Textbook of Endocrinology
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Textbook of Endocrinology

Mala Dharmalingam MBBS, MD, DM (AIIMS)
Editor
Professor of Endocrinology
Department of Endocrinology
MS Ramaiah Medical College
Bengaluru, India

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Contributors

AG Unnikrishnan DM
Assistant Professor
Department of Endocrinology and Diabetes, Amrita Institute of Medical Sciences
Cochin, India

GR Sridhar DM
Consultant
Endocrine and Diabetes Center
15-12-16 Krishnanagar Vishakhapatnam, India

Himanshu M MBBS
Registrar,
MS Ramaiah Medical College
Bengaluru, India

Jubbin Jagan Jacob MD
Senior Registrar
Department of Endocrinology and Diabetes, Amrita Institute of Medical Sciences
Cochin, India

Mala Dharmalingam MBBS MD DM (AIIMS)
Editor and Professor of Endocrinology
MS Ramaiah Medical College
Bengaluru, India

Manisha Sahay MD
Professor of Endocrinology
Head
Department of Endocrinology
Osmania Medical College
Hyderabad, India

Murali Mohan S
MCH Neurosurgery
Neurosurgeon, Columbasia, Bengaluru, India

MV Muralidharan DM
Professor of Endocrinology
Amrita Institute of Medical Sciences
Cochin, India

Nihal Thomas DNB
Associate Professor
Department of Endocrinology
Christian Medical College and Hospital
Vellore, India

Philip Finny DNB
Amrita Institute of Medical Sciences
Cochin, India

Pramila Kalra DM
Assistant Professor
MS Ramaiah Medical College
Bengaluru, India

Priya Chinnappa DBIM
Consultant Endocrinologist
Mallya Hospital
Vittal Mallya Road
Bengaluru, India

Radha Reddy ABIM (American Board)
Consultant Endocrinologist
Chaparral Medical Group
10837 Laurel Avenue
Ranetio Cucamonga
CA 91730
USA

Rakesh K Sahay DM
Professor of Endocrinology
Head
Department of Endocrinology
Osmania Medical College
Hyderabad, India

Rekha Bhat MD DM
Endocrinologist
ACEER
Chennai, India

Rohit S Warrier MBBS
Registrar
MS Ramaiah Medical College
Bengaluru, India

RV Jayakumar DM
Professor
Department of Endocrinology and Diabetes
Amrita Institute of Medical Sciences
Cochin, India

Sriram Mahadevan DM
Endocrinologist
ACEER
Chennai, India

Sudeep K MD DM
Professor
Department of Endocrinology and Diabetes
Amrita Institute of Medical Sciences
Cochin, India

Usha Sriram DBIM
Endocrinologist
Chicago, USA

Vageesh Ayyar S DM
Associate Professor of Endocrinology
St John’s Medical College and Hospital
Bengaluru, India
Preface

The study of endocrinology is basic to understanding medicine. Endocrinology is a subject which has not been dealt with adequately in the undergraduate and postgraduate syllabi. The uniqueness of this book is the fact that the chapters are dealt with a view of understanding and diagnosing the disorders. The object of the book is to present the disorders in a simple and interesting manner and is well illustrated with pictures and algorithms.

The chapters on Thyroid deal with hyperthyroidism, hypothyroidism and thyroid cancer. These are the most common problems faced by physicians next to diabetes. They are comprehensive and help the reader not only in diagnosis but also in management.

The chapters on Reproductive Endocrinology, Polycystic Ovarian Syndrome, Primary Amenorrhea, Male Hypogonadism give insight into the next most common problems that occur in society.

The chapters on Bone Disorders, Rickets and Osteomalacia and Parathyroidism are written with very practical aspects to diagnosing these difficult disorders. The chapters on Pituitary Disorder encompass pituitary lumps and short stature. These have been approached to keep it simple for the physician and the postgraduate.

Adrenal disorders like Cushing’s syndrome and endocrine hypertension have been dealt with length and simplicity, because these are again problems that every physician should know how to approach. Some topics on endocrinology like sexual differentiality, osteoporosis, have been consciously left out as they are complex and may not be relevant to a physician for management.

This book is essentially suited for a physician to easily understand the diagnosis of common problem. The book has been kept simple with plenty of algorithms and tables to make it interesting and aid the physician in problem solving.

Mala Dharmalingam
Acknowledgments

I would like to express my deep gratitude to the SEACON (South Endocrine Associates) members of which have contributed the chapters for the book.

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Dr Rakesh K Sahay for his chapter on Rickets and Osteomalacia.

Dr Pramila Kalra for her chapter on Hyperparathyroidism and Hypoparathyroidism.

I wish to thank my daughter for her patience when this book was getting done and also helping me to compile this book.

I also wish to acknowledge the publishers M/s Jaypee Brothers Medical Publishers (P) Ltd., New Delhi for bringing out this book in a very good manner.
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INTRODUCTION
Before elaborating the approach to short stature, definitions and various terms used in this context are briefly described.

DEFINITION
Height that falls 2 or more standard deviations below the mean for age, gender and preferably ethnic population.

Phases of Normal Growth
a. Infantile: During the first 2 years of life there is rapid growth resulting in gain of 30 to 35 cm.
b. Childhood: During this phase the gain in height is nearly 5 to 7 cm per year.
c. Puberty: Growth results from the combined effects of growth hormone and gonadal steroid surges. The gain in height is up to 8 to 14 cm per year.

Prediction of Adult Height
a. From the height of parents:
   Target height = mid parental height minus 6.5 cm for girls
   Target height = mid parental height plus 6.5 cm for boys
   Target height ± 8.5 cm represents 3rd and 97th centiles for the adult height.
   The difference between the average heights of boys and girls is nearly 13 cm. This difference is taken into account while subtracting 6.5 cm in the case of girls, and adding 6.5 cm in the case of boys, to the mid parental height.
b. From the bone age: The predicted adult height can be read off from Greulich-Pyle or Bayley-Pinneau charts (Table 1.1).
Table 1.1: Prediction of adult stature: Bayley and Pinneau chart

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Approach to Short Stature

Evaluation of Short Stature

The single most important point in the evaluation of short stature is a good physical examination.

i. Is the child really short?
   The height of the child should be plotted on an appropriate growth chart (Figs 1.1 and 1.2). A height that falls below the 3rd centile requires evaluation.

ii. Is there dysmorphism?
   This could suggest:
   - Chromosomal abnormalities
     • Down syndrome
     • Turner’s syndrome
   - Nonchromosomal disorders
     • Noonan syndrome
     • Russel-Silver syndrome
   - Endocrine abnormalities
     • Pseudohypoparathyroidism
     • Pseudo-pseudohypoparathyroidism
     • Laron dwarfism

iii. Is the short stature disproportionate?
   - Short trunk – Spondyloepiphyseal dysplasias
   - Short limbs – Achondroplasia
     • Rickets
     • Childhood or untreated juvenile hypothyroidism

iv. Is the growth rate velocity low?
   Growth rate velocity can be judged by plotting height velocity against time (Figs 1.3 and 1.4).
   A normal growth rate velocity indicates a familial short stature or a constitutional delay in growth and puberty. Growth rate velocity is calculated by measuring height at an interval of 6 months to 1 year. Intervals less than 6 months are too short and should not be used as children do not grow in a linear manner.

v. Is the child too obese?
   Obesity with short stature is seen with endocrine disorders such as:
   • Cushing’s disease
   • Primary hypothyroidism
   • Growth hormone deficiency

vi. Is the child thin?
   A thin and pathologically short child probably has malnutrition or a chronic systemic illness like uncontrolled bronchial asthma, malabsorption, renal tubular acidosis, etc.

Investigations

Determination of bone age is the most important investigation. When coupled with physical examination it holds the key to evaluation of short stature in majority of cases.
2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

Mother's stature | Father's stature
---|---
Date | Age | Weight | Stature | BMP
---|---|---|---|---

*To calculate BMI: Weight (kg) + Stature (cm) + Stature (cm)
x 10,000

Published May 30, 2000 (modified 11/21/00)
Source: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000)

Fig. 1.1: Growth chart—girls
Approach to Short Stature

Fig. 1.2: Growth chart—boys
A normal bone age suggests an intrinsically short growth pattern.\(^3\) This is seen in
- IUGR
- Turner syndrome
- Pseudohypoparathyroidism
- Skeletal dysplasias
- Familial short stature

Bone age is significantly delayed when the growth pattern is delayed or attenuated.\(^4\) In the former, growth rate is normal and in the latter, it is subnormal.

Delayed growth is seen in
- CDGP
- Chronic disease
- Malnutrition

Attenuated growth is characteristic of endocrinopathies.

If clinical examination points towards a specific condition, appropriate investigations should be ordered.
a. Cushing’s disease
   Overnight dexamethasone suppression test or 24-hour urine free cortisol
b. Hypothyroidism
   Serum T₄ and TSH
c. Pseudohypoparathyroidism
   Fasting serum calcium, phosphorus, albumin, alkaline phosphatase, intact PTH
d. Rickets
   Fasting serum calcium, phosphorus, albumin, alkaline phosphatase, 25 hydroxy vitamin D
e. Growth hormone deficiency
   Serum IGF-1, IGFBP3
   Growth hormone stimulation tests

If clinical examination is normal apart from reduced height, the following basic investigations should be ordered:
a. Bone age
b. Complete blood picture
c. Renal function tests
d. Serum electrolytes
e. Fasting calcium profile
f. Liver function tests
g. Urine analysis
h. Free T₄ and TSH
Management

Treatment is directed at the underlying etiology. Malnutrition should be corrected. Underlying systemic illness, if any, should be treated. Hormones, if deficient must be replaced – thyroxine in hypothyroidism, growth hormone in growth hormone deficiency. Conditions considered as normal variants must be explained. Many patients and their caretakers are reassured by this alone.

Low dose gonadal steroids can be offered if puberty is delayed beyond 13 years in girls and 14 years in boys. This will not only promote the development of secondary sexual characters but also cause a mild growth spurt without compromising the final height. A suggested regimen is 5 µg ethinyl estradiol everyday, orally, for girls and depot testosterone 50 mg per m² IM, monthly, for boys. Their height, development and predicted height must be reevaluated at the end of 6 months and a second course may be given if deemed necessary.

Growth hormone therapy is approved for:
- Growth hormone deficiency – 0.18 to 0.3 mg per kg per week
- Turner’s syndrome – 0.375 mg per kg per week
- Chronic renal failure – 0.35 mg per kg per week
- Short stature following IUGR – 0.48 mg per kg per week
- Prader-Willi syndrome – 0.24 mg per kg per week
- Idiopathic short stature – 0.37 mg per kg per week

Growth hormone therapy can be monitored with serum IGF-1 and IGFBP-3

GROWTH HORMONE DEFICIENCY

Most cases of GH deficiency are isolated and idiopathic. Growth hormone deficiency can be caused by:
- Genetic abnormalities of GH production, secretion, or bioactivity
- Genetic abnormalities resulting in combined pituitary hormone deficiency
  - Septo-optic dysplasia
  - POU1F1 deficiency
  - PROP1 deficiency
- Trauma involving the pituitary
- Inflammation involving the pituitary
- Tumors involving the pituitary

The diagnosis of GH deficiency is primarily a clinical one, aided by laboratory support.

Laboratory Evaluation

- Serum levels of insulin-like growth factor 1 (IGF-1)
- GH testing

  Normal levels of IGF-1 are reassuring but do not rule out partial GH deficiency. Random levels of GH are not helpful for the diagnosis of GH deficiency. GH must be measured in
response to a provocative stimulus like insulin, clonidine, arginine, GHRH, L-dopa, etc. Normal children respond with GH concentrations above 10 µg/L. Failure to achieve this level is consistent with the diagnosis of classic GH deficiency. The child must have fasted overnight, be euthyroid, and have no underlying chronic disease or psychosocial deviation. In addition, at least two tests are generally performed using different stimulating agents.

Treatment

Growth hormone replacement is the treatment of choice. A total of 0.18 to 0.3 mg per kg is administered per week by daily subcutaneous injections. Children diagnosed and treated at an earlier age have a better height prognosis than those whose therapy is initiated later. Replacement is continued until a bone age of 15 years in boys and 14 years in girls.

GROWTH HORMONE INSENSITIVITY

The birth weight and length are normal. There is severe growth failure in the postnatal period. Puberty is delayed, but sexual function and fertility are normal. The forehead is prominent, orbits are shallow, nasal bridge is hypoplastic, the sclera may be blue and the voice is high-pitched. These children have a high basal GH levels (>5 µg/L) but low IGF-1 (<50 µg/L). They are treated with IGF-1, if available.

TURNER’S SYNDROME

Any girl with short stature and pubertal delay must be evaluated for Turner’s syndrome. An absent or structurally abnormal second X chromosome causes Turner’s syndrome. The syndrome is characterized by:

- Micrognathia
- “Fishmouth” appearance
- High-arched palate with dental abnormalities
- Epicanthal folds
- Ptosis
- Low-set or deformed ears
- Short neck with low hairline
- Webbing of neck
- Recurrent otitis media
- Broad shield-like chest
- Short fourth metacarpals
- Cubitus valgus
- Extensive pigmented nevi
- Cardiovascular anomalies like coarctation of the aorta, aortic stenosis and bicuspid aortic valves
- Abnormal pelvocaliceal collecting systems, abnormal position or alignment of the kidneys
- Autoimmune diseases, such as Hashimoto’s thyroiditis and Graves’ disease.
Treatment

Treatment is with unopposed estradiol or conjugated estrogen for a year or more, followed by cyclic estrogen and progestins. The short stature of girls with Turner’s syndrome is treated with growth hormone. The outcome is more favorable when growth hormone is initiated at a younger age.

REFERENCES

INTRODUCTION
Before proceeding with the tumors of the pituitary gland, it is essential to know the regional anatomy of the sella and its contents, as the clinical presentation of pituitary tumors depends on the pattern of involvement of these structures, apart from endocrine disturbances.

ANATOMY OF THE PITUITARY GLAND AND ITS SURROUNDINGS
The pituitary gland (hypophysis cerebri) lies in the pituitary fossa, also known as hypophyseal fossa of the sphenoid bone (Fig. 2.1). It is made up of two parts, viz. the adenohypophysis and the neurohypophysis, which have different embryological, morphological and functional characteristics. It is continuous with the infundibulum, which is a conical projection from the inferior aspect of the tuber cinereum (hypothalamus).

![Fig. 2.1: Sphenoid sinus](image-url)
The normal adult pituitary gland is a horizontally positioned ovoid body measuring about 12-15 mm in transverse diameter, 8-10 mm in anteroposterior diameter and 5-7 mm in height.\(^1\) It weighs about 0.5-0.7 gm in an adult male. The weight in a non-pregnant woman is about 100 mg more than in a man. During pregnancy, its weight increases to an average of 0.8-1.0 gm.\(^1,\,2\) The gland is continuous with the infundibulum, which arises from the inferior surface of the tuber cinereum. The infundibulum or the hypophyseal stalk contains an inner core, called infundibular stem, which contains the neural connections of the hypophysis. It is continuous with the median eminence of the tuber cinereum. The neurohypophysis is normally taken to include the median eminence, the infundibular stem and the posterior lobe of the pituitary gland. The adenohypophysis is made up of the pars tuberalis (which surrounds the neural infundibular stem) and...
the anterior lobe of the pituitary gland, which is divisible into pars anterior and pars intermedia.

The pituitary gland has a dual blood supply (Figs 2.3B and C). There is a direct arterial supply common to the anterior and posterior lobes and a portal supply exclusive to the anterior lobe. Luschka described the inferior and superior hypophyseal arteries in 1860. Popa and Fielding described in 1930, the portal system of the pituitary. The arterial supply to the anterior lobe of the pituitary gland may be divided into two groups in relation to the diaphragma sella. The infradiaphragmatic supply to the gland is a capsular network, which also vascularises the diaphragm. The network is made up of branches of the inferior hypophyseal artery, which arises from the meningohypophyseal trunk and direct branches from the intracavernous segment of internal carotid artery (the inferior and anterior capsular arteries). Occasionally, direct branches from the stem of the inferior hypophyseal artery supply the posterolateral part of the anterior lobe and penetrate deeper into the gland than the capsular arteries. The inferior hypophyseal artery is the most important artery supplying the pituitary gland, its diameter being larger than any other arterial structure coursing through the region. The supradiaphragmatic supply is through the middle hypophyseal artery, which is a branch of the superior hypophyseal artery. The vessel is paired and runs on the anterior surface of the stalk. The end arteries of these vessels are found mainly in the subcapsular peripheral zone and the lateral wings of the anterior lobe.

The anterior lobe of the gland receives the portal system, which originates from the capillary bed of the lower infundibular stem. There are two groups of portal vessels, the long and the short, each with their own area of supply. Blood flowing in these two groups of veins do not mix. The long portal vessels supply approximately 90 percent of the parenchyma of the anterior lobe, mainly the anterior and the central portions. The short portal vessels supply a small part of the anterior lobe lying adjacent to the posterior lobe. The blood derived from the portal vessels reaches the sinusoids, which form the vascular bed of the gland and lie between secretory cells. The significance of the portal system is that it carries the hypothalamic regulating hormones to the anterior lobe, thus controlling the secretion of the anterior pituitary hormones. The infundibulum and the posterior lobe of the pituitary are supplied by branches from the superior and the inferior hypophyseal arteries, which form a confluent capillary bed extending from the median eminence through the infundibulum to the posterior pituitary. The medial and lateral branches of the inferior hypophyseal artery form an arterial ring around the infundibular process of the neurohypophysis, while the superior hypophyseal artery supplies branches, termed the arteries of the trabeculae, to the lower infundibular stem. The venous drainage of the anterior lobe of the pituitary is via the inferior hypophyseal veins. The possibility of flow reversal in the portal system raises the possibility of the short portal system acting as a drainage system and providing the short loop feedback for endocrine secretory control. All these veins in turn drain into the anterior and posterior, intercavernous sinus.
Embryology

The adenohypophysis or the anterior pituitary is believed to arise from a diverticulum of the stomatodeum (primitive foregut), prior to the rupture of the oropharyngeal membrane. A saccular recess arise from the lining of the roof of the stomatodeum (the ‘pouch of Rathke’), which later forms a closed vesicle, but remains connected for some time to the ectoderm of the stomodeum by a solid cord of cells. A diverticulum from the floor of the diencephalon grows caudally towards the pouch of Rathke to form the posterior hypophysis. The walls of this hollow diverticulum increase in thickness till the contained cavity is obliterated, except at its upper end, which persists as the infundibular recess of the III ventricle. The posterior lobe becomes invested by the anterior, which extends laterally on either side of it. The anterior lobe also gives off two processes from its ventral wall, which grows along the infundibulum and fuse with it. This forms the tuberal portion of the hypophysis. The original cavity of the stomodeum remains as a cleft and is easily identified in the fully formed gland. The dorsal wall of the stomodeal part fuses with the posterior lobe and forms the intermediate lobe of the pituitary.

Some adenohypophyseal cells have been found to be capable of amine precursor uptake and decarboxylation, thus forming part of the APUD system. These cells are believed to take origin from the neural crest. Takor and Pearse suggest that the ‘ventral neural ridge’ gives rise to the adenohypophysis and is, therefore, of neuroectodermal origin contrary to the classical view. The finding of occasional hypothalamic neurons capable of synthesizing ACTH and MSH lends support to the theory that the posterior and anterior hypophysis shares the same embryonal origin.

Histology

Pars Anterior

Chromophil cells

1. Acidophil (α-Cells)
   - Somatotrophs: These are ovoid and usually grouped along the sinusoids and are the largest and most abundant class of adenohypophyseal chromophils, secreting the protein somatotropin or growth hormone (GH). They stain strongly with orange-G, and ultrastructurally are seen to contain numerous electron-dense, spherical, secretory granules, 350-500 nm in diameter, and a well developed Golgi complex with a central nucleus.
   - Mammatrophs: These cells secrete the polypeptide hormone prolactin (PRL), and are hypertrophy during pregnancy and lactation. They have the largest secretory granules of all hypophyseal cells (over 600 nm in diameter), during pregnancy and lactation. However, it is smaller (200 nm) and fewer in nonpregnant females and in males. These granules are evenly dense, ovoid or irregular, the latter form resulting from fusion. Excess granules fuse with lysosomes to form autophagic vacuoles which degrade unused granules. In active cells, granular endoplasmic reticulum and a Golgi complex are prominent.
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• **Mammosomatotrophs:** These cells are predominantly present in the pars anterior, are characterized by the presence of secretory granules shown contain both GH and PRL, as shown by immuno-electron-microscopy.

2. **Basophils (β-Cells)**

• **Corticotrophs:** The identification of the cells which secrete adrenocorticotropin (ACTH) was difficult to achieve until it was realized that a precursor molecule, pro-opio-melanocorticotropin, is cleaved into a number of different molecules including ACTH, beta-lipotropin and beta-endorphin; the functions of the latter two substances in the pituitary are not known, although the opio-melanocorticotropin complex is also synthesized in neurons of the CNS and has neuromodulator functions. This precursor is glycosylated, making the granules periodic acid-Schiff (PAS) positive; they are also weakly basophilic. These cells are irregular in shape and have short dendritic processes which are inserted among other neighboring cells. Their granules are also small (about 200 nm) and difficult to detect by light microscopy.

• **Thyrotrophs:** These secrete thyroid stimulating hormone (TSH). They are polygonal cells, and lie in clusters towards the adenohypophyseal center. They usually form cellular cords and are not in direct contact with sinusoids. They stain selectively with aldehyde fuchsin. They are characterized by peripherally placed irregular granules that are less electron-dense than in other basophils, measuring about 100-150 nm in diameter and are the smallest granules in adenohypophyseal cells.

• **Gonadotrophs:** These cells are larger than thyrotrophs and are rounded. Usually situated next to sinusoids, these cells have secretory granules with an affinity for PAS stain. In some cells, usually peripheral in the lobe, the granules stain purple while in others, more central, they stain red; it has been suggested that the former secrete FSH and the latter LH or ICSH. Gonadotrophs have pleomorphic nuclei and spherical granules about 200 nm in diameter which tend to gather in lines under the cell surface during secretory activity.

**Chromophobe Cells**

Chromophobe cells constitute the majority of the cells of the adenohypophysis (about half the population of epithelial cells) but, because of their small size and lack of reaction to routine stains, they are not a conspicuous feature of the pituitary. They appear to consist of a number of different types of cells, including degranulated secretory cells of the types described above, stem cells capable of giving rise to chromophils and follicular cells containing numbers of lysosomes and forming cell clusters around cysts of various sizes.

**Folliculostellate Cells**

These are supporting cells and are also involved in trophic and catabolic processes, apart from aiding macromolecular transport. Various peptides with growth factor or cytokine activity have been identified in these cells, which include vascular endothelial growth factor. FS cells express a broad spectrum of cytokeratins indicative of their epithelial nature and supporting the generally accepted but recently challenged hypothesis that the...
adenohypophysis is derived from Rathke’s pouch. They are stellate in shape, detectable by the presence of major histocompatibility complex (MHC) class II determinants and the calcium ion binding protein S-100.

**Pars Intermedia**

This has many β-cells and follicles of chromophobe cells surrounding PAS-positive colloidal material, some of these being derived from pouches of the embryonic intrahypophyseal cleft (of Rathke); Secretory cells of the pars intermedia have granules containing either α-endorphin or β-endorphin scattered uniformly. These cells have also been shown to contain various peptide hormones including ACTH and α-MSH.

**Pars Tuberalis**

This area is characterized by large number of blood vessels, between which cords of undifferentiated cells are admixed with some α- and P-cells. Electron microscopic and immunohistochemical investigations of the human pars tuberalis at have identified gonadotrophs and thyrotrophs. Functional receptors for the pineal hormone melatonin, known to influence circadian systems and photoperiodicity via the hypothalamo-hypophyseal-gonadal axis, have been found in the pars tuberalis. Depending on the amount of melatonin secreted by the pineal gland and the receptivity of cells of the pars tuberalis to it, the latter seems able to respond by varying its secretion of a peptide hormone which modulates the gonadotrophic and thyrotrophic activity of the pars anterior reaching it via the portal plexus.

**SELLA TURCICA (FIG. 2.4)**

The pituitary gland is housed in the hypophyseal or pituitary fossa of the body of the sphenoid bone. There are many variations in the bony surroundings of the pituitary gland due to the complex embryology of the region. The pituitary fossa is delineated in front by the tuberculum sella and chiasmatic sulcus. The dorsum sella and the posterior clinoidal processes form the posterior relationship. The sellar floor, which separates the sellar contents from the underlying sphenoid sinus, extends from the tuberculum sella in front to the base of the dorsum sella posteriorly. Renn and Rhoto found the thickness of the sellar floor to be equal to or less than one mm in 82 percent of specimens and more than one mm thick in 18 percent. Occasionally, the floor was very thin, only a few microns thick. The pituitary fossa has a depth of 10-12 mm with an upper limit of 13 mm; an anteroposterior diameter of 5.16 mm with an upper limit of 17 mm and a width of 10-15 mm. DiChiro and Nelson have found the mean sellar volume to be 594 cu mm using their simplified mathematical formula:

\[
\text{Volume (in cu cm)} = \frac{0.5 \times \text{length} \times \text{width} \times \text{depth in mm}}{1000}
\]
The diaphragma sella forms the roof of the pituitary fossa. It is a fold of dura mater, more often rectangular than circular and has a central opening, which transmits the infundibulum. Anatomical variations of the diaphragma sella are frequent. These have been classified by Busch (Fig. 2.5) into Type I—a funnel shaped depression of the diaphragma sella; Type II—incomplete closure of the diaphragm around the pituitary stalk; Type III—a wide defect in the diaphragm so that there is only a peripheral rim of tissue measuring less than 2 mm in width. This may leave the pituitary gland completely exposed and covered only with arachnoid (IIIa) or may be associated with symmetrical or asymmetrical indentation of the pituitary gland by the herniated arachnoid pouch (IIIb) or there may be a complete remodelling or flattening of the pituitary gland (IIIc). The last defect has been found in 5.5 to 6.7 percent in autopsy series. Bergland et al found anatomical defects in the diaphragma sella of greater than 5 mm in 37 percent of consecutive autopsy cases without pituitary disease. These defects in the diaphragma sella occur six times more in females than in males. Through the defect in the diaphragm, the arachnoid invariably extends and spreads out on the upper surface of the anterior lobe of the pituitary gland. This CSF filled space, called the pituitary cistern, usually enlarges with advancing age. The cistern can extend for a variable distance forwards and laterally and, occasionally, can even cover the posterior lobe. The diaphragm is usually thick at the periphery and thin at the center.
Sphenoid Sinuses

The sphenoidal sinuses are described as paired cavities lying side by side in the body of the sphenoid bone. They are separated by a bony septum, which is commonly deflected to one side or the other. The cavities vary in shape and size, are usually asymmetrical and are subdivided by minor septae. The main septum separating the sinus into the two major cavities was seen in 68 percent of Renn and Rhoton’s specimens. It is usually directed anteroposteriorly and may be vertical in 25 percent. The position of the septum can be located by tomograms and if located near the midline, can be used as a guide during the trans-sphenoidal approach to the pituitary fossa. However, the major septum has been seen to be away from the midline in up to 46 percent. In 43 percent, only the anterior part lies in the midline, while the rest of the septum is S, C or L shaped. The septum lies in the midline only in 27 percent. Accessory septae arising from the synchondroses of the sphenoid are found in 76 percent. In 48 percent they are unilateral, while in 28 percent they are found bilaterally.

Hamberger et al classified the sphenoid sinus into three main anatomical types (Fig. 2.6): (a) The “Conchal” type is usually found in children, but may be seen in up to 3 percent of adults. In this type the sinus does not extend into the body of the sphenoid. It is small, and between it and the pituitary fossa is spongy bone, which may be as thick as 10 mm. (b) The “Presellar” type is found in 11-20 percent of adults. Here, the sphenoid sinus does not penetrate the body of the sphenoid bone beyond a plane perpendicular to the planum sphenoidale. The anterior wall of the sella, therefore, does not bulge into the sphenoid sinus. (c) “Sellar” type of sphenoid sinus occurs in 80-86 percent of adults. In this type, the sella has a thin floor and bulges into the sinus and, occasionally, the sinus can extend from the dorsum sella to the upper clivus.
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Carotid Arteries
The proximity of the carotid arteries to the midline is extremely important in pituitary surgery. The carotid arteries bulge into the superolateral wall of the sphenoid sinus in 71 percent. These are usually covered by bone, but, in 4 percent, there may be no bone between the carotid arteries and the mucosa of the sinus. The average distance between the intracavernous portions of the two carotid arteries is 12-14 mm. However; the carotid siphon can be quite tortuous, sometimes narrowing the distance to 4 mm or occasionally, coursing laterally to an intercarotid distance of 23 mm. The intercavernous venous connections traverse the anterior surface of the pituitary gland in 76-85 percent of cases or the posterior surface in 37 percent.

Venous Sinuses (Fig. 2.7)
The Cavernous Sinuses, one on each side of the sphenoid bone, are trabeculated structures beginning at the superior orbital fissure and stretching as far as the apex of the petrous parts of the temporal bones. The internal carotid artery passes forward on the most medial aspect of each sinus, and just lateral to it is the abducens nerve. In the lateral wall are the oculomotor, trochlear and the ophthalmic and maxillary divisions of the trigeminal nerves. Tributaries to the cavernous sinuses include the superior and inferior ophthalmic veins, superior middle cerebral vein, inferior cerebral veins and the sphenoparietal sinus (with the central vein of the retina sometimes a direct tributary as well). The cavernous sinuses drain chiefly into the internal jugular vein via the inferior petrosal sinuses and into the pterygoid plexuses via several small emissary veins.
The **Intercavernous Sinus (Circular Sinus)** forms a venous collar around the stalk of the pituitary gland and connects the two cavernous sinuses.

The **Superior Petrosal Sinuses** connect the cavernous with the transverse sinuses and run in the margin of the tentorium cerebelli, crossing the trigeminal nerve. They receive veins from the tympanic cavity, cerebellum and inferior parts of the cerebrum.

The **Inferior Petrosal Sinuses** begin at the cavernous sinuses, pass through the jugular foramen and enter the internal jugular vein. Each receives the labyrinthine veins and veins from the medulla oblongata, pons and cerebellum.

The **Basilar Plexus** lies over the basilar portion of the occipital bone. The plexus consists of interlacing venous channels, communicates with the two inferior petrosal sinuses and drains blood from the anterior vertebral plexuses.

### SUPRASELLAR ANATOMY (FIG. 2.8)

The anatomy of the suprasellar region can be conveniently studied in relation to the optic nerves and chiasm and the circle of Willis. Basic to this anatomy is an understanding of the relationship between the carotid artery, the optic nerve and the anterior clinoid process. The carotid artery and the optic nerve are medial to the anterior clinoid process. The artery exits the cavernous sinus beneath and slightly lateral to the optic nerve.

**Optic Nerve**

The optic nerve pursues a posteromedial course towards the chiasm and the carotid artery. The optic nerve enters the optic canal through its anterior opening in the apex of the orbital
Anatomy of the Sellar and Suprasellar Region

roof about 5 cm posterior and 1.5 cm inferior to the supraorbital margin. This anterior opening is called the ‘optic foramen’. The optic canal itself is formed by the union of the two roots of the lesser wings of the sphenoid bone. The proximal (orbital) opening of the optic canal may be round, but it is usually elliptical in shape and the distal (intracranial) opening is always elliptical with its widest diameter in the horizontal plane. There is a gradual widening of the canal from its orbital to its intracranial end. The canal is about 10 mm in length, with the lateral wall being shorter (9 mm) than the medial wall (about 14 mm).21-23

Each optic canal runs posteriorly and medially at an angle of about 35 degrees with the midsagittal plane, continuing in the direction of the lateral orbital wall, so that, if each continued posteriorly, they would meet at the center of the dorsum sella. The distance between the two proximal orbital openings averages 28 mm; between the two distal intracranial openings it is 14.7 mm. Each canal transmits the optic nerve, the ophthalmic artery, and some filaments of the sympathetic carotid plexus and the orbital extension of the cranial leptomeninges. Above each optic canal is a plate of bone that separates it from the frontal lobe of the brain in the region of the olfactory tract. Medially, the sphenoid sinus and the posterior ethmoidal air cells border the canal.24

The intraorbital optic nerve moves freely as the eye moves; however, the intracanalicular optic nerve is tightly fixed within the optic canal.25, 26 The dura is adherent to the bone of the canal on one side and the optic nerve on the other. Thus, small lesions arising within the optic canal or at either of its openings may compress and significantly damage the optic nerve while still quite small and difficult to visualize even with thin-section CT scanning and MR imaging.
Distal to its exit from the optic canal, the optic nerve is covered by a reflected leaf of dura, the falciform process, which extends medially from the anterior clinoid process across the top of the optic nerve. The length of nerve covered by dura only, at the intracranial end of the optic canal, may vary from less than 1 mm to as much as 1 cm. Compression of the optic nerves against the sharp edge of the falciform process may result in a visual field deficit even if the compressing lesion does not damage the nerve enough to cause visual loss. 

The intracranial part of the optic nerve exits from the orbit and optic canal past a firm fold of dura that covers it superiorly and to some extent on both sides. Bergland et al (1968) found that the distance between the optic nerves as they exit from the optic canal averages 13 mm. The two nerves then run posteriorly, superiorly and medially to join at the optic chiasm. The length of the intracranial segment of the normal optic nerve varies considerably. It is usually about 15 mm long, but it may be as short as 3 mm or as long as 18 mm. This portion of the nerve is about 4.5-5 mm in average diameter, but it is flattened and, thus, is wider in the horizontal plane than in the vertical plane. When the intracranial optic nerve is shorter than about 12 mm, the optic chiasm is positioned anteriorly, sits directly over the sella turcica and is called “pre-fixed”. When the intracranial optic nerve is long (over 18 mm), the chiasm is positioned posterior to the dorsum sella and is called “post-fixed” (Fig 2.9). The variation in the length of the optic nerve is extremely important with respect to the visual deficits caused by tumors in the suprasellar region. A sellar tumor with suprasellar extension will cause the classical bitemporal hemianopia or a bitemporal superior quadrantanopia when the optic nerves are of normal length and position. However, with short optic nerves and the chiasm in a pre-fixed position, the same tumor would cause pressure on one or both optic tracts, causing a homonymous hemianopia.
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The leptomeninges that surround the optic nerve—the dura mater, arachnoid and pia mater—are continuous with the leptomeninges of the brain and are known collectively as the vaginal sheaths of the optic nerve. As the dural sheath approaches the globe, its anterior rim splays out slightly and fuses with the sclera surrounding the optic nerve. At the apex of the orbit, this sheath is continuous with the periorbita of the optic canal and passes through the foramen where it fuses with the intracranial dura that lines the base of the skull. Thus, the intracranial portion of the optic nerve is surrounded only by arachnoid and pia mater, not dura. The arachnoid that surrounds the optic nerve consists of a trabeculum of collagenous and elastic fibers that is identical with arachnoid tissue elsewhere in the CNS. It is lined with typical endothelial cells. The pia mater, also composed of collagenous fibers, elastic fibers and a fused glial layer, invests the nerve and sends fibers into it to form characteristic septa. The pia is a very thin and delicate membrane that is adherent to the nerve. Behind the globe, the pia joins the sclera and choroid; posteriorly, it continues through the optic foramen to form the single covering of the intracranial optic nerve. The space between the arachnoid and the pia mater is continuous with the intracranial space and is a repository for CSF, which flows from intracranial spaces through the subarachnoid space along the optic nerve.

Optic Chiasm

The position of the optic chiasm varies. Schaeffer\textsuperscript{29} found it lies (a) in the sulcus chiasmaticus in 5 percent and (b) over the diaphragma sella in 12 percent. When the chiasm lies in either of these two positions it is called a “pre-fixed chiasm”. The chiasm lies over the dorsum sella, which is its normal position in 79 percent. In the “post-fixed position” the chiasm lies over and behind the dorsum sella and this is found in 4 percent of cases. The chiasm is related postero-superiorly to the lamina terminalis of the III ventricle. Lying partly on the superior surface of the optic chiasm is the anterior cerebral artery complex.

Arteries of the Suprasellar Region (Fig. 2.10)

All the arterial components of the circle of Willis and the adjacent carotid artery lie in the suprasellar region and multiple perforating branches originate from them. The anatomical relationships may get distorted when these vessels get stretched over tumors with suprasellar extensions.\textsuperscript{16} The supraclinoid portion of the carotid artery, in addition to giving off the posterior communicating and anterior choroidal arteries, also gives off perforating branches, which include the superior hypophyseal artery and other branches passing to the optic nerve, chiasm, anterior hypothalamus and anterior perforated substance. The posterior circle of Willis and the terminal basilar artery also send a series of perforating arteries through the suprasellar area into the diencephalon and midbrain and these arteries may become stretched over tumors in this region. The internal carotid artery (ICA) enters the dura and the carotid cistern inferomedial to the anterior clinoid process. The process covers the proximal part of the ICA to a varying degree.\textsuperscript{30} The ICA then runs upwards, laterally and posteriorly to its bifurcation, describing a lazy curve in relation to the optic nerve. This relation to the nerve is important in surgical exposure of lesions in the suprasellar region.
Hyperplasia refers to a non-neoplastic increase in cell number. Although physiologic hyperplasia of the pituitary is a well known fact, the occurrence of pathological focus of pituitary cell hyperplasia has long been questioned. Until recently, this issue was controversial, but now it has been proved conclusively that pathological forms of hyperplasia do occur and that on rare occasions they can produce both pituitary enlargement and a hypersecretory state in the absence of an adenoma. Pituitary cell hyperplasia is not a precursor of adenoma, though a zone of hyperplastic cells is observed around the adenoma. Even when present, pituitary hyperplasia can be difficult to diagnose. The small, fragmented nature of surgical specimens coupled with the normal histological pattern of pituitary cells, significantly complicates identification of hyperplastic foci. Hyperplasia is best recognized on reticulin stains and on immunohistochemical studies. The essential pathological feature is expansion of acini with retention of the acinar morphological features. It generally involves cells of a single type; rarely, several cell types may be affected simultaneously.

**PRL Cell Hyperplasia**

The most common form of PRL cell hyperplasia is physiologic and occurs during pregnancy and lactation. In this context, proliferation of PRL cells results in more than a 100 percent increase in the size of the gland. Another common form of PRL cell hyperplasia occurs as a result of the stalk section effect (i.e. interruption of dopamine delivery to the anterior lobe as a result of any of a variety of sellar and suprasellar lesions). The presence of PRL hyperplasia adjacent to some corticotroph adenomas remains unexplained. In cases of long-standing primary
hypothyroidism, PRL cell hyperplasia may be caused by the trophic effects of thyrotropin-releasing hormone. Isolated lactotroph hyperplasia as the primary case of hyperprolactinemia is extremely rare, as is the coexistence of PRL cell hyperplasia with a prolactinoma.

**GH Cell Hyperplasia**
GH cell hyperplasia is a rare phenomenon. In almost all instances, somatotroph hyperplasia occurs as the result of an extra-pituitary GHRH-producing tumor (e.g. pancreatic islet cell tumor, pheochromocytoma, bronchial or intestinal carcinoid, or small cell carcinoma of the lung). In response to the stimulatory effect of this trophic peptide, pituitary somatotrophs enlarge, proliferate, produce excess GH, and cause clinical acromegaly. The same phenomenon occurs with GHRH-producing hypothalamic hamartomas and neuronal choristomas of the pituitary. Although GHRH-producing tumors are rare causes of acromegaly, they always must be considered in the differential diagnosis of acromegaly. Idiopathic GH cell hyperplasia has yet to be demonstrated conclusively as a cause of acromegaly.

**Corticotroph Hyperplasia**
Considerable debate surrounds the role of idiopathic corticotroph hyperplasia as a cause of Cushing’s disease. Corticotroph hyperplasia alone, or in combination with a corticotroph adenoma, is responsible for as many as 15 percent of all cases of pituitary-dependent Cushing’s disease. Such cases of Cushing’s disease are more refractory to cure by all but total hypophysectomy because hyperplastic foci either remain or are newly induced from the ongoing hyperplastic stimulus. Development of corticotroph hyperplasia in response to various extra-pituitary corticotropin releasing hormone-producing tumors (e.g. neuroendocrine neoplasms and hypothalamic or adenohypophyseal gangliocytomas) is well documented. In these cases, the hyperplasia may produce such an enlarged pituitary that the disease may mimic a pituitary adenoma.

**Thyrotroph Hyperplasia**
Hyperplasia of TSH-producing cells occurs exclusively in the context of long-standing hypothyroidism. Frequently, the hyperplasia enlarges the pituitary and simulates an adenoma. The surgeon should be aware of this lesion because numerous cases of thyrotroph hyperplasia have been treated inadvertently with surgical resection without the benefit of medical therapy. Thyroid hormone replacement alone is curative in some cases. Given the trophic effect of thyrotropin-releasing hormone on PRL cells, PRL cell hyperplasia often accompanies thyrotroph hyperplasia in this setting.

**Gonadotroph Hyperplasia**
Hyperplasia of gonadotrophs is extremely rare and difficult to recognize even in pronounced cases. Although it has been reported in the pituitaries of patients in whom primary hypogonadism commenced at a young age, it is unlikely predecessor to adenoma formation.
REFERENCES

29. Schaeffer JP. Some points in the regional anatomy of the optic pathway, with special reference to the tumours of the Hypophysis cerebri and resulting ocular changes. Anat Rec 1924;28:243.
INTRODUCTION

Optimal functioning of the human body demands a constant internal environment including a constant tonicity. A great deal of the stability of this internal environment depends on the adequacy and dependability of water metabolism. In spite of the large variation in the intake of water and/or solutes, a remarkable relatively narrow range of osmolality is maintained. This accomplishment is contingent on multiple factors, including hypothalamic Osmoreceptors, Arginine vasopressin (AVP) and vasopressin receptors in the renal tubules. Deficient secretion or action of AVP results in diabetes insipidus (DI), while its inappropriate secretion results in syndrome of inappropriate ADH (SIAD).

History

In 1895, Oliver and Schafer reported potent hypertensive effect of fresh pituitary gland extracts injected intravenously. The pressor activity was subsequently shown to reside solely in the neurohypophysis. The renal effects of these extracts were described later, with the demonstration that they could reverse the polyuria caused by mechanical injury to the pituitary. The efficacy of pituitary extracts in the treatment of patients with diabetes insipidus was described in 1913. Verney in 1947 was the first to propose that secretion of the pituitary antidiuretic hormone was regulated by the osmolality of body water.

Neuroanatomy

The posterior lobe of the pituitary gland is an extension of the forebrain. It contributes to 20% of pituitary gland weight. It consists of nerve fibers, nerve endings with neurosecretory granules containing vasopressin, oxytocin and neurophysins and glial cells. It has a affluent arterial blood supply independent of the anterior lobe. It gets its blood supply from the inferior hypophyseal arteries, which is a branch of internal carotid arteries. Antidiuretic hormone (ADH) is nonapeptide often referred to as arginine vasopressin (AVP) in humans. It is produced by large neurons that originate in the supraoptic (SON) and paraventricular
nucleus (PVN) of the hypothalamus and projects through the pituitary stalk to terminate on capillary plexuses scattered throughout the posterior pituitary. These plexuses deplete into the systemic circulation through the cavernous sinus. AVP is resultant from a large 145 amino acid precursor molecule comprising a signal peptide, AVP, AVP specific neurophysin and a glycosylated moiety. The gene that encodes AVP is located on chromosome 20. After synthesis in the cytosol of magnacelluar neurons, the precursor is translocated into the endoplasmic reticulum. As this precursor complex migrates along the neuronal axons, it undergoes specific cleavage to form AVP which is stored as neurosecretory granules in the posterior pituitary. It is released by an excitatory stimulus along with its specific neurophysin in equimolar quantities to the systemic circulation. It has half-life of about 20 minutes. After release it circulates unbound to proteins in the blood but does bind to platelets. It gets metabolized by enzymatic cleavage and at least four main sites of enzymatic cleavage have been identified on its molecule. During pregnancy, an extremely active cysteine amino peptidase or vasopressinase of placental origin degrades it rapidly.

**Neurophysiology**

*Control of Secretion*

Neurophysiological hormone release is mediated by sensory signals. The key regulatory influences under physiologic conditions are the effective osmotic pressure and extracellular fluid. The relationship of the SON and PVN with autonomic afferents and CNS nuclei are responsible for osmo-and baro-regulation of AVP.

*Neurotransmitters*

Two major classes of substances, the biogenic amines and peptides act as neurotransmitters that regulate the secretion of AVP. The roles of individual neurotransmitters in the regulation of neuro-hypophyseal hormone production are difficult to define. This reflects the intricacy of the neurophysiologic processes involved and the complexity in integrating experimental data from disparate models.

Dopamine is an inhibitory neurotransmitter in the posterior pituitary. Central norepinephrine fibers stimulates AVP release via alpha receptors. Acetylcholine, nitric oxide synthase, excitatory amino acids glutamate, aspartate and Angiotensin II stimulate AVP release. Many other substances have been implicated in the neurotransmitter control of AVP, but their physiologic significance remains uncertain.

*Osmoregulation*

Plasma osmolality is the most imperative determinant of AVP secretion. The osmoregulatory system for thirst and AVP secretion maintains plasma osmolality within the fine limits of 284 to 295 mOsm/kg. Increases in plasma osmolality increase plasma AVP concentrations in a linear manner. The plasma osmolality habitually starts to increase at 284 mOsm/kg and this
is the mean osmotic threshold for AVP release. Despite sizeable inter-individual variation in both threshold and sensitivity of AVP release, these constants remain unmoved within an individual over a short period of time.

Pregnancy causes a lowering of the threshold of AVP secretion without alteration of the gain of the osmoreceptors which accounts for the hypo-osmolality of pregnancy. A similar though inconsequential change occurs in the luteal phase of the menstrual cycle. The response of the osmoreceptor or solutes other than sodium chloride is incoherent. A plasma AVP concentrations of 0.5 pmol/L or less, achieves utmost diuresis. And ceiling antidiuresis is achieved at plasma AVP concentrations of 3-5 pmol/L, which approximates a urine osmolality of 1200 mOsml/Kg and a urine flow of 10 ml/kg/d. The aging process has a substantial effect on osmoregulation. Basal circulating AVP concentrations increase with age and there is enhanced response of AVP to osmotic stimulation.

Baroregulation
Blood volume and pressure are generally recognized as having an influence on AVP secretion. A 10-20% fall in blood pressure is crucial to stimulate AVP secretion and the relationship between blood pressure and AVP is exponential. These hemodynamic effects are mediated by neural pathways that originate in pressure sensitive receptors in the walls of the left atrium and large arteries. They seem to have little or no influence on AVP secretion under customary conditions, but probably contribute significantly to the osmoregulatory abnormalities found in conditions associated with hypovolemia.

Other Regulatory Mechanisms
Nausea, emesis, abdominal manipulation, neuroglycopenia and stress are other potent stimuli to AVP secretion. However, the precise role of AVP in the stress response remains divisive.

Biological Action of Arginine Vasopressin

Renal effects: Although AVP has manifold actions, their principle physiological effect is in the regulation of water reabsorption in the medullary thick ascending limb and the collecting tube. This effect is mediated via receptor V₂. The increase in water permeability is mediated by a cascade of events which increases the hydro-osmotic permeability of the cell by perforating its luminal surface with pre-formed water channels known as ‘Aquaporins’.

Cardiovascular effects: AVP is a potent pressor agent, its effects mediated via a specific membrane receptor V₁. The systemic effects on arterial blood pressure are only apparent at high concentrations due to compensatory buffering hemodynamic mechanisms. Nevertheless, AVP is essential in maintaining blood pressure in mild volume depletion.

Effects on the pituitary: AVP is an ACTH secretogogue, acting through pituitary corticotroph specific V₁ receptors. AVP and corticotrophin releasing factor (CRF) act synergistically, though the effect is weak in isolation.
**Distribution and Clearance of AVP**

Plasma AVP is determined by its volume of distribution and the rate at which it is excreted and metabolized. Most AVP is degraded, probably in the liver. About 15-20% of AVP is filtered by the glomerulus and then variably reabsorbed and destroyed in the proximal tubules or excreted in the urine. Under normal circumstances the urinary clearance of AVP is approximately 15% of creatinine clearance.

**Thirst and AVP**

Thirst and the drinking response to thirst are key components maintaining fluid homeostasis. Thirst is also regulated primarily by hypothalamic osmoreceptors that are exquisitely sensitive to changes in the effective osmotic pressure. The only difference is that the osmotic threshold at which thirst begins is about 5-10 mOsm/kg higher than the threshold for AVP release; therefore over thirst and polydipsia are not stimulated until an increase in sodium intake or water loss raises plasma osmolality by 1-2 %—a change that is normally enough to evoke a maximum antidiuretic response.

### DIABETES INSIPIDUS

**Definition and Classification**

Diabetes insipidus or polyuria can be defined by the excretion of copious urine, in excess of 3 L/24 hrs ( > 40 ml/kg/24 hr in adults, >100 ml/kg/24 hrs in infants). There is large volume of urine that is hypotonic, dilute and tasteless. Four pathologic mechanisms related to vasopressin produce the following conditions:

1. Hypothalamic (central, cranial, pituitary or neurohypophyseal) DI (HDI) with inability to secrete and usually to synthesize vasopressin in the neurohypophyseal system.
2. Nephrogenic DI (NDI), in which there is an inappropriate renal response to vasopressin.
3. Gestational DI (GDI) produced by the accelerated metabolism of AVP.
4. Dipsogenic DI (DDI) in which the preliminary pathophysiology involves the ingestion of fluid rather than the excretion of fluid.

**Hypothalamic DI (HDI)**

HDI is an uncommon disorder, with an estimated prevalence of 1:25000 with an equal gender distribution. Destruction of at least 80% of hypothalamic neurons synthesizing AVP is necessary before expression of symptoms. Though persistent polyuria can lead to dehydration, given free access to water, most patients can maintain water balance through an intact thirst mechanism.

**Etiology:** The preponderance of causes of HDI is acquired. Trauma produces HDI through damage to hypothalamus, pituitary stalk or posterior pituitary. Pituitary stalk trauma may lead to a triphasic disturbance in water balance; an immediate polyuria characteristic of HDI followed within days by a more lingering period of antidiuresis indicative of AVP surplus. This phase can be followed by reversion to HDI or recovery. Not all phases of the response
may be perceptible. Though primary pituitary tumors rarely cause HDI, hypothalamic or pituitary metastases can present with HDI. In childhood, hypothalamic tumors are reasonably common causes of HDI. Familial forms account for 5% of HDI. Wolfram or DIDMOAD syndrome (DI, Diabetes mellitus, optic atrophy and deafness). Autosomal dominant familial HDI is caused by mutations in the AVP gene on chromosome 20.

**Nephrogenic DI (NDI)**

NDI is due to renal resistance to the antidiuretic effects of AVP (Table 3.1). Primary familial forms are rare. The X-linked form usually presents in the first year of life and is caused by mutations of the V2 R gene on the X chromosome. The Autosomal recessive and dominant forms are due to novel mutations in the aquaporin 2 gene (AQP2). More commonly, NDI is due to a array of acquired metabolic or drug effects. The final common pathway producing NDI in many of these is down regulation of AQP2 expression. Table 3.1 gives a classification of diabetes insipidus.

<table>
<thead>
<tr>
<th>Table 3.1: Classification of diabetes insipidus</th>
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<tbody>
<tr>
<td><strong>Hypothalamic diabetes insipidus</strong></td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>• Genetic (autosomal dominant)</td>
</tr>
<tr>
<td>• DIDMOAD (Wolfram) syndrome</td>
</tr>
<tr>
<td>• Idiopathic</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
<tr>
<td>• Head injury</td>
</tr>
<tr>
<td>• After cranial surgery</td>
</tr>
<tr>
<td>• Tumors (craniopharyngioma, pinealoma, germinoma, pituitary macroadenoma, hypothalamic metastases)</td>
</tr>
<tr>
<td>• Granulomata (sarcoidosis, histiocytosis)</td>
</tr>
<tr>
<td>• Infections (meningitis, encephalitis)</td>
</tr>
<tr>
<td>• Infundibuloneurohypophysitis</td>
</tr>
<tr>
<td>• Vascular (infarction, aneurysms, sickle cell anemia)</td>
</tr>
<tr>
<td>• Pregnancy (associated with vasopressinase)</td>
</tr>
<tr>
<td>• Autoimmune</td>
</tr>
</tbody>
</table>

| **Nephrogenic diabetes insipidus**            |
| Primary                                       |
| • Genetic (X-linked recessive, V2 receptor gene) |
| • Genetic (autosomal recessive, aquaporin-2 gene) |
| • Idiopathic                                  |
| Secondary                                     |
| • Chronic renal disease (polycystic kidneys, obstructive uropathy) |
| • Metabolic disease (hypercalcemia, hypokalemia) |
| • Drug induced (lithium, demeclocycline)      |
| • Osmotic diuresis (glucose, mannitol)        |
| • Systemic disorders (amyloidosis, myelomatosis) |
| • Pregnancy                                  |

| **Dipsogenic diabetes insipidus**            |
| Primary hyperdipsia                          |
| • Idiopathic                                  |
| • Associated with psychosis                   |
| • Hypothalamic disease (sarcoidosis)         |
| • Drug induced (anticholinergic, tricyclic antidepressants, lithium) |
| • Autoimmune (multiple sclerosis)            |
**Posterior Pituitary and Disorders of Water Homeostasis**

**Gestational DI (GDI)**

GDI is due to a primary deficiency of plasma AVP resulting from accelerated degradation of the hormone by a vasopresinase produced in the placenta. This syndrome has been referred to as vasopressin resistant diabetes insipidus of pregnancy. The symptoms occur only during pregnancy and usually remit 3 to 6 weeks after delivery. An underlying deficiency in AVP secretion may also be involved in some, if not all patients.

**Dipsogenic DI (DDI)**

It is a syndrome of excess fluid intake and consequent polyuria. It is a manifestation of primary hyperdipsia, psychiatric disease or secondary to drug effects. DDI in the absence of other identifiable illness is compulsive water drinking (Up to 20% of patients with chronic schizophrenia have polydipsia). It is associated with abnormalities of thirst perception, including a low osmotic threshold for thirst; an exaggerated thirst response to osmotic challenge; and an inability to suppress thirst at low osmolalities. The structural and/or functional basis for any of these abnormalities have not been identified. Confirmation of the diagnosis of DDI is through direct or indirect concealment of normal osmoregulated AVP release and antidiuretic action.

**Differential Diagnosis**

In all types of chronic DI maximum urinary concentrating capacity is reduced by polyuria per se. This blunting is comparative to the severity of the DI and may be the result of washout of the medullary concentration gradient or inhibition of synthesis. It usually corrects within 24 to 72 hours if the polyuria is eliminated for that length of time; however it further complicates the interpretation of urine osmolality data during fluid restriction or other short tests commonly used for the differential diagnosis of DI. When suspected from the clinical history, the diagnosis of DI should be verified by measuring the volume, osmolality and creatinine content of a 24-hour urine collection. The osmolality or specific gravity of a random urine sample is less reliable because the values in patients with or without diabetes insipidus can be transiently elevated or depressed by short-term changes in fluid intake, posture or other activities.

The key to the laboratory differential diagnosis of diabetes insipidus is to determine whether the antidiuretic response to an osmotic or non-osmotic stimulus is deficient and if so, whether the deficiency is caused by a primary defect in the secretion or action of AVP. The test commonly used clinically is a dehydration test in a controlled environment, followed by a response to administered vasopressin or to the analogue desmopressin. If the patient has mild polyuria, the test may begin in the evening with the majority of dehydration taking place overnight. If patient gives a history of large volumes of urine during the night, it is best to perform the test during the day. A standard protocol is outlined in Table 3.2.
HDI can be distinguished by urine osmolality less than 300 mOsm/kg accompanied by plasma osmolality greater than 290 mOsm/kg after dehydration. Urine osmolality should rise above 750 mOsm/kg after desmopressin. In contrast, failure to increase urine osmolality above 300 mOsm/kg after dehydration or desmopressin is diagnostic of NDI. Patients with DDI should concentrate urine appropriately during dehydration without significant rise in plasma osmolality.

In reality, however, many patients have incomplete defects and mild forms of DI. The dehydration test can be a poor discriminator in these circumstances. An accurate diagnosis of HDI can be made by direct measurement of plasma AVP during the controlled osmotic stress of a hypertonic 5% saline infusion. Patients with HDI have undetectable AVP. In NDI, plasma AVP is inappropriately high for the prevailing urine and plasma osmolality indicating AVP resistance. In DDI, the relationship of plasma AVP to osmolality is normal.

Direct measurement of plasma AVP in response to osmotic stimulation differentiates HDI from other causes of polyuria. However, access to reliable AVP assays is limited. Thus, a dynamic test using a surrogate end point of AVP release has been developed. Imaging of the hypothalamus, pituitary and surrounding structures is essential in patients with HDI. MRI is the modality of choice. HDI is associated with the loss of normal hyperintense signal of the posterior pituitary on T₁-weighted images. Signal intensity is correlated strongly with AVP content of the gland.

The different types of diabetes insipidus can also be distinguished by a two-day trial of desmopressin on libitum fluid intake. However, this approach to the diagnosis should be used with great caution because it usually results in water intoxication in patients with primary polydipsia. For all practical purposes, the therapeutic trial should be conducted in a hospital when the possibility of primary polydipsia cannot be excluded.

<table>
<thead>
<tr>
<th>Protocol for water deprivation test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparation</strong></td>
</tr>
<tr>
<td>- Fluid given overnight prior to test</td>
</tr>
<tr>
<td>- Avoid caffeine and smoking</td>
</tr>
<tr>
<td>- Weigh patient</td>
</tr>
<tr>
<td><strong>Dehydration phase</strong></td>
</tr>
<tr>
<td>- Draw blood and collect urine for osmolality and urine volume measurements at 8 A.M.</td>
</tr>
<tr>
<td>- Restrict fluids up to 8 hr</td>
</tr>
<tr>
<td>- Weigh patient at 2-hr intervals</td>
</tr>
<tr>
<td>- Collect blood and urine for osmolality and volume measurements at 2-hr intervals</td>
</tr>
<tr>
<td>- Stop test if weight loss exceeds 5% of starting weight or thirst is intolerable</td>
</tr>
<tr>
<td>- Supervise patient closely to avoid surreptitious drinking</td>
</tr>
<tr>
<td><strong>Desmopressin phase</strong></td>
</tr>
<tr>
<td>- Inject 1g if desmopressin intramuscularly</td>
</tr>
<tr>
<td>- Allow patient to eat and drink up to 1.5-20 times the volume of urine passed during dehydration phase</td>
</tr>
<tr>
<td>- Collect urine for osmolality and volume at 9 P.M.</td>
</tr>
<tr>
<td>- Draw blood and collect urine for osmolality ad volume measurements at 9 AM the next day.</td>
</tr>
</tbody>
</table>
Treatment

HDI

With severe HDI, profound polyuria is a great inconvenience and may lead to bladder distention, pyeloureter, hydronephrosis and secondary NDI. The treatment of choice for these patients is desmopressin, a synthetic, long acting vasopressin analogue that possesses minimal pressor activity and has twice the antidiuretic potency of AVP. It can be administered as an intranasal spray (5 to 100 \( \mu \)g daily) or parenterally (0.5 to 2 \( \mu \)g daily), but the individual variation in the dose required to control symptoms is considerable. Desmopressin may also be administered orally in the dose range of 100-1200 \( \mu \)g/day in divided doses. To avoid the potential complication of dilutional hyponatremia, desmopressin should be withdrawn at regular intervals, perhaps once weekly to allow patients to become polyuric and avoid hyponatremia. If desmopressin is too potent, then lysine vasopressin can be prescribed which acts up to 4 hours but has the disadvantage of possessing considerable pressor activity. Pitressin tannate in oil for intramuscular administration or pitressin snuff is poorly tolerated and has been replaced by desmopressin.

Patients with mild forms of HDI can be managed with adequate fluids to quench thirst. Others with mild HDI may be treated with a variety of oral agents. Chlorpropamide (250 to 500 mg daily) has been the most frequently used agent and appears to potentiate the antidiuretic action of AVP. However, it can produce niggle hypoglycemia and hyponatremia. Thiazides, carbamazepine, clofibrate and tolbutamide increase antidiuresis in some patients with HDI but are generally less effectual than chlorpropamide.

NDI

Occasionally, NDI can be “cured” by eliminating an underlying cause, such as hyperkalemia, hypercalcemia or lithium. Treatment is usually limited to a low sodium diet and administration of standard doses of hydrochlorothiazide, indapamide, amiloride or indomethacin. The optimum combination and dose should be determined empirically for each patient. In most cases, treatment will reduce urine volume by 50 to 70%. Tenfold higher doses of desmopressin are effective in patients with partial NDI, but the expense and inconvenience of this treatment make it impractical. Novel strategies for correcting the AVP receptor defect in some X-linked forms of congenital NDI has been proposed and tested \textit{in vitro}, but they are still undergoing clinical trials and are not available for general use.

DDI

The signs and symptoms of DDI cannot be relieved completely with desmopressin because doses sufficient to eliminate the compensatory water diuresis completely almost always result in water intoxication. As with many conditions, the treatment of DDI should address the underlying disorder. This can be difficult. Clozapine has been shown to reduce polydipsia in patients with refractory schizophrenia and a history of hyponatremia.
Desmopressin is the only therapeutic agent recommended for treatment of GDI. Desmopressin is not destroyed by the vasopressinase in the plasma of pregnant women and is reported to be safe for both mother and fetus.

**SIADH (SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE)**

**Background**

Inappropriate antidiuretic hormone secretion was proposed many years ago to account for serum hyperchloremia observed in tuberculosis, but it emerged as a syndrome associated with a variety of conditions described and defined by Bartter and Schwartz. Studies have now confirmed a variety of abnormalities of AVP secretion in the syndrome.

**Pathophysiology**

Hyponatremia (serum sodium < 130 mmol/L) is common in about 15% of hospitalized patients. Hyponatremia is not invariably associated with a low serum osmolality. High concentrations of other circulating osmolytes (e.g. glucose) or a reduced plasma aqueous phase secondary to dyslipidemia can result in hyponatremia but normal plasma osmolality. Moreover, even when hyponatremia is a true indicator of hypo-osmolality, it may reflect an appropriate physiological response. In order to maintain circulating volume in hypovolemia, baroregulated AVP release proceeds despite plasma osmolality well below the osmotic threshold of AVP release. However, an individual with hypo-osmolar plasma but a normal circulating volume in whom the plasma AVP concentration is high for the prevailing plasma osmolality, has a syndrome of inappropriate antidiuresis. A variety of conditions are associated with SIADH and to date four patterns of abnormal AVP secretion have been identified as shown in Table 3.3. Absolute plasma AVP may not be strikingly high, the key finding is that they are inappropriate for the prevailing plasma osmolality.

<table>
<thead>
<tr>
<th>SIADH</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH type A</td>
<td>Wide fluctuations in plasma AVP concentration, independent of plasma osmolality. Accounts for 35% of SIADH</td>
</tr>
<tr>
<td>SIADH type B</td>
<td>Osmotic threshold for AVP release subnormal. Patients osmoregulate around subnormal plasma osmolar set point. Accounts for 30% of SIADH</td>
</tr>
<tr>
<td>SIADH type C</td>
<td>Failure to suppress AVP release at low plasma osmolality, normal response to osmotic stimulation</td>
</tr>
<tr>
<td>SIADH type D</td>
<td>Normal osmoregulated AVP release, but unable to excrete a water load. Accounts for less the 10% of SIADH.</td>
</tr>
</tbody>
</table>
Etiology

In most patients with SIADH, the defect in urinary dilution is caused by ectopic production, exogenous administration or osmotically inappropriate neurohypophyseal secretion of AVP. Many conditions associated with hyponatremia have been reported in which the cause has been attributed to SIADH (Table 3.4).

Table 3.4: Causes of the syndrome of inappropriate antidiuretic hormone secretion

<table>
<thead>
<tr>
<th>Neoplastic disease</th>
<th>Chest disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Carcinoma (bronchus, duodenum, pancreas, bladder, ureter, prostate)</td>
<td>• Pneumonia</td>
</tr>
<tr>
<td>• Thymoma</td>
<td>• Tuberculosis</td>
</tr>
<tr>
<td>• Mesothelioma</td>
<td>• Empyema</td>
</tr>
<tr>
<td>• Lymphoma, leukemia</td>
<td>• Cystic fibrosis</td>
</tr>
<tr>
<td>• Ewing's sarcoma</td>
<td>• Pneumothorax</td>
</tr>
<tr>
<td>• Carcinoid</td>
<td>• Asthma</td>
</tr>
<tr>
<td>• Bronchial adenoma</td>
<td>• Aspergillosis</td>
</tr>
<tr>
<td><strong>Central nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>• Head injury, neurosurgery</td>
<td></td>
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<tr>
<td>• Brain abscess or tumor</td>
<td></td>
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<tr>
<td>• Meningitis, encephalitis</td>
<td></td>
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<tr>
<td>• Guillain-Barré syndrome</td>
<td></td>
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<tr>
<td>• Cerebral hemorrhage</td>
<td></td>
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<tr>
<td>• Cavernous sinus thrombosis</td>
<td></td>
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<tr>
<td>• Hydrocephalus</td>
<td></td>
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<tr>
<td>• Cerebellar and cerebral atrophy</td>
<td></td>
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<tr>
<td>• Shy-Drager syndrome</td>
<td></td>
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<tr>
<td>• Porphyria</td>
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<tr>
<td>• Peripheral neuropathy</td>
<td></td>
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<tr>
<td>• Epilepsy</td>
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<tr>
<td>• Subdural hematoma</td>
<td></td>
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<tr>
<td>• Delirium tremens</td>
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<tr>
<td><strong>Chest disorders</strong></td>
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<tr>
<td>• Pneumonia</td>
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<tr>
<td>• Tuberculosis</td>
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<tr>
<td>• Empyema</td>
<td></td>
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<tr>
<td>• Cystic fibrosis</td>
<td></td>
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<tr>
<td><strong>Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>• Vasopressin and analogues</td>
<td></td>
</tr>
<tr>
<td>• Oxytocin</td>
<td></td>
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<tr>
<td>• Chlorpropamide</td>
<td></td>
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<tr>
<td>• Clofibrate</td>
<td></td>
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<tr>
<td>• Vincristine, vinblastine, cisplatin</td>
<td></td>
</tr>
<tr>
<td>• Thiazides</td>
<td></td>
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<tr>
<td>• Phenothiazides</td>
<td></td>
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<tr>
<td>• Monoamine oxidase inhibitors</td>
<td></td>
</tr>
<tr>
<td>• Selective serotonin reuptake inhibitors</td>
<td></td>
</tr>
<tr>
<td>• “Ecstasy”</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>• Idiopathic</td>
<td></td>
</tr>
<tr>
<td>• Psychosis</td>
<td></td>
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<tr>
<td>• AIDS</td>
<td></td>
</tr>
<tr>
<td>• Abdominal surgery</td>
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</table>

Diagnosis

Clinical features of hyponatremia (Table 3.5), develop as serum sodium falls slowly below 115 mmol/L or if there is a very rapid decrease in serum sodium. Otherwise, patients can remain asymptomatic. Values of serum sodium around 100 mmol/L are life-threatening. Clinical assessment identifies the extracellular volume status of most patients, although problems can arise in distinguishing mild form of hypervolemia and hypovolemia from euvolemia. Pseudohyponatremia due to excessive concentrations of blood glucose, proteins or lipids are readily excluded because plasma is not hypotonic.

The cardinal features for diagnosis of SIADH are given in the Table 3.6. The most frequent difficulty in practice is in distinguishing SIADH from chronic, mild hypovolemia. In both groups, urine osmolality tends to be higher than plasma osmolality and plasma AVP concentrations will be detectable or elevated. Neither is therefore diagnostic of SIADH. Measurement of urinary sodium concentrations is helpful as this differentiates
SIADH from hypovolemia. A pragmatic classification of hypotonic hyponatremia is given in Table 3.7.

### Treatment

Chronic asymptomatic SIADH with plasma sodium concentrations larger than 125 mmol/L may not necessitate specific treatment to raise plasma sodium. With more severe degrees of hyponatremia, predominantly if symptomatic some form of intervention may be essential.
Treatment directed to the underlying cause is most suitable. If this fails or is unfeasible the patient requires therapy. Fluid intake should be restricted to 500 ml/day aiming to raise serum sodium slowly to 125-130 mmol/L. Prolonged fluid restriction is upsetting and additional actions may be required. Traditionally these have attempted to either block the release of AVP or generate renal resistance to its antidiuretic actions. Drugs to suppress AVP secretion (like phenytoin) have met with limited success. SIADH can be treated by inducing NDI with either demeclocycline (600-1200 mg/day) or lithium carbonate (600-1800 mg/day). Lithium is less reliable and more toxic. Both may take up to six weeks to have a maximal effect.

An alternative is to raise plasma osmolality directly by enhancing water excretion while providing a sodium load. This can be achieved with oral frusemide (40 to 80 mg/d) together with salt loading (3 g/d). Chronic severe hyponatremia (100-110 mmol/L) can be treated with a controlled infusion of hypertonic saline. Plasma sodium concentration should rise no more than 0.5 mmol/hour with an increment of no more than 10 mmol/L/24 hours to attain a final concentration of 125 mmol/L. Symptomatic hyponatremia of less than 3 days duration may be corrected more quickly, but not faster than 2 mmol/L/hour with a limit on the incremental rise in sodium to 25 mmol/L during the initial 24-48 hours. Both the rate and magnitude of the increase in sodium during correction are risk factors for the development of osmotic demyelination syndromes.

A new class of agents, AVP receptor antagonists, have been recently introduced as a method of correcting hyponatremia by blocking the binding of AVP to V2 receptors in the kidney. AVP receptor antagonists are highly effective in producing a safe and predictable increased excretion of free water that increases the serum sodium in hyponatremic patients. Because these agents induce excretion of free water without accompanying natriuresis or kaliuresis, this effect has been termed “aquaresis,” to differentiate it from the increased water and solute excretion produced by traditional diuretic agents. Several AVP receptor agonists are under clinical investigation for use in euvolemic hyponatremia: conivaptan (YM-087), lixivaptan (VPA-985), satavaptan (SR-121463), and tolvaptan (OPC-41061). This new class of agents will greatly improve the management of this often difficult condition.

### HYPODIPSIA

**Definition and Clinical Characteristics**

Hypodipsia and Adipsia are characterized clinically by chronic or recurrent bouts of severe hypertonic dehydration associated with an inappropriate lack of thirst. The hypernatremia is often well tolerated and may be an unexpected finding on routine laboratory tests. Severe disorders can lead to somnolence, seizures, coma and renal failure.

**Etiopathology**

Hypodipsia is caused by selective defect in the hypothalamic osmoreceptors that regulate thirst and fluid intake. The conditions producing these conditions are outlined in Table 3.7.
Aneurysms of the anterior communicating artery are a particularly frequent cause because this vessel is the source of short perforating arteries that provide the only blood supply to the anterior media hypothalamus. The lack of osmotically mediated thirst may have little or no effect on water balance when urinary and insensible losses are minimal because such losses usually approximate the water content of a standard diet and may not require increased drinking to compensate. When urinary water losses are large, severe and fatal hypertonic dehydration develops. If losses are gradual, it may remain unrecognized for long periods, in which case it is usually associated with hypokalemia, azotemia and other signs of chronic hypovolemia. Almost all patients with hypodipsia and adipsic hypernatremia also have distinctive defects in the osmoregulation of AVP regulation. Four distinct patterns of osmoregulated thirst and associated AVP release are recognized. These are outlined in Table 3.8. The neurohypophysis and its other regulatory afferents are usually unaffected because the posterior pituitary bright spot is normal on MR imaging.

<table>
<thead>
<tr>
<th>Table 3.8: Causes of adipsic/hypodipsic syndromes</th>
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<tbody>
<tr>
<td><strong>Genetic</strong></td>
</tr>
<tr>
<td>• Autosomal recessive (Schinzel-Giedion syndrome)</td>
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<tr>
<td><strong>Congenital</strong></td>
</tr>
<tr>
<td>• Midline malformations (septo-optic dysplasia, agenesis corpus callosum)</td>
</tr>
<tr>
<td>• Microcephaly</td>
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<tr>
<td><strong>Acquired</strong></td>
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<tr>
<td>• Vascular (Occlusion of the anterior cerebral artery)</td>
</tr>
<tr>
<td>• Tumors (craniopharyngioma, pinealoma, germinoma, meningioma, glioma, metastatic breast, lung)</td>
</tr>
<tr>
<td>• Granulomas (neurosarcoïd, histiocytosis)</td>
</tr>
<tr>
<td>• Psychologic (psychotic depression)</td>
</tr>
<tr>
<td>• Other (hydrocephalus, cysts, aging, Alzheimer's disease)</td>
</tr>
<tr>
<td>• Idiopathic</td>
</tr>
</tbody>
</table>

**Treatment**

Treatment of hypodipsia is to recommend an obligate fluid intake of about 2 l/day, with suitable adjustment for climate and season. If fluid balance cannot be maintained during intercurrent illness, hospitalization may be required to administer free water in amounts sufficient to replenish the deficit. The latter can be estimated from the formula:

\[
\text{Water Deficit} = \frac{(S.Na - 140)}{140} \times 0.5 \times \text{Body Weight (kg)}
\]

The estimated water deficit should be administered over 24 to 48 hours along with enough additional water to cover ongoing urinary and insensible losses. This fluid should be given
by mouth if the patient is able and willing to drink. Otherwise, it may be given intravenously as one-half normal saline urine output and plasma sodium should be monitored closely during rehydration. If a water diuresis develops before the correction of hypernatremia, desmopressin should be given to minimize fluid replacement needs.

Once the dehydration is corrected, attention should be directed to prevent recurrence. The most convenient way is to monitor changes in weight and to adjust fluid intake accordingly. If diabetes insipidus develops, it should be treated with desmopressin. This regimen should be followed closely, with periodic plasma sodium checking and fluid intake should be adjusted accordingly.

**SUGGESTED READING**

INTRODUCTION

Pituitary adenomas are the third most common primary intracranial tumor (preceded by glioma and meningioma). They account for about 10-15% of primary brain tumors in various surgical series. Autopsy series show 20-25% of general population to harbor small pituitary adenomas. The discrepancy between the surgical and autopsy series are due to the presence of clinically silent tumors (‘incidentaloma’), which can be picked up imaging studies.\(^1\)\(^3\)

These tumors are uncommon in pediatric age group. They usually occur between 3rd to 6th decades. Functioning adenomas occur more often in younger age group and non-functioning adenomas in elderly. Women have a higher incidence, especially the pre-menopausal age group. Majority of these tumors occur sporadically. Rarely genetic transmission has noted, except in MEN – type I (Multiple endocrine neoplasia).\(^5\)

PATHOLOGY

Five different types of cell population have been described in the adenohypophysis (Fig. 4.1). They are somatotrophs which secrete growth hormone, Lactotrophs which secrete prolactin, Corticotrophs which secrete adrenocorticotropic hormone and Gonadotrophs that secrete follicular stimulating hormone and luteinizing hormone. On gross inspection of the adenoma, they appear yellowish-gray to purple in color and have a soft, fluid to creamy texture, in contrast to the normal gland which is firm. Routine histology has no diagnostic or prognostic significance. The tumors are usually densely populated and have a diffuse or sinusoidal or papillary pattern. They have cellular monomorphism and lack the acinar pattern seen in the normal gland. Though these tumors may show prominent nucleoli, mitotic figures or occasional giant cells, none of these are considered to be reliable indicators of aggressiveness (unlike tumors elsewhere). Immunohistochemistry is considered the standard procedure for diagnosing and typing pituitary adenomas. Electron microscopy further aids in subclassification of the tumors.\(^4\)\(^6\)
CLASSIFICATION

Clinically these tumors can be classified as functional and non-functional adenoma. Pathologically they were earlier classified as acidophilic, basophilic and chromophobe adenomas. However, this classification has been given up presently following the advent of immunohistochemistry and electron microscopy. Present pathological classification based on these studies. 5,7

Radiologically, the tumor can be classified as microadenoma and macroadenomas. Tumors measuring less then 1 cm are considered as microadenoma and those measuring more than 1 cm in any plane are considered as macroadenoma. Double contour of the sellar floor and small crescentic bulging of the anteroinferior wall of the sella turcica were considered the early radiographic changes suggestive of pituitary microadenomas. An anatomic/radiologic classification of the alterations sella turcica in 4 grades has been described (Fig. 4.2), which has a great utility for surgical prognostication. 8,9

To avoid the confusion existing with multiple classification systems, WHO has proposed a unified approach based on following 5 characteristics: (A) Clinical presentation and secretory activity, (B) Size and invasiveness, (C) Histology, (D) Immunohistochemistry and (E) Ultrastructure. 5

CLINICAL PRESENTATION2,10-18

Broadly the clinical presentation of a pituitary adenoma can be divided into 4 categories as follows:

I – Pituitary Hyperfunction
PRL : Amenorrhea, galactorrhea, infertility
GH : Gigantism, acromegaly
ACTH : Cushing’s disease
TSH : Secondary hyperthyroidism.
II – Pituitary Hypofunction

This occurs secondary to chronic compression by the tumor on the normal gland. The order of failure occurs as follows: Gonadotrophs, Thyrotrophs, Somatotrophs and lastly Corticotrophs. Irrespective of the size or invasiveness of the tumor, posterior pituitary failure does not occur. In pituitary apoplexy, hypopituitarism can occur as an acute manifestation.

III – Mass Effect

**Headache:** Occurs due to stretching of the diaphragma sella.

**Visual disturbance:** Depends upon the tumor size, invasiveness, texture and position of the optic chiasm. Classically begins as bitemporal superior quadrantanopia and proceeds to bitemporal hemianopia. Other manifestations possible are junctional scotomas (due to specific involvement of von Willebrand’s knee within the optic chiasm), monocular blindness, afferent papillary defect, papilledema and optic atrophy.

**Hypothalamic dysfunction:** Invasion/pressure on the hypothalamus can lead to rare ‘tertiary hypopituitarism’ due to disturbance in secretion of hypothalamic-pituitary releasing factors. Vegetative disturbance in the form of altered sleep pattern/eating habits or emotional behavior may be seen occasionally.
Hydrocephalus: Large tumors compressing the third ventricle or obstructing the foramen of munro may cause obstructive hydrocephalus (Fig. 4.3), with features of raised intracranial tension such as early morning headaches, projectile vomiting and visual disturbance.

Anterior cavernous sinus syndrome: Parasellar extension of the tumors (Fig. 4.4) in to the cavernous sinus can result in ptosis, diplopia and facial pain.

Partial complex seizure: Parasellar extension (Fig. 4.5) with compression of medial temporal lobe structures can result in temporal lobe epilepsy characterized by aura and automatism.

Stalk effect: Compression of the Infundibulum results in net decrease in dopamine (a hypothalamic releasing factor). This causes disinhibition of lactotrophs resulting in hyperprolactinemia (less than 150 ug/ml).

IV – Incidentalomas
Clinically silent adenoma picked up on incidental imaging (Fig. 4.6).

THERAPEUTIC PRINCIPLES
Endocrine (Hormonal assay – basal/dynamic and provocative tests) and anatomical (X-ray, CT and MRI scan) assessments are required for complete preoperative diagnoses of pituitary adenoma.

Treatment of pituitary adenoma is based on following principles:
1. Reversing endocrinopathy
2. Elimination of mass effect
3. Elimination/minimizing the possibility of recurrence
4. Definite histological diagnoses.
**Fig. 4.4:** Parasellar extension with involvement of cavernous sinus

**Fig. 4.5:** Parasellar extension with compression of temporal lobe
The options available are Surgery (transsphenoidal and transcranial), Pharmacotherapy, Conventional Radiotherapy and Radiosurgery. The goal of surgery differs depending upon the clinical presentation, tumor size, invasiveness, choice of surgical approach and the effectiveness of adjuvant therapy. In microadenomas and small pituitary tumors total excision should be the goal as it is curative. However, in large- nonfunctional pituitary tumors presenting with visual symptoms, having significant extension into suprasellar and parasellar ‘eloquent’ regions, decompression of the optic apparatus and safe excision of the tumor as much as possible may be done, followed by adjuvant therapy. A surgeon may also employ ‘two step’ surgeries to address the intrasellar and suprasellar portions, separately. A written informed consent about the nature of the tumor, proposed surgery and the possible outcomes must be obtained before surgery.

**Indications** for surgery are as follows:

1. **Apoplexy**: Most urgent indication. It occurs secondary to hemorrhage or acute necrosis of the tumor. Patients present with sudden onset severe headache, precipitous visual loss, ophthalmoplegia, altered level of consciousness and acute adrenal insufficiency. Immediate glucocorticoid replacement followed by surgical decompression is line of treatment.
2. Progressive mass effect with hydrocephalus/visual loss secondary to a macroadenoma.
5. Need for definite tissue diagnosis.
REFERENCES

GH secreting pituitary adenomas occurs in 4th and 5th decades with equal frequency in males and females. They are heterogeneous group of pituitary tumors characterized by hypersecretion of growth hormone, clinically presenting with features of gigantism and acromegaly.\textsuperscript{1,2}

**Clinical Presentation (Fig. 5.1)\textsuperscript{1,2}**

Gigantism is rare as this tumor seldom occur in younger individuals. Acromegaly is the commonest clinical presentation, characterized by following findings:

1. Coarse facial features with thickened lips, fleshy nose, frontal bossing and prognathism, corrugated and furrowed scalp.
2. Macroglossia, snoring and sleep apnea, low and deep pitched voice.
3. Spade like enlargement of hands and feet, thickened fingers and increased soft tissue in palm and sole.
4. Oily and malodorous perspiration.

![Fig. 5.1: Clinical features of acromegaly](image-url)
5. Arthropathy, Crippling spinal canal stenosis and Barrel chest deformity.
6. Cardiomyopathy, arrhythmia and hypertension.
7. Colonic carcinoma.
   All the above decreases the life expectancy of the patient significantly, in the absence of treatment.

Pathology$^3$\textsuperscript{4}
They have been distinguished by their relative incidence, immunohistochemical profiles, ultrastructural morphological features and differences in biological behavior into six different types of adenomas.

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
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<tr>
<td>Densely granulated GH cell adenoma</td>
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<tr>
<td>Sparsely granulated GH cell adenoma</td>
</tr>
<tr>
<td>Mammosomatotroph adenoma</td>
</tr>
<tr>
<td>Mixed GH cell - PRL cell adenoma</td>
</tr>
<tr>
<td>Acidophil stem cell adenoma</td>
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<tr>
<td>Unclassified plurihormonal adenoma</td>
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Pure GH secreting adenomas account for 17% of all pituitary tumors, and are distinguished by both microscopic and ultrastructural characteristics into two groups: Sparsely and Densely granulated adenomas, both of which occur in equal frequency. Sparsely granulated variant exhibits a more aggressive biological profile; it is often large, invasive and refractory to surgical cure.

Densely Granulated GH Cell Adenoma
These represent the classic ‘acidophilic adenoma of acromegaly’, and accounts for approximately 8% of all pituitary adenomas. They are characterized biologically by a relatively slow growth rate and limited invasiveness. An abundance of GH-containing secretory granules renders this tumor strongly acidophilic on routine hematoxylin and eosin stains. Immunopositivity for GH is typically intense and diffuse. It is a well differentiated tumor, which can be appreciated by electron microscopy which can demonstrate the ultrastructural properties that are similar to normal somatotrophs. The cells and their nuclei are of uniform shape and size, and cytoplasmic organelles are very well developed. The most striking ultrastructural property is the abundance of large (300 – 600 nm), spherical granules that are distributed diffusely throughout the cytoplasm with increased concentration at the periphery.
Growth Hormone Secreting Pituitary Adenomas

Sparsely Granulated GH Cell Adenoma

These tumors generally appear chromophobic on hematoxylin and eosin stains and are characterized by their relative paucity of cytoplasmic secretory granules. Nuclear pleomorphism with increased mitosis is a constant feature. Immunopositivity for GH is scant. Electron microscopy demonstrates cells that are irregularly shaped with bizarre, eccentrically placed crescentic nuclei. Virtually diagnostic of this tumor is the presence of fibrous bodies which are spherical aggregates of cytokeratin filaments typically found in a paranuclear location. Although the function of these fibrous bodies remains unknown, they serve as useful diagnostic marker and provide reliable evidence of somatotroph differentiation in an otherwise featureless chromophobic adenoma. The secretory granules are small (< 250 nm), sparse and without any characteristic features.

Although the densely and sparsely granulated GH adenomas are indistinguishable from the standpoint of endocrine dysfunction, the sparsely granulated variant is recognized for its aggressive nature and invasive tendency. Their rapid growth rate generally precludes their recognition in microadenoma stage and most of these would have invaded parasellar structure at the time of diagnosis. In contrast, densely granulated GH adenomas are detected in the microadenoma stage in majority of the patients.

Hyperprolactinemia has been demonstrated in approximately 40% of acromegalic patients. In some patients PRL elevations are mild to modest (<150 ng/ml), within the range attributable to the so called Stalk section effect, however in a significant proportion of patients PRL levels may exceed 150 ng/ml, that can be explained only by tumoral hypersecretion. Three distinct varieties of pituitary adenoma are noted for dual secretion of GH and PRL. They are: Mammosomatotroph adenoma, Mixed GH cell - PRL cell adenoma, and Acidophil stem cell adenoma.

Mammosomatotroph Adenoma

Mammosomatotrophs have been demonstrated with certainty in normal gland, they are transitional cells which appear to share common lineage with somatotrophs and lactotrophs and has the ability of reversible interconversion between these two phenotypes. Mammosomatotroph adenoma is an uncommon tumor, presumably derived from neoplastic transformation of mammosomatotrophs within the normal pituitary. They account for less than 2% of all pituitary adenomas. They are small, well differentiated and biologically silent lesions with minimal invasive potential. Clinically the patients present with features of acromegaly with moderate hyperprolactinemia. The immunohistochemical profile correlates with the clinical presentation by their intense GH immunopositivity and variable PRL staining. Immunoelectron microscopy reveals granules containing both GH and PRL staining which confirms that the single cell population comprising this tumor is responsible for co-secretion of both GH and PRL.
Mixed GH Cell - PRL Cell Adenoma
They represent 5% of all pituitary adenomas. They are characterized by bihormonal (GH and PRL) and bimorphous (distinct cell populations secreting GH and PRL) picture. The dominant endocrine presentation is acromegaly, though varying degrees of hyperprolactinemia can occur. Immunohistochemically, two distinct cell population are recognized, one immunoreactive for GH, and the other for PRL. The most common cellular combination includes densely granulated GH cells and sparsely granulated PRL cells, although any combinations can occur. Usually considered to be an indolent in nature, however gross invasion have been found in up to 30% of these tumors.

Acidophil Stem Cell Adenoma
They are an aggressive form of pituitary neoplasia characterized by an accelerated growth rate and invasiveness. They are presumed to originate from primitive acidophil precursor cells of the pituitary. They are rare lesions representing less than 1% of all pituitary adenomas. Although both GH and PRL are produced, the dominant endocrinologic disturbance is hyperprolactinemia; acromegaly is an uncommon accompanying feature. Rapidity of its growth causes profound mass effect resulting in neurological and visual deficits, which are the commoner presenting symptoms. At the time of presentation majority of these tumors have already eroded sella with parasellar extension, and also have tendency to grow downwards, typically eroding the skull base to involve the sphenoid sinus. Histologically, most acidophil stem cell adenomas are chromophobic. Immunohistochemical studies demonstrate strong positivity for PRL and only scant positivity for GH. Electron microscopy highlights its ‘primitive’ nature, which includes cells of varying size and shapes, irregular nuclei, sparsely granulated cytoplasm, primitive Golgi apparatus and poorly organized rough endoplasmic reticulum.

Endocrine Diagnosis

**Step 1:** Demonstration of elevated basal level of GH. A morning serum sample with levels greater then 5 ng/ml is considered hypersecretion of GH.

**Step 2:** Insufficient suppressability of GH (> 2 ng/ml) on OGTT (oral glucose tolerance testing).

**Step 3:** Elevation of serum IGF-1 levels (adjusted for the age).

Acromegaly can rarely occur due to a non pituitary cause as a result of pathological conditions elsewhere such as GH secreting carcinoids of GIT/small cell carcinoma of lung or secondary to hypothalamic hamartoma secreting excess GHRH.

The above tests confirm the excess secretion of growth hormone which is not physiological; but fails to distinguish between GH secreting tumors and GHRH secreting tumor. GHRH secreting tumors are rare, but may be excluded diagnostically by performing radioimmunoassay of GHRH.
About one-third of these patients also have hyperprolactinemia, either due to stalk effect or due to the plurihormonal nature of the tumor. Hypopituitarism due to mass effect also needs to be ruled out. Hence PRL, T3, T4 and TSH, morning and evening levels of Cortisol, FSH and LH levels are also performed.

**Radiological Diagnosis (Fig. 5.2)**

X-ray of the skull, lateral view or coned views demonstrate the sella. The presence of a microadenoma can be made out by double flooring of the sella in a true lateral view. Larger tumor shows evidence of sellar expansion/destruction. They are important for assessing the extent of pneumatization of the sphenoid sinus, which helps the surgeon to plan the surgical approach.

CT scan is not required for all cases. It is ideal for studying the bony anatomy, especially in invasive tumors. They are the choice of investigation to demonstrate pituitary apoplexy.

MRI of the brain is the imaging modality of choice as the soft tissue anatomy is well defined. The entire extent of the tumor, its suprasellar/parasellar and retrosellar extension with involvement of critical structures such as the internal carotid arteries, cavernous sinus, optic nerve – chiasm complex, hypothalamus, upper brainstem and the presence of hydrocephalus can be appreciated. In microadenoma, a gadolinium contrast scan helps to differentiate the tumor from the normal pituitary gland. In immediate scans, the normal gland enhances richly with the contrast, and the tumor is seen as a small area of non-enhancement. In delayed scans, the tumor picks up the contrast, while the enhancement in the gland fades.

**Treatment Option**

1. Surgical resection
2. Pharmacotherapy
3. Radiotherapy.

Usually any single line of treatment is ineffective and a combination of treatment is often required.
SURGERY

It is the first choice of management. The effectiveness depends upon the tumor size, invasiveness and preoperative GH levels.

Intrasellar tumors with GH levels less than 50 ng/ml are ideal cases and surgery can give a cure. In other cases, adjuvant therapies are often required.

If the surgery is effective, the patient would have relief of headache and improvement in visual status immediately. Hyperhidrosis, paresthesias and regression of soft tissues occur over few days. Diabetic status reduces over longer duration. Hypertension does not respond to successful therapy and often require lifelong treatment.

Criteria for Endocrine Remission:
1. Suppression of GH levels to less than 1ng/ml during OGGT and
2. Normalization of age adjusted plasma IGF-1 levels and
3. GH levels below 2.5 ng/ml.

Remission following surgery is higher in microadenomas; it drops in macroadenoma and reduces significantly in invasive tumors.

Medical Management

Two group of drugs are used in management of GH secreting pituitary adenomas:

1. Somatostatin Analogs

Somatostatin is a physiological inhibitor of GH secreting pituitary somatotrophs. Octreotide, an 8 amino acid analog of Somatostatin is 45 times more potent. It decreases the GH secretion in pituitary adenoma, but do not decease or shrink the size of the tumor. However, it arrests further proliferation.

Plain formulation needs to be administered by multiple subcutaneous injections (100 – 500 ug, 8th hourly). Long acting formulation (Octerotide LAR) and be administered as depot intramuscular injections, once in 28 days.

2. Dopamine Agonist

Bromocriptine has only moderate effects and is often used as adjuvant along with somatostatin analogs.

RADIOThERAPY

Radiotherapy is anti-proliferative and effectively halts tumor progression. It can either be used as a primary treatment or as an adjuvant to surgery/pharmacological treatment. Following RT, the GH levels drops to 50% the baseline by 2 years, and to 75% by 5 years. The latent interval following RT, for endocrinological remission (GH below 2.5 ng/ml) is 10 years. Pharmacological treatment is used following RT due to this latent period.
Radiosurgery is now being increasingly used, it has fewer side effects than RT, but it is costly. GH levels normalize by 1.4 years.

REFERENCES

Hypercortisolemic state secondary to excess secretion of ACTH by a corticotroph adenoma causes Cushing’s disease. More than 80% of these adenomas are microadenomas and these evade detection even with the most sophisticated imaging techniques. Sixty percent of the macroadenomas producing Cushing’s disease are grossly invasive. They have a female preponderance with a ratio of 3:1 to 10:1 in various series, and occur in 3rd to 5th decade of life. Seventy percent of Cushing’s syndrome in adults is secondary to corticotroph adenoma, whereas in pediatric age group, Seventy percent of Cushing’s syndrome occurs due to adrenal adenoma.1-3

**PATHOLOGY**

Neoplastic transformation of the anterior pituitary corticotrophs appears to be the basis for four distinct adenoma subtypes that collectively accounts for 15% of all pituitary adenomas. For convenience they are grouped into endocrinologically ‘active’ and ‘silent’ tumors.

**FUNCTIONAL CORTICOTROPH CELL ADENOMA**

These tumors secrete ACTH and other endorphin-related peptides, and occur as two pathological types: Densely and Sparsely granulated ACTH adenomas. The former of the two is more common and better differentiated; it is PAS positive and represents the classical ‘basophilic’ adenomas causing Cushing’s disease and Nelson’s syndrome. Sparsely granulated ACTH adenomas are uncommon and less well developed. These tumors are PAS negative, chromophobic and have high invasive potential.

Immunoreactivity for ACTH and endorphins are present in both tumor types, but are intense and diffuse in densely granulated variant. On electron microscopic studies these two tumors are easily distinguished. The densely granulated tumor is composed of medium-sized angular cells with oval nuclei, a well developed rough endoplasmic reticulum and Golgi complex, and abundant teardrop-shaped variably electron-dense, cytoplasmic secretory granules (450 nm) that characteristically accumulate beneath the cell membrane. Parallel
Corticotroph Adenomas

Perinuclear bundles of type 1 microfilaments are another diagnostic feature. In comparison, the ultrastructure of the chromophobic sparsely granulated Corticotroph adenoma demonstrates smaller, poorly developed cytoplasmic organelles with few secretory granules or type I microfilaments.

In the presence of Cushing’s disease or other hypercortisolemic states, a conspicuous morphological change occurs, characterized by massive cytoplasmic accumulation of keratin microfilaments, a phenomenon referred to as “Crookes’ hyalinization”. This alteration is a useful morphological indicator of sustained hypercortisolemia. Although once thought to be a finding restricted to non tumorous corticotrophs, Crookes’ hyalinization also may occur within adenomatous cells. In exceptional cases, such microfilament accumulation may be so extreme that the tumor is aptly termed Crookes’ change, either within the tumor or within peritumoral non-neoplastic tissue, does not appear to be of any prognostic significance.

'SILENT' CORTICOTROPH ADENOMAS

Three subtypes with distinct clinicopathological entities termed as ‘Silent Corticotroph adenomas’ have been described, all of which bear a morphological and immunological resemblance to hormonally active Corticotroph adenomas.

‘Silent’ corticotroph adenoma type 1 is histologically and ultrastructurally indistinguishable from the classic densely granulated Corticotroph adenoma of Cushing’s disease. They show strong immunoreactivity for ACTH and pro-opiomelanocortin related peptides. Usually they are often large macroadenomas at the time of presentation. Interestingly, these tumors are associated with high incidence of apoplectic hemorrhage and infarction.

‘Silent’ Corticotroph adenoma subtype 2 is morphologically and immunologically similar to the subtype 1, except that it predominantly occur in men, more often as large nonfunctioning sellar masses, with moderate degrees of hyperprolactinemia, ascribed to autonomous secretion of PRL, apart from stalk effect.

‘Silent’ Corticotroph adenoma subtype 3, though no longer considered to be corticotrophic in nature, has been included for completion sake. Their histological appearance varies from chromophobic to acidophilic. They demonstrate coexpression of GH, PRL, ACTH, endorphins and alpha subunit. The ultrastructure resembles a well-differentiated glycoprotein producing adenoma then one of corticotrophic adenoma. They appear in equal frequency in men and women.

Differential Diagnosis of Cushing's Syndrome

1. ACTH dependent causes (80%)
   a. ACTH secreting pituitary adenoma (70%)
   b. Corticotroph carcinoma (4%)
   c. Corticotroph hyperplasia (10%)
   d. Ectopic ACTH secreting lesions (15%)
      Bronchial and GI carcinoids, Small cell carcinoma lung, pheochromocytoma
e. CRH (Corticotrophin releasing hormone) secreting tumors (1%)
    Hypothalamic glioma/hamartoma

II. ACTH independent causes
   a. Adrenal adenoma
   b. Adrenal carcinoma
   c. Nodular adrenal hyperplasia
   d. Exogenous steroids

III. Pseudo Cushing’s state
   a. Depression
   b. Alcoholism
   c. Obesity
   d. Polycystic ovarian disease.

Clinical Features\(^{1,2,7}\)

Endocrine presentation: Cushing’s disease
1. Moon like facies and Buffalo hump.
2. Truncal obesity and weight gain: Centripetal in distribution (‘lemon on match stick appearance’).
3. Skin changes: White and purple striae, capillary fragility and easy bruisability.
4. Impaired glucose tolerance.
5. Cardiovascular changes: Atherosclerosis, hypertension, coronary artery disease and cardiomyopathy.
7. Decreased Host resistance, Cell mediated and Humoral immunity; Prone for fungal infections.
8. Menstrual irregularities in women, decreased libido in men and Infertility in both.

Without treatment, historical data reveals a case fatality of about 50% in 5 years time, from the time of initial diagnosis.

Majority of these tumors are microadenoma, hence they don’t present with features of mass effect.

Endocrine Diagnosis\(^{9-11}\)

3 Cardinal steps

Step 1: Establishment of Hypercortisolism
   a. Measurement of free Cortisol in a 24 hours urine specimen.
      - Highly sensitive
      - Easy and specific for non iatrogenic causes.
   b. Low dose dexamethasone suppression test
      - Low dose : 1 – 4 mg
      - 0.5 mg of dexamethasone is given 6th hourly for 48 hours.
Corticotroph Adenomas

- The next day morning cortisol levels are suppressed to less than 5 ug/dl in normal individuals.
- In hypercortisolemic states, this suppression does not occur.

Step 2: Distinguishing ACTH dependent/Independent causes:

a. ACTH assay
- Plasma ACTH levels are decreased in Adrenal causes due to negative feedback inhibition.
- Increased moderately in Corticotroph adenoma (80 – 200 pg/ml).
- Levels over 200 pg/ml is usually seen in ectopic ACTH secretion (however, this is not very specific).

Step 3: Differentiating corticotroph adenoma from ectopic ACTH secretion.

a. High dose dexamethasone suppression test
- High dose: 16 mg
- 2 mg is given 6th hourly for 48 hours. The next day morning urinary cortisol levels falls by 50% of its baseline value, it is suggestive of corticotroph adenoma.
- Alternatively, 8 mg dexamethasone at 11pm, followed by assessment of morning plasma cortisol levels. A reduction in values below 50% from previous baseline is suggestive of corticotroph adenoma.

Based on the principle that corticotroph adenoma retains its responsiveness to hypothalamic influences and negative feedback exerted by glucocorticoids, though at supra normal threshold level (hence high dose). Ectopic ACTH secreting tumors donot respond to these because they are not derived from corticotrophs.

b. CRH stimulation test
- Not done routinely.
- IV administration of Ovine CRH (Corticotropin Releasing Hormone) results in 50% increase in plasma ACTH and 20% increase in plasma Cortisol levels in Corticotroph adenoma.
- No response is suggestive of ectopic ACTH secretion (as pituitary corticotrophs are chronically suppressed by persistent hypercortisolemic state.

If high dose dexamethasone test and CRH stimulation test are combined, a diagnostic accuracy of 98% for Corticotroph adenoma is achieved. It is essential to determine the source of ACTH because, majority of these tumors are microadenoma and are difficult to identify on imaging studies.

c. Inferior petrosal sinus (IPS) sampling of ACTH

If the above tests are conflicting and inconclusive, then transfemoral catheterization under Cathlab guidance and sampling of blood from IPS may be done. This test is based on the principle that pituitary secretions are lateralized to the IPS. An IPS sample : Peripheral sample ration of greater then 2, is diagnostic of corticotroph adenoma.
This test is always done bilaterally. It may give an idea of the side of the tumor, if the two IPS samples are different. A ratio more than 1.5 is significant.

**Imaging Diagnosis**

As most of these tumors are microadenomas, imaging diagnosis are only secondary to endocrine diagnosis. Gadolinium enhanced MRI is the modality of choice, where a hypointense spot (Fig. 6.1) with delayed contrast enhancement is suggestive of adenoma.

**Treatment**

*Surgery* is the treatment of choice. Selective, complete removal of adenoma, with preservation of the normal gland is the surgical goal. Identification of the adenoma during surgery can pose difficulties. In such cases, a systematic dissection of sellar contents is done. If no evidence of adenoma is found, then subtotal hypophysectomy (leaving behind a stump of anterior lobe attached to the Infundibulum) is performed in male patients. Surgery has a cure rate of over 90% in microadenoma and 60% in macroadenoma. Surgical cure is evident by 3rd postoperative day. A morning cortisol level of less than 5 ug/dl and undetectable levels of ACTH is the criteria for cure. As a rule, if the postoperative cortisol levels remain high or falls down dramatically to normal range, it is considered as ‘Failure’. For considering treatment to be successful, the cortisol levels must be subnormal (below 5 ug/dl).\textsuperscript{12-15}

\textbf{Fig. 6.1: Microadenoma—hypointense spot}
Radiotherapy is another option available. There is a 50% chance of remission that occurs at an interval of about 2 years. Patient might develop pan hypopituitarism as a complication. Radiosurgery has similar results, but the time of response is less than 1 year.  

Medical therapy has only temporary role. They are used in only two scenarios: (1) moribund patient with high anesthetic risks, waiting for surgery and (2) During waiting period following RT.

2 classes of drugs are used:
  a. Centrally acting drugs: Cyproheptadine, bromocriptine, cabergoline and somatostatin analogs. Response to these drugs is variable and often poor.
  b. Peripherally acting drugs (adrenal blockade): Mitotane, Metyrapone, Ketoconazole, Etomidate, and Trilostane. These drugs are more effective and cause pharmacological adrenalectomy. Persistent adrenal insufficiency is a potent risk.

Combination therapy using Somatostatin analogs and dopamine agonist have been tried. The use of Cabergoline and Lanreotide together was demonstrated to be of benefit, especially when an escape from treatment with only Cabergoline occurs.

In cases of treatment failure with primary surgery or adjuvant therapy, bilateral adrenalectomy may be performed to relieve the patient from persistent Hypercortisolemic state. These patients have to be followed with lifelong mineralocorticoid and glucocorticoid supplements. Hence bilateral adrenalectomy is performed as a last resort, when all other therapies have failed. This procedure is now done laparoscopically, which has decreased the morbidity and mortality associated with the procedure.

Nelson’s syndrome refers to a disorder where in a Corticotroph adenoma manifests only following bilateral adrenalectomy for Cushing’s disease. It is an iatrogenic condition and occurs in less then 10% of the patients treated for Cushing’s disease. The incidence of this condition has come down with advancement in imaging modalities increasing pituitary microsurgery. Morphologically, Corticotroph adenoma occurring in the setting of Nelson’s syndrome are virtually indistinguishable from those causing Cushing’s disease, these are biologically very invasive and are resistant to surgery and radiotherapy. These tumors grow rapidly and present as a rapidly enlarging sellar mass. Along with ACTH, they also secrete other peptides such as MSH (melanocyte stimulating hormone), which causes hyperpigmentation. Such aggressive behavior has been attributed to the loss of negative glucocorticoid feedback resulting from adrenalectomy. Treatment is difficult and often not curative. About 20% of these patients succumb to uncontrolled local growth.

REFERENCES
Prolactinomas are a heterogeneous group of pituitary tumors characterized by hypersecretion of prolactin and are the most common primary adenohypophyseal tumor. They account for 30% of all pituitary adenomas and are more common in women. They have a varied spectrum of presentation, from slow growing microadenoma to large macroadenomas with invasive potential.\(^1\)\(^-\)\(^3\) They have been distinguished by their ultrastructural morphological features into two different types of adenomas: ‘Densely’ granulated PRL cell adenoma and ‘sparsely’ granulated PRL cell adenoma. Other pituitary adenomas with PRL secreting potential are Mammosomatotroph adenoma, Mixed GH cell PRL cell adenoma, acidophil stem cell adenoma and Unclassified plurihormonal adenoma.\(^4\)

**Pathology**

The tumor cells are classically chromophobic. Immunohistochemical staining of the “Golgi pattern” is quite unique. Condensed PRL in the Golgi regions near the nuclei is known as ‘Nebenkern’ or Golgi pattern. The most frequent tumor type is sparsely granulated type and these usually show high response to dopamine agonists.\(^4\) Densely granulated adenomas are rare, and are composed of acidophilic to chromophobic cells with abundant and diffuse cytoplasmic PRL granules.

**Clinical Features**

Clinically they present with endocrine hyperfunction with features of hyperprolactinemia. Women present with secondary amenorrhea and menstrual irregularities, infertility and galactorrhea. Men present with loss of libido, infertility and decreased facial hair growth. Osteoporosis sets in early in these patients due to hypogonadism. Macroadenomas in addition present with features of mass effect in the form of headache, visual disturbance, ophthalmoplegia, hypopituitarism, hydrocephalus or partial complex seizure.\(^1\)\(^-\)\(^6\)
Diagnosis
An increased serum prolactin level beyond 150 ng/dl is considered significant. A normal value in non-pregnant women is less than 20 ng/dl. Values up to 150 ng/dl can occur secondary to infundibular compression by macroadenoma (Fig. 7.1), resulting in disinhibition of hypothalamic influence on lactotrophs. This is often referred to as ‘stalk effect’. High values such as 1000 ng/dl or more is suggestive of invasive prolactinoma. In patients with very large prolactinomas, the initial prolactin level may be read erroneously as normal or only mildly elevated. In such patients, it is important to confirm that the laboratory performed multiple dilutions of the blood sample to avoid this error known as the ‘hook effect’. When dilutions are performed on such a blood specimen, the actual prolactin level which may be much higher is revealed. Clinicians should be aware of this laboratory phenomenon when evaluating large pituitary or parasellar masses. When the hook effect is suspected, dilution testing of prolactin samples may prevent incorrect diagnosis.7

MRI of the brain is the imaging modality of choice as the soft tissue anatomy is well defined. CT scan is not required for all cases. It is ideal for studying the bony anatomy, especially in invasive tumors (Fig. 7.2).

A raise in serum PRL level may also occur in several other conditions listed below.

Differential diagnosis for causes of hyperprolactinemia²

Hypothalamic diseases
Tumors (craniopharyngioma, meningioma, dysgerminoma, third ventricle tumor, cyst, glioma, hamartoma, and metastasis)
Infiltrative diseases (sarcoidosis, tuberculosis, Langerhans’ cell histiocytosis, and eosinophilic granuloma)
Cranial irradiation
Functioning and nonfunctioning adenomas, MEN 1
Empty sella syndrome
Lymphocytic hypophysitis.

Drugs
Neuroleptics (Phenothiazines, Atypical antipsychotics)
Antidepressants (Tricyclic antidepressants, MAO inhibitors and SSRI s)
Antihypertensive medications (Verapamil, M ethyldopa and Reserpine)
Gastrointestinal medications (Metoclopramide, Domperidone and H2 blockers)
Opiates, Cocaine.
Estrogens
Toxins
Organic mercury, Lead, Cadmium, Uranium, Arsenic, Barium

Others
Physical or psychologic stress
Hypothyroidism
Chronic renal failure
Cirrhosis
Adrenal insufficiency
Polycystic ovary syndrome.

Treatment
Prolactinomas have a proven primary role for medical therapy. As dopamine is the hypothalamic factor that inhibits the lactotrophs, dopamine agonists (Bromocriptine and Cabergoline) are used clinically to treat these patients. A spectrum of tumor response to these drugs, from a decrease in PRL levels to reversal of hypogonadism, subjective and objective improvement in vision to ‘complete resistance’ to treatment can occur with dopamine agonists. Bromocriptine is generally considered to be the agent of choice in the treatment of prolactinoma. As a dopamine agonist, it decreases the synthesis and secretion of PRL. It also decreases the rate of tumor cell division and the growth of individual cells. Typically, it is administered at an initial dose of 1.25 mg with food at bedtime, and is gradually increased to 2.5 mg twice daily in over 1-2 weeks, as tolerated. Doses larger than 7.5 mg/d are seldom needed except in the treatment of macroadenomas. Common adverse effects include nausea, nasal stuffiness, and dizziness associated with orthostatic hypotension. Others include vasospasm in the peripheral circulation and exacerbation or unmasking of depression and psychosis. Once normalization of PRL levels is achieved and sustained, the dose of Bromocriptine is gradually tapered to 2.5 mg/day. Cabergoline is along-acting, nonergot dopamine agonist. It is usually better tolerated and has a superior efficacy profile than Bromocriptine. It offers the convenience of twice-a-week administration, with a usual starting
dose of 0.25 mg biweekly to a maximum dose of 1 mg biweekly. Cabergoline appears to be more effective in lowering prolactin levels and restoring ovulation. Up to 70% of patients, who do not respond to Bromocriptine, respond to Cabergoline. The only problem is the cost. Side effects are somewhat fewer than with Bromocriptine and include headache, nausea, postural hypotension, and fatigue.

Dopamine agonists not only reverse the endocrinopathy, they also reverse the effects of mass effect, as the tumors shrink within days to weeks following initiation of therapy. These medications however are not tumoricidal. They only exert pharmacological control. Hence, all the effects of medications are reversed following cessation of therapy. Pituitary adenomas are usually soft and friable in consistency. Following dopamine agonist therapy, these tumors become firm and fibrotic. This change is not reversed even following cessation of dopaminergic drugs.

Indications for Surgery

In microadenomas, surgery is indicated only if the primary treatment fails (resistance or suboptimal response to pharmacotherapy), there is intolerance to dopamine agonist or if the patient prefers surgery over long-term medications.

In macroadenomas,
1. Surgery may be offered as a combined modality of treatment.
2. Pituitary apoplexy (Fig. 7.3).
3. Cystic pituitary adenomas (Fig. 7.4).
4. When there is extensive erosion into the sphenoid sinus as the patient can develop CSF rhinorrhea following tumor shrinkage secondary to pharmacotherapy (Fig. 7.5).
5. Females desiring pregnancy, surgery may be done to reduce the eventual risk of pregnancy induced tumor enlargement.
7. For establishing definite tissue diagnosis (relative indication).
Outcome of surgery depends upon the preoperative PRL levels. Best results are seen if PRL levels are below 100 ng/dl. The chances of recurrence, increases in direct proportions to PRL levels above 200 ng/dl. Radiotherapy is generally reserved for recurrent cases.

**Prolactinoma and Pregnancy**

Management of pregnant patients with prolactinoma is shown in the flow chart. The problems related to pregnancy are as follows:

1. **Difficult conception**: Irregular menstrual cycles and secondary amenorrhea.
2. **Risk of tumor growth during pregnancy**: Physiological pituitary hyperplasia during pregnancy can occur in neoplastic lactotrophs; this is more significant in macroadenoma.
3. **Effects of pharmacological treatment on fetal development**: Though Bromocriptine is considered safe during pregnancy, the policy is to expose the drug as minimum as possible to the fetus. Due to risk of tumor growth during pregnancy, it is better to continue Bromocriptine as it is less dangerous than surgery during pregnancy. Safety of Cabergoline is not established.

**REFERENCES**

GLYCOPROTEIN HORMONE – PRODUCING ADENOMA
These are rare adenomas producing excess of glycoprotein hormones [TSH, FSH, and LH]. They are heterodimers, composed of an alpha subunit which is common to all glycoprotein hormones and a hormone specific beta subunit, which are unique and confer functional, biochemical and immunologic specificity. In the normal state, the alpha and beta subunit are synthesized independently and subsequently are conjugated to produce the biologically active hormone. Glycoprotein hormone producing adenomas are of following subtypes: Thyrotroph adenomas, gonadotroph adenomas and the plurihormonal adenomas.¹,²

Thyrotroph Adenoma (Thyrotropinoma)
They are rare tumors, representing less than 1% of all pituitary adenomas. Fewer than 100 cases have been reported in literature so far. They have no gender preponderance and occur in equal frequency in both males and females. Most of these tumors are chromophobic adenomas. Often they are large and invasive macroadenomas, with suprasellar and parasellar extension at the time of diagnosis. Patients often present with hyperthyroidism which is often misdiagnosed to be ‘primary’ hyperthyroidism. Apart from endocrine dysfunction, these tumors present with mass effect in the form of optic nerve compression. 70% of these tumors also secrete other anterior pituitary hormones (GH and PRL). Patients have raised TSH, T3 and T4 levels. Since alpha subunit of this glycoprotein hormone is secreted in excess, a ratio of alpha subunit to TSH of more than 1 is considered significant and has diagnostic value. Surgery is the first option of treatment. Radiotherapy is often administered as adjuvant therapy.³⁵

Gonadotroph Adenomas
Most of these tumors do not produce a characteristic hypersecretory syndrome. Since some of these are hormonally active, they produce measurable elevations in serum gonadotrophin
Other Pituitary Adenomas

Levels, particularly FSH. They account for 5 to 15% of all surgically removed pituitary adenomas. These adenomas occur commonly in elderly age group, with equal frequency in males and females. They are slowly growing macroadenomas often presenting clinically with visual disturbance and varying degree of hypopituitarism. They are less invasive and recurrence after surgical excision is infrequent. Histologically they are chromophobic.6–7

Plurihormonal Pituitary Adenomas

Most of the pituitary adenomas synthesize and secrete a single hormone. However, a number of pituitary adenomas produce two or more hormonal products, which are termed as plurihormonal pituitary adenomas. A tumor is designated plurihormonal if nonfocal immunopositivity for two or more hormones can be identified within the same tumor cell (monomorphous plurihormonal adenomas) or if the tumor is composed of multiple cell populations, each producing a different hormone (plurimorphous plurihormonal adenomas). Fifty percent of all tumors producing the acromegalic state are plurihormonal adenomas which secrete both GH and PRL (mammosomatotroph adenoma, mixed GH cell-PRL cell adenoma and acidophil stem cell adenoma). Besides acromegaly, the other principal class of plurihormonal tumors is that composed of cells resembling glycoprotein hormone-producing cells, which express any combination of LH or FSH, alpha subunit, TSH, GH, and occasionally PRL. Secretion of ACTH with other hormonal products also may occur but are rare. Majority of the plurihormonal pituitary adenomas are macroadenomas at presentation, and more than 50% of all plurihormonal pituitary adenomas are grossly invasive at the time of diagnosis.1,2,8,9

Null Cell Adenomas and Oncocytomas

25% of all adenomas are non-functional, show scant if any hormonal immunoreactivities, and are ultrastructurally devoid of specific differentiation attributable to any of the five principal cell types of the pituitary. By definition, such tumors are designated ‘null cell adenomas’. Oncocytomas are a variant form of null cell adenoma in which mitochondrial accumulation exceeds 10% of the cell volume. Oncocytosis in relation to pituitary pathology is more a descriptive term without apparent biological or clinical significance, referring solely to the intracellular accumulation of large numbers of dilated mitochondria. Most null cell adenomas are chromophobic lesions. Because mitochondria readily take up acidic stains, oncocytomas often appear acidophilic. Null cell adenomas and oncocytomas typically occur in elderly patients and account for 17 and 6% of all pituitary adenomas, respectively. These slow-growing tumors remain undetected until they become large enough to produce significant mass effects. Virtually all are macroadenomas at presentation. The most common clinical presentation includes headache, visual impairment, and hypopituitarism.1,2,9–21

Ectopic Pituitary Adenomas

A small ectopic focus of anterior pituitary tissue, considered to be the remnants of the Rathke’s pouch is usually located deep within the mucosa or periosteum near the vomerosphenoidal
articulation. This ectopic focus has no endocrinologic significance, except that on rare occasions it may be the site of pituitary adenoma formation. GH-producing tumors have been reported most commonly, followed in frequency by PRL and ACTH producing adenomas. With true ectopic pituitary adenomas, the intrasellar pituitary should be normal. Another rare site of ectopic pituitary adenomas is the suprasellar region. Such ectopic tumors presumably arise from anterior lobe cells attached to the supradiaphragmatic portion of the pituitary stalk.22-24

**INVASIVE PITUITARY ADENOMAS**

When sufficiently large, most pituitary adenomas present with mass effect by simple mechanical compression; however, a sizable proportion of these tumors also exhibit frank invasion of surrounding dural, vascular, osseous, and neural structures. The degree of invasion varies and may range from minute tumor foci permeating adjacent dura to frank, destructive infiltration of parasellar structures. The aggressive behavior of invasive adenomas is not reflected in its histology. Hence, it’s a standard practice to designate adenomas as invasive on the basis of radiological or intraoperative evidence of gross invasion, rather than microscopy (Fig. 8.1). Although not always easily distinguished, ‘invasion’ implies destructive infiltration, whereas ‘extension’ denotes directional growth with compression. In general, invasive adenomas exhibit both qualities and hence have diminished surgical cure rates.25-27

**CARCINOMAS OF THE PITUITARY GLAND**

Metastasizing pituitary tumors are very rare, with fewer than 40 cases reported so far. Pituitary carcinoma is a precisely defined entity that includes only adenohypophysial
Other Pituitary Adenomas
tumors with demonstrated craniospinal and/or systemic metastases. The usual histological
criteria for malignancy (nuclear atypia and pleomorphism, mitotic activity, necrosis,
hemorrhage, invasiveness) are insufficient to permit a diagnosis of pituitary carcinoma.
Pituitary carcinomas primarily affect adults and develop slightly more often in females.
The clinical presentation is characterized by a protracted course, often punctuated by
multiple local recurrences, followed by metastatic dissemination. Although both
hormonally active and nonfunctional pituitary carcinomas have been described, the former
appear to predominate. Pituitary carcinomas composed of ACTH cells, particularly in
the context of Nelson’s syndrome are most frequent. Mode of spread in craniospinal
involvement appears to begin with invasion of the subarachnoid space and subsequent
dissemination by cerebrospinal fluid flow. Extracranial spread of pituitary carcinomas
involves both hematogenous and lymphatic routes. Invasion of the cavernous sinus
provides the necessary venous access. Although the pituitary itself lacks lymphatic
drainage, invasion of the tumor into the skull base provides access to a rich lymphatic
network that in turn aids systemic dissemination.28-30

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from meninigiomas and craniopharyngiomas by positron emission tomography with [18F] fluoroethyl-
INTRODUCTION

The thyroid is a butterfly-shaped gland in the neck that produces two important hormones: thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>). The predominant thyroid hormone secreted by the gland is T<sub>4</sub>; only a small amount of T<sub>3</sub> is produced by the thyroid gland. In the peripheral tissues, T<sub>3</sub> is the active form of the hormone. All the circulating T<sub>4</sub> needs to be converted into T<sub>3</sub> for its action in peripheral tissues. Thyroid hormones are necessary for several functions: brain development, growth, puberty, fuel metabolism, gastrointestinal functions, reproduction and circulation. Deficiency of thyroid hormones is called hypothyroidism, and this can affect the function of virtually every system in the body.

BASIC CONSIDERATIONS

Thyroid hormone production by the thyroid gland is controlled by thyroid stimulating hormone (TSH) produced from the pituitary gland, which in turn is controlled by TSH-releasing hormone (TRH) production by the hypothalamus. The thyroid is a collection of small functional units called follicles. These follicles are globular, and consist of a central proteinaceous material called colloid enclosed in a nest of follicular cells. The follicles are the sites of synthesis of thyroid hormones. The process of thyroid hormone synthesis is detailed in Figure 9.1. The process begins when iodide enters the thyroid gland via a channel protein called the sodium-iodide symporter (NIS). The activity of the NIS is stimulated by thyroid stimulating hormone (TSH) secretion from the pituitary. Once iodide enters the cell, it is converted into iodine by a process called organification. The iodine is then thrown out into the colloid by a protein called pendrin. Later, it is incorporated into the thyroglobulin molecule within the colloid structure of the follicle. The iodine is later bound to tyrosine in a series of steps to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). A molecule of MIT couples with DIT to form triiodothyronine (T<sub>3</sub>); 2 molecules of DIT combine similarly to form thyroxine (T<sub>4</sub>). These steps from organification to iodination are catalyzed by the enzyme
thyroid peroxidase (TPO), which acts at the colloid-cell interface. Thyroglobulin is then taken up by the follicular cell by a process of endocytosis and T3 as well as T4 are released from thyroglobulin. The small amount of iodine that is generated is re-used by the cell. A small amount of T3 and a large amount of T4 are directly secreted by the thyroid gland into the bloodstream; in the blood T4 is more protein bound than T3. Thyroxine-binding globulin or TBG is the major hormone binding to thyroid hormones, albumin is a minor binder. In the peripheral tissues, T4 is deiodinated to form T3 by enzymes called deiodinases.

**ETIOLOGY**

Hypothyroidism can be classified into primary, secondary and tertiary forms. Primary hypothyroidism is due to abnormalities intrinsic to the thyroid gland, while secondary is due to pituitary disease which impairs TSH production and tertiary hypothyroidism is due to hypothalamic, i.e. TRH deficiencies. TSH is the major hormone stimulating thyroid hormone
Hypothyroidism

production, and whenever the thyroid gland fails, the production of thyroid hormone becomes suboptimal. Due to the positive feedback from low thyroid hormone level, the TSH concentration rises, and this characterizes primary hypothyroidism. Sometimes the rise in TSH can stimulate the thyroid gland to keep thyroxine in the normal range, a condition called subclinical hypothyroidism. When the thyroid gland fails completely and the high TSH is unable to keep thyroid hormone level in the normal range, overt primary hypothyroidism occurs. In certain situations, like in pituitary damage, the secretion of TSH becomes low, and this TSH hypo-secretion leads to secondary failure of the thyroid gland; this is called secondary hypothyroidism. TSH deficiency can be due to pituitary disease or hypothalamic disease due to a low TRH production. In practice it is not important to distinguish between secondary and tertiary hypothyroidism, as the management rarely differs. The various causes of adult hypothyroidism, the focus of this article, are listed in Table 9.1.

<table>
<thead>
<tr>
<th>Table 9.1: Etiology of hypothyroidism in the adult</th>
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<td><strong>Primary Hypothyroidism</strong></td>
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<td>Postpartum thyroiditis</td>
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<td>Drugs: e.g. lithium</td>
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<td><strong>Secondary Hypothyroidism</strong></td>
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<td><strong>Rare causes</strong></td>
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<td>Recovery from primary thyrotoxicosis</td>
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<td>Withdrawal of thyroid hormone therapy</td>
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<td>Resolving thyroiditis</td>
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**EPIDEMIOLOGY**

The Whickham Survey, the most comprehensive study on the prevalence of the illness, showed that primary hypothyroidism is very common, occurring in about 1% of the population. The incidence rises with age, and across all adult age groups, the disease is commoner amongst women. About 6% of women and 2.5% of men older than 60 years have serum TSH levels which are higher than twice the upper limit of normal. Worldwide, the most common cause of primary hypothyroidism is Hashimoto’s thyroiditis or chronic autoimmune thyroiditis and this will be discussed in detail.

**CHRONIC AUTOIMMUNE THYROIDITIS OR HASHIMOTO’S THYROIDITIS**

In the classic form of the disease described by Hashimoto, the thyroid gland is enlarged due to lymphocytic infiltration. The gland is described as being “rubbery”. Hypothyroidism is due to autoimmune damage to the thyrocytes. Typically, there is an elevated titer of antibodies to thyroid antigen, among them, the most striking increase is seen in the levels of antibodies to TPO or anti-TPO antibodies as they are called. However, in many cases of chronic
autoimmune thyroiditis, the gland is not enlarged. This is termed atrophic thyroiditis and is due to extensive fibrosis of the gland; it is believed to be an end-stage of chronic autoimmune thyroiditis. In a small proportion of subjects, antibodies that block the TSH receptor also lead to hypothyroidism.

**Clinical Features**

In severe cases of hypothyroidism, the diagnosis is readily apparent to the clinician. The patient often complains of weight gain, and facial puffiness. There is also a history of intolerance to cold weather, and constipation. There is weight gain despite a relative lack of appetite. In view of body swelling, attributable to a combination of fluid retention and glycosaminoglycan deposition, severe hypothyroidism has also been called myxedema. In addition to generalized edema, even pericardial, pleural and ascitic fluid collections have been described. The skin becomes dry, and hair loss occurs. The patient is slow in thought, speech and action. In women, menorrhagia is the commonest menstrual irregularity, but almost any type of menstrual disturbance is seen with hypothyroidism. The voice is coarse, and thick. Often, there is a history of excessive snoring and daytime somnolence. On examination, a rubbery goiter may be present in many cases of thyroiditis, but goiter is absent in atrophic thyroiditis (see above). Classically, the ankle jerks relax slowly after contraction. Sometimes, hearing disturbances may be an associated clinical feature: this may be due to either sensorineural deafness, or conductive deafness due to thickening of the eardrum/middle ear effusions. Cardiomegaly and pericardial effusions are occasional findings.

In children and adolescents, presentation may be more atypical. Children may present with growth failure, declining academic performance, delayed dentition, pubertal delay, menstrual irregularities, or even, rarely, precocious puberty. The presentation is more complex in neonates, and any newborn/infant with the following features must undergo thyroid function testing: hoarse cry, prolonged jaundice, mottled skin, umbilical hernia, constipation, poor feeding and failure to achieve milestones. In contrast to primary hypothyroidism, subjects with secondary hypothyroidism behave a little differently. Features of fluid retention are less striking, and weight gain is not prominent. The skin appears pale. As pituitary disease of diverse etiologies can result in secondary hypothyroidism, these patients also could have features of other pituitary hormone deficiencies, or of an underlying pituitary tumor which can result in secondary hypothyroidism. Unlike primary hypothyroidism, there is no cardiomegaly in cases of secondary hypothyroidism.

With increasing awareness and suspicion of hypothyroidism, the diagnosis is now made early. As a result subjects are being picked up with very subtle and even unusual symptoms. For instance, primary hypothyroidism can be associated with hyperprolactinemia, and present with galactorrhea. In this setting, a high TRH level can stimulate prolactin secretion. Thus, hypothyroidism can lead to a high prolactin level, which in turn can cause amenorrhea, galactorrhea, and other menstrual abnormalities. Levothyroxine alone will suffice to correct these abnormalities in these cases.
LABORATORY INVESTIGATIONS

The diagnosis of primary hypothyroidism is confirmed by measuring the T₄ and TSH levels (Table 9.2). Hypothyroidism is characterized by a low T₄ and a high TSH level. For adults, for most laboratories, the upper limit of normal TSH secretion is 5 uIU/ml. When the TSH is high, but the T₄ is normal, this condition is described as subclinical hypothyroidism. Most of the subjects with subclinical hypothyroidism will go on to develop complete or overt thyroid failure. T₃ is not routinely measured in the diagnosis of hypothyroidism. This is because, in milder forms of hypothyroidism, the increased TSH stimulates the selective production of T₃ and this may result in a high/normal T₃. However, in severe varieties of hypothyroidism, the T₃ is also low. Free hormone estimations (which estimate the concentration of thyroid hormones that are not bound to circulating proteins), are advantageous as they measure the metabolically active component, and also because they are not affected by conditions which increase or decrease the levels of thyroid-hormone binding proteins. For instance, malnutrition and the nephritic syndromes are associated with a low level off thyroid binding globulin; pregnancy and oral contraceptives are associated with higher levels: by measuring the freeT₄ level, the active, unbound component of thyroxine can be estimated more accurately. The diagnosis of chronic autoimmune thyroiditis is essentially clinical, but is supported by the following findings: high levels of anti-TPO antibodies or a fine needle aspiration study of the enlarged gland showing features of lymphocytic thyroiditis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subclinical (Primary) Hypothyroidism</th>
<th>Overt Primary Hypothyroidism</th>
<th>Secondary Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₄</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>TSH</td>
<td>High</td>
<td>High</td>
<td>Low/Normal</td>
</tr>
</tbody>
</table>

In addition to hormonal estimations, a variety of other tests are abnormal in hypothyroidism. For instance low sodium, due to hypothyroidism-induced inappropriate release of ADH is sometimes seen. Raised creatinine phosphokinase levels too are seen. Lipid profile estimations show a raised LDL and triglyceride level. Sometimes the ECG shows ST-T changes; this in combination with cardiomegaly and raised cardiac enzymes has been called myxedema heart. A high prolactin is seen in primary hypothyroidism, because the increase in TRH (caused by thyroid gland failure) stimulates prolactin levels. This hyperprolactinemia, which may even be accompanied by galactorrhea or pituitary enlargement due to TRH-induced hyperplasia, may even sometimes be the cause for seeking medical help.

Diagnosis of neonatal hypothyroidism: Ideally, serum TSH and T₄ are estimated from an elute of whole blood collected on filter paper by a heel prick between 4th to 6th days of life. Before the 4th day, TSH and T₄ levels are physiologically elevated. If only one test is feasible, then TSH based screening is superior, because, though T₄ estimations have also been used for screening, about 10-20% hypothyroid subjects may have T₄ in the low-normal range, and if
the cut off for T$_4$ is raised, then this would result in more subjects being recalled for subsequent TSH testing. T$_3$ estimations are usually normal and should not be used for screening. If the screening blood TSH is more than 40 mU/l, then immediate treatment is required after collecting samples for confirmation. If TSH is 20-39 mU/l then, the child is called for periodic retesting, but treatment is not indicated unless rising levels are documented, because the overwhelming majority of these children have normal thyroid function when tested many weeks later. Usually, isolated rise in TSH levels subside over 3-9 months.

**MANAGEMENT**

Thyroid hormone actions are very important, and even the correction of mild thyroid dysfunction can have a positive impact on health. In many cases, hypothyroidism is suspected early, but sometimes it is diagnosed only when obvious symptoms and signs occur, e.g. goiter, weight gain, cold intolerance, or constipation. The treatment of choice is levothyroxine (LT$_4$), which is one of the most widely prescribed drugs.

The dose of levothyroxine depends upon the age, and also the body weight. The desirable initiating dose in healthy adults is 1.7 ug/kg/day. For the elderly, or in subjects with heart disease, one should start with 12.5 to 25 ug/day and increase the dose by 12.5 ug every 6 weeks. In the elderly, the final dose required may be less than 1 ug/kg/day.

Thyroxine has a narrow therapeutic range. In other words, even a small change in T$_4$ levels can have significant effects. Therefore, even small changes in levothyroxine can cause changes in the clinical well-being, and also result in larger-fold changes in TSH levels; TSH is the preferred test for monitoring. TSH normalization may take about 8 to 12 weeks. Levothyroxine has a half-life of 7 days, which means that the T$_4$ levels too could normalize by about 6 weeks. TSH is the most sensitive indicator of T$_4$ effect, as TSH level rises significantly in response to minor declines in T$_4$ which stimulate the TSH-producing cells in the pituitary. While interpreting thyroid function tests, it is important to remember that several non-thyroidal illnesses and drugs can alter free and total hormone levels (see above). Several drugs can interfere with levothyroxine absorption. This includes cholestyramine, ferrous sulfate, sucralfate and aluminum hydroxide. Other agents like the antitubercular drug rifampicin and anticonvulsants can accelerate the metabolism of l-thyroxine; hence, dose adjustments may be needed in these situations. In practice, frequent re-testing is important, because monitoring can also prevent over-treatment with levothyroxine, which is associated with bone loss, atrial fibrillation and thyrotoxicosis.

The required dose of levothyroxine might also depend upon the etiology of hypothyroidism. Subjects with chronic thyroiditis or total thyroidectomy may need higher l-thyroxine doses as compared to subjects with Graves, disease who have undergone $^{131}$I therapy or surgery; in the latter situation, some residual functional thyroid tissue might be present. It has been argued that T$_3$-alone replacement is unphysiological, as both T$_4$ and T$_3$ are thyroid hormones. Moreover, T$_3$ is the more-active hormone, and so, it has been argued that both T$_4$ and T$_3$ need to be replaced. To address the controversial issue of “perfect” thyroid hormone replacement, a recent study compared the use of a combination of triiodothyronine and
Hypothyroidism

levothyroxine (i.e. T₃+T₄) vs. isolated levothyroxine therapy; the results show no definite advantage of the combination therapy. In fact this study showed that such treatment increases the risk of subclinical hypothyroidism, due to fluctuations in the steady-state free T₃ serum concentrations. Both T₄ and T₃ preparations are commonly available, and in the body, T₄ needs to be converted into T₃ for tissue action. The issue of combination therapy is still controversial and for the present, levothyroxine alone is the treatment of choice.

For neonatal hypothyroidism, therapy is begun at a high dose of 50 ug/day (10-15 ug/kg/day), for replenishing diminished reserves, and after a week, is reduced to 37.5 ug/day. After 6 months the daily dose is decreased to 6-8 ug/kg and later 5ug/kg between 1-12 years. Testing should be performed weekly for a month, followed by monthly for 6 months, then every 3 months up to 2 years of age, and annually thereafter. T₄ is best given once daily to the neonate; the tablets crushed in breast milk and fed 30 minutes prior to feeds. If a dose is missed, then it is better to take another dose the next day rather than skip the tablet altogether. T₄ levels reach 10 ug/dl in about 2 weeks, but TSH usually normalizes only by 4 weeks of therapy.

Treatment considerations in secondary hypothyroidism are the same, but if associated cortisol deficiency is suspected, then levothyroxine therapy must be instituted only after achieving a eucortisolemic state. Similar considerations are important in cases of suspected polyglandular autoimmune disease, where hypoadrenalism and hypothyroidism can coexist.

Myxedema coma: This is a life-threatening complication of hypothyroidism, and refers to severe coma following severe, untreated thyroid failure. Precipitating factors include cold exposure, general anesthesia, infections, or stress. Clinical features, in addition to classic hypothyroid features, are hypoventilation, bradycardia, hypothermia and carbon dioxide narcosis. The treatment is to replace T₃ or T₄ or a combination intravenously. Where intravenous preparations are not commonly available, as in most of India at the time of writing the article, LT₄ is given at a bolus dose of 600 ug orally or through the Ryle’s tube, followed by 100-200 ug per day. Steroid therapy with intravenous hydrocortisone too is desirable, as it can cover for a sudden increased metabolic demand incurred by the starting of thyroxine therapy, and also cover for any coexisting adrenal insufficiency. Usually, positive pressure ventilation is required and broad-spectrum antibiotic therapy based on cultures is also needed. Mortality, however, remains high, at about 50%. Therefore, the condition must be suspected and treated early on.

Subclinical Hypothyroidism

When the FT₄ is normal and the TSH is high, this state is termed subclinical hypothyroidism. As a rule, there must be no history of thyroid dysfunction or therapy. Clinical evidence of thyroid dysfunction is often scant or lacking. In this situation, if the TSH is more than 10 mU/L, thyroxine therapy is indicated. In cases where the TSH is above normal (usually this means above 5 mU/L) but below 10 mU/L, a variety of criteria indicate the need to
therapy (Table 9.3). The evidence in favor of treating these disorders with thyroxine is not very well established, but available literature suggests that at least a trial of therapy is warranted. There are three principal reasons for starting therapy in subclinical hypothyroidism: firstly, to avert the symptoms of eventual thyroid failure. Secondly, to reverse the effects of mild thyroid deficiency on many organ systems and relieve subtle signs and symptoms caused by thyroxine deficiency, thus improving the patient’s quality of life; this is controversial. Finally, as in Table 9.3, therapy is indicated in specific scenarios. The dose required for treating subclinical hypothyroidism may be only about 50 to 75 ug/day.

Table 9.3: Subclinical hypothyroidism: Indications for therapy

- Positive anti-thyroid antibodies
- Goiter
- Dyslipidemia
- Depression
- Infertility
- Pregnancy
- Obesity
- Carpal tunnel syndrome
- Unexplained hyponatremia
- Menstrual irregularities
- Short stature

Pregnancy, Fertility and Hypothyroidism

In general, there is an increased need for thyroid hormones during pregnancy. Also, patients with a previous history of unexplained infertility or frequent miscarriages must have a sensitive TSH measurement before and during pregnancy. In pregnancy, the preferred initiating dose did not alter. During pregnancy, the follow-up is to be more intensive, i.e. every 4 to 6 weeks, to keep FT₄ within normal limits. In pregnancy, given the increase in thyroid binding globulin, it is better to monitor with free T₄ rather than total T₄ levels. Due to increased demand, dosage of levothyroxine may need to be increased by about 30-50% during pregnancy, in order to keep the free T₄ within normal limits. There is now accumulating evidence to suggest that universal screening should be done to detect hypothyroidism before pregnancy. For the present the following three groups should be screened prior to pregnancy: women more than 35 years, those with a family history of thyroid disorders or those with coexisting autoimmune disorders. After delivery, the pre-pregnancy dose can be resumed.

Hypothyroidism, Dyslipidemia and Cardiovascular Risk

More than 90% of subjects with primary hypothyroidism have increased levels of cholesterol and/or triglycerides. On the other hand about 13% of all subjects with lipid abnormalities have thyroid disease. The degree of dyslipidemia has generally correlated well with the severity of thyroid failure. Dyslipidemias should be screened for hypothyroidism. Subclinical
or overt hypothyroidism if associated with dyslipidemia, warrants levothyroxine therapy. In addition to lipid modulation, both subclinical and overt hypothyroidism can reduce cardiac function. Both changes in systolic time intervals, as well as ST-T changes have been reported: these cardiac alterations are reversible with levothyroxine therapy. Lipid abnormalities in subclinical hypothyroidism are reversible with levothyroxine therapy; treatment even improves carotid intima-media thickness, a marker of atherogenic risk.

**SUGGESTED READING**


24. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004 ;291(2):228-38.


INTRODUCTION
Graves’ disease, also known as Parry’s or Basedow’s disease is a common autoimmune disorder, characterized by diffuse goiter, thyrotoxicosis, infiltrative ophthalmopathy and occasionally infiltrative dermopathy. In an individual patient the thyroid disease and the infiltrative disease may occur singly or together, but run courses that are largely independent.

EPIDEMIOLOGY
Graves’ disease is the most common cause of hyperthyroidism and accounts for 60 to 80 percent of spontaneous hyperthyroidism, depending on regional factors, especially iodine intake. It is more common in women than in men (10:1) and tends to become more prevalent after puberty. The annual incidence in women over a 20-year period is around 0.5 per 1000, with the highest risk of onset between the ages of 40 and 60 years.

ETIOLOGY
Graves’ disease is an organ specific autoimmune disorder, with involvement of both T and B cell mediated immunity against thyroid antigen. The etiology of Graves’ disease is multifactorial, caused by a complex interplay of genetic, hormonal and environmental factors that lead to the loss of immune tolerance to thyroid antigens and to the initiation of sustained autoimmunity.

Genetic Susceptibility
Graves’ disease is an oligogenic disorder with number of genetic loci that may contribute to disease susceptibility. Inheritance of MHC Class II molecule, HLA-DR3 gene, was found to confer increased risk of getting Graves’ disease up to 5.7-fold. In contrast, inheritance of HLA DRβ1*07 appears to be protective. Graves’ disease is also associated with polymorphisms of the cytotoxic T-lymphocyte antigen 4 (CTLA-4) gene in several racial
groups.\textsuperscript{5} Linkage studies of Graves’ family members have suggested the susceptibility locus on chromosome 14q31, 20q11 and Xq21-22, which has been named GD-1, GD-2 and GD-3 respectively.\textsuperscript{6}

**Infection**

It has been suggested that Graves’ disease is associated with various infectious agents like \textit{Versinia enterocolitica}, \textit{Leishmania} and \textit{Mycoplasma}.\textsuperscript{7} Molecular mimicry has been invoked to explain the associations between these infections and Graves’ disease. Though epidemiologic evidence indicates that infection might play a role in causation of Graves’ disease, the definitive identification of the organism and the reasonable explanation for the microbe to precipitate disease is lacking.\textsuperscript{8}

**Stress**

Psychic stress has long been considered to be a possible etiology of Graves’ disease.\textsuperscript{9} There are many experiences and reports associating major stress with onset of Graves’ disease and in fact, in Perry’s original report, a crippled woman, who was injured when her nanny allowed her wheelchair to fly down a flight of stairs, had rapid onset of thyrotoxicosis. A mechanistic route from stress to the development of Graves’ disease is not obvious. Aggressive weight loss programs have also been reported to induce Graves’ disease.

**Gender and Gonadal Steroids**

As most of the autoimmune diseases, Graves’ disease is more prevalent in females with an incidence roughly eight to ten times greater in women than in men. One possibility is that female reproductive activity somehow stresses the thyroid. Another possibility is that estrogen might have some influence on the immune system and also on promoter for certain genes such as Class II HLA molecules.\textsuperscript{10}

**Pregnancy**

Pregnancy is a time of immunosuppression and rebound from the immunosuppressant effect of pregnancy may contribute to the development of postpartum thyroid disease. The risk of developing thyroid disease increases four-fold to eight-fold in the postpartum period. As many as 30% of young women give history of pregnancy in the 12 months before the onset of Graves’ disease.\textsuperscript{11}

**Iodine and Drugs**

Iodine and iodine containing drugs such as amiodarone may precipitate Graves’ disease or its recurrence in a susceptible individual. Iodide itself has been thought to induce Graves’ disease, thus leading to the term “Jod Basedow” that refers to the occurrence of thyrotoxicosis following supplementation of iodide in medicinals or by salt iodinization. Possibly increased
Graves’ Disease

iodide intake can actually augment thyroid autoimmunity and iodine can also damage thyroid cells directly, thus releasing thyroid antigens to the immune system.\textsuperscript{12}

**PATHOGENESIS**

Graves’ disease shares many immunologic features with autoimmune hypothyroidism and though the TSH receptor antibody (TRAB) are the ultimate cause of both goiter and hyperthyroidism in Graves’ disease, the nature of immune dysfunction involves many aspects of immune system, including changes in both B-cell and T-cell function.\textsuperscript{7} In Graves’ disease, T lymphocytes become sensitized to antigens within the thyroid gland and stimulate B lymphocytes to synthesize antibodies to these antigens (Fig. 10.1). One such antibody is directed against the TSH receptor site and binding of anti-TSHR autoantibody to the TSHR on thyroid membranes, results in thyroid hormone hypersecretion. The serum concentrations of these antibodies vary among patients and there is no direct correlation between serum concentrations of TRAB and serum thyroid hormone concentrations in patients with Graves’ hyperthyroidism but the presence of these antibodies is positively correlated with active disease and with relapse of the disease.

The close relation between Graves’ hyperthyroidism and ophthalmopathy suggests that both result from an autoimmune response to one or more antigens located in the thyroid and orbit.\textsuperscript{13} The currently favored candidate antigen is the thyrotropin receptor, expressed

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig_10.1.png}
\caption{Pathogenesis of Graves’ disease and ophthalmopathy}
\end{figure}
by the preadipocyte subpopulation of orbital fibroblasts. Regardless of the self-antigen that causes the local accumulation of lymphocytes, the proximal events in the pathogenesis of ophthalmopathy and dermopathy appear to be cytokine-mediated activation of fibroblasts; secretion of glycosaminoglycans by these cells and the edema is due to the hydrophilic action of glycosaminoglycans secreted by fibroblasts. The inflammation is due to infiltration of the extraocular muscles and orbital connective tissue by lymphocytes and macrophages. The increase in the volume of retrobulbar tissue is responsible for most of the clinical manifestations of ophthalmopathy. The muscle cells are normal until the late stages of ophthalmopathy, when they may become atrophic or fibrotic. Dermopathy is characterized by lymphocytic infiltration of the dermis, the accumulation of glycosaminoglycans, and edema.

**CLINICAL MANIFESTATIONS**

Graves’ disease displays an array of possible clinical patterns extending from that of goiter and thyrotoxicosis with or without ophthalmopathy, to that of ophthalmopathy without goiter or thyrotoxicosis. The severity and duration of Graves’ disease and the age of the patient determine the manifestations of hyperthyroidism. The clinical manifestations of Graves’ disease can be divided into those common to any form of hyperthyroidism and those specific to Graves’ disease like ophthalmopathy and dermopathy.

The most common symptoms are nervousness, fatigue, palpitations, heat intolerance, hyperdefecation, weakness, emotional instability and weight loss; these symptoms are present in more than half of all patients who have the disease. Weight loss and decreased appetite become more common, whereas irritability and heat intolerance are less common as age advances. Atrial fibrillation is rare in patients who are younger than 50 years of age, but occurs in up to 20 percent of older patients. Anorexia rather than hyperphagia occurs in about one-third of the elderly patients and contributes to a picture of apathetic thyrotoxicosis. Approximately 80 percent of have a soft to firm, diffuse goiter of variable size. The nails are soft and friable and separation of distal margin of the nail from nail-bed (plumbers nail) with irregular recession of the junction (onycholysis) is sometimes seen.

Clinically evident ophthalmopathy occurs in about 50 percent of patients. Eye signs of Graves’ disease may be divided into two components; the spastic and the mechanical. The former includes the stare, lid lag, and lid retraction and accounts for the “frightened” facies. The mechanical component consists of proptosis of varying degree with ophthalmoplegia and congestive oculopathy characterized by chemosis, conjunctivitis, periorbital swelling, and the potential complications of corneal ulceration, optic neuritis, and optic atrophy. The eye signs may be unilateral early but usually progresses to bilateral involvement. The degree of exophthalmos can be measured by Hertel exophthalmometer, the upper limit of normal being 20 mm, although in African Americans it could be up to 22 mm. The eye changes in Graves’ disease is classified by the American thyroid association using a mnemonic NOSPECS (Table 10.1).
Graves’ Disease

The activity of the eye disease is assessed by the clinical activity score (>4) that is determined by points for the presence of retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle and eyelid edema. The course of Graves’ ophthalmopathy is largely independent of thyroid status, although it tends to be more severe in patients in whom hyperthyroidism is poorly controlled. Typically there is a period of worsening over 12 to 18 months, followed by a period of stabilization; spontaneous improvement of mild ophthalmopathy occurs in approximately 60 percent of patients.

Dermopathy occurs in 5-10% of patients with Graves’ disease almost always in the presence of severe ophthalmopathy. The dermopathy consists of thickening of the skin, particularly over the lower tibia but it can occur at other sites, especially after trauma. 14

Nonspecific laboratory findings include high serum concentrations of bilirubin, ferritin, aminotransferases, and sex hormone–binding globulin. The rate of bone resorption is increased. Hypercalciuria is frequent, but hypercalcemia is rare. Glucose intolerance and, rarely, diabetes mellitus may accompany hyperthyroidism. 15 Among patients who are treated with insulin for diabetes, hyperthyroidism increases the insulin requirement.

DIAGNOSIS

In its classic form, the diagnosis of Graves’ disease is usually easily made. The signs of ophthalmopathy or dermopathy are sufficient to confirm the diagnosis of Graves’ disease in a patient with hyperthyroidism and a diffuse goiter. Occasionally, Graves’ disease occurs in a patient with preexisting nodular goiter, causing confusion. In some cases, the thyroid might not be enlarged and ophthalmopathy may be absent or clinically undetectable. Symptoms of hyperthyroidism may be less evident in the elderly people who often have the apathetic variant of thyrotoxicosis. Graves’ disease must also differentiated from other conditions in which thyrotoxicosis is present like toxic multinodular goiter, toxic adenoma, trophoblastic tumor, increased TSH secretion, thyrotoxicosis factitia, subacute thyroiditis and struma ovary (Fig. 10.2).

INVESTIGATIONS

Once the question of thyrotoxicosis has been raised, laboratory data are required to verify the diagnosis, to assess the severity of the condition and assist in planning therapy. A single

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No physical signs or symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Only signs, no symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Soft tissue involvement (Both signs and symptoms)</td>
</tr>
<tr>
<td>3</td>
<td>Proptosis &gt; 22 mm</td>
</tr>
<tr>
<td>4</td>
<td>Extraocular muscle involvement</td>
</tr>
<tr>
<td>5</td>
<td>Corneal involvement</td>
</tr>
<tr>
<td>6</td>
<td>Sight loss (Optic nerve involvement)</td>
</tr>
</tbody>
</table>

Table 10.1: Showing NOSPECS classification of thyroid ophthalmopathy
Fig. 10.2: Algorithm showing approach to a patient with thyrotoxicosis

A test such as the TSH or free T4 may be enough. TSH should be less than 0.1 µU/ml in significant thyrotoxicosis, although values of 0.1-0.3 µU/ml are seen in patients with mild illness. The serum T3 is proportionally more elevated than the serum T4 levels. It is preferable to measure the free hormone levels wherever facilities are available rather than total T3 and T4.

Thyroglobulin antibodies and thyroid peroxidase antibodies are seen in 90% and 60% of the patients with Graves’ disease, but both antibodies can be detected in 25% of normal subjects, especially in elderly women or in patients with nodular goiter and thyroid carcinoma. Hence, these antibodies have limited diagnostic value and are useful only in confirming the presence of autoimmunity. TRAB is very specific and sensitive for hyperthyroid Graves’ disease and is positive in more than 90% of the individual. It is useful in certain special situations when clinical picture or thyroid function tests are not clear like in the differential diagnosis of thyrotoxicosis in pregnancy, nodular variant of Graves’ disease and in patients with exophthalmus without Graves’ disease.

Thyroid ultrasound is useful in accurate measurement of the of thyroid size, to confirm autoimmunity and color flow Doppler studies are further helpful in assessing the vascularity of the thyroid gland in Graves’ disease. Thyroid radionuclide studies may be indicated to distinguish between Graves’ hyperthyroidism and thyrotoxicosis caused by painless, destructive (autoimmune) thyroiditis, especially in a women postpartum. Radioactive iodine uptake studies are also required in patients with Graves’ disease before planning for radioiodine ablation treatment to calculate the dose of radioiodine needed.
Graves’ Disease

TREATMENT
The aim of treatment in Graves’ disease includes correction of thyrotoxicosis in all cases, relief of compressive symptoms from large goiters and treatment of complications like ophthalmopathy and dermopathy when present. Current treatments for Graves’ hyperthyroidism consist of antithyroid drugs, radioactive iodine, and surgery. There is regional variation in their use as for example; radioactive iodine is favored in North America and antithyroid drugs nearly everywhere else. Apart from regional preferences, patient age, sex, degree of hyperthyroidism and ophthalmopathy, the presence of coexistent medical conditions (such as severe heart disease) and exposure to excess stable iodine (such as amiodarone or contrast media) all influence the choice of primary treatment.

Antithyroid Drugs
Antithyroid drugs can be used either as a primary management tool in an attempt to induce long-term remission or as preparatory treatment before surgery or radioiodine (Fig. 10.3).

Fig. 10.3: Algorithm showing management of Graves’ disease
Thionamides

The major action of thionamides is to inhibit the organification of iodine and coupling of iodothyronines and thus blocking the synthesis of thyroid hormones. Carbimazole is not active as it is, but is completely converted to methimazole for its action. Propylthiouracil has an additional effect of partially inhibiting the conversion of T\(_4\) to T\(_3\) in peripheral tissue. Antithyroid drugs do not block the release of preformed thyroid hormones and so euthyroidism is not obtained until the intrathyroidal hormone and iodine stores are depleted, which would require 1-6 weeks, depending on factors such as disease activity, initial levels of circulating thyroid hormones, intrathyroidal hormonal and iodine stores. Thionamides are also proposed to have a direct effect on the immune system.

The pharmacologic properties of methimazole and propylthiouracil are summarized below (Table 10.2). Both the drugs are very effective in controlling hyperthyroidism and drug selection is largely determined by local practice. Treatment is started with high doses (20 to 40 mg of methimazole or 200 to 400 mg of propylthiouracil per day) and doses are titrated with thyroid function test performed every 1 to 3 months to maintain euthyroidism with minimum effective dose. Treatment is maintained for 12 to 24 months, after which thionamide treatment is usually discontinued. Approximately 30 to 40 percent of patients who are treated with an antithyroid drug remain euthyroid 10 years after the discontinuation of antithyroid drug therapy, which means that the Graves’ disease has remitted. Whether the remission is entirely spontaneous or is due to amelioration of hyperthyroidism or to an immunomodulatory action of these drugs is unclear. Factors that favor long-term remission include T\(_3\) toxicosis, small goiter, and decrease in goiter size during therapy and also negative TRAB levels.

<table>
<thead>
<tr>
<th>Property</th>
<th>Methimazole</th>
<th>Propylthiouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative potency</td>
<td>10 to 50</td>
<td>1</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Absorption</td>
<td>Almost Complete</td>
<td>Almost Complete</td>
</tr>
<tr>
<td>Binding to serum proteins</td>
<td>Negligible</td>
<td>75%</td>
</tr>
<tr>
<td>Serum half-life (hours)</td>
<td>4-6</td>
<td>1-2</td>
</tr>
<tr>
<td>Duration of action (hours)</td>
<td>&gt;24</td>
<td>12-24</td>
</tr>
<tr>
<td>Transplacental passage</td>
<td>Low</td>
<td>Lower</td>
</tr>
<tr>
<td>Levels in breast milk</td>
<td>Low</td>
<td>Lower</td>
</tr>
<tr>
<td>Inhibition of deiodinase</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The main problem with thionamide treatment is the high relapse rate of 60 to 70% depending on duration of follow-up. Most hyperthyroidisms relapse within 3-6 months after medical therapy is discontinued and more than two-thirds of patients who relapse do so within first 2 years. Relapse of hyperthyroidism after a full cycle of thionamides is a strong indication for alternative treatment like radioiodine or thyroidectomy. Late evolution to primary hypothyroidism can be observed as well, mainly in patients who remain euthyroid after discontinuation of therapy.
Graves’ Disease

Side effect record is similar with both the drugs and about 6% of patients report minor side effects like pruritis, urticaria, arthralgias, but resolve spontaneously despite continues treatment. Agranulocytosis (granulocyte count less than 500/mm³) can occur in 0.003% of patients and has been reported more frequently in elderly patients, though it can occur in any age. It is detected within the first 3 to 4 months after therapy is started and can develop very suddenly. It is manifested by fever and evidence of infection, most often in upper respiratory tract. In addition to prompt discontinuation of the antithyroid drugs, treatment includes broad spectrum antibiotics and growth factors to stimulate bone marrow. Patients usually recover in 2 to 3 weeks, but some death has been reported due to this serious side effect. Cholestatic (with methimazole) or necrotic (with propylthiouracil) hepatitis, vasculitis and lupus like syndromes are another rare but severe complication of thionamide treatment that would require prompt withdrawal of the drug. There is a risk of cross reactivity between methimazole and propylthiouracil and switching of drugs is not recommended when serious side effects are encountered and alternate treatments of thyrotoxicosis should be sought.

Iodine and Iodine Containing Compounds

Lugols iodine or saturated solution of potassium iodide decreases its own transport into thyroid, inhibits iodine organification and blocks release of $T_4$ and $T_3$ from the gland. Iodine also decreases vascularity of the thyroid gland in Graves’ disease. The effects of iodine are only transient and its effect loses with time (iodine escape). Enrichment of glandular iodine stores may also retard the clinical response to subsequent radioiodine treatment or thionamide treatment. Iodine is useful mainly for short periods in patients with actual or impending thyrotoxic crisis, severe thyrocardiac disease or actual surgical emergencies. The usual dose of lugols iodine is 3 to 5 drops 3 times a day and SSKI is 1-3 drops 3 times a day.

Oral iopanoic acid and sodium ipodate produce a very rapid fall in the serum concentration of thyroid hormones. Apart from inhibiting the release of thyroid hormones, these drugs completely inhibit the peripheral conversion of $T_4$ to $T_3$. They are used in a dose of 0.5 to 1 gm per day. As with iodine itself, withdrawal of the drug carries the risk of exacerbation and hence large doses of antithyroid drugs should be administered concomitantly. It is not useful in long-term management, due to escape of thyroid hormone synthesis from the blocking effect of iodine.

Lithium

Lithium has direct inhibitory action on hormone release and also on intrathyroidal iodine turnover, but does not interfere with accumulation of radioiodine. In a dose of 300 mg every 8 hours lithium has been shown to provide temporary control of thyrotoxicosis and it has been shown to be beneficial in Graves patient undergoing radioiodine treatment.
Textbook of Endocrinology

Glucocorticoids

Glucocorticoids in high doses (Dexamethasone 2 mg every 6 hours) inhibit the peripheral conversion of T4 to T3. They also decrease the T4 secretion by the thyroid, possibly by immune suppression. Because of the significant side effects associated with long-term use of glucocorticoids and the effectiveness of the alternate treatment, the use of glucocorticoids in Graves’ disease is restricted to thyroid storm, and in the management of ophthalmopathy and dermopathy. Concurrent use of propylthiouracil, SSKI and dexamethasone can cause rapid reduction in thyroid hormone levels often to within the normal range within 24 to 48 hours.

β-adrenergic Antagonist Drugs

Many of the manifestation of the thyrotoxicosis are due to hyperactivity of the sympathetic nervous system and hence beta blockers are important in early management of thyrotoxicosis. These drugs should not be used alone in Graves’ disease, except for short periods before or after radioiodine therapy and adrenergic antagonists are helpful, especially when tachycardia is contributing to cardiac insufficiency. Propranolol is the most widely used agent and has the additional advantage of mild inhibition of the peripheral conversion of T4 to T3. It is given orally at a dose of 20-80 mg over 6 or 8 hrs. It is contraindicated in patients with bronchial asthma, chronic obstructive airway disease, heart block and in cardiac failure. Calcium channel blockers like deltiazem can be used when β-blockers are contraindicated.

Radioiodine

Radioiodine produces thyroid ablation without the complication of surgery. 131I is the preferred radioiodine in the treatment of thyroid hyperfunction, because of its short half-life and its favorable emission profile. Radioactive iodine is contraindicated in pregnant women and those who are breastfeeding, and it can induce or worsen ophthalmopathy, particularly in smokers.

Attempts have been made to standardize the radiation delivered to the thyroid gland according to the size of the gland and the uptake of 131I, but most physicians prefer to give fixed doses of 5 to 15 mCi. After oral administration radioiodine is rapidly absorbed, concentrated and organified in the thyroid follicular cells. Thyroid cells are then destroyed by the ionizing effects of beta particles. Control of hyperthyroidism requires at least weeks to months to be achieved after a single dose of radioiodine. Patients with mild or moderate hyperthyroidism do not require treatment with an antithyroid drug before or after radioactive iodine therapy; their symptoms can be adequately ameliorated with a beta-adrenergic antagonist until the radioactive iodine takes effect. Patients with severe hyperthyroidism should be treated with an antithyroid drug for four to eight weeks before radioactive iodine is given because the drug reduces thyroid secretion rapidly and thereby reduces the slight risk of the development of a thyrotoxic crisis soon after radioactive iodine administration. An antithyroid drug should be given after radioactive iodine therapy in patients whose hyperthyroidism is poorly controlled at the time of the administration of radioactive iodine.
Graves' Disease

Some patients may require a second treatment to with $^{131}$I to cure their hyperthyroidism and if so 1.5 times the first dose of $^{131}$I is administered.

The principal disadvantages of radioiodine are the influence of radiation on Graves' ophthalmopathy and the high frequency of late hypothyroidism. The cumulative incidence of postradioiodine hypothyroidism steadily increases at a rate of 2 to 3% new cases/year. The overall incidence of postradioiodine hypothyroidism approaches to total of 40% at 5 years and 60% or more at 10 years. Hypothyroidism is regarded as a common outcome of radioiodine treatment, rather than a true complication. There is no established teratogenic risk of radioactive iodine, but conception should be deferred for at least four months after treatment.

Transient exacerbation of mild to moderate preexisting Graves' ophthalmopathy can occur in few months after radioiodine treatment and can effectively be controlled by short course of prednisone 0.5 mg/kg one month before $^{131}$I treatment, with gradual tapering over 3 to 4 months, but radioiodine may not be a treatment of choice in patients with severe ophthalmopathy. Radioiodine treatment can rarely cause radiation induced acute thyroiditis that can be clinically manifested 3-4 days after administration of radioiodine by pain and swelling in the neck. This is benign and self-limited and can be treated with short course of anti-inflammatory drugs.

Thyroidectomy

Subtotal thyroidectomy is preferred by some patients with Graves' hyperthyroidism, especially those with a large goiter, and it may be indicated in patients with a coexistent thyroid nodule with suspicion of malignancy or patients requesting for surgery. The patient should be treated with an antithyroid drug until euthyroidism is achieved; inorganic iodide is also usually administered for seven days before surgery. The rate of postoperative hypothyroidism is higher when near-total thyroidectomy is performed than with subtotal thyroidectomy, and it is higher in patients with high serum thyroid peroxidase antibody concentrations.

Treatment of Graves' Ophthalmopathy

The majority of Graves' disease patients have a mild and non-progressive ocular involvement that does not require any specific or aggressive treatment, also because non-severe ophthalmopathy often tends to improve spontaneously.

In mild cases, local therapeutic measures (artificial tears and ointments, sunglasses, nocturnal taping of the eyes, prisms) can control symptoms and signs. In severe forms of the disease (3–5%), aggressive measures are required. If the disease is active, high-dose glucocorticoids and/or orbital radiotherapy, or orbital decompression represent the mainstay of treatment. Prednisone at doses 40 to 80 mg daily, with the dose tapered over a period of at least 3 months with or without initial intravenous pulses of hydrocortisone or methylprednisolone can be highly effective. Orbital decompression is effective in patients with optic neuropathy and exophthalmos, either as the initial treatment or after the failure
of glucocorticoid treatment. Novel treatments such as somatostatin analogs or intravenous immunoglobulins are under evaluation. Rehabilitative (extraocular muscle or eyelid) surgery is often needed after treatment and inactivation of eye disease. Correction of both hyper- and hypothyroidism is crucial for the ophthalmopathy. Antithyroid drugs and thyroidectomy do not influence the course of the ophthalmopathy, whereas radioiodine treatment may cause the progression of preexisting ophthalmopathy, especially in smokers. The exacerbation, however, is prevented by glucocorticoids.

**Treatment of Thyroid Dermopathy**

The treatment of dermopathy is usually symptomatic. Given the relatively benign nature of this problem, topical corticosteroids are more likely to be used than systemic therapy. Strengths of topical corticosteroids range from mid potency steroids, such as fluocinolone acetonide, to high-potency steroids, such as clobetasol propionate. Topical corticosteroids have had their absorption further enhanced with hydrocolloid or plastic wrap occlusive dressings. In general, occlusion is applied for at least 12 h each day. Duration of these treatments varies. A trial of 4–6 wk may be reasonable but must be followed carefully to watch for signs of adverse effects from the topical steroids (e.g. atrophy, telangiectasis, and ecchymoses).

**GRAVES’ DISEASE IN PREGNANCY**

Ideally, women with Graves’ hyperthyroidism should avoid pregnancy until their hyperthyroidism is adequately treated, because the rate of fetal loss in untreated women is high. When Graves’ hyperthyroidism occurs or recurs during pregnancy, an antithyroid drug should be given in the lowest dose necessary to maintain the woman’s serum free thyroxine concentration in the upper part of the normal reference range. Combination therapy with an antithyroid drug and thyroxine must be avoided because the dose of antithyroid drug needs to be higher in patients who are also receiving thyroxine therapy, and little of the thyroxine reaches the fetus, resulting in fetal hypothyroidism. There is little difference between propylthiouracil and methimazole in terms of the potential of causing fetal hypothyroidism, despite the theoretically lower risk of transplacental transfer of propylthiouracil as a result of higher levels of drug binding to serum proteins. There is a weak association between aplasia cutis congenita and maternal use of methimazole or carbimazole during pregnancy. Properly monitored treatment with an antithyroid drug is safe in pregnant women, but hyperthyroidism can be present in the fetuses and neonates of 1 to 5 percent of women who had Graves’ disease during pregnancy, which might be caused by the transplacental passage of thyroid-stimulating antibodies.

**THYROID STORM**

Thyroid storm, also referred to as thyrotoxic crisis, is an acute, life-threatening, hypermetabolic state induced by excessive release of thyroid hormones in individuals with thyrotoxicosis. Thyroid storm appears most commonly following infection like pneumonia, upper respiratory...
Graves’ Disease

tract infection and enteric infections, which seems to induce an escape from control of the thyrotoxicosis, in patients poorly prepared for surgery and rarely after radioiodine treatment. The decreased incidence of thyroid storm can be largely attributed to the improved methods of diagnosis and therapy available today.

In its pure form the manifestations are due simply to the action of excess thyroid hormone. Diagnosis is primarily clinical, and no specific laboratory tests are available. There is fever, tachycardia, tremor, nausea, vomiting, diarrhea, dehydration, and delirium or coma. Precise criteria for the diagnosis have been formulated by Burch and Wartofsky.23 Fever is perhaps the most characteristic feature; the temperature may rise above 41°C. Occasionally, patients have a true toxic psychosis or a marked deterioration in previously abnormal behavior. Sometimes thyroid crisis takes a strikingly different form, which has been called apathetic storm. This condition is characterized by extreme weakness, emotional apathy and confusion. Signs and symptoms of decompensation in various organ systems may be present.

Treatment of thyroid storm consists of supportive as well as specific therapy. Supportive therapy includes rest, mild sedation, fluid and electrolyte replacement, nutritional support and vitamins as needed, antibiotics, cooling and cardiac support. Specific therapy includes drugs like propranolol (20 to 200 mg orally every 6 hours, or 1 to 3 mg intravenously every 4 to 6 hours), antithyroid drugs (150 to 250 mg PTU or methimazole 15 to 25 mg, every 6 hours), potassium iodide (100 mg KI every 12 hours) and dexamethasone (2 mg every 6 hours). Death may be caused by cardiac arrhythmia, congestive heart failure, hyperthermia, or other unidentified factors.

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INTRODUCTION
Papillary and follicular (differentiated) carcinomas of the thyroid are among the most curable cancers and together with medullary carcinoma and anaplastic carcinoma of the thyroid account for around 1% of all human cancers.

EPIDEMIOLOGY
Although thyroid nodules are very common, thyroid carcinomas are relatively rare. The annual incidence rate from various parts of the world ranges from 0.5 to 10 cases per 100,000 population. Thyroid cancers are rare in children and adolescents and their incidence increases with age. The median age at diagnosis is 45 to 50 years. Thyroid cancers are two to four times as frequent in women as in men. Data from our hospital with differentiated carcinoma over the last four years has shown a median age at presentation of 39 years with a M: F ratio of 1:1.8 (Graph 11.1). In our patients with medullary thyroid carcinoma the mean age of presentation was 41 years.

Thyroid microcarcinomas (diameter <1 cm) are found in 5-30% of adults at autopsy. These microscopic tumors maybe detected incidentally following surgical removal of the thyroid gland for some other indication.

Among patients with differentiated thyroid carcinomas papillary carcinoma are more common. The ratio that is conventionally described is 2:1; however in our series it was much more common with a ratio of 4.6:1. Five percent of thyroid carcinomas described in literature are medullary carcinoma. Over a period of 20 years we were able to identify only 40 patients with medullary carcinoma compared to over 70-80 patients of differentiated carcinoma per year accounting for 2.5% of thyroid cancers.

CLASSIFICATION
From thyroid follicular cells (differentiated):
1. Papillary carcinoma and variants
2. Follicular carcinoma and variants
From other cells:
1. Medullary carcinoma of thyroid
2. Lymphoma
3. Others including squamous cell, sarcoma and teratoma
   Anaplastic carcinoma (Undifferentiated)

**PATHOGENESIS**

**Oncogenes and Differentiated Carcinomas**

Rearrangements of the tyrosine kinase domains of the RET and TRK genes are found in some papillary carcinomas. RET rearrangements are found in 3-33% of sporadic papillary carcinomas and in over 60% of those occurring after radiation exposure. The frequency of TRK gene rearrangements is much lower.\(^4\)

RAS gene point activating mutations are found in a similar frequency in follicular malignancies. Other rare mutations include activating mutations in the thyrotropin receptor, the alpha subunit of the G protein and inactivating mutations of the p53 tumor suppressor gene.

**Genetic Abnormalities in Medullary Thyroid Carcinoma (MTC)**

There are four types of clinical MTC. MTC that is sporadic or MTC which is part of a familial MTC syndrome, MEN2A syndrome or MEN2B syndrome. Germline mutations of the RET Proto-oncogene were identified in all three familial syndromes of MTC. Somatic mutations of the RET proto-oncogene have been identified in 25-30% of sporadic MTC.\(^5\) Hereditary
MTC accounted for 25% of patients with MTC in our institution. Familial MTC accounted for 40% of the hereditary MTC and the rest had MEN 2.³

**Thyroid Irradiation**

External radiation to the region of the neck in childhood increases the risk of papillary carcinoma. The risk increases with the dose given. In children exposed to a dose of 1 Gy to the thyroid the risk of thyroid carcinoma is increased by 7.7.⁶

There does not appear to be any increased risk of thyroid malignancies associated with diagnostic and therapeutic usage of iodine-131. However, the number of children exposed to Iodine-131 is still very small to rule out a carcinogenic effect. There has been a 100 fold increase in the incidence of thyroid cancer in Belarus and Ukraine following the Chernobyl nuclear accident.⁷

**Iodine Intake**

There is no difference in the incidence of thyroid cancers in countries which are iodine deficient compared to countries which are iodine sufficient. But there appears to be a relative increase in the incidence of follicular and anaplastic cancers in iodine deficient areas.⁸

**PATHOLOGICAL FEATURES**

**Papillary Carcinoma**

Papillary carcinoma is an unencapsulated tumor with papillary (leaf-like structures) (Fig. 11.1) with characteristic overlapping nuclei that have a ground glass appearance and longitudinal grooves with invaginations of the cytoplasm into the nuclei ("Orphan Annie" appearance-based on a cartoon character in the 1930s with large clear eyes) (Fig. 11.2).⁹ The tumor is multicentric in over 20-80% of patients and bilateral in around 1/3rd of patients. Lymphatic spread is common either intrathyroidal or to regional lymph nodes or rarely to the lungs. The variants described include encapsulated, follicular, tall cell, clear-cell and diffuse sclerosing.

Among our patients the follicular variant was seen in 20% of patients. Lymph node spread was seen in over 90% and distant metastasis in 12% of patients.²

**Follicular Carcinoma**

The follicular lesions have a distinct capsule and capsular and vascular invasion is the key feature to distinguish between an adenoma and a carcinoma. The lesion is characterized by follicular differentiation without the nuclear changes seen in papillary carcinoma.⁹ Multicentricity and lymphatic spread is less frequent. Hematological spread occurs to the lung and bone. Variants described include the Hurthle cell variant (Fig. 11.3) which is rare and was seen in 1% of differentiated carcinomas in our series. Lymph node metastasis was seen in 7% with distant metastasis in 34% of patients in our series.²
Fig. 11.1: H & E staining of thyroid showing papillary carcinoma. Black arrow; finger-like projection of the tumor and inset reveals evidence of extracapsular invasion (© 2006 Department of Endocrinology, Christian Medical College, Vellore) (For color version, see Plate 1)

Fig. 11.2: Characteristic Orphan Annie nuclei (Black arrow) with inset picture of the cartoon character "Orphan Annie" (© 2006 Department of Endocrinology, Christian Medical College, Vellore) (For color version, see Plate 1)
Medullary Carcinoma

Medullary carcinoma is located typically at the junction of the upper third and the lower two thirds of the thyroid gland. The tumor consists of sheets of spindle-shaped, round or polygonal cells separated by a fibrous stroma. The nuclei are uniform in shape with rare mitotic figures. There is positive immunohistochemical staining for calcitonin and carcinoembryonic antigen (Fig. 11.4). Amyloid deposits are seen in 75% of patients. Almost half the patients will have cervical lymph nodes which are palpable and distant metastasis to the lung, liver and bone maybe seen in 20% of patients. Fifty percent of patients in our series had lymphadenopathy at the time of presentation and in 15% of the patients the lymph node enlargement was not associated with any thyroid swelling.

CLINICAL PRESENTATION

The most common presentation of differentiated carcinoma is that of an asymptomatic thyroid nodule (Fig. 11.5A). The diagnosis is not usually evident on clinical examination. The following features increase the suspicion of a thyroid malignancy in a nodule.

1. Children, adolescents and patients older than 60 years
2. If the nodule is hard and irregular
3. Any progressive increase in size or a recent increase in size
4. Enlarged locoregional lymph nodes
5. Compressive symptoms including any history of hoarseness of voice
6. Males
7. Previous exposure to head and neck radiation
Fig. 11.4: Calcitonin immunostaining of a section of tissue from a medullary thyroid carcinoma (© 2006 Department of Endocrinology, Christian Medical College, Vellore) (For color version, see Plate 2)

Figs 11.5A and B: Clinical presentation. (A) Asymptomatic solitary nodule (Black arrow). (B) Multinodular goiter (© 2006 Department of Endocrinology, Christian Medical College, Vellore) (For color version, see Plate 2)
Other presentations include:

1. Multinodular goiter with increase in size of a particular nodule or presence of a hard nodule (Fig. 11.5B)
2. Cervical lymphadenopathy (Fig. 11.6A)
3. Compressive symptoms like hoarseness of voice, dysphagia, cough and dyspnea
4. Occasionally distant bone and lung metastasis (Figs 11.6B and 11.7)
5. Incidental diagnosis in a surgical specimen of the thyroid

Medullary carcinoma maybe suspected on initial examination in several situations; the location of the nodule at the junction of the upper 1/3rd with the lower 2/3rd of the thyroid lobe, pain on palpation, a diarrheal syndrome or symptoms of flushing and a family history of thyroid or neuroendocrine tumors.10

Figs 11.6A and B: Clinical presentation. (A) Local lymphnodal metastasis. (B) Distant skull metastasis with evidence of thyroid enlargement (Black arrow) (© 2006 Department of Endocrinology, Christian Medical College, Vellore) (For color version, see Plate 2)

MANAGEMENT

The Role of FNAC

Whatever the presentation fine needle aspiration cytology remains the single most important test to distinguish benign and malignant lesions. Provided the sampling is adequate three possible cytological results are possible: benign, malignant and indeterminate. In over 250 patients with differentiated carcinomas seen in our center the FNAC was suggestive of malignancy in 75% of patients.2 About 20% of patients with an indeterminate FNAC report have a malignancy (Graph 11.2).11
Prognostic Factors

The survival rate at 10 years for middle-aged adults with differentiated thyroid carcinoma is about 80-95%. The prognostic indicators of recurrence of the disease and deaths were age, grade and extent of tumor and the histological subtype. Poor prognosis was observed when the age at the time of diagnosis was > 70 years and the tumor was poorly differentiated.
Thyroid Cancers

(grade 3 and above). The prognosis was poorer in patients with follicular cancers and worst with the Hurtle cell variant of follicular cancers. Gender, stage of the tumor and nodal status did not influence the prognosis.11

Therapy for Differentiated Cancers

Surgery

The goal of surgery is to remove all tumor tissue in the neck. There are strong arguments in favor of a total or near total thyroidectomy in all patients. They are:

1. Lower recurrence rates since many papillary carcinomas are mutlifocal.
2. Facilitates remnant ablation with radioactive iodine.

There is a definite increase in the risk of recurrent laryngeal paralysis and hypoparathyroidism with this approach. However, this is minimized by surgical experience.12

In patients with papillary carcinoma, lymph nodes in the central neck compartment and the ipsilateral supraclavicular area should be dissected. A modified neck dissection is performed if there are palpable lymph nodes in the jugulo-carotid chain. Among patients with a follicular cancer lymph node dissection is performed only if lymph nodes are palpable during surgery.

Radioactive Iodine Therapy

Iodine-131 is given for two major reasons postoperatively for all patients with differentiated carcinomas.

1. Destroys any remaining normal thyroid tissue and thereby improves the use of whole body Iodine scans and thyroglobulin for detection of remnant disease or recurrence.
2. Destroys occult foci of cancer and decreases long-term chances of recurrence.

The first scan is done about 6 weeks after surgery with the patient off levothyroxine therapy in the interim. If uptake is detected anywhere in the thyroid bed or anywhere in the body a therapeutic dose of Iodine-131 is administered. The usual dose used in our institution is 50-100 MBq. Patients are replaced with large doses of levothyroxine (usually 300 micrograms/day) and followed after 6 months. Whole body Iodine scans are repeated at 6 months and if the uptake persists then the patient undergoes a second sitting of radioactive Iodine ablation. Among our patients over 50% of patients went into remission after a single sitting of radioactive I-131 therapy. The mean total dose required for achieving remission was 123 mC of I-131.2 Patients are considered to be in remission only once two consecutive whole body imaging scans done at six monthly intervals do not detect any residual lesions. Common acute adverse effects with therapeutic doses of iodine-131 include nausea and sialadenitis but they are usually mild and resolve rapidly. Radiation induced pulmonary fibrosis may develop in individuals with pulmonary metastasis if the doses are large or closely spaced.13 Radiation thyroiditis may develop in patient with large remnants. This is also self-limiting and if the patient has pain, a few days of therapy with glucocorticoids maybe required.
External Radiotherapy

External radiotherapy to the neck and upper chest is indicated in patients in whom surgical excision is incomplete and the tumor tissue does not take up radioactive iodine.

Follow-up

The goals for follow-up include:
1. Adequate levothyroxine replacement
2. Early detection of recurrences or persistence of disease
   
   Recurrences are usually detected in the first-five years of therapy, however, they maybe detected later in some cases. Long-term follow-up is mandatory.

Levothyroxine Therapy

Tumor growth is TSH dependent and inhibition of TSH by levothyroxine improves recurrence and survival rates. Levothyroxine is given in adults at the dose of 2.5 micrograms/kg body weight. We routinely give 200 to 300 micrograms of levothyroxine to all patients depending on body weight. The goal of therapy is to suppress TSH to less than 0.1 Microunit/ml and keep the free T₄ in the normal range.

Clinical Examinations

Patients should be followed up every six months in first-two years and subsequently seen once a year. Examination should include palpation of the thyroid bed and cervical lymph nodes to detect any evidence of recurrence. Any suspicious nodules should be biopsied under ultrasound guidance. Routine chest X-rays are not indicated.

Serum Thyroglobulin (TG) Measurements

An annual thyroglobulin measurement is an excellent marker to detect recurrence of disease. Patients with undetectable serum thyroglobulin have been free of relapse over the last 15 years. Thyroglobulin measurements are usually obtained after withdrawing thyroid hormone therapy for a period of 4 weeks. Oral T₃ therapy (Cytomel™) 20 micrograms thrice daily can be used for the first-two weeks to minimize the effects of hypothyroidism. Alternatively recombinant TSH injection (an expensive agent) can be administered prior to taking blood for thyroglobulin measurements. Fifteen percent of patients with thyroid cancers have anti-thyroglobulin antibodies which may interfere with the measurement. Testing for antibody levels should be performed simultaneously to account for any interference with the assay. Among patients seen in our hospital the peak thyroglobulin levels had a significant association with the presence of metastasis and the levels were directly related to the number of ablations required per patient. Follicular carcinomas had higher peak TG levels when compared to papillary carcinomas.
Thyroid Cancers

Therapy for Medullary Carcinoma of Thyroid

Surgery

Similar to the therapy of differentiated carcinoma the primary therapy for medullary carcinoma is surgical removal of all neoplastic tissue in the neck. This includes total thyroidectomy and bilateral lymph node dissection. Surgery should only be performed after careful exclusion of a coexisting pheochromocytoma. In patients with adrenal medullary disease thyroid surgery should only be done after resection of the adrenal tumor.

Postoperative Management

Levothyroxine therapy is given in normal replacement doses as the patient is athyreotic. Serum Calcitonin (CT) measurements are done 2-3 months after surgery. If basal CT is normal then a stimulated CT value following pentagastrin administration is done. Patients with undetectable pentagastrin stimulated CT values are likely to be free of disease. In patients with local disease 75% will have undetectable CT values but in those with lymph node involvement the chances of biochemical cure is only 20-30%. Postoperative Calcitonin levels were elevated in a majority of patients in our series and it did not predict poor prognosis (Graph 11.3).

In patients with high CT levels postoperatively various localization procedures including ultrasound neck and liver, Abdominal CT, MRI neck, I-131 MIBG scanning, thallium 201 scanning and octreotide scanning all have variable sensitivity. Selective venous sampling with CT measurements appears to be most sensitive. In our series we have used MIBG scanning extensively preoperatively to confirm the diagnosis of MTC, identify coexisting pheochromocytomas, identify metastatic disease and postoperatively to locate the source of hypercalcitoninemia (Fig. 11.8).

Graph 11.3: Calcitonin was persistently elevated in 70% of subjects and this may not indicate poor prognosis (© 2006 Department of Endocrinology, Christian Medical College Vellore)
Radiotherapy

Radioactive iodine therapy does not have a role as the Parafollicular cells do not have the ability to concentrate and trap iodine. In patients with functioning thyroid tissue there maybe some benefit of the scatter radiation on parafollicular cells.

External radiation therapy appears to benefit two selected group of patients;
1. Patients with inoperable tumors it induced long-term stabilization
2. Patient with persistently elevated postoperative CT levels after complete thyroid surgery.

Follow-up

After initial treatment, patients should be on a lifelong follow-up as for differentiated cancers. Serum CT should be checked once every 6 months for the first two-years and subsequently once a year lifelong. If CT levels are found to be elevated persistently a complete work-up is done. A detectable CT level is compatible with long-term survival. Screening for pheochromocytoma and hyperparathyroidism should be continued on follow-up in familial cases and in all patients below the age of 40 years.

CONCLUSIONS

1. Most patients with differentiated thyroid cancers can be cured with appropriate and adequate surgery followed by radioiodine therapy.
2. Meticulous follow-up for life is vital to detect and treat recurrences early.
3. Lifelong supraphysiological thyroid hormone replacement is required to decrease chances of recurrence.
4. Chances of a complete cure for MTC depend on early diagnosis followed by complete thyroidectomy with bilateral neck dissection.

REFERENCES

Adrenal Gland and Cushing’s Syndrome

DEVELOPMENT – EMBRYOLOGY

Adrenal gland arises from mesenchymal cells attached to coelomic cavity lining adjacent to urogenital ridge. Adrenal cortex is first noted at 6th week of gestation and its size in mid-gestation is larger than the kidneys (Fig. 12.1).

Cells destined to form the medulla migrate from the sympathetic ganglia. The fetal cortex regresses and definitive cortex with zonulation occur. This zonulation is under control of transcription factors. The adult gland weighs 4 gm and is $2 \times 5 \times 1$ cm in dimension. The gland receives blood supply from inferior phrenic, aorta and renal arteries. It receives 6 to 7 ml blood/gm/minute. Venous drainage goes directly to inferior vena cava on the right side and renal vein on the left side.

Fig. 12.1: Development of adrenal gland
**STRUCTURE**

The gland consists of cortex which is steroidogenic and medulla derived from enterochromaffin tissue producing catecholamines, epinephrine and norepinephrine. The cortex is further divided into three zones, zona glomerulosa secreting aldosterone (the major mineralocorticoid) which forms 15% of width of adult gland, zona fasciculata secreting hydrocorticone (the major glucocorticoid) forming 75% of adult gland size and zona reticularis producing adrenal androgen constitute the rest (Fig. 12.2).

![Fig. 12.2: Structure of adrenal gland](image)

**Cell Apoptosis and Regeneration**

Cell division to replace senescent cells occur from the zona glomerulosa-fasiculata junction while apoptosis occur by migration into reticularis. Factors controlling this process is poorly understood.

**STEROIDOGENESIS (FIG. 12.4)**

All hormonally active steroids in man are derived from cholesterol (C27) (Fig. 12.3). Circulating cholesterol as LDL is trapped by adrenal cortical cells by receptor mediated uptake. Internalized LDL–receptor complex fuse with lysosome liberating free cholesterol. Adrenal cortical cells can synthesize cholesterol de novo from acetyl CoA. The rate limiting step in formation of all biologically active steroids is transport of intracellular cholesterol from outer to inner mitochondrial membrane, a process regulated Steroid Acute Regulatory Protein (30 Kd) (StAR). This protein is induced by cAMP generated when ACTH bind with adrenal cell surface receptors.

Cholesterol (C27) is cleaved by enzyme Desmolase (sccP450) to yield Pregnanolone and Isocaprialdehyde. Pregnanolone is the precursor of all biologically active steroids. Depending on the need, pregnanolone is preferentially channeled into mineralocorticoid (z. glomerulosa), Glucocorticoid (z. fasciculata) or Androgenic (z. reticularis) pathways. Each zone possesses set of enzyme for formation of the appropriate type of steroid.
Regulation of Adrenal Steroid Biosynthesis

Adrenal steroid formation is controlled by ACTH and Angiotensin II. ACTH regulate production of glucocorticoids by z. fasciculata which secrete 15 to 20 mg of the hormone while z. glomerulosa, under influence of angiotensin II produces 100-150 ug of aldosterone. Most abundantly secreted adrenal steroids are androgens, DHEA and Androstenedione, the daily secretion rate exceeding 20 mg. Each class of steroid is synthesized in a zone specific manner as the enzymes are selectively distributed in each zone for synthesis of a particular class of steroid.
Adrenal Gland and Cushing’s Syndrome

Aldosterone synthesis is facilitated by angiotensin II, serum K and minimally by ACTH. It is inhibited by somatostatin, dopamine, atrial natriuretic peptide and heparin. Cyp 11B2, unique enzyme needed for synthesis of aldosterone is expressed only in Z. glomerulosa. However, corticosterone and its deoxymetabolites with moderate mineralocorticoid activity can be formed in the z. fasciculata as well and become clinically significant in some disease states like Cushing’s syndrome, congenital adrenal hyperplasia and adrenal carcinoma which are associated with hypertension. Both angiotensin II and K increase transcription of Cyp 11B2 in the cells of Z. glomerulosa. While K cause membrane depolarization permitting entry of Ca into the cells activating calmodulin kinases while angiotensin II activate phospholipase C.

Z. reticularis synthesize around 20 mg of androgens which include DHEA, DHEAS and androstenedione. DHEA is transformed into androgen or estrogen in the target tissues. This conversion produce 50% androgens in female and smaller fraction in males. In males, major source of androgen is testosterone from testes, the production starting at the time of puberty. Androgenic activity of DHEA in males become significant in situations like CAH responsible for isosexual precocious puberty. DHEA levels are high at birth and fall with involution of fetal zone, rising again between 6 and 8 years (Adrenarche) and levels fall to very low levels in old age (Adrenopause). Secretion of adrenal androgen is primarily regulated by ACTH and show circadian variation similar to that of cortisol but of lesser magnitude due to longer half-life of DHEA.

CIRCADIAN RHYTHM AND HYPOTHALAMO HYPOPHYSEAL ADRENAL AXIS

Pituitary cortitroph is under the influence of CRH (41 amino acid peptide) secreted by parvocellular neurons of paraventricular nucleus and Vasopressin and oxytocin produced by the magnocellular neurons of paraventricular and supraoptic nuclei. CRH act on the corticotrophs through G protein coupled receptors causing expression of POMC gene and its product. POMC is converted to 1-39 amino acid residue (ACTH) and beta lipotropin by enzyme prohormone convertase I. Corticotrophs lack Convertase II enzyme which is necessary for the production of MSH. This enzyme is expressed in the intermediate lobe and certain areas of brain. Vasopressin and oxytocin act on the corticotrophs through the V3 receptors. Circadian rhythm of cortisol secretion is a property of the HPA axis, the rhythm being triggered by suprachiasmatic nucleus. Lowest levels of cortisol is noted around 11 pm while highest levels are observed around 4 am. This is associated with change in the activity of HPA axis and sensitivity of cortitrophs to circulating levels of CRH, Vasopressin and Oxytocin. Disruption of circadian rhythm occur by change or shift of activity timings, sleep deprivation and ageing. Glucocorticoid Nadir is deeper in elderly with its metabolic effect of increased visceral fat and weight gain and mortality.

Disease states like Cushing’s syndrome and depressive illness also alter the circadian rhythm. Blunted nadir cortisol is observed in depressed persons is not just an epiphenomenon but modulation of cortisol levels would improve the psychological disturbance.

Stress also influences the HPA axis activity. Usually, physical stress has their effect mediated through somatosensory, viscerosensory and osmosensory inputs through the
brainstem while psychological stress influence HPA axis through forebrain – prefrontal cortex and subiculum. Input received from various sources are translated by hypothalamus by secretion of CRH, oxytocin or vasopressin. All modalities of stress activate the CRH neurons, psychological stress selectively activate PVN oxytocin neurons. Hypotension and change in volume or osmolar factors mainly affect vasopressin and oxytocin producing neurons while metabolic factors like hypoglycemia activate dominantly CRH secretion. Chronic stress, when show diminished response to repeated stress (habituation) show enhanced response to new form of stress (facilitation). HPA response to chronic stress is mediated by vasopressin and GABA activity.

Activity of HPA axis is controlled by feedback regulation at pituitary and hypothalamic levels. Rapid and slow negative feedbacks are reported. Glucocorticoids alter hypothalamic neuronal electrical activity in the PVN cells within seconds responsible for acute feedback. Subacute feedback operate by inhibiting protein synthesis at corticotroph and hypothalamic levels. Areas involved in stress are paraventricular nucleus (PVN), prefrontal cortex and hippocampus.

HPA system is also influenced by cytokines (Interleukins, interferons, TNFs and colony stimulating factors). This may be important in regulating the activity of the system in infections and inflammation. Leptin, hormone secreted by adipocyte, negatively influences the HPA system to conserve or utilize energy.

**Action of Adrenal Steroids**

Glucocorticoids and mineralocorticoids enter the cells and bind to cytosolic receptors. These receptors are similar to the one binding thyroid hormones and has a C terminal ligand binding domain, central DNA binding area which bind to specific transcription area of DNA and N terminal hypervariable area. Binding of glucocorticoid receptors to the DNA cause tissue specific activation or repression of transcription explaining the differential action of glucocorticoids in different tissues. GR$\alpha$ is predominantly activate transcription while GR$\beta$ represses transcription.

Ninety percent of glucocorticoids are bound to cortisol binding globulin (CBG) which is an $\alpha2$ globulin secreted by liver. Levels rise in pregnancy, estrogen therapy and some liver diseases like chronic active hepatitis while low values are noted with glucocorticoid therapy, nephritic syndrome, cirrhosis liver and thyroid hormone excess. Genetically determined excess or deficiency of CBG is rare but can be associated with changes of total cortisol estimated. Only free cortisol is transported into tissues and hence biologically active. Free cortisol is filtered by the kidneys and urinary free cortisol accounts for 1% of total cortisol secretion.

Plasma half-life of cortisol is 70 to 120 min. It is inactivated by formation of cortisone (by enzyme 11-$\beta$ Hydroxysteroid dehydrogenase or by reduction of double bond between C4 and C5 to tetrahydrocortisol (THF). Inactivated metabolites are rapidly conjugated with glucoronic acid and excreted in the bile. Mineralocorticoids are also metabolized in a similar manner.
11-β hydroxysteroid dehydrogenase is a crucial enzyme which determine the tissue specific activity of glucocorticoids. Tissues which express this enzyme, inactivate cortisol to inactive metabolite cortisone. Two isoforms of this enzyme exists – 11β HSD1 active in liver, adipose tissue, bone, brain, gonads muscle and eyes which respond mainly to glucocorticoids while tissues like kidney, colon and salivary gland express 11β HSD2 which respond to aldosterone. Dysregulation of these isoenzymes are considered to be responsible for certain forms of mineralocorticoid excess situation and hypertension like inherited form of endocrine hypertension, salt sensitive essential hypertension and hypertension with locorice ingestion.

**Biological Effects of Glucocorticoids**

Glucocorticoids have wide ranging biological effects. Major influence of glucocorticoids of clinical significance arise from their action on intermediary metabolism, immune and inflammatory response and muscle and bone structure (Fig. 12.5).

**Intermediary Metabolism**

*Carbohydrates:* In supraphysiologic levels, glucocorticoids increase hepatic glycogen by increased formation and decreased breakdown on glycogen. It promotes gluconeogenesis with increase in hepatic glucose output and cause tissue insulin resistance resulting in hyperglycemia and diabetes. Diabetes is noted in one-third of subjects receiving pharmacologic doses of glucocorticoids.
Fat cell and fat metabolism: Glucocorticoids enhance lipolysis in adipose tissues with release of FFA. This results in increase in triglycerides and cholesterol. Adipocyte differential and redistribution of adipose to tissue to central areas (Trunkal obesity) occur with glucocorticoid excess.

Protein metabolism: Glucocorticoids cause protein breakdown. Amino acids from this process is channeled into gluconeogenic pathways. Protein wastage in skin cause dermal fragility and collagen breakdown in subepidermal region results in purple striae. In the bone, protein removal cause decreased bone osteoid and bone fragility and pathological fractures. Tissue deposition, characteristic of growing children is inhibited by decreased formation of IGF 1 due to glucocorticoid excess account for short stature. This is reported even with inhaled corticosteroids used in asthma and topical steroids used in dermatology.

Immune System and Inflammation
Suppression of immune and inflammatory response by glucocorticoids is the basis of use of these agents for a variety of situations outside endocrine practice. Acute administration of glucocorticoids cause drop in T and B lymphocytes by extravascular migration to bone marrow, spleen and lymphoid tissues. There is fall in eosinophil count and increase in polymorphs. Apoptosis of lymphocytes increases with glucocorticoid administration. Cytokine production, which is an important step in immune reaction and inflammation is blocked by binding of glucocorticoids with NFkB. NFkB play central role in production of cytokines. Glucocorticoids also reduce the transformation of monocytes to macrophages and reduce the phagocytosis by macrophages.

Miscellaneous
In the nervous system, depression is observed in 50% of patients with Cushing’s syndrome. Depression, euphoria, psychosis, lethargy and apathy are noted with steroid excess. Glucocorticoids cause neuronal death in areas like hippocampus. This would result change in cognitive function and memory. Ophthalmic effects of glucocorticoids include rise in intraocular pressure, chemosis, cataract and proptosis (due to retrobulbar fat deposits). In the gastrointestinal system, glucocorticoids are implicated in formation of peptic ulcer and pancreatitis.

DIAGNOSIS OF CUSHING’S SYNDROME
Etiology
Incidence of Cushing’s syndrome has been reported variedly between 2 to 5 cases per million population. The symptoms and signs are so subtle and varied that the diagnosis is often delayed or missed. Failure to diagnose and treat would result in high mortality with relative risk of 3.8 to 5 times of normal population. When diagnosed by clinical grounds or by workup, poor prognosis is noted in cases which could not be cured by surgery or in cases associated with malignancy.
Usual causes of Cushing’s syndrome include:
1. Pituitary dependant disease
2. Adrenal adenoma or carcinoma
3. Ectopic ACTH producing lesions.
   Iatrogenic Cushing’s syndrome will have somatic features of Cushing’s syndrome but would show Addisonian features when exogenous steroids are withdrawn.

**Clinical Features**
- Central obesity, supraclavicular and nuchal pad of fat
- Facial plethora, acne, hirsutism
- Thin skin, purple striae more than 1 cm diameter, fungal infection, easy bruising (Fig. 12.6)
- Short stature, lanugo hair
- Proximal myopathy
- Diabetes mellitus, hypertension, hyperlipidemia and polycystic ovaries (Metabolic syndrome X)
- Menstrual dysfunction, infertility, decreased libido and impotence
- Pathologic fractures
- Incidental adrenal mass
   A patient presenting with one or more of these features need to screened for hypercortisolism and fully evaluated if screening tests are abnormal.

**Diagnostic strategy for hypercortisolism would be as follows:**
1. Screening and confirmatory tests to demonstrate the presence of hypercortisolism
2. Identify the source of excess cortisol.

**Screening Tests**
Tests employed in screening and confirmation of hypercortisolism are based on the following principles.
   There is elevated levels of cortisol in all subjects with Cushing’s syndrome.
   Normal diurnal variation of cortisol is lost with blunting of nadir of cortisol around midnight.
Abnormalities are noted in the suppressibility of HPA axis with exogenous dexamethasone. However, the following factors should also be considered before confirmation or elimination of diagnosis of Cushing’s disease:

Even in established cases of Cushing’s, cyclical increase and normalisation of secretion of cortisol occur.

Physiologic states like stress and exercise, disease states like depression, mania and drugs which alter the metabolism of cortisol could interfere with interpretation of these tests. Sensitivity and specificity depend on the nature of the test, method used for analysis of samples and cut off points used and mode of collection of sample when fragile molecule like ACTH is being analyzed.

**Urinary Steroid Metabolites**

Historically, urinary metabolites of adrenal steroids were used for the diagnosis of Cushing’s syndrome in the past. 24 hours urinary 17-ketosteroids, ketogenic steroids and 17 hydroxycorticoids were used. Variability of test results and the fact that these steroids represented only part of glucocorticoid secretory status with problems of urine collection has made urinary steroid metabolites for evaluation of Cushing’s syndrome as obsolete tools.

**Urinary free cortisol:** Free cortisol is filtered by the kidney and is not absorbed or metabolized. When binding capacity of cortisol by CBG is exceeded (at 25 ug/dl normally) increase in UFC proportion to free plasma cortisol occur. However, in mild cases of Cushing’s syndrome, rise in urinary free cortisol is noted only during night and 24 hours measurement may not reflect a small rise at night. Timed urine collection done during would improve the sensitivity of urine cortisol measurements. Procedure is less cumbersome with only one or two urine specimen to be collected. Accurate measurement with simultaneous measurement of urine creatinine improve the specificity of the test. Methods used for measurement include direct RIA without chromatographic separation and HPLC separation followed by RIA or tandem mass spectrometry and fluorimetry. Drugs like carbamazepine and fenofibrate would interfere with chromatographic methods. Normal UFC is around 100 mcg in 24 hours and values in Cushing’s syndrome usually exceed 400 mcg in 24 hours in values in the border range. Repeat measurements done later as the steroid excretion rate vary cyclically in some patients, who have other clinical features of the disease. Assay specificity is 100% while sensitivity vary from 50 to 75%.

**Circadian Rhythm Alterations**

One of the early abnormalities in Cushing’s syndrome is the loss of diurnal variation. This phenomenon is used for the diagnosis of Cushing’s syndrome in different ways.

**Midnight cortisol:** Elevation of midnight cortisol strongly suggest the diagnosis of Cushing’s disease. Inability to procure a blood sample at this time with stress elimination make this test impractical.
Adrenal Gland and Cushing’s Syndrome

Midnight salivary glands: This can be used as a surrogate when midnight plasma cortisol estimation is difficult. However, the test can be influenced by stress, sleep disturbances, emotional factors and hence lack specificity. Sensitivity and specificity approach 95% and may become an important tool for the diagnosis of Cushing’s syndrome.

Suppression test: The concept behind this test is that the normal hypothalamic hypophyseal system is highly sensitive to exogenous glucocorticoids like dexamethasone. 2 mg overnight suppression and 0.5 mg four times day for 48 hours suppression are used for this purpose with cut-off point of 5 ug in the morning. With this dose of dexamethasone, only normal pituitary will be suppressed while cortisol output in pituitary basophil adenoma, ectopic ACTH producing lesions and adrenal tumors will not be suppressed. The test is frequently performed for evaluation of Cushing’s syndrome but its validity is being questioned. By lowering the cut-off point to less than 1.8 ug/dl, some improvements in sensitivity and specificity and can be expected and the test need further evaluation. A number of factors can make the interpretation of the test difficult (Fig. 12.7).

<table>
<thead>
<tr>
<th>Dexamethasone suppression – falacies</th>
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<tbody>
<tr>
<td>Drugs altering DXM metabolism</td>
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<tr>
<td>Slowing metabolism – spontaneous suppression:</td>
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<tr>
<td>Benzodiazepines, Estrogens</td>
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<tr>
<td>Accelerating metabolism – lack of suppression :</td>
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<tr>
<td>Barbiturate</td>
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<td>Phenytion</td>
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<td>Carbamazepine</td>
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<td>Rifampicin</td>
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<tr>
<td>Spurious lack of suppression :</td>
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<tr>
<td>Pseudo-Cushing’s states</td>
</tr>
<tr>
<td>Alcohol, Exercise, Affective diseases</td>
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<tr>
<td>Liver diseases</td>
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</table>

Fig. 12.7: Drug interaction causing falacies

Combined tests: As each of the test used for screening has some advantages and pitfalls, combination of tests can be used to improve diagnostic accuracy.

Low Dose Dexamethasone Suppression Test (LDDST) with Corticotrophin Releasing Hormone Test

This test is based on the principle that only abnormal corticotrophs will respond to CRH when under suppression by dexamethasone. Starting at 12 noon, 8 doses of dexamethasone 0.5 mg administered, last dose being at 6 am on the third day. At 8 am, 1ug/kg of CRH administered and blood collected at 15 mins interval for one hour for cortisol and ACTH estimation. Cortisol value above 1.4 ug/dl suggest Cushing’s disease.

LDDST with late night salivary cortisol is another test which can be used for diagnosis of Cushing’s disease. Salivary cortisol is a surrogate of plasma free cortisol and indicate the cortisol status of the individual. However, this test also has the same fallacies as plasma cortisol and needs further validation.
ACTH ESTIMATION (Fig. 12.8)

Collection and Transport
When ACTH is used, blood should be kept in ice water bath, rapidly centrifuged and aliquoted into samples for estimation. Some laboratories use protease inhibitors like trasylol for preventing ACTH degradation.

Assay Method and Sensitivity
Laboratories use monoclonal antibody with sandwitch technique with greater precision and specificity. However, these assays fail to detect some case of ectopic ACTH and hence polyclonal assays measuring entire ACTH molecules and fragments are recommended by many. Assay should have adequate sensitivity at values below 10 pg/ml.

Imaging
In ACTH independent Cushing’s syndrome, abdominal CT of high resolution to pick up masses below 1 cm is useful. Masses below 4 cm diameter is more likely to be benign while masses larger than 6 cm are more likely to be malignant. Overproduction of cortisol by adenoma or carcinoma will cause atrophy of contralateral gland. Bilateral nodular lesions, diffuse type with enlargement of adrenals are noted in Primary pigmented nodular adrenal disease (PPNAD).
ACTH Dependant Cushing’s—Diagnostic Work-up

Once it is identified that the Cushing’s syndrome is ACTH dependant, it becomes mandatory to identify the source of ACTH – from pituitary or from some ectopic source. This is achieved by a combination of procedures which include:

1. Bilateral inferior petrosal venous sinus sampling (IPPS sampling) (Fig. 12.9) through the femoral route done before and after CRH stimulation with 1ug/kg of CRH. When pituitary is the source of ACTH, sinus samples will have higher levels of ACTH and it will increase further on CRH as corticotrophs respond to CRH. However, in ectopic ACTH syndrome, central and peripheral samples does not show any gradient and there is no response to CRH.

2. High dose dexamethasone suppression test: Some suppression occur with basophil adenoma while no suppression is seen in adrenal lesions or ectopic ACTH syndrome is responsible for Cushing’s syndrome.

3. Metyrapone stimulation test: Metyrapone, inhibitor of 11 hydroxylase block the final step in cortisol production. Metabolites prior to block, especially compound S accumulate when the drug is administered at dose of 750 mg 4 hourly for six doses. This causes increased ACTH production and increase in plasma compound S >10 ug/L. The test can be used for distinction of pituitary adenoma from adrenal causes of Cushing’s syndrome.

4. CRH stimulation test: When ovine or human CRH is injected IV, corticotropinomas respond with incremental output of ACTH. This can be used for distinction between pituitary dependant and adrenal cause of Cushing’s syndrome.
Imaging Studies

Pituitary Lesions
Choice of imaging procedure is MRI which has higher delineation power. Corticotropinomas are small lesions. The lesion has same characteristics as normal pituitary tissue and hence not enhanced by contrast. Up to 10% of normal population can have incidentalomas on MRI and hence, it cannot be used as a single modality for diagnosis.

Ectopic ACTH Syndromes
Usual ectopic sites where ACTH is produced are lung and bronchi, pheochromocytoma, carcinoids, gastrinomas and medullary carcinoma. X-rays, ultrasounds CT and MRI are used for localization of lesions. Tumor markers like calcitonin, metanephrine, 5 HIAA and gastrin are surrogate markers of these tumors.

Somatostatin receptor scintigraphy: Corticotrophs retain receptors for somatostatin and hence can be used for localizing occult tumors producing ACTH.

\(^{18}\)F Fluorodeoxy glucose PET has been used for localizing ACTH producing lesions. This procedure does not offer any advantages over already existing imaging modalities.

TREATMENT OF CUSHING’S DISEASE
Management of Cushing’s disease depend on the cause.

Adrenal Disease

Incidentaloma and Subclinical Cushing’s Syndrome
With the availability of high precision imaging, adrenal mass lesions are detected when patients are investigated for unrelated diseases. When worked up, some of them show mild to moderate increase in plasma cortisol, but often below the diagnostic cut-off for classical Cushing’s syndrome. These patients are some time referred to as subclinical Cushing’s syndrome. Theoretically, these patients have same risk profile as classical Cushing’s but large scale experience regarding their long-term outcome, diagnostic work-up and treatment modality are yet to be worked out. Recommendation at present would be close follow-up of these cases and intervene when classical features of Cushing’s develop. Guidelines for diagnosis and management can be drawn when large scale experience and data are available regarding the validated procedure for diagnosis, cost effectiveness of diagnostic and therapeutic strategy and mortality and morbidity of treatment versus observation of these cases.

Adrenal Adenoma or Carcinoma
When unilateral adenoma or carcinoma is responsible for Cushing’s disease, surgery is the treatment of choice. Cotralateral adrenal is often nonfunctional due to suppression of HPA
Adrenal Gland and Cushing’s Syndrome

axis by high cortisol levels. Replacement with cortisol may be needed in the postoperative periods and for long duration in some cases. Long-term prognosis when radical surgery can be done is good when replacement therapy is given till time of recovery of HPA axis which may not occur at all in some cases. When surgery cannot be done because of inoperable adrenal functioning carcinoma, medical therapy has to be considered.

Medical Therapy

Drugs used for medical management of Cushing’s disease include:

A. Those drugs which inhibit adrenals enzymes involved in the steroidogenesis
B. Agents which reduce the ACTH drive on adrenals at hypothalamic or pituitary levels.

Agents Blocking Steroidogenesis

1. Mitotane
2. Trilostane
3. Ketoconazole
4. Aminoglutethemide
5. Metyrapone

These drugs reduce plasma cortisol by inhibiting steroidogenesis at one or more steps in the steroidogenic pathways. Two forms of medical therapy exist. In one case, total blockade of adrenal with replacement with hydrocortisone to avoid adrenal insufficiency is advocated. Similarly, dose of drug is titrated to provide eu cortisolemic state.

Mitotane (o, p DDD): This drug blocks all the enzymes involved in cortisol synthesis. Desmolase, 3 beta HSD, 11 and 18 hydroxylase are blocked. The drug has also adrenolytic effect and hence useful for treatment of adrenal cancer. Starting with a dose of 0.5 to 1 gm per day, dose is titrated up-to 12 gm per day. Even at lower levels, GI side effects like nausea, vomiting and diarrhea occur, becoming universal at dose exceeding 4 gm. At higher dose levels, neurological side effects like fatigue, gait disturbance, giddiness, vertigo, confusion and problems in language expression occur. Due to long half-life, the drug may remain in the body for many months and hence not advisable for women desiring fertility within next 3 years. Other rare side effects include fatigue, gynecomastia, skin rash, hyperlipidemia and hyperuricemia. These side effects are temporary and reverse on stoppage of drug. Mitotane increases metabolic clearance of exogenous cortisol and 50% increase in hydrocortisone dose is needed when patient needs replacement therapy.

Ketoconazole: This antifungal agent also block steroidogenic enzymes like side chain cleavage enzyme, 17, 20 lyase, 11 beta and 17 beta hydroxylase. Recommended dose is 400 to 1500 mg daily in three to four divided doses. Side effects include GI upset, gynecomastia, menstrual irregularity and mild abnormality of liver enzymes. Idiosyncratic major liver dysfunction occur in an occasional patients and drug should be discontinued if liver enzyme rise above three times the basal levels. Coadministration of proton pump inhibitors or H₂ receptor blocking drugs block conversion of drug to active compound and hence loss of drug effect.
Metyrapone: This drug is a 11 beta hydroxylase inhibitor. It is given in a dose of 1 to 2 gm in divided doses. Due to enzyme block, androgenic and mineralocorticoid metabolites accumulate with side effects like hypertension, acne, menstrual disorders. These side effects are dose dependant and less common at doses below 2 gm.

Aminoglutethemide: Blocks the conversion of cholesterol to pregnanolone. Starting at 500 mg in divided doses, dosage titrated upto 2 gm depending on clinical effect. Main side effects includes neurological problems (Somnolence, dizziness, blurred vision, depression), morbilliform rash and fever and thyroid dysfunction and goiter.

Other drugs include Trilostane (3 Beta HSD inhibitor), Etomidate (anesthetic agent with ability block side chain cleavage and 11 beta hydroxylase). Only limited experience exist with these agents.

Agents Reducing at Hypothalamus or Pituitary by Reducing Secretion of ACTH
1. Dopaminergic agents – bromocryptine and cabergoline
2. Somatostatin and analogues
3. Cyproheptadine
4. Valproic acid

All the above agents have been used. No large scale trials reports attesting consistant ACTH reducing effect is available and failure rate is usually high. Hence, these agents are not usually considered as primary mode of therapy for management Cushing’s disease resulting from ACTH overproduction from pituitary or ectopic source.

Surgery
Adrenal Surgery
Unilateral adrenal surgery is the procedure of choice in adrenal adenoma or carcinoma causing Cushing’s disease. Bilateral adrenal resection is done when Cushing’s syndrome result from overproduction of ACTH and source of ACTH cannot be eliminated (Unsuccessful pituitary surgery or failure to locate or treat ectopic source of ACTH). Mortality with transabdominal procedure vary from 1 to 20% depending on severity of Cushing’s syndrome and associated co-morbid states, especially cardiovascular problems. With laparoscopic resection in experienced hands, mortality is as low as 0.2%. Contraindications for laparoscopic procedure include tumors larger than 10 cm diameter and presence of adrenal carcinoma. Adrenalectomy is also used in pigmented nodular adrenal disease and bilateral nodular adrenal hyperplasia causing Cushing’s syndrome. Immediate normalization of plasma cortisol occur. Failure of normalization of cortisol indicate incomplete procedure.

Pituitary Surgery
When the cause of Cushing’s disease is pituitary driven, the treatment of choice is trans-sphenoidial surgery. When performed by experienced surgeon, mortality and morbidity is
negligible. Comorbid medical conditions like diabetes, hypertension, associated coronary artery disease and increased coagulability of blood also would influence the prognosis. Postoperative problems include damage to optic nerve, neurologic deficits, CSF rhinorrhea, meningitis, diabetes insipidus hypopituitarism and venous sinus thrombosis.

Outcome of surgery: Following surgery, patient may go in for permanent remission or relapse immediately or later. In good centers, 70 to 80% results are achieved. When tumor can be located by MRI prior to surgery, outcome is usually better. When no lesions are observed, rough localization of ACTH over producing area of pituitary is done with IPSS data and repeated frozen section during surgery yield better outcome. Immediately after surgery, the patient shows hypoadrenocorticism as the normal corticotroph is suppressed by the adenoma. Slow recovery of HPA axis occurs in 12 to 15 months.

After surgery, patient may achieve remission of the disease which may be permanent or temporary. A subset of patient fail to show fall in cortisol due to failure of surgery when re-exploration can be considered. Even after remission following surgery, re evaluation of patient from time to time is indicated to make early onset of recurrence which is one of the features of transsphenoidal surgery. Most of the patients may need long-term follow-up for relapse. Overall 10 relapse rate is around 25% while it is 7% for microadenoma and 45% for macroadenoma. Prediction of relapse can be done with any of the tests which are used for initial diagnosis of Cushing’s syndrome. After surgery, patient may develop impaired secretion of other pituitary hormones. This has to be evaluated and treated appropriately.

If relapse occur, treatment options include repeat surgery, medical therapy to block adrenal steroidogenesis, pituitary radiation and bilateral adrenalectomy. Each of these modalities of treatment has its own limitation.

Radiation

Radiation is one modality of treatment for Cushing’s disease. Type of pituitary radiation used are conventional external radiation, stereotactic focused radiation using a linear accelerator (Linac based system, Gamma knife), fractionated stereotactic radiation, particle therapy (proton beam, alpha particle) and implantation of radioactive materials (radioactive gold and yttrium). Usually, radiation is used as an adjunct for unsuccessful surgery for a pituitary lesion. Most common problem associated with pituitary radiation using conventional external radiation is damage to neurological structures in the radiation path. This is avoided to an extent with new modalities of radiation treatments used now with linear accelerator based system. Even with this modality of radiation treatment, damage to optic nerve occur if the distance of optic nerve system is less than 5 mm from tumor margin. Additional problems include hormone deficiency, failure of treatment and formation of second tumor after radiation.

Success of radiation treatment is assessed by low 24 hours urinary free cortisol or morning plasma cortisol less than 2 to 3 ug after one mg overnight dexamethasone suppression.
Occurrence of hypopituitarism after surgery is assessed by estimation of hormone in question (Free T4 for thyroid failure) or by provocative tests like metyrapone or insulin tolerance test under medical supervision. Use of ACTH stimulation would give adrenal response to ACTH but may not reflect pituitary hypothalamic reserve which may be altered in radiation therapy.

Other side effects of radiation include damage to optic nerve, brain structures and oculomotor nerves. Visual assessment before and periodically after radiation is recommended. MRI would delineate brain damage after radiation.

Benefit from therapy occur in delayed manner. Benefit is dose dependant. Relapse rate are higher with low dose (20Gy) compared to conventional dose of 50 Gy. Side effects of radiation depend on whether radiation is given in single or multiple sitting spread over a period of several weeks. Time taken for response varied from 4 to 26 months. As high cortisol levels for such periods are harmful, medical blockade of adrenal steroidogenesis with o,p DDD or ketoconazole is recommended in the interim period. Time taken for remission is shorter with Gamma knife therapy. Adequate remission of hypercortisolism occurred in less than one year in most of the cases. Occasionally, one may need more than one session with Gamma knife. Even with this modality of treatment, hypopituitarism occur and need periodic assessment and replacement of hormones which are deficient. Other problems include fertility after pituitary radiation. In women, ovulation induction can be attempted with varying results when in case of adult men, sperm banking of ones semen can be done before radiation.

**SUGGESTED READING**

BRIEF HISTORY OF ADDISON’S DISEASE

Thomas Addison (1795-1860) has been credited with the discovery of Addison’s disease. He published a book on diseases of suprarenal capsule that expanded on his earlier accounts of Addison’s disease. He also announced the discovery of another new disease called Addisonian anemia, now called Pernicious anemia. This hailed the discovery of the clinical condition, Addison’s disease, now more commonly recognized in clinical practice. Addison’s disease holds key importance in India, because it is estimated that 1/4th of patients with tuberculosis have adrenal involvement.

NORMAL NEGATIVE FEEDBACK LOOP

Glucocorticoid is controlled as below:

Fludrocortisone is controlled by the renin angiotensin system. This hormone system regulates BP, water balance. When blood volume is low, kidneys secrete rennin. Renin stimulates production of angiotensin (causes blood vessels to constrict). Also causes increase secretion of aldosterone from zona glomerulosa. This restores blood volume by sodium retention. This again inhibits further aldosterone production by negative feedback mechanism.
ETIOLOGY

The cause of hypocortisolism is divided into 2 categories, Primary and Central adrenal insufficiency.

Central adrenal insufficiency includes both secondary (pituitary) and tertiary (hypothalamic).

PRIMARY ADRENAL INSUFFICIENCY

Some of the common causes include:
- Autoimmune destruction (70-80%)
- Tuberculosis (20% cases)
- Adrenal destruction by hemorrhage (Waterhouse Frederickson syndrome).
- Infarction
- Tumors
- Infections
- Surgery
- Radiation
- Drugs
- Amyloidosis
- Sarcoidosis
- Histoplasmosis
- Congenital anomalies (CAH).

![Diagram](image)

Autoimmune (associated with HLA Dr3, B8 tissue type)

Polyglandular syndrome  Sporadic

Type 1 : Addison’s disease hyperparathyroidism
- Chronic mucocutaneous candidiasis

Type 2 : Primary hypothyroidism
- Primary hypogonadism
- Type 1 Diabetes mellitus
- Pernicious anemia
- Addison’s disease
- Vitiligo

Reference: Davidson’s Principles-19th edition
CENTRAL CAUSES OF INSUFFICIENCY

1. Withdrawal of exogenous steroids (most common)
2. Pituitary adenoma/infarction
3. Hypothalamic abnormalities
4. Following cure of Cushing’s disease.

The enzyme defects include CAH (21 Beta Hydroxylase deficiency).

Drugs like aminoglutethimide, metyrapone, etomidate, ketoconazole are known to cause adrenal insufficiency.

There is recent evidence suggestive of IgG blocking the stimulation of Cortisol production by ACTH hormone. The phenomenon of receptor ab’s causing clinical syndrome is well known in Myesthania Gravis, Graves’ disease. So, consequently, the presence of ab’s for Addison’s disease may also be predicted.

Receptor ab’s could be stimulatory (more common), like in Graves’ disease where ab’s mimic the action of TSH. On the other hand, inhibitory ab’s have also been demonstrated in primary hypothyroidism. So, we consider the possibility of including ab’s of Addison’s in the inhibitory category.

Typically, it has been noticed that in these patients with Addison’s (autoimmune), the cortical epithelial cells undergo atrophy, with attempts to regenerate and are surrounded by lymphoid cells with plasma cells.

Recent evidence has shown that in a particular group of patients, these ab’s that act on adrenal cortex also interfere with steroid producing cells in ovary, testis, placenta. Most of these patients suffered from premature menopause, also ovarian atrophy, but in striking contrast, there was no evidence of hypogonadism in males.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Adrenal virilism is also known to cause hypocortisolism in newborn children. Typically, adrenal hyperplasia starts between 12th week, 5th month of fetal life that gives rise in females to male pseudohermaphroditism, and in males to macrogenitosomia praecox. Here, there is no conversion of 17-hydroxyl progesterone to 17-hydroxycorticosterone and accumulation of former causes androgenic effect. Deficient glucocorticoid function is unusual in cases of CAH. More often, deficient salt regulation is seen presenting with vomiting, dehydration, reduced serum sodium levels, high serum potassium levels, or maybe chronic, with loss of weight with diarrhea, vomiting.

Also, here is a concept of “pseudohypoadrenalism”, seen in varied types of shock after surgeries. Typically, these patients would have previously undergone long-term steroid therapy; here, if the condition improves of IV cortisol, the diagnosis almost certain. Here, the cause of shock is not adrenal failure. Most of them have normal levels of 11- hydroxylcorticosterone.
**CLINICAL FEATURES (TABLE 13.1)**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness, fatigue</td>
<td>Hyperkalemia (mild)</td>
</tr>
<tr>
<td>Anorexia, weight loss</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>GI problems: vomiting, diarrhea,</td>
<td>Hyperpigmentation (buccal mucosa, skin folds, new scars)</td>
</tr>
<tr>
<td>abdomen pain</td>
<td></td>
</tr>
<tr>
<td>Salt craving</td>
<td>Vitiligo, adrenal calcification.</td>
</tr>
</tbody>
</table>

Source: "Medical Secrets"-4th ed, Anthony J. Zollo

The manifestations of central insufficiency are similar to primary except, hyperpigmentation not seen (due to no hypersecretion of melanocyte stimulating hormone).

Electrolyte abnormalities are not typically seen in central disease because aldosterone is intact.

Central disease may involve other features of hypopituitarism. Hypoglycemia is more seen here due to presence of ACTH, GH deficiency.

Some cases of Addison’s where a person with normal light skin may be mistaken for another race with darker pigmentation (Table 13.2).

**Table 13.2: Comparing various parameters in central/primary disease**

1. Hypopituitarism/Withdrawal of Exogenous Steroids

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mineralocorticoids</td>
<td></td>
<td>CRH</td>
<td>Glucocorticoids, adrenal androgens, serum sodium, ACTH, serum potassium, renin</td>
</tr>
<tr>
<td>2. Addison’s Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>ACTH, serum potassium, CRH, renin</td>
<td>Glucocorticoids, Mineralocorticoids, adrenal androgens, serum sodium</td>
</tr>
<tr>
<td>3. CAH (21 Beta Hydroxylase Deficiency)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>Adrenal androgens, ACTH, serum potassium</td>
<td>Glucocorticoids, mineralocorticoids, serum sodium</td>
</tr>
</tbody>
</table>

Reference: Harrison’s Internal Medicine 15th ed
Hypocortisolism

SCREENING TESTS AND DIAGNOSIS (FLOW CHART 13.1)

To assess the function of hypothalamic-pituitary-adrenal axis, ACTH stimulation test is most commonly done. Here, baseline cortisol is drawn, then 250 microgram LV synthetic ACTH (Cosyntropin) is given. Blood samples are collected at 30, 60 minutes. A normal response is a cortisol level of more than 20 microgram/dl. A normal response rules out adrenal insufficiency in most cases. Lack of a normal response indicates reduced adrenal reserve but does not differentiate between primary and central causes. To differentiate between these two, ACTH levels are measured.

Recently, because 250 microgram is supraphysiological dose (so, difficult to rule out adrenal insufficiencies), 1 microgram ACTH stimulation test is being done. ACTH stimulation test holds value especially in adrenal crises. If not in crisis, cortisol, ACTH, aldosterone, renin, serum potassium, serum sodium levels are tested from blood sample before deciding whether ACTH stimulation test needs to be done.

Previously, Insulin-Tolerance Test (ITT) was the gold standard test. The idea here is to induce hypoglycemia (plasma glucose < 40 mg/dl) with IV insulin which causes production of ACTH, cortisol, GH. Since ITT is cumbersome, it is not being preferred now.

X-ray/CT adrenal may also be done as an investigative methodology.

If autoimmune origin is suspected, then 21-hydroxylase auto ab’s is done.

Flow Chart 13.1: Diagnosis of adrenal insufficiency

Source: Davidson's Principles, Practice of Medicine 19th ed
Lately, Lysine vasopressin has caused interest because it causes increase in basal cortisol levels in plasma. This is caused due to corticotrophin release from pituitary gland. Therefore, there is a possibility of using this as potential diagnostic test. The mechanism of action of this molecule is not very clear, maybe it acts on hypothalamus, or higher centers, on the anterior pituitary or on adrenal cortex. Experiments on rats have shown that hypophysectomy removes effect of vasopressin. This test could be used to distinguish between pituitary and hypothalamic reasons for central hypocortisolism.

**TREATMENT OF HYPOCORTISOLISM (TABLE 13.3)**

Prior to 1950s, Addison’s disease used to be treated with cortical extracts by injection. Now, with the advent of cortisone, patients have the capacity to regularize carbohydrate metabolism with no more hypoglycemic attacks (which used to be common with DOCA). Treatment has been made possible with advent of fludrocortisone (small doses being sufficient, around 0.1 mg/day).

Patients with Addison’s disease typically need both glucocorticoid, mineralocorticoid replacement, whereas patients with central adrenal insufficiency need only glucocorticoids because here mineralocorticoid secretion is usually not affected. In patients who are not critically ill, cortisol is given by mouth, 15 mg on waking, 5 mg at 18:00 hrs; precise dose should be adjusted for each patient. Excess weight gain indicates over replacement, while persistent lethargy is due to inadequate dose. Not to forget to increase steroid dosage at times of illness.

**ADRENAL CRISIS**

Adrenal crisis is a medical emergency, which needs LV hydrocortisone succinate 100 mg; IV fluids (NS, 10 % Dextrose for hypoglycemia). Parenteral hydrocortisone is continued (100 mg IM/6 hrs) until GI symptoms abate before starting oral therapy.

Complications of glucocorticoid therapy, other than gastritis, are rare. Complications of mineralocorticoid therapy include hypokalemia, hypertension, cardiac enlargement, sometimes even CHF. So, regular measurements of body weight, serum potassium levels, BP are useful.

<table>
<thead>
<tr>
<th>Relative potency (Anti-inflammatory agent)</th>
<th>Relative sodium retaining potency</th>
<th>Duration of action</th>
<th>Equivalent dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>Short</td>
<td>20</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>Short</td>
<td>25</td>
</tr>
<tr>
<td>Fluidrocortisone</td>
<td>10</td>
<td>Short</td>
<td>—</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>Intermediate</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>Intermediate</td>
<td>5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>Intermediate</td>
<td>4</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>Intermediate</td>
<td>4</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>Long</td>
<td>0.75</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>Long</td>
<td>0.75</td>
</tr>
</tbody>
</table>
CONCLUDING STATEMENTS

Never overlook persistent vague complaints, especially when other autoimmune diseases are present. Also, hyperpigmentation maybe absent in autoimmune cases, which may lead to misdiagnosis.

Also, in clinical settings if BP does not return to baseline in spite of inotropic support, check for any hidden pathology.

In a patient recently diagnosed with primary hypothyroidism, not to forget to look out for possibility of Addison’s disease. The features that should alert the clinician skin, mucosal pigmentation, postural hypotension, weight loss, hyperkalemia. Failure to do so may result in adrenal crisis if thyroxine is given before glucocorticoid replacement.

In pregnancy, usual steroid dosage to be maintained. Occasionally, dose adjustments maybe needed depending on patient’s well-being and the presence or absence of symptoms of adrenal insufficiency. Pregnancy increases the production of Cortisol Binding Globulins (CBG), therefore bound cortisol. Free cortisol is proportionately increased, so no dose adjustments needed.

Also, during labor, delivery (vaginal, cesarean), parenteral stress dose steroid coverage should be given as at other times of major stress. Here, the preferred mode of steroid administration is by continuous IV infusion, and then rapid dose tapering to the usual maintenance dose when clinical situation allows.

Patients are asked to wear medical alert bracelet/pendant for their identification of the Addisonian status.

SUGGESTED READING

2. Lesson of the week: Deterioration of symptoms after start of thyroid hormone replacement.
3. Lesson of the week: Addison’s disease.
11. Student BMJ (Beyond the name: History of Addison’s Disease).
INTRODUCTION

Polycystic ovarian syndrome is a common endocrine disorder affecting women of reproductive age group. PCOS has a wide spectrum of clinical manifestations encompassing oligomenorrhea, amenorrhea, infertility, hirsutism, acanthosis nigricans and obesity. Hence, considerable proportions of patients seek treatment from Gynecology and Dermatology practitioners, apart from Endocrinologists. Accurate prevalence of PCOS worldwide is not known due to heterogeneity in design of epidemiology and clinical studies along with ambiguity in case definition. However, most authors in literature suggest a prevalence of 5 to 8% among women of reproductive age group worldwide.\(^1\)

Though androgen excess in women has been recognized since the time of Hippocrates, it was only in 1935 that Stein and Leventhal described the symptomatology. They reported a series of cases of women with amenorrhea, infertility and hirsutism with ovarian polycysts. Wedge resection of ovaries in these women resulted in resolution of symptoms.\(^2\) Since this report, it was widely believed that the pathology of this disease spectrum lies in the ovaries. The condition was now known as Stein Leventhal disease or Polycystic Ovarian Disease (PCOD).

With passage of time PCOD was also described in association with type 2 diabetes mellitus. With advancement of assay procedures and sonography in 19th century, biochemical, clinical, and endocrinologic studies have revealed an array of underlying metabolic abnormalities including insulin resistance. Hence this condition is now referred to as Polycystic Ovarian Syndrome.

Diagnosing PCOS is often a clinical challenge because patients manifest with a spectrum of clinical presentations, characteristics of a syndrome. Signs and symptoms are such that each has to be considered separately and other causes of that (sign/symptom) have to be ruled out. Not all women present with a set of symptoms. Often, there is only one symptom and no sign at all. Thus a physician has to depend on biochemical assays and sonography to make an accurate diagnosis of PCOS. Nevertheless, research in recent times has helped experts
to formulate a crisp guideline, which helps in the diagnosis of PCOS. Treatment goals are different for every patient as severity of each component of the syndrome is different. Therefore, treatment is often customized. Understanding the little known pathophysiology would help in differential diagnosis and in initiating the right treatment regimen.

**OVARIAN PHYSIOLOGY**

The primary defect in women with PCOS does not lie in the ovaries but in metabolism involving insulin, lipids and growth factors. However, the major fall out of this defect in metabolism is on the ovary and HPO axis. Most of the clinical manifestations are secondary to change in ovarian physiology. Thus it is appropriate to briefly discuss the ovarian physiology before understanding the pathogenesis. Only processes relevant to PCOS are noted here.

Normally, human ovaries produce one ovum each menstrual cycle. The cyclical activity in the endometrium is a reflection of cyclical activity in growth and development of dominant follicles in the follicular phase of the cycle. The cyclic activity in ovaries is largely gonadotropin regulated. Estrogen and Progesterone, secreted by dominant follicle and corpus luteum respectively regulate the endometrial cycle.

After puberty all primordial follicles develop into preantral follicles which now have several layers of granulosa and thecal cells. Granulosa cells now possess FSH receptors but the process is independent of FSH. Growth factors produced locally in the ovaries and granulosa cells are responsible for growth of preantral follicle. Any further development of preantral follicle is dependent on FSH. The recruitment of dominant follicle is described in three stages, i.e. recruitment stage where a cohort of follicles are recruited, selection stage where one follicle is selected and finally dominant stage where the selected follicle develops to release the ovum. Apart from gonadotropins and sex steroids, Insulin, Insulin like growth factor-1 and 2 (IGF-1, 2), epidermal growth factors, plasma proteins, proteoglycans and non-steroidal ovarian factors and Inhibin A, B influence dominant follicle growth and maturation. Hyperandrogenism, polycysts and anovulation of PCOS is a result of metabolic derangements in this process of graftian follicle development.

**Role of Follicle Stimulating Hormone**

Follicle stimulating hormone (FSH) is secreted by anterior pituitary gland. It plays a principle role in the mechanisms of selection and development of dominant follicle. Secretion of FSH is regulated by Gonadotropin releasing hormone (GnRh). During the last few days of menstrual cycle, there is a fall in levels of sex steroids and Inhibin A due to decline in secretion by corpus luteum. Consequently, there is an increase in GnRh pulsatile secretion pattern which leads to increase in FSH levels. This event initiates folliculogenesis. FSH binds to the receptors on granulosa cells in the preantral follicle and initiates the selection process. The preantral and early anterol follicles produce more amounts of androgens in relation to estrogens. Thus the microenvironment is androgenic. In one of the follicle, there
is a shift from androgenic microenvironment to an estrogenic microenvironment, which becomes a dominant follicle. Once the dominant follicle stage is reached, the other recruited follicles undergo atresia. The dominant phase is characterized by sustained mitotic division of granulosa cells. Several other growth factors are known to act along with FSH to stimulate the mitotic process. As the number of granulosa cells increase, FSH induces the production of the enzyme – P450 aromatase and 3β hydroxysteroid dehydrogenase (3βHSD). This process is seen exclusively in the dominant follicle and is responsible for the shift to estrogenic microenvironment from relative androgen excess. The quantity and activity of aromatase progressively increases and peak during late follicular phase. Aromatase converts thecal derived androstenedine to estrone which is then converted to estradiol 17β, catalyzed by 3αHSD. Thus FSH induced aromatase expression in granulosa cells is responsible for progressive increase in estrogen secretion during days 7 and 12 of menstrual cycle. During FSH induced development, the granulosa cells acquire luteinization potential. Granulosa cells express large amounts of Steroid Acute Regulatory Protein (StAR), the P450 side chain cleavage (P450scc) and 3β-hydroxysteroid dehydrogenase (3β-HSD), all of which confer luteinization potential. The expression of these enzymes is induced by FSH. Estrogen now produced in the granulosa cells are believed to initiate this induction. The granulosa cells begin to secrete small quantities of progesterone and 17-hydroxyprogesterone (17-OHP) which is believed to exert a positive feedback on the pituitary to secrete Luteinizing hormone. Though the luteinization capacity is obtained in the early phases of follicular development, it remains suppressed by oocyte derived inhibitors, until prior to ovulation. These inhibitors, particularly GDF-9 is known to be dysregulated in PCOS leading to dysregulation of steroid production and consequent increased LH secretion.

FSH induces production and recruitment of Luteinizing hormone (LH) receptors on membranes of granulosa cells. As estradiol levels increase, it induces a positive feedback on the pituitary to secrete LH. Thus LH surge ensues, resulting in ovulation. The LH surge brings about further luteinization of follicle resulting in increased production of progesterone. Increasing levels of progesterone induces positive feedback on pituitary to increase secretion of FSH. Consequently, a mid cycle FSH surge ensues.

**Role of Luteinizing Hormone**

Luteinizing hormone is produced by the anterior pituitary in a pulsatile fashion with pulse frequency and amplitude being constant in early follicular phase and increasing during ovulation. Luteinizing hormone receptors are located on theca cells during all stages of the menstrual cycle in contrast to granulosa cells. LH is responsible for differentiation of thecal cells although insulin and lipoproteins act in synergy. Thecal cells express receptors of insulin, LDL, HDL, and IGF-1 and a battery of enzymes which catalyses androgen production from cholesterol. LH in synergy with insulin, HDL, LDL, inhibin stimulates androstenedione production and to a lesser degree testosterone production in the theca cells. HDL is the most potent of all factors know so far. Activin, GDF-9, BMP-4 are known to inhibit androgen...
production.\textsuperscript{16} Androstenedione is then transported to the granulosa cells where it is aromatized to estrone and finally converted to estradiol by 17-beta-hydroxysteroid dehydrogenase type I. This is known as the two-cell, two-gonadotropin hypothesis of regulation of estrogen synthesis in the human ovary.\textsuperscript{22} Multiple abnormalities of mechanisms involved in growth, differentiation and steroid production in the dominant follicles are responsible for hyperandrogenism, anovulation, polycysts and its consequences.

**PATHOPHYSIOLOGY**

As mentioned earlier, PCOS has a heterogeneous clinical presentation reflected by its heterogeneous hormonal and metabolic abnormalities. Hence understanding the little known pathophysiology of PCOS is pivotal to initiate a customized treatment regime. There is no single, well described, comprehensive pathological pathway. However, over the years several interrelated mechanisms have been described. With accrual of knowledge with time, many theories have been explained.\textsuperscript{23}

- A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude.
- A defect of androgen synthesis that results in enhanced ovarian androgen production.
- An alteration in cortisol metabolism resulting in enhanced adrenal androgen production.
- A unique defect in insulin action and secretion that leads to hyperinsulinemia and insulin resistance.

However, today it is clear that none of the above mechanisms are starting points of pathology but interlinked components with varying severity. These mechanisms can be studied under three primary components as insulin resistance, hyperandrogenism, obesity and two secondary components as LH, FSH dysregulation and anovulation and menstrual irregularity. These components result from polygenic abrasions coupled with environmental factors. We now discuss each component in detail.

**The Concept of Insulin Resistance**

Insulin resistance is defined as resistance to the glucose-stimulating effects of insulin in organs such as muscles, liver, and fat.\textsuperscript{24} It was in 1921 that Achard et al first published the association of Diabetes Mellitus and hirsutism in young women even before PCOD was described. They called it ‘Diabetes of bearded women’.\textsuperscript{25} Clinically conditions associated with insulin resistance like acanthosis nigricans, central obesity, ovarian polycysts were recognized with PCOS even before a relation between Insulin resistance and PCOS was described. In 1976, Kahn et al reported a syndrome of severe hyperandrogenism, acanthosis nigricans, and insulin receptor defect which was later described as HAIR AN syndrome by Barberi et al in 1983.\textsuperscript{26, 27} Case report of Kahn et al and a study by Burghen et al (1980) which reported PCOS women with glucose stimulated hyperinsulinemia suggested the role of Insulin resistance in pathology PCOS.\textsuperscript{28}
Polycystic Ovarian Syndrome

Thereon, several euglycemic clamp studies have demonstrated decreased insulin sensitivity in obese and non-obese PCOS women. Some studies have reported increased insulin resistance in obese women compared to non-obese PCOS women. Few studies have also shown PCOS women to have normal insulin sensitivity. However, these discrepancies can be attributed to absence of standard definition and diagnostic criteria for insulin resistance, ethnic variability, study size and case definitions. For example, studies using homeostasis model to quantify insulin resistance have shown less prevalence of insulin resistance in PCOS. Nevertheless, the euglycemic clamp model of assessment is considered to be more sensitive in PCOS.

Several studies with euglycemic clamp model have shown that insulin resistance in PCOS is independent of obesity. Some studies have shown the degree of insulin resistance to be consistent with degree of hyperandrogenemia. But not all people with insulin resistance have hyperandrogenism. Insulin resistance, selective to ovary has also been reported. Thus, collectively it is apt to believe that insulin resistance is a common finding in PCOS patients but may not be profound to the degree seen in patients with type 2 diabetes and in some cases selective to ovaries. It is also postulated that mechanism of insulin resistance in PCOS patients is different from that seen in metabolic syndrome.

Insulin resistance in PCOS subjects has been described as type A insulin resistance where there is a defect in post-receptor mechanisms in insulin receptor signaling. An abnormality of insulin receptor autophosphorylation, is seen in about 50% of PCOS subjects. This abnormality is characterized by increased serine phosphorylation, which inhibits the intrinsic tyrosine kinase activity of the insulin receptor. The increased serine phosphorylation of the insulin receptor is known to be a result of activity of a serine kinase, extrinsic to the receptor. Further, studies on fibroblasts from PCOS subjects have shown that insulin resistance is selective, inhibiting the metabolic but not mitogenic and steroidogenesis pathways of insulin signaling. This is known as selective insulin signaling (Table 14.1).

Due to decreased insulin sensitivity, hyperinsulinemia ensues as a compensatory mechanism. The relation between hyperandrogenism and hyperinsulinemia, secondary to insulin resistance has been debated ever it was first reported in 1921. Recently, prospective

<table>
<thead>
<tr>
<th>Table 14.1: Effects of insulin on ovarian function (modified from Poretsky et al 1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly stimulates steroidogenesis acting in synergy with LH and FSH</td>
</tr>
<tr>
<td>Stimulates 17α-hydroxylase</td>
</tr>
<tr>
<td>Up-regulates LH receptors</td>
</tr>
<tr>
<td>Up-regulates type I IGF receptors or hybrid insulin/type I IGF receptors</td>
</tr>
<tr>
<td>Promotes ovarian growth and cyst formation synergistically with LH/hCG</td>
</tr>
<tr>
<td>Inhibits IGFBP-1 production and increases IGFBP protease activity</td>
</tr>
<tr>
<td>Proliferates keratocytes in synergy with IGF-1 causing Acanthosis Nigricans</td>
</tr>
<tr>
<td>Promotes central obesity</td>
</tr>
</tbody>
</table>
studies which used different modalities of reducing insulin resistance in PCOS, including calorie restriction and weight loss, have shown a significant reduction in circulating androgen levels.38-41 On the other hand, studies that have used only by anti-androgen drugs have showed no improvement in insulin resistance. 42, 43 However, few studies have shown marginal drop in insulin levels in PCOS patients after been treated with anti-androgens and androgen suppressants.44, 45 Theoretically, there has to be a reduction in insulin resistance in the ovaries for it to begin normal functioning.

Hyperinsulinemia, secondary to insulin resistance is known to cause several metabolic dysfunctions. Excess of insulin inhibits production of Sex steroid binding globulin (SHBG) in the liver, consequently increasing levels of bioactive androgens. Further, serine phosphorylation, as discussed above is reported to modulate the activity of the key regulatory enzyme of androgen biosynthesis, P450c17, present in both the adrenal and Thecal cells.46 Thus, serine phosphorylation has been shown to increase enzyme activity and androgen synthesis. It is therefore believed that a single defect – serine phosphorylation – produces both the insulin resistance and the hyperandrogenism in a subgroup of PCOS women. Thus it is now believed that one part of hyperandrogenism is secondary to insulin resistance.

The role of IGF-1,2/Receptor system has also been described in PCOS. Hyperinsulinemia is known to inhibit production of IGF Binding protein 1 in the liver. It is also known to increase protease activity of IGFBP’s in circulation thus increasing free IGF-1 in circulation.47-49 This process has been well described in the ovaries. IGF-1 and insulin being potent growth factors, now in increased levels, stimulate excess androgen production (in synergy with LH) and follicle development as described previously. Thus high levels of insulin and free IGF-1 acts in synergy with FSH to recruit more preanteral follicles, initiate mitosis at a faster pace. Preanteral follicles, during maturation acquire a cavity filled with a fluid and grow relatively bigger due to excess growth factors.

Mediation of insulin in functions of anterior pituitary has also been reported. Though there are conflicting results, it is believed that insulin increases the number of LH receptors on thecal cells and increases sensitivity of pituitary cells to GnRh.50

Excess insulin and free IGF-1 stimulate IGF-1 receptors present on keratocytes leading to their proliferation. This results in hyper pigmentation of skin and is particularly seen in areas of skin folds. This condition is called Acanthosis Nigricans.51,52 Other consequences of Insulin resistance like obesity, type 2 Diabetes mellitus (DM), vascular changes, coagulation dysfunctions and cardiac diseases have been reported in association with PCOS. They are considered later in the chapter.

Hyperandrogenism

Hyberandrogenism is the sine qua non of PCOS. Ovary is the primary source of hyperandrogenism in PCOS. About 25% of the testosterone in the blood of women arises directly from the adrenals, 25% from the ovaries and 50% from peripheral conversion of precursors to testosterone by enzymes such as 5α-reductase in the skin and fat cells.54
Depending on the androgens measured and the technique employed, 50 to 90% of women with PCOS have been reported to have elevated serum androgen levels, mainly testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS). There is, however, significant individual variation and some subjects may have completely normal androgen levels. Major component of excess androgens is secondary to hyperinsulinemia as explained above. Hyperandrogenism independent of insulin resistance has been explained in PCOS and related disorders while underlying mechanisms are not yet clear. Polygenetic abrasions in androgen coding genes have been reported.

Ovarian androgens produced in theca cells and diffuse across the basement membrane to the granulosa cells, and are converted to estradiol as explained earlier. During the recruitment stage of preanterior follicles, androgen is produced in excess due to excess insulin/IGF-1 stimulation create an overt androgenic microenvironment. As explained earlier, these follicles are bigger in size and are fluid filled. A conversion of microenvironment to estrogentic is essential for selection of dominant follicle. But it has been seen that androgen in excess inhibit aromatase enzyme function of converting androgens to esterone to some extent. Thus the process of dominant follicle selection and development is stalled. Thus oocyte maturation and anovulation does not occur leading to alteration in menstrual cycle. Excess androgens are also known to increase size and number of potentially recruit able follicles by at least 2 to 3 times than normal ovary in primates. Hence we have multiple follicles passed the preanterior phase, larger than normal due to excess growth factors and filled with fluid. These are polycysts characteristic of PCOS. Normally, androgens induce atresia in non-dominant follicles. But due to unknown reason the polycysts in PCOS remain active and responsive to FSH.

Amongst active androgens, free testosterone and DHEA are found to be elevated in PCOS women. DHEAS is found to be elevated in a minority of PCOS population. As mentioned above there is a decrease in production of SHBG leading to increase in free testosterone. Researchers have shown enhanced $5\alpha$-reductase activity in PCOS women. This steroidogenic enzyme is responsible for both $5\alpha$-reduction of testosterone to $5\alpha$-dihydrotestosterone in skin and cortisol to $5\alpha$-dihydrocortisol in liver. Therefore, it is suggested that increased activity of $5\alpha$-reductase mediates both hirsutism and enhanced hepatic cortisol metabolism.

Excess androgen in circulation favors a central/visceral pattern of body fat distribution, although other genetic factors may also play important roles. Visceral fat has increased lipolytic activity and free fatty acid levels are increased in PCOS. Thus hyperandrogenemia may favor visceral body fat distribution, which results in relative increases of free fatty acids, which induce skeletal muscle insulin resistance. This is the minor component of excess androgens influencing insulin resistance. As fat cells proliferate, excess androgens in circulation are converted to estrogens by aromatase enzymes present in adipocytes. Thus hyperestrogenic state ensues. This excess estrogen stimulates increased LH release which further augments androgen secretion in the recruited follicles. Thereby, PCOS is a state of excess androgens and excess estrogens. Hence the pathophysiology is best described as vicious circle.
LH and HPO Axis

LH hypersecretion both basally and in response to GnRH administration – is a characteristic hallmark of PCOS. Many hypothesis have been proposed to explain this phenomenon. Initially this phenomenon was considered to be the primary abnormality in classic PCOS and thus, the cause of androgen excess. It is believed that the elevated LH levels are partly due to an increased sensitivity of the pituitary to GnRH stimulation, manifested by an increase in LH pulse amplitude and frequency, but mainly amplitude. The gonadotrophin pattern (high LH and low to normal FSH) can also be due to increased pulse frequency of GnRH secretion), attributed to a reduction in hypothalamic opioid inhibition because of the chronic absence of progesterone. In PCOS, LH/GnRH pulses are persistently rapid and favor LH synthesis, hyperandrogenemia and impaired follicular maturation. However, recently it has been shown that LH abnormalities are largely secondary to androgen excess and insulin resistance. A steady and sustained level of estrogen favors increased release of LH while small amounts of estrogen favors FSH release and inhibits LH secretion through feedback mechanisms. In PCOS, high amounts of estrogen are in circulation due to peripheral conversion of excess androgens by adipocytes. This excess estrogen is believed to cause LH hypersecretion. Previously increased LH to FSH ratio was used as a marker of PCOS. However, they have no place in modern diagnostic guidelines as follows.

Obesity and Lipid Abnormalities

There is a strong association of obesity and PCOS. Worldwide, at least 50% of PCOS women are obese and have higher abdominal fat than weight matched controls. Androgens are largely implicated in android fat distribution as mentioned above. Lean PCOS patients are also found have higher amounts of fat with android type distribution compared to weight matched controls. Lipocytes secrete estrogens as explained above along with several other metabolites including adiponectin. Estrogens inturn promotes liopocyte proliferation. This vicious cycle may explain the difficulty experienced in PCOS women to lose weight.

Obese and Lean PCOS women are found to have marginal lipid abnormalities. Though this is not a characteristic feature, it is not uncommon to find it in clinical practice. Higher total cholesterol with high LDL, Triglycerides, VLDL and low HDL levels are common findings. Increased hepatic lipase activity has also been reported in PCOS. These metabolic abnormalities have largely been attributed to increased insulin resistance and adiposity while role of excess androgen is debated.

Anovulation and Irregular Menstruation

The etiology of anovulation in PCOS is often explained by high intraovarian androgen levels which prevent the emergence of a dominant follicle as explained above. Further, though aromatase enzyme in granulosa cell is inhibited to some extent by excess androgens, increased LH mediates production of small amounts of estrogen and inhibit. Insulin is also thought to be involved in this process. Thus with excess androgens from enlarged follicles, excess
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estrogen from adipocytes, negative feedback to pituitary is absent resulting in no FSH rise. Thus dominant follicle selection is stalled and ovulation does not occur. Hence disturbance in HPO axis and anovulation leads to irregular menstruation.

**Genetics of PCOS**

Familial clustering of PCOS and functional hyperandrogenism was first reported by Cooper et al in 1968. Since then, several studies have reported variable prevalence of PCOS in sisters and second degree relatives of PCOS women. Due to absence of well defined male phenotype of PCOS, the precise pattern of inheritance has been difficult to define. About 50% of sisters of PCOS probands have hyperandrogenemia with or without anovulation, which suggests an autosomal dominant inheritance for a factor predisposing to ovarian hyperandrogenism. No single gene has been implicated in pathology of PCOS and most studies suggest an obligate role of environmental factors in expression of the genotype. Many studies have also identified familial aggregation of insulin resistance consistent of a specific genetic trait. However, results of genetic studies have been heterogeneous. Role of IGF-1 and Insulin receptor genes are under study.

**CLINICAL PRESENTATION**

Spectrum of clinical presentation has been associated with polycystic ovarian syndrome. Irregular menstruation, hirsutism and infertility are common symptoms. Clinical presentation depends on the severity of individual components of pathology. Hirsutism is often the only symptom in young females, just past puberty (Table 14.2).

<table>
<thead>
<tr>
<th>Frequent symptoms</th>
<th>Less frequent symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular menstruation</td>
<td>Unable to lose weight</td>
</tr>
<tr>
<td>Male pattern hair growth</td>
<td>Pigmentation in skin folds</td>
</tr>
<tr>
<td>Unable to conceive</td>
<td>Deeping of voice</td>
</tr>
<tr>
<td></td>
<td>Increased scalp hair loss</td>
</tr>
<tr>
<td><strong>Major signs</strong></td>
<td><strong>Minor signs</strong></td>
</tr>
<tr>
<td>Hirsutism with FG score &gt; 12</td>
<td>Male pattern baldness</td>
</tr>
<tr>
<td>Male pattern obesity</td>
<td>Acanthosis nigricans</td>
</tr>
</tbody>
</table>

**HIRSUTISM**

PCOS is the most common cause of hirsutism. It refers to the presence of course terminal hairs in androgen-dependent areas on the face and body in women. It correlates best with excess levels of DHEA. It is differentiated from hypertrichosis, which is excessive growth of thin vellus hair at any body site. Hirsutism develops when follicles in androgen sensitive areas start to form thick, pigmented terminal hair as opposed to thin, short, non-pigmented vellus hair normally seen in those areas in women.
Excess hair growth in women is of cosmetic concern. Women present with excess hair growth on upper lip, chin, cheeks, anterior chest, abdomen, inner thighs and lower extremities. Often excess hair growth may be seen only in one body segment. Women often complain of male pattern hair growth despite mechanical removal. Excess hair growth, though subjective, can be clinically assessed by modified Ferriman-Gallwey (F-G) score. This system evaluates nine body sites. Each body site is scored from 0-4 based on the amount of terminal hair present. A score > 8 is consistent with the diagnosis of hirsutism. However, in India, a score of 12 is considered hirsute. This scoring system has prognostic value.

Virilization

It is not common to find virilization in women with PCOS as there is a relative increase in free testosterone rather than total testosterone in PCOS. It is common in women with variants of PCOS like ovarian hyperthecosis and syndromes of extreme insulin resistance like PCOS. Of various signs of virilization, deepening of voice is most common symptom in clinical practice.

Irregular Menstruation and Infertility

Amenorrhea and oligomenorrhea are common presenting symptoms in PCOS due to anovulation and disturbed HPO axis. Generally, delay in menstruation is progressive, occurring once in 45 days and decreasing in frequency up to or more than 365 days. However bleeding can be unpredictable, heavy and prolonged in some women due to unstable endometrial proliferation, by excess estrogen, unopposed by progesterone. PCOS is known to be the most common cause of infertility.

INVESTIGATIONS AND DIAGNOSIS (TABLE 14.3)

Diagnosis of PCOS is often a clinical challenge due to heterogeneity in presentation and signs being common to other endocrinopathies. Till recently there was a lack of a universally accepted definition of PCOS as a result of disagreement concerning the relative merits of ovarian sonography, endocrinology and clinical features as well as the recognized genetic heterogeneity of the condition. However in 2003, an international group have issued a diagnostic criteria which has been largely acceptable. Criteria for diagnosis of polycysts by ultrasonography has also been published.

<table>
<thead>
<tr>
<th>Table 14.3: 2003 Diagnostic criteria for PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS can be diagnosed after the exclusion of other medical conditions that cause irregular menstrual cycles and androgen excess and determination that at least two of the below conditions</td>
</tr>
<tr>
<td>- Oligoovulation or anovulation usually manifested as oligomenorrhea or amenorrhea.</td>
</tr>
<tr>
<td>- Evidence of hyperandrogenemia reflected by elevated levels of circulating androgens or clinical evidence of hyperandrogenism.</td>
</tr>
<tr>
<td>- Polycystic ovaries as defined by ultrasonography (see below).</td>
</tr>
</tbody>
</table>

Note: Functional polycystic ovaries need not be present to make a diagnosis and conversely, their presence alone does not establish the diagnosis.
**Differential Diagnosis (Table 14.4)**

It is essential to exclude other disorders that have similar clinical presentations. Most of the disorders to be considered are other causes of hyperandrogenism. Apart from androgen excess disorders and thyroid dysfunction, syndromes of severe insulin resistance have to be considered if clinical presentation is suspicious.

<table>
<thead>
<tr>
<th>Table 14.4: Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Androgen excess</strong></td>
</tr>
<tr>
<td>• Late onset adrenal hyperplasia</td>
</tr>
<tr>
<td>• Cushing syndrome</td>
</tr>
<tr>
<td>• Androgen secreting tumors of ovaries or adrenals</td>
</tr>
<tr>
<td><strong>Menstrual disturbances and infertility</strong></td>
</tr>
<tr>
<td>• Thyroid dysfunction</td>
</tr>
<tr>
<td>• Hyperprolactinemia</td>
</tr>
<tr>
<td>• Hypogonadotrophic hypogonadism</td>
</tr>
<tr>
<td>• Premature ovarian failure</td>
</tr>
<tr>
<td><strong>Hyperinsulinemia</strong></td>
</tr>
<tr>
<td>• HAIR-AN syndrome</td>
</tr>
<tr>
<td>• Insulomas</td>
</tr>
</tbody>
</table>

**Ultrasonography Findings (Table 14.5)**

The PCOS ovary has a thickened tunica and about twice the cross-sectional area of normal ovaries. They contain follicles of size 2 mm to 9 mm in size and 2 to 3 times the number in normal ovaries.\(^{58}\) Polycystic ovaries is defined on ultrasound by 10 or more 2-8 mm follicles and an increased, echodense stromal area.\(^{78}\)

<table>
<thead>
<tr>
<th>Table 14.5: Concise 2003 guidelines for ultrasound assessment of PCOS, Balen AH et al(^{79})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The PCO should have at least one of the following</td>
</tr>
<tr>
<td>• 12 or more follicles measuring 2±9 mm in diameter or</td>
</tr>
<tr>
<td>• Increased ovarian volume (&gt;10 cm(^3)).</td>
</tr>
<tr>
<td>• If there is evidence of a dominant follicle (&gt;10 mm) or a corpus luteum, the scan should be repeated during the next cycle.</td>
</tr>
<tr>
<td>2. The subjective appearance of PCOs should not be substituted for this definition. The follicle distribution should be omitted as well as the increase in stromal echogenicity and/or volume.</td>
</tr>
<tr>
<td>3. Only one ovary fitting this definition or a single occurrence of one of the above criteria is sufficient to define the PCO. If there is evidence of a dominant follicle (&gt;10 mm) or corpus luteum, the scan should be repeated next cycle. The presence of an abnormal cyst or ovarian asymmetry, which may suggest a homogeneous cyst, necessitates further investigation.</td>
</tr>
</tbody>
</table>

**Laboratory Findings (Table 14.6)**

Certain hormonal assays are essential to establish diagnosis according to above mentioned criteria. Metabolic parameters may be required depending on prevalent risk factors. Below are a battery of tests suggested as a work up for PCOS. It should be noted that not all tests mentioned below are required to be done in a given patients. Physicians should discretely choose assays based on clinical presentations.
Table 14.6: Modified from Richardson RM (2003)\(^7\)

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone</td>
<td>&lt; 20 ng per dL (&lt; 0.7 nmol per L)</td>
<td>Exclude androgen-secreting neoplasm</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>20 to 30 years—0.06 to 2.57 pg per mL</td>
<td>Establish diagnosis or monitor therapy</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>0.4 to 2.7 ng per mL (1.4 to 9.4 nmol per L)</td>
<td>Establish diagnosis</td>
</tr>
<tr>
<td>DHEAS</td>
<td>600 to 3,400 ng per mL (1.6 to 9.2 µmol per L)</td>
<td>Exclude androgen-secreting neoplasm</td>
</tr>
<tr>
<td>17-hydroxyprogesterone</td>
<td>Follicular phase &lt; 2 µg per L (6.1 nmol per L)</td>
<td>Exclude late onset CAH</td>
</tr>
<tr>
<td>Prolactin</td>
<td>&lt; 20 ng per mL (&lt; 20 µg per L)</td>
<td>Exclude hyperprolactinemia</td>
</tr>
<tr>
<td>TSH dysfunction</td>
<td>0.5 to 4.5 µU per mL (0.5 to 4.5 mU per L)</td>
<td>Exclude thyroid</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>&lt; 20 µU per mL (&lt; 144 pmol per L)</td>
<td>Exclude hyperinsulinemia</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Glucose: insulin ratio &gt; 4.5</td>
<td>Exclude insulin resistance</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td>Exclude lipid abnormalities</td>
</tr>
<tr>
<td>Diabetes screening</td>
<td></td>
<td>Exclude type 2 DM</td>
</tr>
</tbody>
</table>

Diagnostic Algorithm (Fig. 14.1)

The following algorithm adapted from David A. Ehrmann, 2005 can be used to diagnose PCOS.\(^8\)

Any two of the following three disorders confirmed:
- Oligomenorrhea or amenorrhea
- Hyperandrogenism (e.g., hirsutism, acne, alopecia) or hyperandrogenemia (e.g., elevated levels of total or free testosterone)
- Polycystic ovaries on ultrasound

All of the following disorders ruled out:
- Hyperprolactinemia
- Nonclassic congenital adrenal hyperplasia
- Cushing's syndrome
- Androgen-secreting neoplasm
- Acromegaly

**Polycystic ovary syndrome**

**Ancillary studies**

- Risk assessment for endometrial carcinoma
  - Endometrial biopsy if risk increased

- Risk assessment for glucose intolerance
  - Oral glucose-tolerance test if risk increased

- Fasting cholesterol, HDL cholesterol, triglycerides, LDL cholesterol

- Risk assessment for obstructive sleep apnea
  - Polysomnography if risk increased

**Fig. 14.1:** Algorithm for diagnosis of PCOS
COMPLICATIONS OF PCOS

Type 2 Diabetes Mellitus
Association of type 2 DM and androgen excess has been reported since 1921. Insulin resistance seen in PCOS may lead to type 2 DM and hypertension. Women with PCOS are said to have 5-10 fold risk to develop type 2 Diabetes. Worldwide, about one-third of women and adolescents with PCOS have impaired glucose tolerance. Though insulin resistance plays a major role in PCOS, only 10% of women with PCOS have found to have DM.

Dyslipidemia
Patterns and prevalence of lipid abnormalities have been mentioned above. They manifest as a result of adiposity, insulin resistance and excess androgens. Dyslipidemia may put PCOS patients at a risk to develop atherosclerosis.

Coagulation and Endothelial Dysfunctions
Some studies have noted variety of disorder in factors involved in coagulation including homocystein and plasminogen activator antigen. These studies are largely inconclusive and are believed to have little clinical significance in the long-term. Reports on endothelial dysfunction have been conflicting.

Cardiovascular Disease Risk
Considering that insulin resistance plays an important role in PCOS, it has been postulated that PCOS women are under high-risk to develop cardiovascular diseases as a complication of metabolic syndrome. Few studies have demonstrated increased prevalence of carotid and coronary plaques in PCOS women. However, two large prospective studies by Wild and Pierpoint, 2000 and Solomon CG, 2002 have shown that women with PCOS do not have significant risk of developing cardiovascular disease but women with PCOS and DM have significant risk of developing DM complications.

Endometrial Cancer
PCOS women are known to have a three fold risk of developing endometrial cancer. The endometrium is constantly exposed to estrogen in hyperandrogenic anovulatory women. Hence endometrium proliferates in excess without the periodic progesterone-induced inhibition and differentiation to secretory endometrium. Thus in women with PCOS with long history of amenorrhea it is recommended to note endometrial thickness. Endometrial biopsy is recommended if there is a clinical suspicion.

TREATMENT
Treatment options in PCOS are several. It is important to have an understanding of pathophysiology and correlate clinical findings with possible underlying mechanism in a
patient. Such a knowledge will help a physician to tackle the right component(s) of pathology. In younger women with hirsutism, PCOS is more of a cosmetic problem. Thus, just reducing androgen levels would suffice. In women with menstrual abnormalities and obesity, treating insulin resistance along with anti-androgens may help. As mentioned above, treating insulin resistance only can reduce androgen levels. Various drugs and their merits are discussed below. Combination of drugs can be used depending on clinical presentation, goals of therapy and drug tolerance.

**Treating Hirsutism**

Hirsutism due to PCOS is best treated medically. Mechanical methods are just symptomatic treatments. Patients with hirsutism generally have high amounts of DHEA. Hence the aim of treatment is to suppress androgen production and/or block androgen receptors and/or reduce conversion of testosterone to DHEA provided testosterone levels are normal. During treatment with androgens, conception should be avoided due to possibility of feminization of a male fetus. The following are various options.

**Androgen Block**

- **Cyproterone acetate**, a competitive inhibitor of testosterone and dihydrotestosterone receptor binding was the first androgen receptor antagonist used clinically. it also has progestational and weak glucocorticoid properties.\(^\text{141,142}\) It is an effective and well-tolerated treatment for hirsutism. Cyproterone acetate with mild estrogen combination is available and are known yield good results.

- **Spironolactone**, initially used as a potassium sparing diruetic was found to competitively block androgen receptor in hair follicles.\(^\text{89}\) In addition spironolactone also inhibits androgen biosynthesis through the cytochrome p450 system and directly inhibits 5α-reductase activity. Spironolactone can be given at a dose of 200 mg/day for 3-6 months. Irregular uterine bleeding can occur in some women. It is best given in combination with an OCP. Polyuria and fatigue are other common side effects.

- **Flutamide**, a nonsteroidal antiandrogen blocks the androgen receptor. Flutamide 250 mg/d for six months is effective in treating hirsutism. Patients with severe hyperandrogenism or alopecia, may respond better to flutamide than to spironolactone.\(^\text{90}\) The most common side effects of flutamide are mild and include dry skin and increased appetite. However, the potential exists for a rare but severe drug-induced hepatitis which limits the usefulness of this medication.\(^\text{91}\) It is advised to monitor liver enzymes when treated with flutamide.

- **Finasteride**, a potent inhibitor of 5α-reductase reduces the conversion of testosterone to DHEA. 5 mg/d for 3-6 months is recommended dose. Finasteride is well tolerated with minimal side effects at the standard dose of 5 mg/day. A randomized, double blind, placebo controlled study by Moghetti et al objectively compared the effectiveness of spironolactone, flutamide and finasteride by using computer
assisted light microscopy determination of hair shaft diameter in hirsute women. At the end of a six-month period all three treatments similarly reduced hair diameter and the Ferriman-Gallwey score compared to the placebo group.92

**Androgen Suppression**

- Oral Contraceptive Pills are effective to treat androgen excess. The progestational component of the OCP inhibits pituitary secretion of LH, which in turn decreases ovarian androgen production. Progestins also decrease adrenal DHAS production, possibly via a negative feedback loop through the glucocorticoid receptor. In addition, the estrogen component of oral contraceptive pills increases production of SHBG thus decreasing the amount of free testosterone available. They are an excellent choice for patients with abnormal cycles and acne but used alone are not the most efficacious therapy for hirsutism.

- Gonadotropin Releasing Hormone Agonists can be used to suppress androgen excess only if all other options of treatment are exhausted. Administration of a long-acting gonadotropin GnRHa such as leuprolide acetate suppresses ovarian androgen production by inhibiting pituitary gonadotropin secretion. However, its adverse effects and bone loss has to be considered before usage.

**Insulin Sensitizing Agents**

- Metformin is the insulin sensitizing agent of choice in PCOS. It is a pregnancy category B drug, and it is begun at 500 mg/day with dinner and is increased by 500 mg increments every 1-2 weeks as gastrointestinal symptoms abate. Metformin treatment usually results in modest weight loss, which may be due in part to its suppression of appetite. Metformin is found to be effective in improving both reproductive and metabolic outcomes in PCOS.

**Lifestyle Modifications**

Weight loss and low calorie diet have shown to improve symptoms in obese and non-obese women. Even non-obese women have to be recommended low calorie diet and weight loss as they are found to have more fat than normal women matched with age. Some studies have shown weight loss to be more effective than metformin in reducing insulin resistance. An improvement in menstrual function has been reported in as many as 80-90% of patients.93 Further, weight loss also has a consistent effect on hyperandrogenism with significant decreases to normal or near normal levels of total and free testosterone and a significant increase in sex hormone-binding globulin.

**Anovulation**

Treating hyperandrogenism and/or insulin resistance will result in spontaneous ovulation. Should the treatment fail, then agents like clomiphene citrate alone or along with
dexamethasone can be used. High rate of spontaneous abortion in PCOS women treated for ovulation induction has been noted.

**Surgery**

Resection of cysts is no longer advocated for PCOS, unless the polycysts in the ovaries cause severe problems that warrants the need of surgery.

**PSYCHOLOGICAL SUPPORT AND PATIENT EDUCATION**

This is an essential aspect of treating PCOS. The patient must be made aware of the disease especially its complications such that patient follows the doctor’s advise and does her best to avoid Diabetes.

Psychological support is essential because the syndrome involves infertility, irregular menstruation and cosmetic problems. A woman with infertility must be reassured that with proper treatment she can conceive and should be counseled with care such that she follows up regularly. Patients with hirsutism, especially the young will be deeply concerned about the cosmetic problem. Thus the immediate solution of hair removal and the remission of hirsutism with anti-androgen therapy should be explained. Also the need of regular menstrual cycle should be explained to the young and middle aged women who do not intend to conceive. The risk of development of endometrial cancer and other problems due to hormonal imbalances should be explained. Reassurance is the key for patients well being and compliance.

**SPECIAL CONCERNS**

- Rule out all disorders that mimic PCOS.
- Carefully monitor while treating an infertility case.
- Never prescribe and anti-androgen to a women wanting to conceive.
- Categorize high-risk groups for diabetes and monitor regularly.
- Recognize patients with high-risk of endometrial carcinoma and take appropriate steps.
- Recognize syndromes of severe insulin resistance like HAIR-AN syndrome.

**RESEARCH IN PCOS**

Scientific world is currently involved in mapping the pathogenesis pathway for PCOS by studying the mutant gene. Also due to the spectrum of clinical presentations, it has ample opportunities for clinical investigations in areas of diagnosis and case management.

Much has changed in the understanding of PCOS since it was 1st described in 1935. As years pass by, hidden errors and malfunctions are unearthed. The diagnosis and case management have been changing over the years and much will change in years to come as the depth of knowledge in PCOS increases.
Polycystic Ovarian Syndrome

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INTRODUCTION

Puberty signals the beginning of transition from childhood to adolescence and adulthood and is accompanied by striking physical and hormonal changes. The most significant event is the return of pulsatile GnRH secretion that leads to increased gonadotropins and sex steroids. Physical changes of puberty include growth spurt, appearance of sexual hair, breast development, onset of menarche and then ovulatory cycles. Most normal girls go through the various stages between age’s 10 to 14 years with normal variations from age 8 to 16 years. Menarche or the onset of menses typically occurs around age 12 years with a trend towards earlier age of onset in overweight girls and in certain ethnic groups.

DEFINITION

Primary amenorrhea is defined as absence of menarche by age 16 years in girls with secondary sexual characteristics and by age 14 in girls without sexual hair or breast development. Ovarian, uterine, vaginal, hypothalamic or pituitary dysfunction may cause primary amenorrhea. Evaluation of the girl can be begun even at an earlier age if signs of an underlying etiologic disorder are evident.

ETIOLOGY

Most large series have shown that ovarian failure of different etiologies accounts for about 35-43%, müllerian agenesis and other outflow tract abnormalities to account for 15-25%, constitutional delay 10-20%, pituitary and hypothalamic disorders about 10-15%.
1. Outflow tract obstruction: Imperforate hymen, vaginal septum
2. Absence of vagina, cervix, uterus
3. Uterine causes: Endometrial damage due to infections, trauma
4. Ovarian pathology: Gonadal dysgenesis, premature ovarian failure, gonadotropin resistant ovaries, chemotherapy, radiation
5. Pituitary disorders: Hypopituitarism, pituitary tumors, hyperprolactinemia, germinomas
7. Other endocrine disorders: Cushing’s syndrome, androgen insensitivity, congenital adrenal hyperplasia, polycystic ovary syndrome
8. Constitutional delay: Though less frequent than in boys, it is usually associated with delay in growth and a family history.

EVALUATION OF PRIMARY AMENORRHEA

Evaluation consists of detailed history and physical exam with special attention to signs of genetic and endocrine disorders that are associated with primary amenorrhea.

History

*Family history:* Primary or secondary amenorrhea, genetic disorders, constitutional delay.

*Birth history:* Newborn salt wasting, genital ambiguity, birth weight, birth defects.

*Childhood illness:* Recurrent otitis media, corticosteroid use, radiation and chemotherapy, growth patterns and psychosocial problems.

*Psychosocial:* Eating disorders, excessive exercise, behavioral changes related to eating, poor school performance.

*Review of systems:* A detailed history of headaches, visual disturbances, weight change, thirst, hirsutism, abdominal striae, fatigue, and skin pigmentation changes, galactorrhea.

Physical Examination

Girls may present with striking clinical features like short stature, webbing of neck, increased carrying angle as in Turner’s syndrome or with a well feminized normal girl who may have mullerian agenesis. A complete physical exam with special attention to Tanner stages of puberty is important.

*Height, Weight, BMI*

*Pubertal stage:* Tanner staging

Stage 1: Elevation of breast papilla only. No pubic hair

Stage 2: Elevation of breast and papilla as a small mound, areola diameter enlarged. Sparse long pigmented hair along labia majora

Stage 3: Further enlargement without separation of breast and areola. Dark, coarse curled hair sparsely spread over mons

Stage 4: Secondary mound of areola and papilla above the breast Adult type hair, limited to mons
Stage 5: Recession of areola to contour of breast.
Adult type spread in quantity and distribution

Genitalia: Clitoral size, introital opening, presence of labial masses, presence of vagina.

Stigmata of Turner’s syndrome: Webbing, increased carrying angle, widely spaced nipples, short stature, ptosis (Figs 15.2A to C).

Stigmata of testicular feminization: Tall stature, lack of axillary and pubic hair, well developed breasts, female external genitalia, scar of inguinal hernia repair (Fig. 15.1).

Signs of constitutional delay: Growth retardation, delay in Tanner stages, normal intellect.

Stigmata of Cushing’s syndrome: Round face, posterior cervical fat pad, abdominal striae, thin extremities, truncal obesity, hirsutism (Figs 15.3A to C).

Stigmata of polycystic ovary syndrome: Obesity, acanthosis nigricans, hirsutism.

Signs of hypopituitarism such as short stature (in growth hormone deficiency), scanty sexual hair, poor or absent breast development, enuchoidal body proportions and tall stature in isolated hypogonadotropic hypogonadism.

Signs of autoimmune disorders like vitiligo, thyromegaly, increased pigmentation, alopecia.

Fig. 15.1: Testicular feminization in four women. Absent body hair, good breasts and female external genitalia
Laboratory Testing and Imaging

Workup of the young girl involves four initial steps that will identify majority of conditions that cause primary amenorrhea. Extensive testing maybe needed only in a small percentage of these girls. Ruling out pregnancy is a very important preliminary step.

Step 1

Pelvic ultrasound: This will establish the presence or absence of müllerian structures and identify streak ovaries, intra-abdominal testes, polycystic ovaries and other pelvic pathology.
Absence of the uterus may signify müllerian agenesis [xx] or testicular feminization [xy]. A karyotype will help differentiate the two.

**Step 2**

Tests to identify androgen excess: In young girls presenting with hirsutism, virilization or features of Cushing’s syndrome, the appropriate tests are free testosterone, Dexamethasone suppression test and 17 alpha hydroxy progesterone. Polycystic ovary syndrome, Cushing’s syndrome, congenital adrenal hyperplasia, adrenal and ovarian tumors may present with primary amenorrhea, hirsutism and virilization.
Step 3: Serum FSH
Elevated FSH indicates ovarian failure. Gonadal dysgenesis [Turner’s syndrome, Swyer syndrome], autoimmune premature ovarian failure, gonadotropin resistant ovaries, 17 alpha hydroxylase deficiency, prior exposure to chemotherapy and radiation. Gene mutations that are responsible for premature ovarian failure have been reported.

Low or normal FSH could indicate pituitary gonadotropin deficiency, hypothalamic GnRH deficiency, anorexia nervosa, chronic illness, malnutrition, exercise induced amenorrhea, hyperprolactinemia or constitutional delay.

Step 4: Serum Prolactin, TSH
An elevated prolactin level could be secondary to a prolactinoma, medications, hypothyroidism, and pituitary stalk interruption due to tumors, stalkitis, and other space occupying lesions. Proper history, thyroid function tests and imaging of the sella are appropriate next steps.

Elevated TSH indicates primary hypothyroidism and is treated with thyroxine. A suppressed TSH needs further evaluation to rule out hyperthyroidism or subclinical hyperthyroidism.

![Diagram of TSH, FSH, and Prolactin levels](image.png)

TREATMENT
This is primarily aimed at the underlying cause and in initiating hormone replacement for induction of puberty and maintenance of adequate estrogen when appropriate. Treatment also includes providing support to the young girl and her parents by having a sensitive and empathic approach.

Counseling regarding the possibility of menstruation, normal sexual function and future fertility potential and genetic counseling are important issues that will need to be addressed. This is especially important in young girls with chromosomal abnormalities and müllerian agenesis.

Surgical therapy is necessary for imperforate hymen and vaginal septum. Vaginal reconstruction or vaginal dilatation may be needed in testicular feminization. Gonadectomy to remove Y containing gonads are recommended in these girls after breast development and linear growth are completed. Adrenal and ovarian tumors need surgical excision. Clitoral reduction and vaginoplasty are done in children with congenital adrenal hyperplasia along with steroids.
Primary Amenorrhea

Girls with Turner’s syndrome, Swyer syndrome [after gonadectomy], testicular feminization [after gonadectomy], premature ovarian failure of any cause [autoimmune, radiation, chemotherapy], and hypogonadotropic hypogonadism [due to hypothalamic or pituitary tumors or inflammation, radiation or post surgical] are all hypoestrogenemic and need initiation of hormone replacement. Estrogen is begun at lower doses and gradually increased to 0.625 to 1.25 mg of conjugated equine estrogen or 1-2 mg of ethinyl estradiol for 25 days of the month. If the uterus is present, progesterone is added for the last 10-12 days in doses of 5-10 mg of medroxy progesterone acetate. Withdrawal bleeding occurs after estrogen and progesterone are stopped. Risk benefit ratio of hormone replacement needs to be discussed. Oral contraceptive pills may be used in the place of estrogen and progesterone after induction of puberty and in those girls desiring contraception.

Girls with polycystic ovary syndrome are encouraged to lose weight. Progesterone withdrawal monthly or every other month may be adequate for shedding of endometrium. Metformin or oral contraceptives are used based on presence of insulin resistance or hirsutism.

Hyperprolactinemia is treated with Bromocriptine or cabergoline. Hypothyroidism is treated with Levothyroxine and hyperthyroidism with antityroid drugs or radioactive iodine. Cushing’s syndrome is treated with appropriate surgery of pituitary or adrenal tumor causing steroid excess.

Anorexia nervosa is managed with nutritional and psychological counseling, limitation of the intensity of exercise and stress reduction helps some girls. Hormone replacement may be necessary for a period of 6 to 12 months till recovery occurs in functional hypothalamic amenorrhea.

 Constitutional delay is managed with reassurance and ruling out other causes of primary amenorrhea.

 Counseling regarding sexual activity needs to be done assuring confidentiality and privacy. Assisted reproduction techniques now make it possible for women with ovarian failure to use donor eggs. Hypothalamic amenorrhea can be treated with pulsatile GnRH or gonadotropins. A surrogate can help women with müllerian agenesis. Girls with Turner’s syndrome can gain height with growth hormone therapy and puberty can be initiated at an appropriate time with estrogen and progesterone.

SUMMARY

Primary amenorrhea can be managed in a timely, cost effective manner by recognizing the symptoms and signs of the various conditions that cause the absence of menarche and by a few simple steps of laboratory testing and imaging. Our understanding of the pathophysiology of these conditions allows us to treat these problems effectively. Hormone replacement and assisted reproduction technologies have improved the quality of life of these young girls tremendously.
INTRODUCTION

The gonads have two primary functions: to produce gametes and secrete hormones for reproduction. Hormones are necessary for adequate sexual function. Their actions are shown outwardly as secondary sexual characters. Gonadal failure may occur at various stages — in utero, before puberty, or later. Hypogonadism or gonadal failure may be also due to dysfunction or destruction of hypothalamus or pituitary. Gonadal failure may result in hormone dysfunction, reproductive dysfunction or both.

This chapter will focus on hormonal deficiency seen in males.

Children with gonadal disorders may present in two ways: Early activation of the gonadal axis (precocious sexual development) or absent or delay in sexual development (hypogonadism). Diagnosis of hypogonadism is easier in adults.

EVOLUTION OF HYPOTHALAMO-PITUITARY GONADAL AXIS

Normal sexual and reproductive function depends on pulsatile secretion of gonadotrophic releasing hormone (GnRH) from the hypothalamus. GnRH is secreted episodically in late fetal and early neonatal life, which in turn stimulates gonadotropin secretion from the pituitary. Gonadotropins further stimulate testicular sex steroid production. Following birth, in the first few years of life, GnRH secretion is low until puberty. The secretion of gonadotropin-releasing hormone by the hypothalamus initiates pulsatile release of gonadotropins, gonadal secretion of sex steroids, pubertal development, and finally, gametogenesis.

As early as 3 years before the onset of puberty, i.e. by 5-7 years of age, sleep-entrained secretion of gonadotropins may occur. They further increase to result in pubertal development. Gonadotropins begin to increase at least a year before the onset of puberty. FSH may have an important role in the early pubertal period. Testosterone levels also increase early morning before the onset of puberty. LH and FSH levels increase due to an increase in pulse amplitude and not due to increased frequency of pulses. Analysis of GnRH and
gonadotropin secretion can be studied by frequent blood sampling over 24 hours, and use of deconvolutional analysis; this technique is based on mathematical repartitioning of measured hormone concentrations. As a result underlying secretion and clearance dynamics can be obtained.

Around the time of puberty the ratio of bioactive to immunoactive LH increases; both LH and FSH act synergistically to produce gonadal development.

**Indian Data on Hypogonadism**
A search on PubMed, using search terms ‘hypogonadism’ and ‘India’ mainly yielded (a) case reports of Laurence-Moon-Bardet-Biedl syndrome, Klinefelter syndrome in South African’s, Indians, where it is reported to be common, occurrence of extraovarian endocrine abnormalities in Indian women with premature ovarian failure, and a study on pituitary-gonadal axis in men with protein calorie malnutrition.

**EDC Data**
From our prospective computerized database on endocrine diseases, we analyzed 40 consecutive men who came principally for evaluation and management of hypogonadism. The age, both median and mode was 23 years (range 15-44 years). Most of them (n:27) presented between the ages of 20 and 30 years (*Table 16.1*). Six each were aged below 20 and between 31 and 40 respectively. The oldest was aged 44 years.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No (n:40)</th>
</tr>
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<tbody>
<tr>
<td>&lt; 20 years</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>20-30 years</td>
<td>27 (67.5%)</td>
</tr>
<tr>
<td>31-40 years</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>&gt; 40 years</td>
<td>1 (2.5%)</td>
</tr>
</tbody>
</table>

*Endocrine and Diabetes Centre, Visakhapatnam*

**Classification of Male Hypogonadism**
Male hypogonadism can result from
1. Failure of testes: Primary hypogonadism
   a. Developmental: Klinefelter’s syndrome, Ulrich-Noonan syndrome, cryptorchidism
   b. Inflammatory: Orchitis due to mumps, leprosy, chemotherapy, trauma, surgery
   c. Other conditions: Myotonia dystrophica, defects of testosterone enzymes, XX male, testicular steroid biosynthetic defects, Sertoli-only syndrome, LH receptor mutation, anorchia
2. Failure of hypothalamus/pituitary: Secondary hypogonadism
   a. Hypogonadotrophic hypogonadism: genetic defects
      i. G protein coupled receptor
      ii. Kallmann’s syndrome-I: X linked Kallmann’s syndrome with anosmia
iii. DAN: With adrenal insufficiency  
iv. GNRHR receptor deficiency  
v. FGRI: Fibroblast growth receptor 1: autosomal dominant Kallmann’s syndrome  
vi. LEP: Leptin and leptin receptor deficiency: associated with obesity  
b. Pituitary and parasellar tumors involving pituitary: craniopharyngioma, germinomas, astrocytomas  
c. Inflammatory: Langerhans histiocytosis, Postinfections and vascular disorders of CNS, following radiation therapy, lymphocytic hypophysitis  
d. Isolated LH, FSH deficiency; multiple pituitary hormone deficiencies including PROP-1 mutation  
e. Miscellaneous disorders: Prader-Willi syndrome, Laurence-Moon and Bardet-Biedl syndromes, chronic systemic disorders (sickle cell disease, AIDS, chronic renal disease, malnutrition)  

3. Combined primary and secondary hypogonadism  

Statistically most boys with delayed puberty do not have serious underlying disorders. Of the minority who have systemic disorders, more boys present than girls. The proportion of primary and secondary hypogonadism varies depending on the catchment area and expertise of the evaluating center.  

CLINICAL APPROACH  

Micropenis  

Pediatricians are likely to encounter boys with small penis. Micropenis is defined as a penis with stretched penile length (SPL) >2.5 SD below the mean for age (with or without cryptorchidism). It can result from hypogonadotrophic hypogonadism or may be a mild form of ambiguous genitalia. Where age-related normal values for stretched penile length are available, isolated micropenis without genital ambiguity can be further subclassified into borderline (SPL between –2.5 and –2.0 SD) and definite (SPL < -2.5).  

If micropenis is due to a deficiency of testosterone in utero, the penis responds to testosterone administration. A recent study suggested boys with isolated micropenis could be given testosterone, beginning even before the age of two years. Testosterone delivery can be either intramuscular (long acting preparations, 25-50 mg every 3 to 4 weeks for 3 to 4 months), or transdermal; the latter has a variable absorption and response. In those who do not respond to testosterone, transdermal dihydrotestosterone may be used.  

Generally hypogonadism is suspected when pubertal changes do not occur at the expected time (by 14 years in boys). Rarely hypogonadotrophic hypogonadism may be considered earlier when a male infant has cryptorchidism or micropenis (normal stretched penile length is 3.5+/-.4 cm in full-term newborn at birth, 4.5-5 cm by age two and 6-6.5 cm by age eight to ten). Micropenis along with midline defects such as cleft lip, cleft palate and renal agenesis may occur with hypogonadotrophic hypogonadism.
Delayed Puberty

Diagnosis of pubertal delay is based on statistical norms (i.e. delay of more than 2 standard deviation from the mean age of pubertal onset). In that way it is sometimes arbitrary. For practical purposes, delay of puberty is considered clinically significant if sexual maturation has not become apparent by age 14 years in boys, or age 13 years in girls.

When as is usual the boy is referred for evaluation of pubertal delay, one must identify the main reason for presentation: often parents seek reassurance that development is normal (i.e. the perceived ‘delay’ is only a variant of normal, which is often the case). It is necessary to identify whether it is merely a psychosocial problem, or is part of a hormonal deficiency. Hormonal deficiency if suspected must be diagnosed. An etiological diagnosis should also be made, especially of serious underlying conditions such as intracranial tumors.

Similarly one must assess whether pubertal delay is bothering the child, the parent or the physician. The relative contribution of concerns about short stature and secondary sexual characters or both must also be considered.

Clinical History

In the more usual case when a boy is brought for delayed puberty, a medical history must be first taken: attention to systemic diseases, frequent episodes of ill health, trauma, surgery, irradiation to skull or chemotherapy must be assessed. Impaired sense of smell may occur in hypogonadotrophic hypogonadism (Kallmann’s syndrome). A family history of delayed puberty may be elicited in families with delayed puberty.

Where hypogonadism is suspected after puberty, information must be obtained about the time and rate of pubertal development, sexual function, and the current altered sexual function.

Physical Examination

Particular attention must be paid to body proportions, fat distribution and pubertal development. Boys with hypogonadism have eunuchoid proportions (upper segment to lower segment ratio is less than 0.9 and arm span is more than height).

Abnormal physical signs may be present: Noonan syndrome, Laurence-Moon-Biedl syndrome, Frohlich’s syndrome, etc. Midline defects such as cleft lip or palate. Neurological examination including ocular fundi and visual fields. Sense of smell must be tested to identify hyposmia and anosmia.

Stretched penile length is measured from the mons pubis to the tip of the penis (Normal ranges have been given earlier). Rugosity and pigmentation of scrotum signifies development of secondary sex characters. Testicular volume of more than 4 ml suggests early pubertal changes have set in (Volume of testis can be measured by comparing with Prader or chidometer, or can be estimated as volume = 0.52 × length × width).
Prepubertal Versus Postpubertal Testicular Androgen Insufficiency

Certain clinical clues can indicate when androgen deficiency occurred. When puberty had not set in at all, the testis is likely to be less than 4 ml in volume or 2.5 cm long, no pigmentation or rugosity of scrotum, peripheral subcutaneous fat, eunuchoid habitus, no terminal face hair, no temporal recession of hair, high pitched voice, delayed muscle mass and a small prostate.

When hypogonadism occurs after puberty, the physical signs are likely to be, normal skeletal proportions, no absence of pubic hair, though it may be scanty, soft small testes, adult sized prostate, though it may be smaller, no change in voice.

Laboratory Evaluation

Once assessment, both clinical and if necessary lab, for systemic diseases is completed, hormonal measurements are necessary. Low serum testosterone for age in boys generally suggests compromised testicular function. Measurement of gonadotropins (LH, FSH) identifies the probable cause. Elevated gonadotropin levels suggest that the primary failure is at the level of the testes. If they are either low or inappropriately normal, further failure of the hypothalamus-pituitary is suggested.

To document hypothalamo-pituitary failure, a GnRH stimulation test is required. It is done by injecting 100 ug of GnRH intravenously, and by assaying the levels of LH, FSH at 0,30,45,60 and 120 minutes. A positive response is evidence that puberty has set in or is likely to set in within six months, consists of LH rise three times above basal level, and or FSH levels 1.5-2 times the basal level, by 30-45 mins of the injection.

In boys with cryptorchidism and low or non-elevated gonadotropin levels hCG test may be done. HCG is given 5,000 IU intramuscularly. Baseline and 72 hours post-injection testosterone levels are measured. A rise of circulating testosterone to >300 ng/dl suggests adequate Leydig cell function.

In suspected Klinefelter’s syndrome, a karyotyping would reveal 47, XXY chromosomal pattern.

Imaging of pituitary and intracranial structures may be necessary to identify intracranial pathological process. Bone densitometry may also be done at baseline, to assess whether bone strengthening agents are required.

TREATMENT

Treatment may aim at correcting hormonal deficiency (always) and at correcting infertility (sometimes, as in hypogonadotrophic hypogonadism). Where fertility is not an issue, or is not possible, replacement of testosterone corrects physical features of hypogonadism: it improves energy, sexual function, increases muscle mass, bone mineral density, and increases hemoglobin levels.

Testosterone is usually given intramuscularly in a dose of 200 mg every three weeks (combination of esters, testosterone propionate, phenylpropionate, isocaproate). Oral
testosterone undecanoate (40 mg/d) has unreliable absorption and may be hepatotoxic. Serum levels can be monitored to maintain testosterone level in the mid-normal range one week after the injection.

Transdermal delivery of testosterone is also possible. The advantages are a smooth maintenance of hormone level, without troughs and valleys. ‘Testoderm’ is available as scrotal patches and ‘Androderm’ as non-scrotal patch.

Oral testosterone preparations, despite the convenience of administration, are poorly androgenic and have hepatic side effects such as liver cysts, cholestasis and hepatocellular adenoma.

Testosterone replacement results in development of secondary sex characters. Sexual function occurs, and is maintained facial hair growth depends on the ethnic background. Side effects such as acne, oily skin, breast enlargement and tenderness may occur. Breast changes are often transient.

A recent meta-analysis of testosterone supplementation for erectile dysfunction showed that response to primary gonadal failure was better; response was better with transdermal rather than intramuscular replacement.

Testosterone modulates male sexual behavior and is necessary for normal sexual activity. However, the precise relationship between serum hormone levels and male sexual behavior is still not completely clear. Therefore, a combination of clinical assessment and lab evaluation is necessary in management. Recent studies have reported that testosterone replacement should maintain not only physiological levels of the hormone, but also of its metabolites such as dihydrotestosterone.

When fertility is desired in individuals with hypogonadotrophic hypogonadism, gonadotropins or pulsatile GnRH may be given. Therapy is initiated with hCG at a dose of 1000 to 2000 IU on alternate days intramuscularly and adequacy of dose assessed by serum testosterone level and on testicular growth for 12 months. Often hMG or recombinant FSH must be added later.

Alternatively pulsatile GnRH may be given by a programmable portable mini-infusion pump, usually at 2-h intervals to mimic the LH pulse frequency observed in normal men. The doses of GnRH can vary from approximately 5–25 ng/kg and are titrated to reach and maintain T levels in the midnormal adult male range. Treatment may have to be continued for at least 12 months. Thus treated, pulsatile GnRH therapy in idiopathic hypogonadotrophic hypogonadal men can induce androgen production and spermatogenesis. Predictors of resulting in adult testicular size and optimizing spermatogenesis are prior history of sexual maturation and absence of cryptorchidism.

Once fertility is achieved, testosterone replacement may be continued.

**Monitoring Therapy**

During the first year, clinical response and side effects should be looked for every 3 to 4 months. To evaluate the adequacy of testosterone dose, serum level should be measured.
midway between injections, to ensure that the level of testosterone is in the midnormal range. On those using testosterone patch, peak hormone values are reached four to eight hours after the application of patch. In elderly men, prostate should be evaluated, along with prostate-specific antigen.

**Adverse Effects**
Serious adverse effects are not common with appropriate replacement dose of testosterone. Gynecomastia may result from aromatization of testosterone to estradiol. Alopecia may worsen. Hyperviscosity due to stimulation of bone marrow erythrocytes is another uncommon complication.

**ANDROPAUSE**
In contrast to women, who have a relatively sudden cessation of gonadal activity (the menopause), aging men do not have a comparable dramatic development. Andropause refers to an age-related decline in testosterone level. It may be associated with physical and emotional changes. Hypogonadism in aging men, which is defined by low levels of free testosterone index, results from reduced testosterone production and increased levels of sex hormone binding globulin levels. Diagnosed is based on clinical symptoms such as decreased muscle mass, loss of libido and laboratory investigations. However, when and whether testosterone replacement is safe and effective is still controversial.

Aging men have lower levels of free testosterone because of a combination of central (hypothalamo-pituitary) and peripheral (testicular) causes. However, other confounding factors exist, including co-morbid conditions, and altered levels of hormones such as growth hormone, cortisol and thyroxine. Besides, diagnosis of hypogonadism in aging men is made difficult by complex biochemical investigations [bioavailable testosterone assay by ammonium sulfate precipitation]; and lack of age-adjusted reference values. Ultimately the diagnosis of hypoandrogenism in elderly males requires a combination of clinical features and low free testosterone levels. Similarly clinical response is a better guide to the dose of testosterone that is required.

A recent review of all published placebo-controlled trials of testosterone supplementation in older men concluded that as of now, testosterone supplementation cannot be recommended for older men with normal or low-normal testosterone and no clinical manifestations of hypogonadism. However, the long-term safety and efficacy remain uncertain. Unless there is unequivocal evidence of hypogonadism in the elderly, testosterone replacement should not be given. Even then, contraindications such as prostate cancer and breast cancer must be excluded.

The advantages of improved muscle strength, energy and well-being must be balanced against the risk of prostatic hypertrophy and cancer. There are yet no large scale trials comparing the safety and efficacy of testosterone for ‘andropause.’
INTRODUCTION
Hypertension (HTN) is a common disorder occurring in approximately 20% of population in developed nations. The prevalence is higher in India and varies between 20 and 50% according to the region studied.\(^1\) Ninety percent of these individuals have essential or primary HTN (Table 17.1). Even though only 10% of patients have secondary HTN, this represents a large number.\(^2\)

Etiology of Essential HTN
The etiology of essential HTN is heterogeneous and involves multiple genetic and environmental factors. Most of the pathophysiological mechanisms have an endocrine basis. Whereas secondary HTN can be broadly divided into renal and endocrine causes with distinct symptoms and signs. HTN refractory to usual line of treatment also prompts a physician to search for secondary causes. It is important to identify individuals with secondary HTN as treatment of primary disorders can often lead to a cure of HTN. This can prevent long-term complications and a need for lifelong treatment.\(^3\)

The pathological hallmark of untreated HTN is atherosclerosis. If untreated about 50% of hypertensive patients die of coronary heart disease (CHD) or congestive heart failure (CHF), 33% of stroke and 10-15% of renal failure.

Pathophysiology of Essential HTN
Mean arterial pressure is a function of cardiac output, systemic blood flow and resistance to blood flow in the perfused organ.\(^4\) These functions are regulated by hormones, neurotransmitters and local factors which are affected by structural and functional abnormalities in the heart and vasculature that occurs with chronic HTN.
Table 17.1: Types of HTN

<table>
<thead>
<tr>
<th>Systolic and Diastolic HTN</th>
<th>Primary, essential or idiopathic</th>
</tr>
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<tbody>
<tr>
<td>Renal</td>
<td>Secondary (identifiable)</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td></td>
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<tr>
<td>Renovascular</td>
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<tr>
<td>Renin producing tumors</td>
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<tr>
<td>Renopriyal</td>
<td></td>
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<tr>
<td>Primary sodium retention</td>
<td>(Liddle syndrome)</td>
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<tr>
<td>Endocrine</td>
<td></td>
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<tr>
<td>Acromegaly</td>
<td></td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Hyperthyroidism</td>
<td></td>
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<tr>
<td>Hypercalcemia (hyperparathyroidism)</td>
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<tr>
<td>Adrenal</td>
<td></td>
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<tr>
<td>Cortical</td>
<td></td>
</tr>
<tr>
<td>Cushing’s</td>
<td></td>
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<tr>
<td>Primary aldosteronism</td>
<td></td>
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<tr>
<td>Congenital adrenal hyperplasia</td>
<td></td>
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<tr>
<td>Apparent mineralocorticoid excess (licorice)</td>
<td></td>
</tr>
<tr>
<td>Medullary: Pheochromocytoma</td>
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<tr>
<td>Extra-adrenal chromaffin tumors</td>
<td></td>
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<tr>
<td>Carcinoid</td>
<td></td>
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<tr>
<td>Exogenous hormones</td>
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<tr>
<td>Estrogen</td>
<td></td>
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<tr>
<td>Glucocorticoids</td>
<td></td>
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<tr>
<td>Mineralocorticoids</td>
<td></td>
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<tr>
<td>Sympathomimetics</td>
<td></td>
</tr>
<tr>
<td>Tyramine containing foods and monoamine oxidase inhibitors</td>
<td></td>
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<tr>
<td>Coarctation of aorta</td>
<td></td>
</tr>
<tr>
<td>Pregnancy induced HTN</td>
<td></td>
</tr>
<tr>
<td>Neurological disorders</td>
<td></td>
</tr>
<tr>
<td>Acute stress</td>
<td></td>
</tr>
<tr>
<td>Increased intravascular volume</td>
<td></td>
</tr>
<tr>
<td>Alcohol and drug use</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased cardiac output</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Paget’s disease of the bone</td>
</tr>
<tr>
<td>Rigidity of the aorta</td>
</tr>
</tbody>
</table>

**Neurohumoral Causes of HTN**

Many patients with essential HTN have an endocrine basis for elevated blood pressure (BP). Increasing circulating hormone levels, changes in responsiveness of target tissues to these hormones and abnormalities in vascular tone can all contribute. It is unclear whether endocrine abnormalities are primary or secondary. Besides a major genetic component, there is a change in response of target tissue to specific hormones with associated adaptive responses contributing to hypertensive processes.
Sympathetic Nervous System Hyperactivity

Increased catecholamines, either alone or through Renin release, increase BP through arterial and venous vasoconstriction, increased cardiac output and alteration of normal renal pressure-volume relationship.\(^6,7\) Vagal inhibitory responses to baroreceptors increase BP by preventing nocturnal fall in heart rate (HR) and BP.\(^8\)

Renin Angiotensin System

The juxtaglomerular apparatus of kidney has specialized cells that secrete renin. Renin release is controlled by changes in renal perfusion pressure potassium (K), angiotensin II and adrenergic nervous system. Angiotensinogen converts renin to angiotensin I which is activated to angiotensin II by ACE inhibitors. Angiotensin II is a potent vasoconstrictor and stimulates aldosterone release. The Renal-Angiotensin-Aldosterone system is linked by a negative feedback loop designed primarily to regulate sodium homeostasis and secondarily to modify arterial pressure.\(^9\) Low Na intake stimulates Angiotensin II which causes renal vasoconstriction and increased Aldosterone release and Na retention (Fig. 17.1).

Fig. 17.1: Factors involved in the control of blood pressure (From: Zipes: Braunwalds Heart Disease; Textbook of Cardiovascular Medicine. 7th ed, 2005)

Although most patients with essential HTN would be expected to have low plasma rennin activity, surveys show only 30% of hypertensives to have low PRA, 50% have normal PRA and 20% high PRA.\(^10\) Classification of HTN according to PRA has fallen out of favor due to a lack of expected response by anti-HTN therapy selected based on this classification.
Hyperinsulinemia/Insulin Resistance

The relationship between hyperinsulinemia/IR/HTN with or without obesity has been seen in many ethnic groups including Asians.

In normal humans, insulin stimulates sympathetic nervous system with increased BP but also causes vasodilatation with decreased BP. Insulin also causes vascular hypertrophy, increased renal Na and structural changes in myocardium. These pressor effects of insulin are blunted in IR due to increased nitric oxide (NO) secretion, leading to HTN. In addition IR is usually associated with syndrome of dyslipidemia /diabetes/ HTN all of which lead to premature CAD.

Endothelial Cell Dysfunction

Reduced vasodilatory response to various stimuli of NO release appear independent of etiology of HTN and degree of vascular structural alteration. This promotes abnormal vascular remodeling and greater vascular damage. The endothelial cells are a source of multiple relaxing and contracting substances which have a local paracrine influence on underlying smooth muscle cells.

SECONDARY CAUSES OF HTN

Renovascular HTN

It is one of the most common secondary causes of HTN being present in 3-5% of total hypertensive population. Renovascular HTN is defined as HTN secondary to unilateral (1%) or bilateral ischemia (2-4%). Although 60% of patients have renovascular disease only a minority develop HTN as greater than 70% of renal artery has to be occluded to develop HTN. Renal vascular disease is due to atherosclerosis (65-75%) or fibromuscular dysplasia (25-30%). RVD secondary to atherosclerosis is more common over age 50 and in men, whereas fibromuscular dysplasia is more common in women and age less than 50.

Inciting event is decreased renal perfusion pressure in affected kidney with stimulation of rennin release, increased Angiotensin II and Aldosterone. This leads to HTN with sodium retention and hypokalemia. It is differentiated from primary aldosteronism by increased plasma renin levels. Although many do not have increased PRA they show decreased BP with angiotensin antagonist (sarlasin) or decreased renal blood flow on renogram in response to Angiotensin Converting Enzyme Inhibitors.

Renal artery stenosis should be considered in individuals with:
- Accelerated HTN
- HTN age < 35 or > 50
- Refractory HTN
- HTN with renal insufficiency
- Abdominal bruit.
Endocrine Hypertension

Treatment includes angioplasty or ACE inhibitors. ACE inhibitors should be used with caution as can cause renal insufficiency in individuals with bilateral renal deficiency.

Other rare causes of renovascular HTN are renin producing tumors (from kidney, ovary and pancreas) or bilateral renal parenchymal disease secondary to diabetes, autoimmune diseases.20, 21

Adrenal Causes of HTN

HTN can be caused by increased secretion of any of the adrenal hormones, i.e. glucocorticoids (GC), mineralocorticoids (MC) and catecholamines.

The zona fasciculata of the adrenal cortex secretes GC in high amounts (cortisol-10-20 µg/day) under control of ACTH. MC are secreted from zona glomerulosa in low amounts (aldosterone 100-150 µg/dl) under control of Angiotensin II. Rarely increased deoxycorticosterone (DOC) is associated with congenital adrenal hyperplasia (CAH). Together these contributes to less than 1% of all causes of HTN, though increased mineralocorticoid related HTN is being more apparent.

Cushing’s Syndrome

Seventy to eighty percent of patients with Cushing’s syndrome have HTN, with greater than 50% of patients having DBP >100 mm of Hg.5, 22 HTN occurs in 17-70% of patients treated with exogenous glucocorticoids.4 The incidence of HTN in patients with Cushing’s syndrome is highest in patients with ectopic ACTH producing tumors and carcinomas.23 Longer the HTN is present, less likely it can disappear when the underlying cause is relieved. Metabolic and vascular damage persist years after normalization of cortisol.22

HTN in Cushing’s is produced via 2 mechanisms:

a. Activation of renin and therefore angiotensinogen and angiotensin II.

b. Retention of sodium by overwhelming the GC inactivating mechanism of kidney, i.e. 11-hydroxysteroid dehydrogenase activity.24, 25

In endogenous Cushing’s syndrome, MC production is usually normal. In Cushing’s disease due to pituitary microadenoma, renin and aldosterone levels are normal and DOC levels are normal or increased modestly.5, 23 In ectopic ACTH syndrome and adrenal carcinoma increased MC activity causing HTN and hypokalemia are the rule as a result of increased DOC and MC effects of high levels of cortisol. In these situations, PRA is generally suppressed.23

Elevation of BP by exogenous GC (which has minimal MC activity) is via these following mechanisms:

• Increased cardiac output.26

• Activating renin-angiotensin systems by increased hepatic angiotensinogen.23

• Block release of arachidonic acid from phospholipids causing reduced synthesis of vasodilatory prostaglandins.

• Enhanced pressor sensitivity to endogenous vasoconstrictors

• Sodium influx into vascular smooth muscle cells.
Patients with suspected Cushing’s syndrome, i.e. truncal obesity, moonfacades, thin skin, muscle weakness, DM, HTN and osteoporosis should be screened. A 1mg overnight Dexamethasone Suppression Test (DST) has a sensitivity of 54% with a post DST cortisol of 5 µg. The sensitivity can be improved to 95% with post DST Cortisol value of less than 2 µg. A 24 hours urine free cortisol (UFC) (80-120 µg) – sensitivity of 70%. Both the low dose DST and 24 hr UFC can be falsely positive in “pseudo Cushing’s syndrome” due to alcoholism, endogenous depression and eating disorders. A midnight salivary cortisol value of > 4.3 nmol/L has a sensitivity of 95%. Specificity is low, but two midnight cortisols that are twice normal, i.e. > 8.6 µg, is considered to have the most reasonable sensitivity and specificity to be recommended as the initial screening test for Cushing’s (Fig. 17.2). Dexamethasone CRH test is very expensive and labor intensive. Hence, it is reserved for mild Cushing’s or patients with equivocal results. It is positive in 50% of anorexics.22, 27

If screening tests are suggestive, Cushing’s is confirmed by doing the two day low dose DST (i.e. 0.5 mg every 6 hours for 48 hours) followed by CRH, and daily measurement of UFC. A lack of suppression confirms Cushing’s. Localization of tumor is by high dose DST (i.e. 2 mg dexamethasone every 6 hours for 48 hours) with daily Plasma Cortisol and 24 hours UFC. In pituitary Cushing’s there will be a >40% suppression of UFC with increased plasma ACTH. In ectopic Cushing’s, UFC remains increased with increased Plasma ACTH. Then, MRI of pituitary and Inferior Petrosal Sinus Sampling (IPSS) with CRH can localize a pituitary lesion. CT adrenals will localize local adrenal pathology.

Surgical removal of the tumor is generally curative without a need for lifelong GC replacement, and permanent relief of HTN. One-third of patients however have residual HTN and thus could reflect underlying essential HTN.28
Primary Mineralocorticoid Hypertension

Primary aldosteronism is the most frequent type of HTN caused by the adrenal gland. It is caused by increased and inappropriate production of aldosterone by the adrenal zona glomerulosa leading to mineralocorticoid excess state. This is associated with the suppression of PRA, increased BP and hypokalemia. Causes of HTN with hypokalemia are listed in Table 17.2. Primary aldosteronism is the cause of HTN in 5-13% of all unselected cases of HTN.29,30

Clinical symptoms are from potassium depletion. Weakness, periodic paralysis, cramps, tetany and paresthesias are common. Despite increased aldosterone they rarely have edema. They may have glucose intolerance. Resetting of osmostat can cause slightly increased serum sodium levels.

Degree of HTN is variable and patients can be refractory to conventional antihypertensives. LVH is disproportionate to degree of HTN. Structural damage to kidney, cerebral circulation and retinal vessels occur. Fifty percent have proteinuria and CRF in 15%.

Etiology for Primary hyperaldosteronism with their frequencies include:

- Aldosterone producing adenoma (APA), including renin responsive adenoma – 65%
- Idiopathic hyperaldosteronism (IH), including bilateral adrenal hyperplasia – 30-40%
- GC remediable aldosteronism – 1-3% (discussed later).
Solitary adenomas are usually less than 2 cm in size. They are benign with a well defined capsule and cells resemble zona fasciculata cells. Bilateral adrenal hyperplasia shows hyperplasia of zona glomerulosa, and aldosterone excess is milder than APA. Enhanced aldosterone response to Angiotensin II is seen. Adrenocortical cancers are rare and usually greater than 6 cm.

Pathophysiology

The renin angiotensin (RAS) system is suppressed. Aldosterone production is autonomous and does not respond to maneuvers that activate (upright) or suppress (salt loading/the RA system). A renin responsive form of adenoma has been reported. IHA is usually responsive to stimuli that activate RA system. Adrenal carcinomas are resistant.

Screening

Serum K can be low or normal and therefore is not a good screening test. PRA is suppressed in almost all patients.(<1 ng/ml/m ) and does not increase appropriately (> 2 ng/ml/hr) with sodium restriction or furosamide administration followed by 90-120 min of upright posture. Normal or high PRA rules out primary aldosteronism.

Increased plasma aldosterone in setting of low PRA makes diagnosis of primary aldosteronism more likely. PA/PRA ratio > 30 is suggestive and PA/PRA >50 is diagnostic of primary aldosteronism (PRA expressed as ng/ml/hr and PA as ng/ml). ACE inhibitors, β blockers and spironolactone should be withdrawn 2-4 weeks (spironolactone - 6-8 weeks) prior to test. Hypokalemia should be corrected as it decreases aldosterone. Blood samples should be obtained after 2 hours of upright posture as it has better diagnostic accuracy.

Captopril suppression test - 50 mg of Captopril is given and blood drawn before and 90 minutes after. In primary aldosteronism, aldosterone levels remain elevated due to autonomous aldosterone production and suppressed PRA. Normal response is >20% reduction of aldosterone to < 410 pmol/L (<15 ng/dl). Sensitivity is 90-100%, specificity is 50-80%.

Three day sodium load followed by 24 hours urine aldosterone reliably discriminates between primary aldosteronism and essential HTN with specificity 93% and sensitivity 96%. The urine aldosterone should be > 28 - 39 nmol/day (10-14 µg/d) in presence of urine Na >250 nmol/d. IV Normal Saline at 500 ml/hr for 4-6 hours with post saline plasma aldosterone > 250 pmol/L (>10 ng/dl) confirms autonomous aldosterone production.

With upright posture, in normal patient and those with essential HTN, plasma aldosterone increases by at least 50% compared to supine position. Accuracy of test is increased by simultaneous measurement of supine and upright cortisol. In primary aldosteronism, a significant decrease in aldosterone with cortisol (anomalous postural response), whereas in IPA there is increase in renin and aldosterone with upright posture. Positive predictive value to differentiate APA versus
Endocrine Hypertension

IPA is - 90%. 18 OH corticosterone levels are > 2800 nmol/ml (100 ng/dl) in APA, lower than IHA. 18 oxycortisol and 18 OH cortisol in 24 hours urine collections are modestly increased in APA, normal in IPA and 10 fold increased in GRA (Fig. 17.3).

After a biochemical diagnosis, spiral CT Abdomen can help differentiate adenoma versus IHA. If CT is not conclusive, NP 59 scan can help localize adenoma’s. Adrenal venous sampling is reserved for cases where imaging and biochemical studies are inconclusive. In APA, ratio of ipsilateral to contralateral aldosterone is >10:1. This procedure can be unsuccessful in 25% of cases.

Therapy

Surgery is the treatment of choice for patients with APA, APRA and primary unilateral adrenal hyperplasia. Cure rates (defined as BP of 140/90 with medication, 6-12 months post surgery) vary between 35-50%. BP and potassium should be normalized preoperatively.

In IHA, spironolactone is treatment of choice. It is used in dose of 150-500/day. It blocks testosterone synthesis in men, resulting in erectile dysfunction, decreased libido and gynecomastia. In women it causes menstrual irregularities. Amiloride is an alternative used at 5-15 mg twice daily dose. Long acting nifedipine (30-90 mg/day) has been used as it inhibits aldosterone biosynthesis in vitro. It may be used as second line.
Genetic Basis for Mineralocorticoid Excess State

Glucocorticoid remediable aldosteronism (GRA) is the commonest heritable form of hyperaldosteronism. Some forms of congenital adrenal hyperplasia (CAH) have a mineralocorticoid component. The steroids responsible for mineralocorticoid excess states include DOC and cortisol. Aldosterone levels are low from suppression of renin-angiotensin systems. Other genetic causes include mutation of enzymes or ion channels mediating activation of aldosterone.

Hypermineralocorticoid Cortisolism with Decreased Plasma Renin

Congenital Adrenal Hyperplasia

CAH results from deficiency in cortisol biosynthesis. Deficiency in both 11β hydroxylase (CYP 11B) and 17α hydroxylase (CYP17) are associated with hypertension and hypokalemia. Increased DOC, which is a potent MC causes retention of sodium and low PRA and aldosterone.

17α hydroxylase deficiency is characterized by HTN, hypokalemia and hypogonadism. Activation of 17 OH progesterone is required for gonadal synthesis of testosterone and estrogen. Its deficiency results in sexual immaturity in both sexes, high gonadotropin levels and low urinary 17-ketosteroids. Females have primary amenorrhea and lack of secondary sexual characters. Males have ambiguous genitalia or female phenotype. 17β hydroxyprogesterone are low and corticosterone and DOC levels are increased. Mutations of CYP17 gene causes 17α hydroxylase deficiency.

11 beta hydroxylase deficiency, there is accumulation of DOC due to impaired conversion to corticosterone. Virilization in females at young age results from shunting to androgen pathway. DOC, 11 deoxy cortisol and adrenal androgen are all increased. Prevalent in Middle Eastern Muslims and Jews. Genetic defect is in the gene that encodes CYP 11B.

Treatment with GC-dexamethasone or prednisone restores normal DOC. Overdosing causing Cushing’s and must be avoided.

Glucocorticoid Remediable Aldosteronism

Inherited as autosomal dominant and characterized by severe refractory HTN, unresponsive to anti HTN treatment. Many individuals are not hypokalemic. Aldosterone production is under control of corticotrophin. Therefore, this condition can be controlled by GC treatment.

GRA is caused by gene duplication from unequal crossing over between 11 beta hydroxylase (CYP 11B) and aldosterone synthetase CYP18 gene. There is ectopic expression of aldosterone synthetase in zona fasiculata, Mineralocorticoid regulation is by corticotrophin instead of angiotensin II. Hence, there is overproduction of Aldosterone, 18 oxycortisol versus 18 OH cortisol.

Screening should be done in individuals with early onset HTN, depressed plasma renin, early hemorrhage or stroke in family or relatives.
Endocrine Hypertension

Treatment is with smallest effective dose of steroids – Hydrocortisone acetate -10-12 mg/m²/day with avoidance of linear growth retardation and maintenance of age specific BP. Alternatives are MC antagonists-Amiloride and spironolactone as monotherapies.

**Syndrome of Apparent Mineralocorticoid Excess—Low PRA**

It is a rare syndrome observed mainly in children. These children present with failure to thrive, short stature, thirst, polyuria, polydypsia secondary to nephrogenic DI induced by hypokalemia. They have HTN, low PRA levels, decreased K, normal plasma cortisol and low plasma aldosterone levels.

Primary defect is impaired activity of 11 betahydroxysteroid dehydrogenase (11β OHSD) with resultant accumulation of cortisol in the kidney. Therefore, cortisol binds to MC receptors in distal tubule, which are usually sight of aldosterone binding. The decreased 11beta OHSD deficiency could also be due to enzyme inhibition by glycyrrhizic acid.

Treatment is difficult and uses high potency GC to suppress endogenous cortisol production. Spironolactone may be used but has anti-androgen and progestrogenic properties precluding long-term use particularly in children.

**Spironolactone Unresponsive Group—Liddle’s Syndrome**

It is inherited as an autosomal dominant condition with HTN, low PRA, low aldosterone and decreased potassium. Spironolactone is not effective, but Amiloride/Triamterene are effective- by blocking sodium reabsorption and potassium secretion and excretion by mineralocorticoid receptor mechanism.

**Licorice Ingestion**

Patients who consume more than 1gm of licorice/day develop a mineralocorticoid excess HTN. The glycyrrhizic acid inhibits 11betahydroxysteroid dehydrogenase activity and results in cortisol exposure to renal mineralocorticoid receptors with resultant HTN, decreased potassium, decreased PRA, decreased plasma and urinary aldosterone. After withdrawal of licorice, in 2 weeks the licorice metabolites are cleared but it takes the renin-angiotensin-aldosterone axis months to normalize.

**Primary or Secondary Glucocorticoid Resistance States**

GCR syndrome occurs as primary genetic deficiency or is induced by treatment with GC antagonists. The defect causes increased production of ACTH with resultant increase in cortisol, DOC and androgens. Women present with acne, hirsutism and menstrual irregularities, HTN, hypokalemia, decreased PRA, decreased aldosterone.

Table 17.3 summarizes biochemical features of HTN syndrome involving MC and GC excess.
Pheochromocytomas are catecholamine producing tumors of chromaffin cells that typically cause HTN. Although thought to be a rare cause of HTN, 1 in 1000 hypertensives, in an autopsy series, about half were diagnosed at postpartum, suggesting that these tumors are not frequently recognized. Diagnosis of pheochromocytomas is important for the following reasons:

1. They are curable causes of HTN by surgical removal of tumors.
2. If untreated, patients can die of lethal HTN paroxysm.
3. 5-10% of pheochromocytomas are malignant, but early detection and surgical removal can prevent metastatic spread.
4. Presence of pheochromocytoma may be a clue to endocrine or non-endocrine familial disorder.

Ninety percent of tumors arise from chromaffin cells of adrenal medulla and are referred to as pheochromocytomas and 10% of those arising from paraganglia are termed extra-adrenal pheochromocytomas or paragangliomas. Paragangliomas can arise from sympathetic ganglia anywhere from neck to pelvis and tend to be more malignant than pheochromocytomas.

**Pathophysiology of Pheochromocytomas**

The autonomic nervous system consists of parasympathetic nervous system (PNS) and sympathetic adrenal system. Neurotransmitter for PNS is acetyl choline and sympathoadrenal systems are Norepinephrine (NE) at the sympathetic nerve terminals of PNS and CNS and epinephrine which is directly secreted from adrenal medulla into systemic circulation. Another catecholamine is dopamine secreted from both CNS and PNS. Sympathetic NS is under direct control of CNS.

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### Table 17.3: Biochemical features of hypertensive syndromes involving mineralocorticoid and glucocorticoid excess

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Blood Pressure</th>
<th>Serum Potassium</th>
<th>PRA</th>
<th>Aldosterone</th>
<th>Cortisol</th>
<th>DOC</th>
<th>ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary aldosteronism</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td></td>
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<tr>
<td>Cushing's</td>
<td>↑</td>
<td>N↑</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↑/N</td>
<td></td>
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<tr>
<td>Pituitary and adrenal</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Ectopic ACTH</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
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<tr>
<td>11β OH deficiency</td>
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<td>↓</td>
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<td>↑</td>
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<tr>
<td>17α OH deficiency</td>
<td>↑</td>
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<td></td>
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<tr>
<td>Apparent mineralocorticoid excess</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Licorice ingestion</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Cortisol resistance</td>
<td>↑</td>
<td>↓</td>
<td></td>
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<td>↑</td>
<td>↑</td>
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</tr>
</tbody>
</table>
Clinical Manifestation of Pheochromocytomas

Pheochromocytomas arising from adrenal medulla and mainly secrete epinephrine with features of systolic HTN, with increased cardiac output, tachycardia, sweating, flushing and anxiety. Norepinephrine secretion is predominantly by paraganglia and has features of both systolic and diastolic HTN due to peripheral vasoconstriction with less tachycardia, palpitation or anxiety.\(^{50,51}\)

Predominant manifestation of most pheochromocytomas are HTN, which is present in 90-100\% of patients. Half of patients have sustained HTN, a third have paroxysmal HTN and one-fifth have normal blood pressure.\(^{52}\) Patients frequently present with triad of headache, diaphoresis and palpitation. More than 90\% of patients have at least two symptoms. Headache may also be associated with pallor and nausea. Episode may occur daily or rarely. Infrequent symptoms may include tremor, angina, Raynaud’s, livedo reticularis or mass effects from tumor.

HTN is due to increased peripheral resistance. Cardiac output is normal and stroke volume is decreased due to intravascular volume depletion. Labile BP is due to episodic catecholamine release, impaired sympathetic reflexes and chronic volume depletion.\(^{53}\)

Orthostatic hypotension results from epinephrine release. Myocarditis, dilated or hypertrophic cardiomyopathy can also result from a pheochromocytoma. Chest pain and various EKG abnormalities including diagnosis of acute myocardial infarction have been documented.

Hereditary Pheochromocytoma

Ninety percent of pheochromocytomas are sporadic, 10\% occur in familial syndromes like MEN 2A and 2B, von Hippel, Lindau disease or neurofibromatosis. MEN 2 and VHL are inherited as autosomal dominant. MEN 2A (Sipple’s syndrome) is characterized by pheochromocytoma, medullary carcinoma of the thyroid, multiple mucosal neuromas and Marfanoid habitus. Mutations of RET proto-oncogene on chromosome 10q11.2 is responsible for MEN 2 syndrome.\(^{54}\)

VHL includes pheochromocytoma, cerebella and retinal hemangioblastomas, renal carcinoma, renal and pancreatic cyst. Gene for VHL is on chromosome 3p25-p26.\(^{55}\)

Pheochromocytomas are presented in 1\% of patients with von Recklinghausen’s syndrome. Inactivating mutation of NFI genes on chromosome 17 causes this disorder.

Hereditary pheochromocytomas are generally bilateral, intra-adrenal, and occur earlier to diagnosis of HTN, compared to sporadic pheochromocytomas. MEN 2 pheochromocytomas predominantly secrete metanephrine and present with episodic HTN compared to VHL tumors that predominantly secrete normetanephrine and present with sustained HTN.

Diagnosis

Several disorders mimic the symptoms of pheochromocytoma, i.e. catecholamine excess states like panic attack, hypoglycemia, drugs, accelerated HTN, etc. Many physiological and
pharmacological stimuli can precipitate a hypertensive crisis in patients with pheochromocytoma. β blockers can cause a paradoxical increase in BP.

Screening for pheochromocytoma should be considered in patients with labile or refractory HTN, episodic HTN, unexplained hypo-or hypertension during surgery, pregnancy or anesthesia, adrenal incidentalomas, familial history of pheochromocytoma and idiopathic cardiomyopathies.

Biochemical measurements of the magnitude of excessive catecholamine production by tumor confirms the diagnosis of pheochromocytoma. There is no consensus on the preferred screening test. Initial screening test is 24 hours urine for free catecholamines, total metanephrine and creatinine. Of all the metabolites, 24 hours urine metanephrine is the most sensitive and specific (sensitivity 97% specificity 96%). A urine catecholamine value that is 2-3 times above normal is diagnostic for pheochromocytoma. Urine VMA has lowest sensitivity at 65%.

Plasma free metanephrine tend to be more elevated than plasma catecholamine. It has a high sensitivity but large numbers of false positives. Plasma metanephrine is diagnostic for pheochromocytoma if it is 3-4 times increased and may be preferred in high risk patients with familial endocrine syndromes.

Labetalol, iodinated contrast, tricyclic antidepressants, prochlorperazine, reserpine, Clonidine, clofibrate should be stopped 2 weeks prior to any test. Dihydroperidine calcium channel blockers can be used for BP control.

Plasma chromogranin-A is elevated in 80% of patients with pheochromocytoma and may be increased in other neuroendocrine tumors. It is generally used for postoperative surveillance of patients after resection of catecholamine secreting tumors.

If initial biochemical screening tests are equivocal but index of suspicion for diagnosis of pheochromocytoma is high, the Clonidine suppression test or Glucagon stimulation test may be used. Normal response to Clonidine 0.3 mg suppression is a decrease in plasma catecholamine by 50% or less than 500 pg/ml (3 nmol/l) after 2 hours. Test has a high sensitivity but poor specificity. Normal response to 1 mg IV glucogon is threefold increase in plasma catecholamines or greater than 2000 pg/ml (12 nmol/l) after 2 minutes. Figure 17.4 outlines an algorithm for diagnosis and management of pheochromocytomas.

Localization

Once biochemical diagnosis of pheochromocytoma is made, MRI, CT abdomen, Octreotide or MIBG scans are used to localize pheochromocytomas. Ninety percent are intra-adrenal. MRI is more specific, but CT has greater sensitivity 93-100%. MRI is preferred for localization of paraganglioma’s. MIBG is used for localization of extra-adrenal pheochromocytomas and postoperative surveillance. Sensitivity of MIBG is 90% and specificity is 100%. Thyroid uptake should be blocked by iodide 3 days prior and 1 week after iodine labeled MIBG. Drugs interfering with catecholamine synthesis should be stopped 72 hours before MIBG. Octreotide scan is also used for identifying extra-adrenal pheochromocytomas and metastatic disease.

Fludrodroamine PET scan shows promise in immediate diagnosis of pheochromocytomas.
Fig. 17.4: Algorithm for diagnosis of pheochromocytoma. CT, computed tomography; MRI, magnetic resonance imaging. From Larsen: Williams Textbook of Endocrinology 10th ed., 2003

* In some institutions, plasma metanephrines are being used for the initial screening, especially in patients with hereditary syndromes. See text for details.

† Repeat 24-hour urine collection may be indicated during a hypertensive crises or a paroxysm in patient with episodic symptomatology.
Management
Surgery is the treatment of choice and usually curative but associated with high morbidity 40% and mortality 2-4%. Outcomes can be improved with preoperative alpha blocker treatment and volume expansion. Phenoxybenzamine is started at 10 mg per day and titrated to keep BP normal, up to a maximum dose of 80-100 mgm per day in divided doses. Phenoxybenzamine blocks catecholamine binding to receptors and therefore minimizes risk of hypertensive crisis. A noncompetitive alpha blocker is preferred as catecholamines can overcome a competitive blocker. Doxazosin has been used without serious side effects. Labetalol should not be used as it is a weak alpha blocker. Patients are typically treated for 10-14 days prior to surgery.

Surgery
Generally, a transabdominal approach is used for bilateral and for familial pheochromocytomas, flank approach for unilateral pheochromocytomas and laparoscopic adrenalectomy for pheochromocytomas less than 6 cm.

Intraoperative hypotension is treated with volume expansion and IV pressors. Intraoperative hemodynamic monitoring with combination fast acting IV vasodilators and beta blockers (sodium nitroprusside and esmolol) and IV vasoconstrictors (norepinephrine and epinephrine) help improve surgical outcomes.

Patients should be monitored postoperatively indefinitely with yearly biochemical test and chromogranin A- as 20% have essential HTN, or can have recurrence of pheochromocytomas versus metastatic disease.

Malignant Pheochromocytomas
This occurs in about 10% and 5-year survival rate is 23-44%. Treatment of choice is surgery or debulking. Although response rate is suboptimal, high specific activity $^{131}$I labeled MIBG in combination with chemotherapy may be used. External beam radiation is used as palliation of bone metastasis. Tumor embolization is also being tried for non-surgical tumors.

OTHER CAUSES OF ENDOCRINE HYPERTENSION
Thyroid Disease
Hypothyroidism may cause diastolic HTN in 1-2% of the general population. This increase in DBP can be due to increase extracellular volume and increase in systolic vascular resistance. Hypothyroidism causes a sympathetic and adrenal activation leading to HTN, which irreversible with thyroid hormone treatment.

Hyperthyroidism causes increased systolic BP with tachycardia, increased cardiac output, increased stroke volume and decreased peripheral vascular resistance.
Acromegaly

One-third of the patients with acromegaly have HTN. It is a negative prognostic factor for mortality in acromegalics.\textsuperscript{67, 68} Growth hormone (GH) is thought to have an antinatriuretic effect with retention of sodium and ECF volume expansion. The prevalence of primary aldosteronism seems to be increased in acromegaly, though in most patients plasma renin is increased but aldosterone is not. Acromegalics with HTN seem to have higher GH levels than those who don’t have HTN.

Treatment of HTN includes reduction of GH levels and diuretics as first line antihypertensives.

Hyperparathyroidism

HTN is present in 30-40\% of patients with hyperparathyroidism and has no correlation to calcium and parathyroid hormone (PTH) levels. HTN may or may not resolve after parathyroidectomy and may be due to nephrocalcinosis.\textsuperscript{5, 69,70} A relationship between renin–angiotensin–aldosterone system and the parathyroid calcium system exists. In hyperparathyroidism due to MEN syndrome HTN can be due to a pheochromocytoma or primary aldosteronism.

Exogenous Causes of Secondary HTN

1. Mineralocorticoids – Fludrocortisone and licorice
2. Growth hormone
3. Gonadal steroids –

<table>
<thead>
<tr>
<th>Table 17.4: Features of “Inappropriate” hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset before 20 or after 50 years of age</td>
</tr>
<tr>
<td>Level of blood pressure &gt;180/110 mm Hg</td>
</tr>
<tr>
<td>Organ damage</td>
</tr>
<tr>
<td>Funduscopic findings of grade 2 or higher</td>
</tr>
<tr>
<td>Serum creatinine &gt;1.5 mg/100 ml</td>
</tr>
<tr>
<td>Cardiomegaly or left ventricular hypertrophy</td>
</tr>
<tr>
<td>Features indicative of secondary causes</td>
</tr>
<tr>
<td>Unprovoked hypokalemia</td>
</tr>
<tr>
<td>Abdominal bruit</td>
</tr>
<tr>
<td>Variable pressures with tachycardia, sweating, tremor</td>
</tr>
<tr>
<td>Family history of renal disease</td>
</tr>
<tr>
<td>Poor response to therapy that is usually effective</td>
</tr>
</tbody>
</table>
Table 17.5: Overall guide to work-up for identifiable causes of hypertension

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal disease</td>
<td>Urinalysis, serum creatinine, renal sonography</td>
</tr>
<tr>
<td></td>
<td>Isotopic renogram, renal biopsy</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>Captopril-enhanced isotopic renogram, duplex sonography</td>
</tr>
<tr>
<td></td>
<td>Magnetic resonance or CT angiogram, aortogram</td>
</tr>
<tr>
<td>Coarctation</td>
<td>Blood pressure in legs</td>
</tr>
<tr>
<td></td>
<td>Echocardiogram, aortogram</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>Plasma and urinary potassium, plasma renin and aldosterone</td>
</tr>
<tr>
<td></td>
<td>Plasma or urinary aldosterone after saline load, adrenal CT and venous sampling</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>Morning plasma cortisol after 1 mg dexamethasone at bedtime</td>
</tr>
<tr>
<td></td>
<td>Urinary cortisol after variable doses of dexamethasone, adrenal CT, and scintiscans</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Plasma metanephrine</td>
</tr>
<tr>
<td></td>
<td>Urinary catechols; plasma catechols (basal and after 0.3 mg clonidine.</td>
</tr>
<tr>
<td></td>
<td>Spot urine for metanephrine</td>
</tr>
<tr>
<td></td>
<td>Adrenal CT and scintiscans</td>
</tr>
</tbody>
</table>

CT = computed tomography.

i. Oral contraceptives – high dose of estrogen and progesterone increase BP, not the current low dose OCP or HRT.71
ii. Androgens in pharmacological doses cause volume expansion and arterial HTN.
4. Sympathomimetic amines (amphetamine, cocaine) due to release of catecholamines.
5. Cyclosporin due to renal vasospasm and volume expansion.
   Oral contraceptives increase BP as estrogen activates renin and Angiotensin II and aldosterone.66 Only genetically predisposed women or those with obesity, renal disease, increased age develop HTN. If HTN develops on OCP, the OCP should be stopped. If OCP are required, they may be given with ACE inhibitors.

**SUMMARY**

Secondary HTN is more frequent than previously thought and usually reversible with appropriate treatment. **Table 17.4** lists symptoms and signs that should clue a physician towards work-up for causes of secondary HTN. **Table 17.5** briefly outlines management strategies for various causes of secondary HTN.

**REFERENCES**


INTRODUCTION
Rickets/osteomalacia is an umbrella term that covers a number of disorders related to the weakening of the bone or impaired mineralization. Bone formation requires deposition of osteoid by osteoblasts, mineralization and remodeling by osteoclasts. In rickets/osteomalacia, there is defective mineralization caused by an imbalance in vitamin D3, calcium and phosphorus. This imbalance may be caused by a lack of one of these three essential elements.
Rickets occurs in children at the growth plates. Osteomalacia is a similar disorder occurring in adults.

PATHOPHYSIOLOGY
The bone tissue consists of cells and extracellular matrix. There are three types of cells in mature bone tissue: osteoblasts, osteocytes, and osteoclasts. Osteoblasts and osteocytes are involved in the deposition of bone matrix. These cells produce collagen type I, which is then calcified. These cells also produce non-collagenous proteins, as well as regulatory factors. Osteoblasts are located at the surfaces of bone tissue, while osteoclasts are located within the calcified matrix of bones. The extracellular matrix can be subdivided into organic matrix composed of collagen fibers and ground substance, and inorganic matrix composed mainly of a complex of calcium and phosphate in the form of hydroxyapatite [Ca-10-(PO-4)-6-(OH)-2]. Osteoblasts are the cells that build bone by secreting bone matrix around themselves. Once surrounded by the matrix, they become osteocytes – the mature bone cells that occupy lacunae in the solid matrix and have cytoplasmic extensions that extend through canaliculi to reach neighboring lacunae containing osteocytes. Osteocytes communicate with each other via gap junctions. They also maintain bone matrix thus playing an important role in homeostasis. Osteoclasts are bone resorption cells. They originate from pluripotent cells within the bone marrow. These pluripotent cells also give rise to macrophage and monocytes. Osteoblasts control the activity of Osteoclasts via RANKL and macrophage colony stimulating factor.
(m-CSF) which are produced by osteoblasts and bind to RANK and m-CSF receptor on osteoclasts.

**Osteoclasts** are involved in the resorption of bone tissue. They are multinucleated giant cells, with multiple vacuoles and lysosomes, and a highly acidophilic cytoplasm. The surface of the osteoclast in contact with the bone being resorbed forms a ruffled border due to extensive infolding. The ruffled border is indicative of an “activated” osteoclast; osteoclasts not currently involved in bone resorption do not display this border. This border increases the surface area of the portion of the osteoclasts plasma membrane in contact with the adjacent bone surface. The osteoclast binds to a portion of bone matrix and induces a drop in pH through the release of hydrogen ions, produced by carbonic anhydrase within the cell. The increased acidity causes the hydroxyapatite crystals of the bone matrix to dissolve. The organic portion of the matrix is subsequently dissolved by proteolysis. This process forms pits on the surface of bones called Howship’s lacunae. Osteogenic cells are the precursors of osteoblasts. They can be found in the inner layers of periosteum and endosteum. In adult bone, they differentiate into osteoblasts under appropriate stimuli, such as mechanical stress, when the need for remodeling or repair arises.

The **extracellular matrix** of bone tissue can be subdivided into organic and inorganic portions. The organic portion is composed of collagen fibers and ground substance. Fibers consist primarily of type I collagen. Ground substance is composed of proteoglycan, aggregates of keratan sulfate, chondroitin sulfate and hyaluronic acid.

The inorganic portion of the matrix is what gives bone its density, and accounts for approximately 65% of the extracellular matrix. It is composed primarily of a complex of calcium and phosphate in the form of hydroxyapatite. Calcium carbonate, citrate, fluoride, magnesium, and sodium are also present as impurities of hydroxyapatite.

If we look at the growing end of the bone, we have an osteoblastic end and an osteoclastic end. Osteoid seam laid down by osteocytes is mineralized continuously in an orderly fashion in the presence of adequate amounts of serum calcium, phosphorus and PTH.

**Calcium Homeostasis**

Most of body’s calcium (i.e. 99%) is in bone, the remaining 1% is extraskeletal, 0.8% being intracellular and 0.2% extracellular. The total extracellular calcium is around 1.3 gm, 50% of which is free or ionized portion and the remaining 50% is either complexed to organic anions or bound to protein. We measure the total calcium. The routine methods adapted by most laboratories measure total calcium which is around 9 to 11 mg/dl, so correction for serum albumin is necessary in order to get the free calcium value which is physiologically important.

Like calcium, major store of body’s phosphorus is again bone (i.e. 85%). Intracellular phosphorus accounts for 14% of total phosphorus. The CO₂ and glucose determines the transport of phosphorus across the cell.

Daily average intake of calcium is around 1 gm, of which 3/4th is excreted through the gut and remaining through the kidney. 150 mg of calcium is actively secreted into the intestines daily, while 350 mg is absorbed into the vascular space.
Phosphorus Homeostasis

Unlike calcium, phosphorus in blood compartment is in two forms, inorganic and organic. The inorganic form is either bound to lipids and protein or is free. The free portion is the one, which is measured by routine methods, which is the most active form.

Average Indian diet contains around 1400 mg of phosphorus daily, out of which 900 mg is excreted through kidney, major route of excretion unlike calcium. This is the reason for elevated plasma phosphorus in renal failure.

Vitamin D Homeostasis

Vitamin D is the prohormone that is activated into two forms:

a. Cholecalciferol (D3) produced endogenously in skin after UV B exposure ergosterol changes to dehydrocholesterol.

b. Ergocalciferol (D2) obtained exogenously from diet.

These activated forms of vitamin D (D2 and D3) are then hydroxylated in the liver and changed to 25 hydroxy vit D (25 HCC), which subsequently are hydroxylated in the kidney to 1,25 dihydroxy vitamin D (1,25-DHCC) via the enzyme 1-alpha-hydroxylase which is produced by the proximal tubule. 1, 25-DHCC, the active form of vit D3 acts on intestine, parathyroid glands as well as on bone to maintain adequate levels of calcium in the blood. In the process it also increases blood phosphorus levels by increasing absorption from intestine.

Parathyroid Hormone

84 amino acid protein produced by parathyroid glands. The functions of parathormone are:

1. Increases serum calcium
2. Increases renal calcium reabsorption
3. Increases skeletal turnover
4. Increases renal production of dihydroxy-vitamin D3.

Calcitonin

1. Produced by thyroid parafollicular C cells
2. Reduces serum calcium
3. Inhibits bone calcium resorption.

CLINICAL PRESENTATION

The presentation of rickets can vary from diffuse bone pains to fractures, progressively increasing skeletal abnormalities like genu valgum and varus, cubitus valgus and varus, widened wrists, rickety rosary, rachitic chest with Harrison sulcus (rib deformity at the site of diaphragmatic insertion), frontal bossing, dental anomalies, stunted growth in young children and muscle weakness. Craniotabes, hot cross bun appearance of the skull may be seen in infants, there may be delayed closure of fontanelles in children.
Osteomalacia may be asymptomatic. When present symptoms include bone pains and muscle weakness. Pain is dull aching and is worsened by activity. It is due to osteopenia or fractures. The most common sites are lower back and hips. Fractures are seen in ribs, vertebrae, long bones and may lead to skeletal deformities. Bone tenderness may be present on palpation.

Muscle weakness may be severe and may be associated with wasting. It generally involves proximal muscles and may lead to a characteristic waddling gait. Muscle weakness is due to hypophosphatemia or secondary hyperparathyroidism.

Rickets/osteomalacia may be broadly classified as hypocalcemic where teeth deformities, muscle pains and tetany are seen and hypophosphatemic where there are generally no enamel problems or tetany.

**DIAGNOSIS (FIG. 18.1)**

Lab evaluation of a child with rickets/osteomalacia includes serum levels of calcium, phosphorus, alkaline phosphatase and renal functions including serum electrolytes. Blood gases to rule out acidosis are needed.

Skeletal X-rays are essential not only to diagnose but to monitor the response to treatment. In rickets some of the X-ray findings of long bones include widened epiphysis, cupping and irregular fraying of metaphysis. Diffuse osteoporosis can be seen. The most common radiographic feature in osteomalacia is reduced bone density, coarsening of trabecular pattern and loosers’ zones or pseudofractures. Loosers’ zones are narrow lines of radiolucency which usually transect and lie either at right angles or obliquely to the cortex of the bone. They are typically bilateral and symmetric. The common sites include axillary margins of scapulae, lower ribs, superior and inferior pubic rami, neck of proximal femora and posterior margins of proximal ulnae. Multiple bilateral loosers’ zones are called Milkman’s syndrome. These fractures occur due to stress which is repaired by poorly mineralized osteoid. Some people believe that these fractures are caused by pressure due to pulsation of arteries which frequently lie closeby.

![Fig. 18.1: Approach to a case of rickets or osteomalacia](https://www.ketabpezeshki.com/66485457-66485438)
Other tests include serum PTH, urine calcium and ALP isozyme levels in special situations. Serum levels of 25(OH) D and 1,25 di (OH) D are done as needed. In hypocalcemic rickets/osteomalacia 25(OH) vitamin D low, PTH is raised-secondary hyperparathyroidism with amino aciduria, while in hypophosphatemic rickets/osteomalacia 25 (OH) D concentration is normal and there is no hyperparathyroidism.

**APPROACH TO RICKETS/OSTEOMALACIA (TABLE 18.1)**

Rickets/osteomalacia can be non-renal (nutritional, liver disease, malabsorption or drug induced) or renal. Nutritional rickets/osteomalacia responds to vitamin D-15000 ug ORAL OR 6 lakh IU IM and this can be used to distinguish between nutritional and non-nutritional (renal) rickets/osteomalacia. If no response occurs the dose may be repeated after 3-4 weeks. Those who respond are put on 400 u or 10 ug of vit D3 orally while those who fail to respond are worked for other (renal) causes of rickets/osteomalacia. Renal rickets may be azotemic, i.e. associated with renal failure or non-azotemic where serum creatinine and GFR are normal. Non-azotemic rickets may be associated with acidosis or without acidosis. The classic example of non-azotemic rickets with acidosis is renal tubular acidosis (RTA) which may be further classified as proximal or distal RTA. Without acidosis, there are various causes of non-azotemic rickets. They are Vit dependent rickets (types I and II), Vit D resistant rickets or hypophosphatemic rickets (see algorithm) (Fig. 18.2).

**Nutritional Rickets**

Vitamin D deficiency is the commonest cause of nutritional rickets is seen in infants breast-fed for prolonged periods without adequate supplementation and in children who lack adequate sun exposure. Breast milk contains 40-60 IU/L of vitamin D and is a poor source and does

<table>
<thead>
<tr>
<th></th>
<th>Distal RTA</th>
<th>Proximal RTA</th>
<th>Vit D Dependent Rickets/Osteomalacia</th>
<th>Hypophosphatemic Rickets/Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys : Girls</td>
<td>1.03:1</td>
<td>6.5:1</td>
<td>1:1.5</td>
<td>1:1.03</td>
</tr>
<tr>
<td>Age at onset (yr)*</td>
<td>3 (2-4) [1 mo-10 yr]</td>
<td>2 (0.7-3.3) [1 mo-10 yr]</td>
<td>1.9 (1.1-2.7) [18 days-9 yr]</td>
<td>2.7 (2.1-3.3) [1-10 yr]</td>
</tr>
<tr>
<td>Onset &lt;1 yr</td>
<td>33%</td>
<td>45%</td>
<td>50%</td>
<td>20%</td>
</tr>
<tr>
<td>Onset &gt;1 yr</td>
<td>66%</td>
<td>55%</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyuria</td>
<td>100%</td>
<td>80%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fractures</td>
<td>20%</td>
<td>–</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Enamel hypoplasia</td>
<td>10%</td>
<td>–</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Seizures</td>
<td>–</td>
<td>–</td>
<td>30%</td>
<td>–</td>
</tr>
<tr>
<td>Families affected</td>
<td>15%</td>
<td>12%</td>
<td>4%</td>
<td>11%</td>
</tr>
</tbody>
</table>
not satisfy the recommended allowance of 200 IU/l daily. If the mother is vitamin D replete the infant may be asymptomatic till the age of 3-4 months and then develops rickets while if the maternal stores of vitamin D are poor, rickets may manifest at birth.

Other causes of Vitamin D deficiency include poor exposure to sunlight and use of sunscreens. The vitamin D content of the diet is poor, especially more so in vegetarian diets. Also diets with a high phytate content (cereal based) interfere with absorption of Calcium from the gut.

The classic lab findings include low calcium, phosphorus and very low Vit D3 levels. Treatment includes Vit D3 supplements at 50-150 micrograms daily. A single dose of 15,000 micro grams of Vit D3 or IM dose of 6 lakh IU will also suffice. This should be followed by recommended daily allowance for Vit D. A demonstrable improvement usually occurs in 2-4 weeks.

Other causes of non-renal rickets/osteomalacia may be malabsorption syndromes, liver disease which impairs vitamin D metabolism and use of antiepileptic drugs.

**Anticonvulsant Induced Osteomalacia**

Osteomalacia occasionally occurs in patients who are receiving anticonvulsants especially phenytoin or phenobarbitone. It is more common with combination therapy. Whereas the incidence of bone disease is low, hypocalcemia, increased alkaline phosphatase and decreased intestinal calcium absorption are more frequent. The clinical spectrum varies from patients with hypocalcemia to those with bone pains and fractures. Osteomalacia or rickets occurs due to interference with conversion of Vitamin D to 25 dihydroxy D, also phenytoin and phenobarbitone impair efflux of calcium from bone, in addition phenytoin also decreases absorption of calcium from the gut. Treatment consists of administration of vitamin D.

**Renal Rickets**

*Renal Tubular Acidosis (Table 18.2)*

The commonest cause of non-azotemic rickets is RTA, which can be either distal (type I) or proximal (type II). The defect in type I is in the cortical collecting tubular cell (i.e. alpha intercalated cell). There is a hydrogen secretory defect either due to mutation in the H+ ATP-ase or H, K ATP-ase on the luminal membrane or in the Cl- HCO₃ exchanger on the
basolateral membrane with resultant acidosis. This syndrome is characterized by hypercalciuria, hypokalemia, increased tendency to renal stone formation and alkaline urine. This is diagnosed by acid load test. d-RTA is treated with supplementation of bicarbonate at a dose of 1-2 mEq/kg/day.

In proximal RTA (type II) there is a mutation in the Na/HCO₃ exchanger on the basolateral membrane, thereby causing bicarbonaturia. In the typical Fanconi syndrome there is, in addition glycosuria, amino aciduria, phosphaturia and uricosuria.

**Acid load test:** If there is severe acidosis (serum bicarbonate <18 mEq/l) if the distal tubule is normal the urine pH should be < 5.5 and the test is not required. Acid load test is done if the serum bicarbonate is more than 18 mEq/l. It detects the ability of the distal tubule to excrete acid. Base line ABG and urine pH are done 0.1 gm/kg of ammonium chloride is given orally after overnight fasting. Urine samples are collected hourly for four hours. Blood pH and bicarbonate are measured at the end of second hour to check whether acidosis has been induced. If urine shows pH of < 5.5 at any point in next 4-5 hours, it indicates that the distal tubule acid secretory capacity is normal. If urine pH fails to fall below 5.5 it denotes distal tubular acidosis.

The cornerstone of treatment of RTA is replacement of bicarbonate. The dose of bicarbonate is 1-2 mEq/kg/day in distal, whereas in proximal large amounts of bicarbonate, i.e. 10-15 mEq/kg/day is necessary to correct acidosis. Bicarbonate is given as tablets (sodamint-4 mEq/tab) or as powder (1g=13 mEq)or as Shohl’s solution (citric acid + sodium citrate + water), which gives 1 mEq/ml. Potassium supplements can be given as required.

**Hypophosphatemic Rickets/Osteomalacia**

**Hypophosphatemic Non-azotemic Rickets/Osteomalacia**

The filtered P is absorbed by the proximal tubule by Sodium phosphate cotransporters. NPT1 and NPT2 genes map respectively to human chromosomes 6p22 and 5q3. Parathormone is phosphaturic. Gene on X chromosome PHEX inhibits a phosphaturic factor, FGF 23 which decreases the number of NPT.

In hypophosphatemic variety of rickets the level of serum phosphorus is low. Normal range for blood phosphate levels.
Rickets and Osteomalacia

0-5 days of life: 4.8-8.2 mg/dl
6 days-4 years: 4.0-6.8 mg/dl
4-11 years: 3.7-5.6 mg/dl
12-15 years: 2.9-3.4 mg/dl

Causes of Phosphate Deficiency

I. Poor intake (urine P is low)
   • Neonatal
   • Aluminium phosphate ingestion

II. Decreased tubular absorption (urine P is high)
   • Primary renal tubular defects
     – Hereditary hypophosphatemic rickets/osteomalacia (HHR/O)
     – Autosomal dominant hypophosphatemic rickets (ADHR/O)
     – Sporadic acquired hypophosphatemic rickets
     – Fanconi’s syndrome
   • Secondary renal tubular defects
   • Primary hyperparathyroidism
   • Secondary hyperparathyroidism
   • Renal tubular acidosis
   • Tumor induced osteomalacia

Urine phosphorus excretion is normally around 11mg/kg/day but may vary with dietary Phosphorus. Hence, better methods to express urine P losses are Tubular resorption of P (TRP%) and tubular maximum for phosphate (Tmp). There is increased fractional excretion of phosphate (TRP) (normally it should be less than 15%) and a high Tmp (tubular maximum for phosphate) in hypophosphatemic rickets due to renal defect.

\[ \text{TRP} \% = \frac{\text{Up} \times \text{Pcr/Ucr} \times \text{Pp}}{1} \]
\[ \text{TMP/GFR} = \frac{\text{Pp} - \text{Up} \times \text{Pcr/Ucr}}{\text{TmPO4/GFR}} \]

Hypophosphatemic rickets/osteomalacia is a genetic disease inherited as either X-linked dominant or recessive or autosomal recessive, XLD being the commonest. The gene associated with XLH, which is located on chromosome Xp22.1, has been identified and is referred to as the PHEX (phosphate-regulating gene with homologies to endopeptidases on the X-chromosome) gene. Hypophosphatemic rickets/osteomalacia, also called vit D resistant non-azotemic rickets/osteomalacia is due to a mutation in a gene called PHEX, which causes
reduced activity of osteoblasts, thereby reducing the osteoid. There is primarily phosphate reabsorption defect in the proximal tubule leading to phosphaturia. In addition there is also a defect in the conversion of 25, HCC to 1, 25 DHCC. It is the commonest variety of non nutritional rickets/osteomalacia. It is characterized by rickets/osteomalacia, dental anomalies, short stature, bone pains, enthesisopathy and dental abscesses, cranial abnormalities, and spinal stenosis (in severe cases). The children present at early age (6 months -1 year) with short stature, waddling gait, coxa vera and genu valgum (lower limbs more affected). The condition is characterized by normal calcium, low phosphorus, and normal PTH. There is increased fractional excretion of phosphate (normally it should be less than 15%) and a high Tmp (tubular maximum for phosphate).

Four other primary phosphaturic conditions have been described:

i. Hypophosphatemic rickets/osteomalacia, autosomal dominant, (ADH)- much less severe than XLH. It is associated with deficiency of Fibroblast Growth Factor (FGF-23). The major renal Na/P cotransporter type IIa is a target for regulation by FGF-23. The FGF levels can be measured by ELISA assay.

ii. Hereditary hypophosphatemic rickets/osteomalacia with hypercalciuria (HHRH/HHOH) autosomal recessive, distinguished by high calcitriol levels not present in XLH or AD form and normocalcemia.

iii. Adult sporadic hypophosphatemic osteomalacia presents first in adolescence or adulthood, severe bone pain, vertebral fractures, myopathy, glycinuria in addition to phosphate leak.

iv. Oncogenous non-azotemic rickets/osteomalacia (OHR/OHO) with phosphaturia occurring due to tumors arising from mesenchyme which produces as yet unidentified substance that elicits phosphaturia and hypophophatemic malacia. Several mesenchymal tumors of bone or connective tissue (including those called nonossifying fibromas, fibroangioma, and giant cell tumors) secrete a phosphaturic substance (parathyroid like protein) that results in non-azotemic renal bone disease. Also seen in breast carcinoma, prostate cancer, lung cancer, multiple myeloma and chronic lymphatic leukemia. The age of onset has been late childhood, adolescence, or young adulthood. The clinical characteristics are similar to those associated with familial hypophosphatemia. Treatment is surgical removal of the tumor, with excellent result. OHR/OHO, also known as tumor-induced osteomalacia, is thus an acquired and rare form of renal P, wasting, with clinical and biochemical features of XLH and ADH. In contrast to XLH and ADH forms, these patients also exhibit muscle weakness, fatigue, and fractures. Recent studies on the molecular analysis of abundantly and differentially expressed genes in tumors led to the identification of phosphatonin candidates, including FGF-23, frizzled-related protein 4 (FRP-4) and mepe (matrix extracellular proteolytic enzymes).

Treatment

Optimal therapy consists of calcitriol 0.5-1.5 mcg/d PO plus a sodium/potassium phosphate mixture to provide 1-3 g PO of elemental phosphate (P) per day in divided doses. For this a
special solution called Joulie’s solution (Dibasic Sod phosphate 1.36 gm/l, phosphoric acid 58.8ml/l) is used. Usually prepared solution contains nearly 30 mg of phosphate in each ml of the solution.

Complete remission of the HHRH/HHOH phenotype is seen after therapy with phosphate alone. Whereas treatment with both phosphate and vitamin D is necessary to ameliorate the symptoms of XLH.

The addition of growth hormone therapy to this regimen is undergoing clinical trial to determine if it produces increased linear growth in these patients, most of whom exhibit short stature.

**Precautions**

Very minor changes in calcitriol dose may produce hypercalcemia and renal damage. The calcium-creatinine (mg/mg) ratio in urine must be monitored closely at first, and then every 3-6 months. It is important that the ratio remain less than 0.25, and ratios higher than 0.4 are dangerous. Too high a phosphate intake may produce secondary hyperparathyroidism.

**Vitamin D-dependent Rickets/Osteomalacia (Pseudo Vit D-deficiency)**

Vitamin D dependent rickets/osteomalacia can be either type I or II.

**Type I Vit D-dependent Rickets/Osteomalacia**

The defect is in the conversion of 25 hydroxy cholecalciferol to 1, 25-dihydroxy cholecalciferol due to defect in the 1-apha hydroxylase gene. The gene defect is located on chromosome 12 and mode of inheritance is autosomal recessive. Diagnosis is by finding low level of 1, 25 DHCC (N=20-75 pg/ml) with normal 25 HCC(20-70 ng/ml). Treatment is with physiological doses of Vit. D2 or D3.

**Receptor Defect or Vitamin D-dependent Rickets/Osteomalacia Type II**

Receptor defect or vitamin D-dependent rickets/osteomalacia type II results from an inherited lack of calcitriol receptor sites (end organ resistance to the actions of Vit D). It is inherited as autosomal recessive trait. Approximately half of patients with Type II rickets/osteomalacia also have alopecia, which sometimes is complete. Patients are hypocalcemic and usually normophosphatemic. Treatment is with high doses of 1, 25 DHCC. Several mutant forms of receptor defect rickets/osteomalacia exist, with a wide range of severity and response to calcitriol therapy, including some totally resistant to therapy. Some patients have benefited from intravenous calcium; a high oral calcium intake plus calcitriol has helped others.

**Azotemic Renal Rickets/Osteomalacia or Renal Osteodystrophy**

Bone metabolism is altered in chronic kidney disease once GFR falls below 60 ml/min/1.73 m². The major pathogenetic mechanisms are:

1. Loss of feedback inhibition of PTH by 1,25 dihydroxy D
2. Renal retention of phosphorus
3. Hypocalcemia
4. Secondary hyperparathyroidism
5. Acidosis

The child manifests with short stature, rickets/osteomalacia, bone pains and fractures. The imaging studies show supperiosteal erosions in phalanges, rugger jersey spine, looser zones, fractures, osteopenia and rickets/osteomalacia. Blood biochemistry reveals increased serum creatinine, low calcium, high phosphate, increased alkaline phosphate with an elevated intact parathormone level.

Treatment includes correction of hypocalcemia, treating hyperphosphatemia with phosphate binders—calcium containing—calcium carbonate, acetate, gluconate, etc. and non-calcium containing—aluminium, lanthanum and sevelamer. Management of secondary hyperparathyroidism entails correction of hyperphosphatemia as detailed above, administration of vitamin D (1,25 form or non-hypercalcemic analogues) and parathyroidectomy in resistant cases.

Hypophosphatasia
It is characterized by abnormally low level of alkaline phosphatase, rickets like changes and increased serum and urine levels of pyrophosphate and phosphoethanolamine. Transmission is autosomal recessive.

Three forms are described—Infantile—severe form with hypercalcemia, hypercalciuria and nephrocalcinosis; less than 50% infants survive. The childhood variety is characterized by premature loss of deciduous teeth, increased susceptibility to infections and craniosynostosis. Adult form shows osteomalacia. There is coarse trabeculation of bones on X-ray and looser zones in adults. Treatment is with vitamin D and phosphorus supplementation with poor response in most cases.

Hypoparathyroidism
Rickets or osteomalacia is rarely seen in hypoparathyroidism. As parathormone is the major regulator of vitamin D synthesis, its deficiency leads to low levels of 1,25 dihydoxy vitamin D and hypocalcemia. Treatment is with vitamin D, in some cases, 1,25 form may be needed.

Pseudohypoparathyroidism
In this condition, resistance to parathormone leads to hypocalcemia, hyperphosphatemia, low 1,25 form of vitamin D and consequently rickets and osteomalacia. As in hypoparathyroidism, some patients can be treated with 1,25 vitamin D.

CONCLUSION
Rickets/osteomalacia is a common problem encountered by clinicians. The causes are multiple, a proper diagnostic approach is necessary and appropriate therapy is rewarding.
SUGGESTED READING

INTRODUCTION

The body has four parathyroid glands. They are small, pea-sized glands, located in the neck just behind the butterfly-shaped thyroid gland. Two parathyroid glands lie behind each ‘wing’ of the thyroid gland. The parathyroid glands release a hormone called parathyroid hormone (PTH). PTH is cleaved to an 84–amino acid protein in the parathyroid gland, where it is stored with fragments in secretory granules for release. Once released, the circulating 84–amino acid protein has a half-life of 2 to 4 minutes. It then is cleaved into N-terminal, C-terminal, and mid-region fragments of PTH, which are metabolized in the liver and kidney. PTH secretion occurs in response to hypocalcemia, hyperphosphatemia, and calcitriol deficiency and is inhibited by severe hypomagnesemia.

This hormone regulates levels of calcium and phosphorus in the body by increasing bone mineral dissolution releasing calcium and phosphorus. It also increases renal reabsorption of calcium and excretion of phosphorus and enhances reabsorption of calcium and phosphorus from gastrointestinal tract indirectly through synthesis of 1, 25 –dihydroxyvitamin D.

Hyperparathyroidism characterized by increased production of PTH is due to hyperactivity of parathyroid glands. Hyperparathyroidism was first described and treated in the 1930s by Fuller Albright of Massachusetts General Hospital.

It can be of three types:
1. Primary
2. Secondary
3. Tertiary

Primary hyperparathyroidism can be sporadic and familial. It is due to autonomously functioning parathyroid adenoma or less commonly due to hyperplasia. Parathyroid carcinoma accounts for an insignificant minority (<0.5% of patients with hyperparathyroidism).

Secondary hyperparathyroidism is caused by diffuse hyperplasia of the parathyroid glands in response to ongoing stimuli such as hypocalcemia or hyperphosphatemia. Secondary hyperparathyroidism, when severe, also can cause hypercalcemia because of increased bone
Hyperparathyroidism and Hypoparathyroidism

resorption. Most patients who have CKD stages 3 to 5 however, are hypocalcemic because of the low levels of calcitriol.

Tertiary hyperparathyroidism is a term used to describe hyperplastic glands that become adenomatous, and therefore unresponsive, over time. This condition usually is seen in patients who have CKD after years of secondary hyperparathyroidism.

**HYPERPARATHYROIDISM**

**Frequency**
Primary hyperparathyroidism is a common disease which manifests in 1 in 500 women and 1 in 2000 men.

**Age**
It manifests mainly in fifth, sixth and seventh decades of life.

**Pathophysiology**
Primary hyperparathyroidism is the commonest causes of hyperparathyroidism and manifests as hypercalcemia. It should be suspected in any patient presenting with hypercalcemia with normal renal functions and no malignancy (Fig. 19.1 and Table 19.1).

The commonest cause of hyperparathyroidism is adenoma found in 80 to 85% of cases and in about 15-20% of cases it is because of hyperplasia of parathyroid glands.

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**Fig. 19.1:** Approach to a case of hypercalcemia
In individuals with parathyroid adenoma the set point for calcium induced suppression of PTH secretion is altered or shifted which causes an inappropriate rise of hormone for the level of calcium on the contrary in hyperplasia the calcium set point is normal but the number of PTH producing cells is increased. Adenomas usually weigh 0.5 to 5 gm in size.

Familial genetic syndromes should be considered when hyperparathyroidism is due to the hyperplasia of the glands. It is due to chief cell hyperplasia. The family members of such patients should be screened for presence of asymptomatic hypercalcemia.

Other uncommon causes could be multiple endocrine neoplasia type 1 and 2, familial hypocalciuric hypercalcemia and hyperparathyroidism jaw tumor syndrome.

Parathyroid carcinoma is usually not aggressive. High calcium levels may be a pointer towards carcinoma.

Also, a syndrome of familial asymptomatic hyperparathyroidism has been reported which usually manifests with mild elevation of serum calcium of the baseline value (within 1 mg/dl) and the PTH value is 1-5 -2 times the normal values.

**Symptoms and Signs (Table 19.2)**

The disorder occurs in all ages with peak between the ages of 60 and 70 years. About 50% of the patients may be asymptomatic with hypercalcemia discovered incidentally.

The symptoms of hyperparathyroidism can be remembered by the rhyme “moans, groans, stones, bones, and psychiatric overtones”:

- “moans” (complaints of not feeling well)
- “groans” (abdominal pain, gastroesophageal reflux)
- “stones” (kidney)
- “bones” (bone pain)
- “psychiatric overtones” (lethargy)
Spectrum of Clinical Features in Different Organs

Central nervous system—Fatigue, lassitude, depression, cognitive impairment, psychosis and depression.

Neuromuscular and articular—Gout, pseudogout, myopathy, chondrocalcinosis and erosive arthritis.

Cardiovascular—Hypertension, left ventricular hypertrophy, short QTc interval, arterial stiffness and arrhythmias.

Gastrointestinal system—Peptic ulcer disease, GERD, cholelithiasis, pancreatitis and constipation.

Skeletal system—Osteopenia, osteoporosis, fractures, brown tumors and bone cysts (Figs 19.2 and 19.3). Renal—Polyuria, nephrolithiasis (40-50%), renal tubular defects.

Hypertension may be reported in about 30-50% of patients.

It is recognized that most patients with primary HPT do not have clear-cut symptomatology but rather experience nonspecific symptoms of fatigue, subjective muscle weakness, and perhaps depression that are difficult to quantify and attribute definitively to primary HPT. Some patients may not manifest typical symptoms of hyperparathyroidism and can only be diagnosed by biochemical investigations.

Investigations (Fig. 19.1)

1. Serum calcium—Hypercalcemia (normal level: 9 to 10.5 gm/dl) is the commonest abnormality seen. Some patients may be normocalcemic. It may be seen in patients who have vitamin D deficiency and if such patients are given vitamin D supplements their serum calcium level may rise. Serum albumin levels should always be measured to calculate corrected calcium.
Fig. 19.2: Hand X-ray showing tufting of distal phalanges and subperiosteal resorption in primary hyperparathyroidism

Fig. 19.3: X-ray skull showing salt and pepper appearance in primary hyperparathyroidism
2. **Hypophosphatemia**—It is seen in about 50% of cases. It is because lowered renal threshold for phosphorus absorption. Urine calcium may be normal or elevated. A urine calcium level of >4 mg/kg body weight is taken as definition for hypercalcemia.

3. **25 (OH) D levels**—In patients presenting with hypercalcemia 25(OH) D levels are to be done to rule out vitamin D toxicity. Bone mineral density—it is decreased in hyperparathyroidism.

4. **Serum PTH levels**—It can be measured by highly sensitive immunoassay the most useful being the one midregion specific or the one which measures intact hormone. A high normal value of PTH when a patient is hypercalcemic is suggestive of hyperparathyroidism as in such case serum PTH level should be suppressed. Thus, even though the PTH may be in the normal range (usually 10 to 65 pg/mL), it is indicative of hyperparathyroidism. Biochemical markers of bone formation may be increased but generally not needed for diagnosis.

**Localization of Parathyroid**
- Ultrasonography-localizes parathyroid enlargement in about 80% cases
- 99mTc Sestamibi scintigraphy—has a sensitivity of about 80% for the localization of adenoma (Fig. 19.4).

![Sestamibi scan showing parathyroid adenoma](https://www.ketabpezeshki.com)
Parathyroid Angiography

Intraoperative parathyroid localization—it is currently being tried using a combination of rapid PTH measurement with Tc 99 MIBI scanning.

Management

Medical Management

Surgical removal of parathyroid is the only definitive treatment for a primary hyperparathyroidism.

No medical therapy has been proven convincingly to be safe and effective for treatment of primary hyperparathyroidism.

Management of Acute Hypercalcemia

Hydration with saline: It is an effective treatment for emergency management of hypercalcemia. This helps in restoring a normal ECF volume and causes an increase in urinary calcium excretion by 100-300 mg/day.

Increase in urinary sodium further increase urinary calcium excretion. After hydration has been achieved a loop diuretic like frusemide can be added in twice daily doses to depress tubular reabsorption of calcium.

Saline can be given up to 6 L in life-threatening hypercalcemia and frusemide can be administered even up to 100 mg every 2 hrly but less severe cases may require only up to 2-3 L of saline in 24 hours and diuretic in twice daily doses.

Bisphosphonates like alendronate, pamidronate, and risedronate can be used for lowering calcium levels. They act by inhibiting osteoclast function. The effect lasts for about 4-6 weeks. Pamidronate can be given in a dose of 60-90 mg over a 4 hours period. Zoledronate can be given in dose of 4 mg over a 15 minutes period. A clinical response takes 2 to 4 days to occur, and the nadir in serum calcium occurs within 4 to 7 days. Such treatment can be offered to patients who are poor surgical risks or those who decline surgery.

Calcitonin which causes rapid inhibition of osteoclastic activity and reduces tubular absorption of calcium can be administered by intravenous route, intramuscular route or by subcutaneous injections at 6-12 hours interval at a dose of 2 to 8 units per kg body weight have been used for the treatment of hypercalcemia.

Cinacalcet—Sensipar (cinacalcet) is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium. It can be given in a dose of 30 mg of cinacalcet orally twice daily which can be increased to 40 to 50 mg twice daily at weeks 4 and 8 according to the serum calcium levels.

Glucocorticoids—are usually given orally beginning at a dosage of 40 to 60 mg/day, are effective first-line agents along with saline diuresis when the hypercalcemia is mediated by elevated circulating levels of calcitriol in granulomatous disorders or lymphoma.
Dialysis can be used in patients with severe hypercalcemia complicated by renal failure.

Estrogen has been shown to act as an antagonist to PTH mediated bone resorption

Administration of orthophosphate salt may be used for hypercalcemia

Plicamycin and gallium nitrate, phosphate can also be used for the treatment of hypercalcemia.

Surgical Management

Surgical removal of parathyroid gland is the definitive treatment.

Indications for surgery in primary hyperparathyroidism.

Serum calcium greater than 1 mg/dL above the upper limit of normal

Studies on mortality in primary HPT show a correlation of higher serum calcium levels and possibly longer duration of the disease with increased risk of premature death, particularly from cardiovascular disease and malignancy.

Twenty-four-hour urinary calcium excretion greater than 400 mg

Urinary calcium excretion varies depending on age, race, and gender and is affected by multiple variables; however, a level of 4 mg/kg of body weight or greater is well above the limit of normal.

Creatinine clearance reduced by 30% compared with age-matched normal persons

It is recommended that baseline creatinine clearance be estimated from a 24-hour urine collection. In patients’ not meeting criteria for surgery, serum creatinine measurement is recommended as a follow-up of renal function with creatinine clearance estimated from Cockcroft-Gault equation.

Bone Mineral Density

Bone density at the lumbar spine, hip, or distal radius that is more than 2.5 SD below peak bone mass.

Parathormone is believed to be catabolic and and it is predominantly so on the appendicular skeleton enriched in the cortical bone (distal radius).

Patients under 50 years of age

Age alone is a risk factor for primary HPT progression and development of complications. Patients in whom medical surveillance is not desirable or not possible.

In those patients who cannot be regularly followed-up surgery should be undertaken.

Surgical Treatment Options

The traditional approach to parathyroidectomy is bilateral neck exploration with visualization of all four glands. The rationale for this approach is that more than one gland is affected in 15 to 20% of patients with primary HPT. The success rate of this approach is 95 to 98%. The reasons for failure are multiple abnormal parathyroid glands, ectopic location of the glands,
supernumerary parathyroid glands, and parathyroid cancer (minimally invasive surgery). With the advances in parathyroid localization techniques, a variety of minimally invasive approaches, either endoscopic or unilateral exploration, have been introduced.

**HYPOPARATHYROIDISM**

Hypoparathyroidism can be due to absolute deficiency of PTH or ineffective action of PTH. The hallmark of hypoparathyroidism is hypocalcemia.

**Frequency**

Primary hypoparathyroidism is rare. Familial cases occur with autosomal dominant, autosomal recessive, and X-linked transmission. With the exception of X-linked transmitted syndromes there is no sex predilection.

**Age**

Maternal hyperparathyroidism resulting in newborn hypoparathyroidism usually manifests by the third week of life, however, cases have been reported as late as 2 months of age. Patients with DiGeorge syndrome present for clinical evaluation between birth and 3 months of age with a variety of symptoms. Patients with polyglandular autoimmune syndrome type I present early in life. These patients typically have candidiasis by age 5 years and hypoparathyroidism by age 10 years. For other forms of hypoparathyroidism, no age predilection is noted.

**Classification of Hypoparathyroid Disorders**

**Iatrogenic Causes**

The most common cause of primary hypoparathyroidism is excision of all parathyroid glands via surgery in the treatment of thyroid, laryngeal, or other neck malignancy. Patients with parathyroid hyperplasia, as observed in the multiple endocrine neoplasia (MEN) syndromes, are treated by surgical removal of the parathyroid glands (Figs 19.5 and 19.6).

Extensive irradiation to the face, neck, or mediastinum may cause destruction of all 4 parathyroid glands, with ensuing primary hypoparathyroidism and hypocalcemia.

The “hungry bone syndrome” develops after a parathyroidectomy for hyperparathyroidism. The body has been accustomed to high levels of PTH, causing hypercalcemia. Much of this hypercalcemic effect is because of resorption of bone. When the parathyroid gland or glands responsible for the hypersecretion of PTH are removed, the PTH level in the blood drops suddenly, and the patient experiences transient hypoparathyroidism.

**Autoimmune Hypoparathyroidism**

It can manifest clinically between early childhood and adulthood. It can occur as part of autoimmune polyglandular syndrome type 1 or as an isolated hypoparathyroid disorder.
APECED (Autoimmune polyglandular endocrinopathy –candidiasis-ectodermal dystrophy) is transmitted as autosomal recessive syndrome.

It is because of mutation in autoimmune regulator gene located on chromosome 21q22.3. The most common associated conditions include mucocutaneous candidiasis and Addison’s disease.

Antibodies to the parathyroids have been detected in up to 30% of patients with isolated hypoparathyroidism and 40% of patients with polyglandular disease.
Hypoparathyroidism due to altered PTH regulation-activating mutations (constitutive activation) of the calcium sensing receptor produces a functional hypoparathyroid state. The calcium sensor-receptor is another target of autoantibodies in hypoparathyroidism. In patients with polyglandular autoimmune syndrome type 1, more than 50% will have this antibody.

**Congenital and Developmental Disorders**
- Isolated primary hypoparathyroidism
- X-linked primary hypoparathyroidism
- X autosomal-recessive primary hypoparathyroidism
- Developmental abnormalities of hypoparathyroid- DiGeorge syndrome causes parathyroid dysplasia or thymic hypoplasia
- Kenny-Caffey syndrome (parathyroid aplasia, growth retardation and medullary stenosis of the long bones) and Barakat syndrome (hypoparathyroidism, nerve deafness and renal dysplasia) can cause hypoparathyroidism
- Kearns-Sayre syndrome (i.e. mitochondrial myopathy, ophthalmoplegia, retinal degeneration, cardiac conduction defects, primary hypoparathyroidism)
- Maternal hyperparathyroidism can result in transient neonatal hypoparathyroidism.

**Secondary Causes**
- Wilson’s disease, hemochromatosis both primary and secondary (thalassemia)
- Transient and infrequently permanent hypoparathyroidism may occur due to $^{131}$I radioiodine therapy for hyperthyroidism
- Destruction of parathyroid glands by tumor metastasis from breasts or granulomatous lesion may rarely cause hypoparathyroidism.

**Symptoms and Signs**
- The clinical features depend on the serum calcium level, age at onset and duration, levels of serum magnesium and potassium.
- Neuromuscular irritability is the hallmark of hypoparathyroidism. Patient can manifest with mild to moderate paresthesias in the extremities to painful muscle cramps and generalized hyper-reflexia. Severe cases may manifest with tetany and carpopedal spasm and with the below mentioned signs.

**Chvostek Sign**
Facial twitching, especially around the mouth, is induced by gently tapping the ipsilateral facial nerve as it courses just anterior to the ear.
Trousseau’s Sign

Carpal spasm is induced by inflating a blood pressure cuff around the arm to a pressure 20 mm Hg above obliteration of the radial pulse for 3-5 minutes.

Patient may also manifest with hoarseness, (due to laryngospasm) wheezing and dyspnea (due to bronchospasm), muscle cramps, diaphoresis, and biliary colic. Seizures may occur in severe cases.

Neuropsychiatric manifestations can occur in the form of anxiety, irritability, depression, psychosis and dementia, hallucinations and depression, disturbance of extrapyramidal system function as choreoathetosis and Parkinsonism.

Severe hypocalcemia may manifest as bradyarrhythmias and prolonged QT interval. Refractory congestive heart failure may occur because of hypocalcemia which may become normal after correction of calcium levels.

The commonest ocular manifestation of hypocalcemia is cataract which can be subscapular, anterior and posterior zonular. Both papilledema and pseudotumor cerebri may occur.

Some skin manifestations like alopecia and Candidiasis are characteristic of hereditary hypoparathyroidism associated with autoimmune polyglandular failure.

The other features may include soft tissue calcification and exostoses. Periarticular deposition of calcium salts is common and may occasionally present as pseudogout and chondrocalcinosis.

PSEUDOHYPOPARATHYROIDISM

It can occur because of resistance to the action of PTH. Patient may present with typical features of hypocalcemia but PTH levels will be high. Resistance may be at the level of skeleton or kidneys with or without Albright’s osteodystrophy phenotype. The treatment modalities are same as hypoparathyroidism.

Investigations

Hypocalcemia

Total serum calcium (normal value-8.5 to 10.5 mg/dl) and the level of ionized calcium (normal value 4.5 to 5.6 mg/dl) should be low for diagnosing hypocalcemia. Serum albumin levels should be done to calculate corrected calcium. Serum calcium should always be repeated if hypocalcemia is present for confirmation of diagnosis.

In patients who have hypoalbuminemia, there is a decrease in the total calcium but not a decrease in the ionized calcium. Thus, before a diagnosis of hypocalcemia can be made, one should estimate the corrected calcium by adding 0.8 mg/dL to the total calcium for every 1 mg/dl decrease in the serum albumin below 4 mg/dl. If hypocalcemia persists, the ionized calcium level should be measured (Table 19.3).

In patients who have excess citrate (from blood transfusions) or acute administration of bicarbonate, the percentage of calcium that is bound to these negatively charged ions increases,
reducing the free ionized calcium, usually with only a minimal change in total calcium. Acute respiratory alkalosis also lowers the ionized calcium.

**Hyperphosphatemia**
Serum phosphorus levels will be high (normal value 3 to 4.5 mg/dl).

**PTH**
Demonstration of little or no PTH in the presence of hypocalcemia confirms the diagnosis.

**Magnesium**
Magnesium depletion can sometimes be seen in patients with hypoparathyroidism. Such patients may show PTH resistance and are also resistant to vitamin D. These patients require correction of magnesium deficit.

High PTH levels with hypocalcemia and hyperphosphatemia are seen in patients with pseudohypoparathyroidism. 25(OH)D levels should be done in all patients presenting with hypocalcemia as vitamin D deficiency could be a cause of hypocalcemia but in these cases serum PTH levels will be high.

**Treatment**

**Acute Hypocalcemia**
Calcium loading is done with 100 mg - 300 mg of elemental calcium in 150 ml of 5% dextrose (10-30 ml of 10% calcium gluconate; 9.8 mg/ml elemental calcium) of calcium over a period of 10-20 minutes and then calcium infusion needs to be given in a dose of 0.5-2 mg/kg/hr of elemental calcium and then adjusted according to the amelioration of symptoms.

For infants 10-20 mg/kg of elemental calcium (1-2 ml/kg of calcium gluconate 10%) should be given IV over 5-10 minutes to control seizures, may be continued as IV infusion at 50-75 mg/kg a day over 24 hours.

Oral calcium supplementation is required in dose of 2-3 gm of elemental calcium per day. Patient should not be given more than 600 mg elemental calcium per dose as the absorption of calcium decreases at higher doses. Severe cases of hypocalcemia require oral calcium supplementation every 3 hourly till serum calcium becomes normal. The commonest preparation used is of calcium carbonate and it has to be taken with food for proper absorption.

Calcium carbonate absorption may be hampered in patients with achlorhydria or in patients taking pharmacological agents which decrease gastric acid secretion. Such patients should be given calcium citrate instead of calcium carbonate.

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1,25(OH)$_2$ D (Calcitriol)

It stimulates absorption of calcium and phosphate from small intestine and promotes release of calcium from bone into blood. Calcitriol is given in a dose of 1-3 μg/day.

Phosphate Binders

If in spite the correction of hypocalcemia the hyperphosphatemia is persisting then patients can be given phosphate binders for lowering high serum phosphorus.

PTH is commercially available for use in the treatment of osteoporosis. Its use for patients with hypoparathyroidism is not approved by the Food and Drug administration.

Surgical Treatment

Patients who are undergoing thyroid surgery may be treated with an autotransplant of a segment of parathyroid gland to prevent hypoparathyroidism after surgery. This autotransplant is usually placed subcutaneously in the forearm or in the neck.

If the autotransplantation fails, patients are treated as any other patient with hypoparathyroidism.

Follow-up

- Patients should be followed up for serum calcium, phosphate levels and should be maintained in the normal range,
- Patient should wear a bracelet indicating primary hypoparathyroidism
- Patient needs to be monitored for development of nephrocalcinosis and nephrolithiasis
- An ultrasound of the abdomen is recommended once every year to see for development of nephrocalcinosis or nephrolithiasis
- Drugs and hypoparathyroidism-The use of any diuretic may alter calcium homeostasis so caution should be exercised in such case.

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