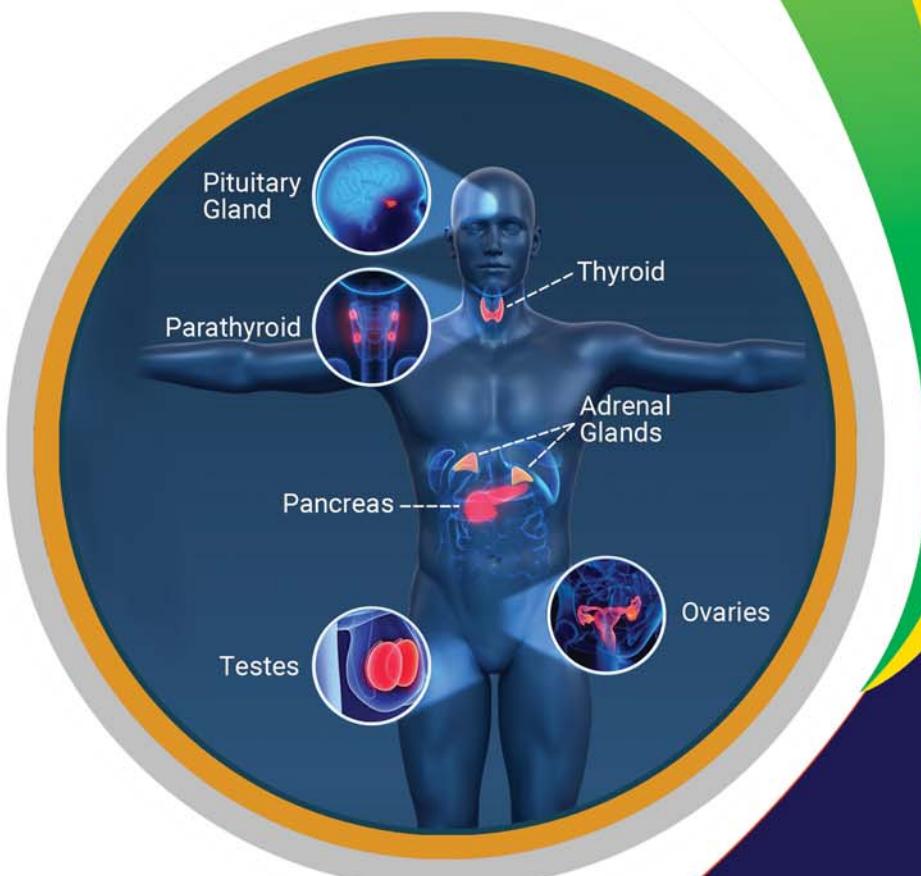




INDIAN MEDICAL ASSOCIATION ACADEMY OF MEDICAL SPECIALITIES

Head Quarters, Hyderabad, Telangana

231st CENTRAL WORKING COMMITTEE OF INDIAN MEDICAL ASSOCIATION (CWC)



ANNALS OF IMA AMS
THEME : ENDOCRINOLOGY

13th & 14th April 2024
CHENNAI, TAMIL NADU



INDIAN MEDICAL ASSOCIATION

**231st Central working Committee
Chennai**

Hosted By

**IMA Tamil Nadu State branch
IMA Tambaram**

Welcomes

IMA National leaders and CWC members

DATE

April 13 & 14 2024

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Theme : ENDOCRINOLOGY

13th & 14th April 2024
Chennai, Tamil Nadu

Dr. Nomeeta Shiv Gupta **Dr. Srirang Abkari** **Dr. Shilpa Basu Roy** **Dr. Rajiv Ranjan Prasad**
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IMA PRAYER



May everybody be happy
May everybody be healthy
May everybody be free from pain
May everybody be free from sorrow
May we be the healing cure
Beyond every greed & lure

FLAG SALUTATION

We, the members of Indian Medical Association
Stand here to salute our National Flag.
Its honour and glory shall be our light and strength
And its course shall be our course.
We pledge our allegiance to it and realizing our responsibilities
As the accredited members of this National organization,
We swear we will dedicate everything in our power
To see it fly high in the comity of Nations.
Jai Hind!

From the Editor's Desk



Dr. Shilpa Basu Roy

MBBS (Hons), MS (General Surgery), MCh (CTVS)
Associate Professor & Consultant Cardiothoracic Vascular & Transplant Surgeon
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As clinicians, the latter has been a very perplexing & cumbersome field, to diagnose the colossal entities which come under its domain. With its varied clinical stigmata & the complex pathophysiology, a deep understanding of the subject is a must for deciphering the checkpoints where targeted therapeutics may as well be initiated. As a surgeon, often for diseases like pheochromocytomas, a Von Hippel Lindau disease, adrenal adenomas, posterior pituitary neoplasms, thyroid & breast neoplasms or even the MEN syndromes to express a few, neoadjuvant onco or the general therapeutics must be initiated to commence a surgery as it is found to be definitive in many cases.

But, as far as my experience with the patients are concerned, therapeutics still are a mainstay of the treatment for a large number of diseases like the diabetes mellitus (I, II, MODY, LADA), addison's disease, cushing's disease or syndrome, hashimoto's thyroiditis, riedel's thyroiditis, acromegaly, the paraneoplastic syndromes or at times the gestational diabetes which has a huge prevalence vis-a-vis a burden on the general population. Therefore a lucid approach to the diseases as outlined in the index has been crafted carefully for a contended understanding which will help the readers to engineer a precise algorithm for diagnosing & treating such.

Endocrine diseases, due to their unique behavior, are deemed to be silent culprit in most of the morbidity & mortality of the patients. Therefore screening the "population at risk" or those who harbour the stigmata of the endocrine disorder which in maximum cases has been seen to maintain both mendelian & the non-mendelian pattern of inheritance is of utmost importance. Overtly studying the genome using advanced methodologies such as Cytogenetics, fluorescent in-situ hybridization (FISH), next generation DNA & RNA sequencing, micro droplet PCRs' to name a few may be judiciously used. For precise and efficacious diagnosis, cross sectional imaging using the computed tomograms, MR images, PE tomogram or photon tomograms along with cell or tissue sampling for the histopathological diagnosis for localizing the lesion & staging of the later along with initiating oncotherapeutics, radiations or definitive surgery would remain the cornerstone. Also to comment on the diseases which would cater judicious use of the "pill" with or without lifestyle modifications, must be generously sought after.

Henceforth, I extend my gratitude to the esteemed authors of the country & under the banner of the Indian Medical Association for their assiduous efforts in crafting the articles & would humbly wish the readers to lend their attention to this issue of the journal.

Regards

Dr. Shilpa Basu Roy, Mch



Dr R V ASOKAN

National President
Indian Medical Association

Message

Dear Dr Rajeev Ranjan Prasad and Shipa Basu Roy

It is with great pleasure and pride that I am penning down this message to you. IMA AMS is one institution of IMA that has been climbing greater heights every year. The Annals published by IMA AMS are of international standards albeit friendly to the reader. I appreciate the fact that IMA AMS is bringing out the Annals on Endocrinology this time. I look forward to release a copy of the same in the ensuing Central Working Committee at Chennai on 13th and 14th of April. I am eager to devour the contents of the Annals as well.

The leadership given by Dr. Nomeeta Shiv Gupat and Dr Srirang Akbari has further expanded the frontiers of knowledge of our members. I take this opportunity to congratulate you both, Dr Rajeev Ranjan Prasad and Dr Shipa Basu Roy whose blood and sweat is this publication.

Thank you on behalf of the medical fraternity.

Dr R V ASOKAN

National President
IMA

09.04.2024

Punalur



INDIAN MEDICAL ASSOCIATION (HQs.)



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Greetings from Indian Medical Association (HQs.)!

I am delighted to learn that IMA Academy of Medical Specialties is releasing Annals on "Endocrinology" at Central Working Committee Meeting of IMA on 13th & 14th April, 2024 at Chennai, Tamil Nadu.

The field of medicine is experiencing an increasing number of inventions and innovations due to the constant advancements in technology. This has made it more important for treating physicians, especially specialists to learn about these innovations so they can provide patients with the best care possible in the quickest amount of time and at the lowest possible cost. The medical field will greatly benefit from publications such as the "Annals" in order to meet the aforementioned needs.



I believe that IMA AMS is doing a great job by providing its members with useful information through the publication of Annals. The members' proficiency and understanding of the most recent advancements in medicine and medical technology will surely grow as a result of this.

As you all know that IMA Aao Gaon Chalen Project was relaunched on 25th June, 2023, all over the country by our Chief Patron Dr. Ketan Desai Sir. In this regard, I request all of you to adopt at least one village and conduct various activities on a regular basis under this project. You are also requested to send a village adoption activity report along with photographs to IMA HQs. so that a compiled document can be created. The Awards for this noble cause will be given by IMA HQs. either after the completion of one year on 24th June 2024 or on the occasion of Doctors Day next year.

Though, IMA had conducted Organ Donation Awareness Camp in the month of August, 2023, to continue it further I request all of you to create awareness about Organ Donation and motivate the donors to donate their organs after their death to save more lives.

I express my heartiest appreciation and congratulations to the whole Editorial Team of Annals.

Long Live IMA !!

Dr Anilkumar J. Nayak
Hony. Secretary General, IMA



"One for All – All for One".... a cohesive, collective, enhance, communicative approach to break all sectorial walls and bring all clinicians at one platform to help in building a Healthy Nation



Dr. Shitij Bali

Hony. Finance Secretary,
IMA

Message

Greetings from Indian Medical Association (HQs.)!

It gives me intense pride to know about the release of our IMA AMS annals on Endocrinology in the upcoming CWC at Chennai on the 13-14 April 2024. The annals would welcome our members to the forefront of endocrinology, where the intricate dance of hormones orchestrates the symphony of life. In this magazine, we embark on a journey to unravel the mysteries of the endocrine system, exploring its profound influence on health, disease, and human physiology. Let's Join as this annals update us into the latest research, clinical insights, and therapeutic breakthroughs shaping the landscape of endocrinology. Together, let's illuminate the pathways to understanding and optimizing hormonal balance for a healthier tomorrow.

Wishing all the best to the IMA AMS Team that has really put in all the hard work for us to enjoy reading the annals.

Long live IMA.

Dr. Shitij Bali

Hony. Finance Secretary, IMA



Dr. Nomeeta Shiv Gupta

Chairman
IMA AMS Hqrs

Message

Dear members,

It gives us great pleasure to present yet another ANNALS from IMA AMS on ENDOCRINOLOGY.

As you are all aware this is a very interesting subject with all new protocols and management strategies coming up

Keeping this in mind, we decided to take up this subject.

I would like to congratulate the whole team at IMA AMS for working so hard to put this together for all of us.

Dr. Nomeeta Shiv Gupta

Chairman, IMA AMS Hqrs



Dr. Srirang Abkari

Hony. Secretary
IMA AMS HQs.

Message

As we continue in our pursuit for academic excellence, it is indeed a happy moment for us to witness the release of yet another Annals of IMA AMS, the theme being Endocrinology. The endocrine system being a very important component in regulating all the bodily functions needs a proper understanding of the normal physiology and the derangements therein. There needs to be a high index of suspicion for diagnosing endocrine disorders. The chapters written by eminent authors in this field with their vast clinical experience will make this issue much a sought after publication.

We are thankful to our Chief Patron, Dr. Ketan Desai for his blessing and guidance in all our endeavours. We are grateful to Dr. RV Asokan, our National President for his visionary leadership, Dr. Anil Kumar J Nayak, Honorary Secretary General for his valuable inputs and encouragement, Dr. Shitij Bali, Honorary Finance Secretary for his timely advice and support.

Our dynamic Chairman, Dr. Nomeeta Shiv Gupta deserves great appreciation for inspiring us to do more, supporting us in all our programs and monitoring its implementation. A special thanks to our Editorial team of Dr. Shilpa Basu Roy and Dr. Rajiv Ranjan Prasad for their contribution for the Annals.

IMA AMS is in the process of rolling out fellowship courses in many specialities all across the country. We request all of you to propagate this information. We also request you to contribute for the re-development of the New IMA Building at New Delhi.

Please join IMA AMS and participate in academic activities across specialities and interact with specialists, update and upgrade your knowledge.

Long Live IMA!

Dr. Srirang Abkari
Hony. Secretary
IMA AMS HQs.



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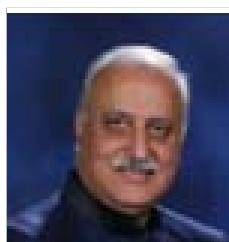


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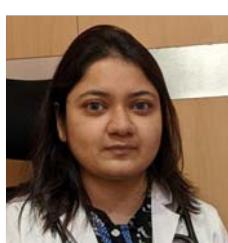
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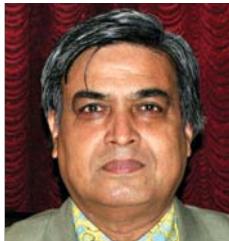
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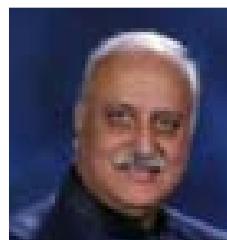
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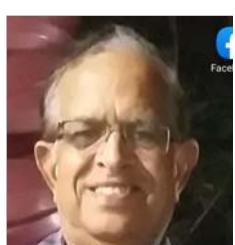
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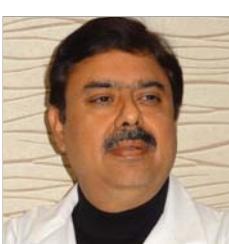
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Type 1 Diabetes- Overview

Dr. Ch. Vasanth Kumar, MD

*Senior Consultant Physician
Apollo Hospitals, Hyderabad*

Introduction

Type 1 diabetes is due to destruction of the pancreatic beta cells, leading to insulin deficiency. It is the commonest endocrine disorder in children.

It is estimated that about 1,97000 individuals suffer from type 1 Diabetes in India. Both genetic and environmental factors are responsible for developing T1DM.

The risk of developing T1DM is significantly increased in close relatives of a patient with T1DM.

Environmental agents like viruses or foods appear to trigger an immune response that causes destruction of the pancreatic beta cells.

Identification of these factors may lead to a better understanding of the pathogenesis of the disease.

Distinguishing type 1 from type 2 diabetes —

Once a diagnosis of diabetes is made, the next step is to distinguish T1DM from type 2 diabetes mellitus (T2DM). T1DM is characterized

primarily by insulin deficiency, whereas T2DM is characterized primarily by insulin resistance with relative insulin deficiency.

As the prevalence of obesity and the incidence of T2DM is increasing in children and adolescents, it sometimes becomes increasingly difficult to clinically differentiate type 1DM from type 2DM.

children with T1DM are less likely to have excess body weight and often have a recent history of weight loss, although up to 25 percent are overweight and Patients with new-onset 2DM may also have a history of recent weight loss.

Age – Patients with T2DM generally present after the onset of puberty, whereas those with T1DM may present at an earlier age. Approximately 45 percent of children with T1DM present before 10 years of age and By contrast, almost all cases of T2DM present after 10 years of age.

Patients with T2DM frequently have acanthosis nigricans which is a sign of Insulin resistance.

Laboratory testing —Pancreatic autoantibodies – Measure autoantibodies against GAD65 (glutamic aciddecarboxylase 65), IA2 (the 40K fragment of tyrosine phosphatase), insulin, and ZnT8(zinc transporter 8) [3]. This panel of tests should be performed at the time of presentation, before or soon after starting insulin therapy.

Most patients with T1DM have one or more of the above pancreatic autoantibodies, indicating autoimmune destruction of pancreatic beta cells; this is sometimes referred to as type 1A diabetes (figure 4) [48]. A minority of patients with clinical features of T1DM have no detectable autoantibodies and are categorized as having type 1B.diabetes. In these patients, there is no evidence of autoimmune beta cell **destruction**.

CPeptide levels strongly correlate with beta cell function

Cpeptide very low and sometimes undetectable in type1 DM.

CPeptide is the most appropriate primary end point for assessing beta cell function in type 1 DM.

T1DM usually presents as follows

Children often present acutely, with severe



symptoms of polyuria, polydipsia, and ketonemia, and approximately a third of them present with diabetic ketoacidosis (DKA).

Older children may have a hyperacute presentation so called fulminant T1DM. In them, autoimmunity is absent, and there is a complete loss of beta-cell function. Adults usually present with a more gradual onset, and the initial clinical presentation may appear consistent with type 2 diabetes mellitus (T2DM).

NUTRITIONAL GOALS

The nutritional goals for people with type 1 diabetes are to maintain as near-normal blood glucose levels as possible, by integrating insulin therapy.

MEDICAL NUTRITION THERAPY

Medical nutrition therapy (MNT) is the process by which the nutrition prescription is customized for each individual based on medical, lifestyle, and individual factors.

Proper attention to diet is important to minimize hypoglycemia and weight gain while achieving glycaemic goals.

Glycemic management has been shown to markedly diminish the likelihood of neuropathy, nephropathy, retinopathy, and coronary artery disease in people with type 1 diabetes [into each individual's diet and physical activity patterns.

Achieve optimal blood pressure and lipid levels.

Provide adequate calories for achieving and maintaining a reasonable body weight, normal growth, and development.

While advising diet to type1DM patients following points have to be considered.

Their Personal dietary preferences and Consistency in day-to-day carbohydrate intake and Dosing insulin for variations in blood glucose Weight management and Nutritional content with balanced protein, carbohydrates, and fats apart from Meal-insulin timing

Presence of other comorbid conditions such as hypertension, hyperlipidemia, and renal, cardiovascular, and celiac disease is important.

Prevention of complications of diabetes, both acute (hypoglycemia and ketoacidosis) and chronic (micro- and macrovascular complications).

Improving overall health through healthful food choices.

Addressing individual nutrition needs, incorporating personal and cultural preferences,

PHYSICAL ACTIVITY/EXERCISE

Benefits of exercise include improved glycemia, weight management, reduction in comorbidities like hypertension, dyslipidemia, and cardiovascular disease.

The timing of exercise has to be advised in relation to insulin dose, type, mode of delivery, and time of injection. People with diabetes should check glucose levels before and after exercising, especially in the beginning of an exercise program, to evaluate their glycemic response to exercise and to adjust insulin and carbohydrate regimens, as needed, to prevent hypoglycemia.

WEIGHT MANAGEMENT

Optimal body weight — Body mass index (BMI) is commonly used to classify weight status

BMI is a good but imperfect indicator of body fat. For example, some athletes may have a relatively high BMI due to high muscle mass. The use of BMI also has limitations in the older adult population, who may have a low muscle mass and fluid retention.

Caloric intake — The relative importance of caloric intake for an individual is dependent on several factors, including:

Lowering caloric intake and inducing weight loss are of major importance for adults with type 1 diabetes who have overweight (BMI e"25 to 29.9 kg/m) or obesity (BMI e"30 kg/m) as the risk of comorbidities associated with excess adipose tissue increases with BMI in these ranges.



We know that the presence of obesity, in particular, can worsen insulin resistance and increase risk of cardiovascular disease, stroke, retinopathy, and nephropathy.

Insulin therapy along with monitoring of glucose is the corner stone of management of type 1 DM.

It includes the coordination of meals/diet and activity with insulin

replacement as physiologically as possible, which involves the frequent monitoring of glucose levels with frequent insulin administration as needed.

Intensive insulin therapy is the standard of care for people with type 1 diabetes.

Glycated hemoglobin – A1C goals in people with diabetes should be individualised balancing the demonstrated benefits with regard to prevention and delay of micro- and macrovascular complications with the risk of hypoglycemia.

For most adults with type 1 diabetes, we aim for an A1C value of 7 percent.

Those individuals who use Blood glucose monitorig (rather than continuous glucose monitoring [CGM]) should test their blood glucose at least four times daily, before meals and at bedtime.

Additional testing may be indicated two to three hours after meals and occasionally at 3 AM (for safety), as well as before and after exercise, before driving, and whenever hypoglycemia is suspected.

CGM should be offered to all adults with type 1 diabetes, and it is especially useful for those who are having frequent or severe hypoglycemia and those who have developed impaired hypoglycemic awareness.

These devices measure glucose continuously from interstitial fluid and different types of them are available but they are out of reach for many of the patients with type 1 DM .

INSULIN REGIMENS

The basic requirements of an optimal insulin

regimen include administration of a basal insulin plus mealtime boluses of a rapid-acting, ultra rapid-acting, or short-acting insulin.

Basal insulin can be delivered by daily or twice-daily injections of an intermediate-acting or long-acting insulin preparation or continuous subcutaneous insulin infusion (CSII) via a pump, typically using a rapid-acting insulin preparation.

The choice between multiple daily insulin (MDI) injections and continuous subcutaneous delivery of insulin via a pump (CSII) is largely a matter of personal preference, lifestyle, and cost. The choice should be given to patients who have to decide depending on their life style and affordability.

Three doses of pre meal short acting insulin and bed time NPH is a practical solution to many of our patients.

Pre mixed insulins should be avoided and it is a big challenge to shift many of these children who are on premixed.

They can be delivered by syringe pen or pump.

Rapid acting analogues and glargine as basal insulin have advantages.

The goal of management of type 1 DM is to avoid acute complications like DKA and severe hypoglycemias while maintaining near normal glucose levels which can prevent the chronic complications.

Patient Education plays an important role and it should include providing comprehensive knowledge of Nutrition, monitoring of glucose and Insulin administration.

Managing Diabetes and blood glucose is always a challenge to the patients when they suffer from acute infections.

Parents are the main care givers in case of DM in young children and counselling them about every aspect of the condition is important.



Newer Drugs in the Treatment of Type 2 Diabetes Mellitus

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INTRODUCTION

The pathophysiology of type 2 diabetes(type 2 DM) is multi-factorial. De Fronzo famously called it the ominous octet, referring to the eight mechanisms leading to type 2 diabetes mellitus. Some of these mechanisms ,like the role of the kidney in the reabsorption of glucose causing high sugar levels ,and the role of the incretin pathway, have been recently added targets for drugs to control diabetes . SGLT-2 inhibitors and GLP-1 receptor agonists are being widely used worldwide in view of their favourable profile in preventing renal and cardiac complications of diabetes , in addition to good glycaemic control.

In this chapter, we will review the evidence regarding why these drugs have become game changers in the management of type 2 DM.

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS

SGLT2 inhibitors are a relatively recent addition to the arsenal of medications used to manage diabetes mellitus. These drugs work by inhibiting the sodium-glucose cotransporter 2 (SGLT2), a protein responsible for reabsorbing glucose in the kidneys. By blocking this transporter, SGLT2 inhibitors promote the excretion of glucose through urine, thereby lowering blood glucose levels. Phlorizin was the first substance discovered to have SGLT inhibitory activity. It was extracted from the bark of apple trees in the 19th century.

However, due to its poor oral bioavailability and non-specificity for SGLT2, it was not suitable for clinical use. SGLT2 inhibitors lower glycated haemoglobin (HbA1c) by 0.6-0.8% (6-8 mmol/mol) without increasing the risk of hypoglycemia and induce weight loss and improve various metabolic parameters including blood pressure, lipid profile and hyperuricemia.

MECHANISM OF ACTION OF SGLT2 INHIBITORS

In the kidney, approximately 180 g of glucose per day is excreted in the urine through glomerular filtration. Most of the glucose in the urine is however completely reabsorbed by SGLT2 and SGLT1 expressed in the proximal tubule, and glucose is not normally excreted in the urine. SGLT2 is responsible for reabsorption of 90% filtered glucose in the proximal convoluted tubule. SGLT2 inhibitors suppress reabsorption of glucose by inhibition of SGLT2, and thereby increase urinary glucose excretion by approximately 60–80 g per day and ameliorate hyperglycemia. (1)

By inhibiting the SGLT-2-dependent glucose and sodium reabsorption, there is an increase in distal tubular sodium load; the resultant inhibition of the renin-angiotensin-aldosterone system and reduction of afterload and preload is cardioprotective.

The mechanism by which SGLT2 inhibitors may be nephroprotective is by increasing distal sodium



delivery and inhibiting tubuloglomerular feedback leading to afferent vasoconstriction and a decrease in intraglomerular pressure. Reduction in intraglomerular pressure leads to a decrease in albuminuria. Interference with proximal glucose reabsorption and proximal sodium reabsorption results in natriuresis.

Excretion of 60–80 g of excess glucose corresponds to 240–320 kcal of energy loss from the body, promoting weight loss. Improvement of obesity/overweight, especially abdominal fat accumulation promotes amelioration of insulin resistance and results in improvement of metabolic parameters such as blood pressure, lipid profile, and serum uric acid level.

SGLT2 INHIBITORS APPROVED BY FDA

Canagliflozin was the first SGLT-2 inhibitor approved on March 29, 2013. Dapagliflozin received FDA approval in January 2014. Shortly following the approval of dapagliflozin, empagliflozin became the third SGLT inhibitor to receive FDA approval in August 2014. Ertugliflozin was approved by FDA in 2017 and is indicated for adult subjects with type 2 DM to improve the control of blood glucose in addition to diet and exercise. The latest drug to be approved by FDA in January 2023 was Bexagliflozin as an adjunct to diet and exercise to improve glycaemic control in adults with type 2DM. (Table 1)

SGLT2 INHIBITORS IN INDIA

Canagliflozin, Dapagliflozin and Empagliflozin are available in India. A new molecule remogliflozin has been approved in India in 2019 after a phase

3 trial proved its efficacy and safety in comparison to dapagliflozin. Despite the disadvantage of twice daily administration, it potentially reduces treatment cost to less than half compared to other molecules of this class.

INDICATION FOR USE OF SGLT2 INHIBITORS

SGLT2 inhibitors are indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.(2) They are indicated for the reduction of the risk of eGFR decline and hospitalization in patients with chronic kidney disease at risk of progression. SGLT2 inhibitors may be a useful option in obese and hypertensive patients because of their weight loss and antihypertensive benefits. They can be used in patients with longstanding diabetes because their action is independent of α -cell function and insulin secretion.

BENEFITS OF SGLT2 INHIBITORS

GLUCOSE CONTROL

When compared with other oral anti-hyperglycemic agents, SGLT2 inhibitors have demonstrated non-inferiority along with additional metabolic benefits. As an example, in a randomized, double-blind study of 1,450 patients, HbA1c decreased "0.65% with canagliflozin 100, decreased "0.74% with canagliflozin 300 mg, and decreased "0.55% with glimepiride 6 or 8 mg over a 104 week period.

Medication	Dose (mg)	Frequency	Do not initiate therapy
Dapagliflozin	5;10	Once Daily	eGFR less than 25 mL/minute/1.73 m ²
Canagliflozin	100;300	Once Daily, before first meal of day	eGFR less than 20 mL/minute/1.73 m ²
Empagliflozin	10;25	Once Daily	eGFR less than 20 mL/minute/1.73 m ²
Ertugliflozin	5; 15	Once Daily	eGFR less than 45 mL/minute/1.73 m ²
Bexagliflozin	20	Once Daily	eGFR <30 mL/min/1.73 m ²

Drug	Manufacturer	Brand name	Dose	Price per tablet (INR)
Canagliflozin	Johnson & Johnson Ltd	Invokana	100	54.5
	USV Ltd	Sulisent	100	55
	Janssen Pharmaceuticals	Motivyst	300	120
Dapagliflozin	Sun Pharmaceutical Industries Ltd	Oxra	10	52
			5	50
	AstraZeneca plc	Forxigo	10	52
			5	50
	Abbott	Gledepa	10	52
Empagliflozin	Lupin Pharmaceuticals, Inc	Gibbulio	25	57
			10	47
	Boehringer Ingelheim	Jardiance	25	57
			10	47
Remogliflozin	Glenmark pharmaceuticals	Remo	100	12.5
		Remo-Zen	100	12.5
	Mankind Pharma Ltd	Sgltr	100	12.6
	Torrent Pharmaceuticals Ltd	Zucator 100	100	12.6

OTHER METABOLIC EFFECTS

In clinical trials of the SGLT2 inhibitors as monotherapy or add-on treatment, weight loss of ~1 to 4 kg occurred over 18 to 104 weeks. To date, all studies with SGLT2 inhibitors have found significant reductions in BP, with greater reductions seen in systolic than diastolic BP. The initial reductions in BP are believed to be due to the diuretic and volume depletion effects. However,

longer-term effects may be attributable to inhibition of the renin-angiotensin system and weight loss. SGLT2 inhibitors may be an ideal class of medications for patients with type 2 diabetes and hypertension.

CARDIOVASCULAR BENEFITS

SGLT2 inhibitors have emerged as promising drugs in the management of heart failure,

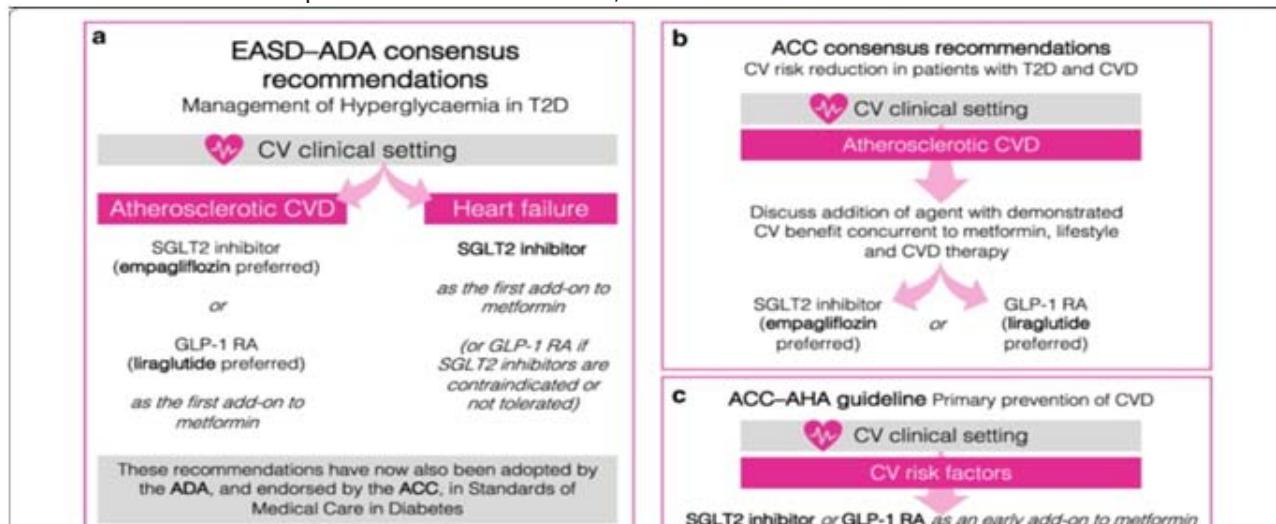


Figure 1 : American diabetes association (ADA) recommendations for diabetic control in high risk individuals for ASCVD

particularly in patients with or without type 2 diabetes. Several large clinical trials like EMPA-REG OUTCOME, DECLARE-TIMI 58, and DAPA-HF demonstrate reductions in heart failure hospitalizations and cardiovascular mortality with drugs like empagliflozin and dapagliflozin even in patients without diabetes. The mechanisms behind these benefits are still under investigation but may involve diuretic effects, improvements in ventricular remodeling, reductions in arterial stiffness, and potential effects on myocardial metabolism. This is the reason why, the ADA and AACE guidelines recommend these drugs as first choice in patients with DM with cardiovascular complications as shown in the cartoon below.

While SGLT2 inhibitors have shown great promise in heart failure management, they are not considered first-line therapy and are typically used as adjunctive therapy alongside other standard heart failure treatments such as beta-blockers, ACE inhibitors/ARBs, and mineralocorticoid receptor antagonists. According to AHA/ACC/HFSA(2022) guidelines, the management for heart failure with reduced ejection fraction (HFrEF) includes sodium-glucose cotransporter-2 inhibitors.

RENAL BENEFITS

Clinical trials like CREDENCE and DAPA-CKD have demonstrated significant renal benefits with drugs like canagliflozin and dapagliflozin. These trials showed reductions in renal failure, end-stage kidney disease, and cardiovascular events, irrespective of diabetes status. Subanalyses of trials like DECLARE-TIMI 58 and EMPA-REG OUTCOME further confirmed the renal protective effects of dapagliflozin and empagliflozin, respectively. These renal benefits are attributed to mechanisms such as reducing glomerular hyperfiltration, intraglomerular pressure, and inflammation. According to a joint consensus from KDIGO and ADA (2022), SGLT2 inhibitors with established kidney benefits are suggested for patients with type 2 diabetes mellitus, CKD, and eGFR >20 mL/min/1.73 m². A reversible decline in the eGFR with the beginning of SGLT2 treatment can occur and is normally not an indication to discontinue therapy. Using an SGLT2 inhibitor in patients with

urinary albumin >200 mg/g creatinine is advised to reduce CKD progression and cardiovascular events.

ADVERSE EFFECTS OF SGLT2 INHIBITORS

1. Genital mycotic infections include vulvovaginal mycotic infections, including candidiasis, vulvovaginitis, vulval abscess, and bacterial vaginitis.(4)
2. Serious urinary tract infections (UTI), including urosepsis and pyelonephritis, are associated with SGLT2 inhibitors. Meta-analysis of 52 RCTs showed that dapagliflozin had a dose-response relationship with UTI.
3. Discontinue SGLT2 inhibitors in case of ulcers and infection of the lower limb. Canagliflozin is especially associated with an increased risk of lower-limb amputation than empagliflozin.
4. SGLT-2 inhibitors are associated with an almost 3-fold increased risk for euglycaemic ketoacidosis. The risk for diabetic ketoacidosis is highest for canagliflozin, followed by empagliflozin and dapagliflozin. Euglycemic DKA is a triad of increased anion gap acidosis, the presence of ketosis, and serum glucose < 250 mg/dL. SGLT-2 inhibitors appear to be associated with euglycemic DKA, possibly due to their noninsulin-dependent glucose clearance, hyperglucagonemia, and volume depletion.
5. Fournier gangrene is a rare but life-threatening necrotizing fasciitis of the perineum demanding urgent surgical intervention.
6. Erythema, rash, pruritus, and angioedema have been reported. Discontinue the SGLT2 inhibitor and monitor until signs and symptoms resolve.
7. SGLT2 inhibitors are associated with an increased bone fracture. Potential mechanisms for fracture include volume



contraction leading to dizziness and falls and possible effects on calcium, phosphate, and vitamin D homeostasis leading to a reduction in bone mineral density.

CONTRAINDICATIONS

SGLT2 inhibitors should not be used specifically for the treatment of hyperglycemia in patients with:

1. Type 1 diabetes
2. Patients receiving dialysis treatment
3. Prior diabetic ketoacidosis (DKA)
4. Hypersensitivity reactions such as anaphylaxis or angioedema

MONITORING

Volume status and renal function should be assessed at baseline before initiating SGLT-2 inhibitors since all four agents can cause intravascular volume contraction, potentially resulting in a symptomatic decrease in blood pressure and short-term transient alteration in serum creatinine. Laboratory monitoring of complete blood count (CBC), blood glucose, HbA1c, lipid panel, and kidney function tests should be performed routinely as changes in serum creatinine, eGFR, hematocrit, hemoglobin, low-density lipoprotein (LDL) cholesterol, serum bicarbonate, serum phosphate, and potassium may occur. Patients should also be monitored for signs and symptoms of "Fournier's Gangrene. Patients with clinical implications and manifestations of metabolic acidosis should be thoroughly investigated for ketoacidosis, as DKA may present even if the serum glucose range is below 250 mg/dL. Patients should be screened for risk factors for lower limb amputations such as peripheral vascular disease, history of amputations, neuropathy and diabetic foot ulcers.

CONCLUSION

SGLT2 inhibitors have emerged as a pivotal therapy for managing blood sugar levels in individuals with type 2 diabetes. They offer the advantages of promoting weight loss and carrying

a low risk of hypoglycemia. Recent research has underscored their significance in treating heart failure and chronic kidney disease, regardless of the presence of type 2 diabetes. Moreover, they have been shown to reduce cardiovascular and renal risk independently of their glucose-lowering effects. Patients using SGLT2 inhibitors should be mindful of common side effects like genital fungal infections, as well as the rare but serious risk of diabetic ketoacidosis. With the expanding scope of their use, SGLT2 inhibitors are poised to play an even greater therapeutic role.

GLP-1 RECEPTOR AGONISTS

INTRODUCTION

One of the most interesting mechanisms in the pathophysiology of diabetes, involves the incretin pathway. These are hormones secreted by the gut, such as glucagon-like peptide 1 (GLP 1) and gastric inhibitory polypeptide (GIP), which increase insulin levels. This pathway is dysfunctional in diabetes, with reduced incretin effect, and this causes hyperglycaemia.

The incretin pathway was used as a target for control of diabetes, by using analogues of GLP1 called Glucagon-like peptide-1 receptor agonists (GLP-1 RA). These drugs mimic the action of GLP 1 in the body, and hence achieve glycaemic targets.

Examples of drugs in this class include Exenatide, Lixisenatide, Liraglutide, Albiglutide, Dulaglutide, and Semaglutide.

Structurally, there are two categories of these agents; human GLP-1 backbone agents and exendin-4 backbone agents.

Human GLP-1 backbone:

- Dulaglutide
- Albiglutide
- Liraglutide
- Semaglutide

Exendin-4 backbone:

- Exenatide (two formulations)
- Lixisenatide

MECHANISM OF ACTION

Glucagon-like peptide-1 is an incretin hormone produced by the intestinal enteroendocrine L-cells which is inactivated by dipeptidyl peptidase-4 (DPP-4). Incretin secretion is stimulated by nutrient ingestion, the most potent activators being glucose and lipids. GLP-1 and GIP levels are low in the fasting state and increase only after food intake. Hence GLP-1 analogues have a low risk for hypoglycaemia as their effect on insulin secretion is on a glucose dependent manner.

It works by stimulating insulin secretion after food intake and inhibits beta cell apoptosis. These lead to increased availability of insulin thus reducing blood glucose levels (5).

Other functions of GLP-1 include early satiety by delaying gastric emptying and by direct actions on the hypothalamus. GLP-1 acts on the neuropeptide Y neurons on the hypothalamus which results in vagal nerve activation. Both these actions promote weight loss.

ADMINISTRATION

Most GLP-1 RA are available as subcutaneous injections which is a major barrier to their usage. Oral Semaglutide is the first oral GLP-1 RA product approved by the FDA for the treatment of type 2 diabetes.

Dosing frequency for some commonly prescribed GLP-1 receptor agonists are mentioned below:

Liraglutide	Once daily
Lixisenatide	Once daily
Tirzepatide	Once weekly
Dulaglutide	Once weekly
Albiglutide	Once weekly
Exenatide QW	Once weekly
Exenatide BID	Twice daily
Semaglutide	Once weekly if subcutaneously and daily if taken orally

Table 1: Dosing frequency of GLP1-RA

INDICATIONS

GLP-1 RA can be used as a first line agent along with metformin for glycaemic management independent of the HbA1C value. It acts by mainly reducing the post-prandial sugar. Hypoglycaemia is very rare unless the GLP-1 RA is combined with insulin or sulfonylureas. Hba1c reduction is about 0.8 to 1.5 percent and hence it is a potent drug for treating diabetes.

In adults with type 2 diabetes and established or at high risk of atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease, a GLP-1 RA is preferred for glycaemic management due to lower risk of hypoglycaemia as patients with CKD are at high risk for hypoglycaemia. Most patients with CKD die of cardiovascular causes, and hence these drugs reduce mortality significantly. GLP-1 RA promotes myocardial glucose uptake and utilisation, reduces oxidative stress and inhibits cardiomyocyte apoptosis. This prevents adverse cardiac remodelling.

GLP-1 RA have a reno-protective effect due to its anti-inflammatory action. It decreases the production of renal tumour necrosis factor- alpha and interleukins thus reducing nephron damage. Liraglutide is known to decrease progression of proteinuria and delay the onset of renal dysfunction in patients with type 2 DM,in a large randomised controlled trial .

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Result (LEADER) trial, which was started in 2010 assessed the efficacy of liraglutide in reducing cardiovascular mortality in patients over a period of 5 years. It was a randomized, double-blind trial that assessed the effect of liraglutide versus placebo on cardiovascular outcomes in 9,340 people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, the LEADER trial showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer

participants in the treatment group (13.0%) than in the placebo group (14.9%). Deaths from cardiovascular causes were significantly reduced in the liraglutide group compared with the placebo group (6)

Liraglutide is used as an adjunct to treat obesity. It is indicated for individuals with a BMI > 30 kg/m² or a BMI > 27 kg/m² who have at least one weight related condition. It is initiated at a dose of 0.6 mg per day and can be titrated up every week until a dose of 3 mg/day is achieved. Semaglutide for weight reduction is started off as a 0.25 mg subcutaneous injection and the dose is titrated every week up to a maintenance dose of 2.4 mg.

In the STEP2 trial conducted to assess the efficacy of Semaglutide (SMG) in treating obesity, more than 1,200 patients with diabetes complicated with obesity were randomly divided into 1mg SMG group, 2.4mg SMG group, or placebo group. The weight loss ranges of the two treatment groups were -6.9 kg (-7%) and -9.7 kg (-9.6%), respectively. The 2.4 mg group lost the most weight, which means that among adults suffering from overweight or obesity and diabetes, SMG 2.4 mg once a week has achieved significant clinically significant weight loss (7)

THE INDIAN PERSPECTIVE OF GLP-1 RA

Commonly prescribed GLP-1 RA in India are Liraglutide, Dulaglutide and Semaglutide.

Liraglutide remains the most widely used GLP-1 RA in India for treating type 2 diabetes mellitus. It is given as 0.6 mg subcutaneously in the first week and can be increased up to a maximum of 1.8 mg per day. Cost is a limiting factor for its usage as the patient will incur a cost of Rs.10,000 per month.

Semaglutide is given as 0.25 mg subcutaneous every week and can be titrated to 1 mg every week slowly for glycaemic control. If glycaemic control is not achieved after at least 4 weeks on 1 mg dose then it can be increased to 2 mg once a week which is the maximum dose.

Oral Semaglutide is given on a daily basis. It is started as a 3 mg per day dose and can be titrated

up to 14 mg per day based on the glycaemic control. Oral Semaglutide was launched in India in 2022, however cost is a limiting factor as each 3 mg pill costs Rs.315 leading to significant cost burden to the patient.

ADVERSE EFFECTS

The most frequently exhibited side effects from GLP-1 RA include nausea, vomiting, and diarrhoea. Dizziness, mild tachycardia, infections, headaches, and dyspepsia may also occur.

Patients should receive counselling that this class of drugs increases satiety, and transient, mild nausea may occur if they attempt to eat while feeling full. Increasing the dosage of these medications should occur slowly if nausea is present. Injection-site pruritus and erythema are also common, most notably with the longer-acting medications in this class.

There is a low risk of minor episodes of hypoglycaemia; however, research has not described any major hypoglycaemic episodes. Combination therapy with GLP-1 agonists and dipeptidyl peptidase-4 inhibitors is not a current recommendation due to statistically insignificant glycaemic improvement and enhanced hypoglycaemic effects. GLP-1 RA can be given along with basal insulin to improve glycaemic control; however, dose reduction of insulin is necessary to prevent hypoglycaemia.

CONTRAINDICATIONS

Contraindications to utilizing GLP-1 RA includes previous history of hypersensitivity to GLP-1 RA and pregnancy as it is a class-C teratogen. Patients with severe gastrointestinal diseases such as gastroparesis and inflammatory bowel disease should avoid GLP-1 RA.

Long-term consequences on the thyroid gland have been a concern. In rodent models, liraglutide stimulated calcitonin release and led to hyperplasia of thyroid gland C-cells and tumours. The effects on humans remain unclear. Hence GLP-1 RA are not recommended in patient populations with a history significant for multiple endocrine

neoplasia 2A, multiple endocrine neoplasia 2B, or medullary thyroid cancer

While the mechanism remains largely unknown, acute pancreatitis, including potentially fatal haemorrhagic and necrotizing types, has been noted in users of GLP-1 RA. Clinical trials by have showed an incidence of 1.6 cases of acute pancreatitis per 1000 patient-years exposure to liraglutide compared to 0.7 cases per 1000 patient-years in placebos. Routine monitoring of amylase and lipase are not recommended unless the patient is symptomatic.

MONITORING

If a GLP-1 RA is added to a regimen already consisting of a sulfonylurea or long-acting insulin, patients require monitoring for hypoglycaemias. A decrease in the insulin dose may become necessary, depending on the GLP-1 RA selected. Patients taking GLP-1 RA should regularly have their haemoglobin A1c measured and have a serial monitoring of blood glucose done at home to assess glycaemic trends. Creatinine can be monitored periodically as with any diabetic patients but the risk of drug induced kidney injury is low.

Healthcare providers should also monitor patients taking GLP-1 RA for signs and symptoms consistent with pancreatitis. The FDA currently has recommended against routinely monitoring calcitonin levels for medullary thyroid cancer.

CONCLUSION

The battle ground for survival has always been fought in the vascular bed, and cardiovascular and renal complications decide hugely the morbidity and mortality in type 2 DM. The search for drugs which thus have benefits beyond just glycaemic control, and impact these aspects , has opened up the road for better prognosis in diabetes . These drugs have cardiovascular and renal benefits, and hence SGLT2 inhibitors ,and GLP 1 analogues , have changed the lives of patients with type 2 DM significantly, and are valued additions to the physicians armamentarium in the control of diabetes and its complications .

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Gestational Diabetes Mellitus - The Peril Of Pregnancy !

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Gestational diabetes mellitus (G D M) , as the name suggests, is any quantum of a glucose intolerance that is detected after 20 weeks of pregnancy. Affecting nearly 10 %- 14.3 % of all the pregnant mothers, with an estimated risk of a whooping 45% - 60 % to develop into frank diabetes mellitus within the next 10 to 20 years, GDM has overtly been a burden of the all cause morbidity & mortality of the patients., therefore this would warrant for an effective screening tool to detect & halter the latter.

Therefore ,we as gynecologists widely rely on the results obtained from the Oral glucose tolerance test (OGTT) , usually performed within 24 – 28 weeks, where for an Indian pregnant woman , where 75 g of oral glucose is administered & a 2 – hour blood sample is collected. Values of a > 140mg / dl would be considered as the G D M & values > 120 mg / dl would bear the nomenclature of 'decreased gestational glucose tolerance (DG GT) . DG GT bear resemblance to the impaired glucose tolerance (I G T) but the latter is used only for non – pregnant woman. This is strictly in accordance with the Diabetes in pregnancy study group India (DIPSI) guideline . **A remarkable property of the guideline as mentioned lies on the virtue of collecting & testing the blood sample irrespective of the weather the patient is fasting or has taken the meal.**

Whereas the World health organization (W H O) performs the OGTT using 75 gm of glucose & a 2 hour post prandial reading of > 140 mg / dl would be considered as a case if G D M straightaway. Though the process of performing the OGTT looks simple & reasonable as only a single blood sample is taken & interpreted ,it musyt be kept in mind

that a random fasting sample of a > 126 mg / dl OR a 2 hr OGTT sample shows a > 200 mg / dl , it may be suspected that the mother had undetected diabetes prior to conception (PG DM) & thus would warrant a further confirmation using a glycosylated hemoglobin sample.

The IAD PSG diagnostic protocol recommends investigations during the first trimester of pregnancy to identify women with overt, undiagnosed Diabetes by measuring fasting glucose resulting in > 126 mg/dL, glycated hemoglobin of >=6.5% or random blood glucose of >=200 mg/dL. A single confirmed changed test result is sufficient for the diagnosis of overt diabetes. They recommend the universal screening of all pregnant women, with no pre-existing diagnosis of overt diabetes, between 24 and 28 weeks of pregnancy. Screening consists of the 75-g OGTT and the collection of three glucose samples (fasting, 1 & 2 h after the glucose overload) where the normal limits are, respectively, 92mg / dl, 180 mg / dl & 153 mg/dL.

Mothers who have a strong family history of diabetes , sedentary lifestyles , high BMI , a previous pregnancy yielding > 4 kg fetal weight , dyslipidemia with triglycerides > 250 mg / dl & HD L < 35 mg / dl , history of Poly cystic ovarian syndrome (PCOS) , Impaired glucose tolerance test , impaired fasting glucose , glycated hemoglobin of > 5.7 % , cardiovascular or the common metabolic syndromes are extremely prone to develop the disease . rendering the HbA1c as an inadequate tool to stamp the diagnosis, OGTT estimations would cater to the need for patients with the G D M .



The offending hormone for such an entity has been deciphered to be the human placental lactogen secreted from the placenta to control & accentuate the nutritional status of the fetus in utero which surprisingly harbors properties to perform alterations on the insulin receptors of the body which reduces uptake of the glucose in the peripheral tissues, thereby leading to the G D M .Complications of GDM as we see in our daily practice would be macrosomia, neonatal hypoglycemia, shoulder dystocia, hyperbilirubinemia, polycythemias , ARDS in the neonate & sometimes tetany in the baby. Complications for the mother would include hypertension, preeclampsia & increased risk of cesarean delivery

Whereas, The ACOG recommended levels of blood glucose in pregnancy is fasting plasma glucose under 95 mg/dL, 1 hour postprandial under 130-140 mg/dL, 2 hours postprandial below 120mg/dL, treatment of the latter is essential. Adherence to the a specific diet chart under the parameters of caloric allotment, caloric distribution, and carbohydrate intake along with 30 mins of moderate aerobic activity for five times a week is the initial prescription , non – resolution of the symptomology , worsening of anti – natal parameters or non-achievement of glycemic control would further essentially need insulin , based on the diet of the patient . Despite of having some standard recommendations to use insulin is 0.7 units/kg/day in the 1st trimester , 0.8 units/kg/day in the 2nd trimester & 0.9 to 1.0 units/kg/ day in the 3rd trimester , we usually recommend the patient the divide the daily requirement of the insulin in two halves , one half to be divided & administered 15 mins before meals for breakfast , lunch & dinner in the form of rapid acting or regular insulins & the other half to be administered in the bedtime using basal insulin . Another point would be the use of metformin, especially in patients of P C O S , started at 500 mg titrated up to 2.5 gms . A recent update regarding the treatment would be the use of long-acting insulins such as detemir, with the pitfall of the latter being

some severe episodes of nocturnal hypoglycemia which can be detrimental for the mother & the baby. In our clinical practice, we usually refrain from using long-acting insulins.

Though there has been some overwhelming research when it comes to gestational diabetes mellitus where IADPSG criteria would be a useful predictor for congenital anomalies of the fetus in utero , where the third-trimester fetal anthropometry would predict adversities in the fetus, where the PROMIS trial based on insulin sensitivities & glucose metabolism would necessarily predict outcomes on the patient with GDM , where secretagogin which is a calcium binding protein would be a future prognostic marker for G DM , where a Mediterranean diet would be beneficial for the mother , such practices still do need strong testimonial evidence to be harbored into the current practice of the treatment of G DM & therefore , we do not harbor such in our day to day clinical practices.

Whereas the need to educate patients hold utmost importance with respect to the prevention of the disease for a healthy pregnancy, such may only be achieved by an integrated approach by a judicious interdependent specialty health care providers as the physicians, specialists, trained nurses & pharmacists. Noteworthily, on Anti natal visits, samples must be taken in the first trimester itself, which, if negative, the tests must be performed on the 24th - 28th week & finally at the 32nd – 34th week of pregnancy for an effective screening. The importance of such an endeavor has been detailed in the ELENA study where information, education & communication (IEC) have been widely recognized as a tool to combat the dreaded disease. Monitoring the progression, advocating a virtuous lifestyle, proper administration & reconciliation of the drug administered, use of radio diagnostics to screen the baby would certainly help to obtain an acceptable product & prevent the further morbidity & the mortality load for the mother



Diabetic Foot Ulcer-a Common Cause of Atraumatic Limb Loss In Current Era

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INTRODUCTION

The burden of diabetes Mellitus has risen dramatically over the past two decades. Based on current trends 642 million individuals will have diabetes by the year 2040 as projected by IDF (1). Diabetic foot ulcer is a common cause of non-healing chronic ulcer and a major public health problem now a days.

The management of chronic foot ulcer with diabetes remains a major therapeutic challenge for doctors throughout the world. Patients with chronic diabetic ulcers have to deal with pain, infection, hospital stays, and amputations. For patients and their families, this results in a poor quality of life. For the community, it results in large healthcare expenditures, which could be reduced if a proper, evidence-based treatment for these chronic ulcers would exist.

EPIDEMIOLOGY

10 percent to 25 percent among diabetic patients has a risk of developing ulcers. 50 to 60 thousands of atraumatic amputations performed in United States due to diabetes. It is estimated that 60 to 70 percent of diabetic ulcers are due to neuropathy. 15-20 percent due to vascular ischemia and rest 15 to 20 percent due to combination of both.

PATHOPHYSIOLOGY

Sequence of events related to development of diabetic ulcers are described as follows. At the beginning due to persistent hyperglycaemia there is both sensory and motor neuropathy. Following this sensory neuropathy there is unrecognised injury in foot due to ill-fitting shoes, foreign body

or other trauma. Associated with motor neuropathy or charcot's foot lead to collapse and dislocation of the interphalangeal or metatarsophalangeal joints, causing pressure on areas with little protection. There is also severe micro and macro vascular circulatory impairment. Once the ulceration occurs there less chance of healing and high chances of recurrence. Autonomic neuropathy causes absence of sweating and loss of skin elasticity making our natural barrier more prone to breakdown and infection.

PROBLEMS WITH DIABETIC ULCER

1. **Peripheral Arterial Disease**- Ischaemia in the form of peripheral arterial disease is a significant contributor to the burden of the diabetic foot (2). Atherosclerosis is not only more prevalent in people with diabetes, but its natural history is also hastened. Peripheral arterial disease exceeds 20% in diabetes when it is identified by an abnormal ankle-brachial index (3).
2. **Chronic Non-Healing Ulcer**- The lifetime risk of developing a diabetic foot ulcer is between 19% and 34% and it is estimated that 9.1 million to 26.1 million individuals with diabetes globally develop foot ulcers every year (4).
3. **Infection**- Diabetic foot ulcers are very vulnerable to infection. About 50%-60% of ulcers develop infection which is the leading pathology that devastates most diabetic feet. Approximately 20% of moderate or severe diabetic foot infections result in amputation at various levels (5). The

incidence of osteomyelitis diagnosed by culture is approximately 20% of diabetic foot ulcers (6). All stages of infection may also be complicated by bacteraemia, resulting in systemic signs of infection.

4. **Limb Loss**-Every 20 s a lower limb is amputated due to diabetes (7). Of all amputations in persons with diabetes, 85% are preceded by a foot ulcer (8).
5. **Mortality**-A recent review has demonstrated 5-year mortality for Charcot neuroarthropathy, foot ulceration, minor and major amputations to be 29.0%, 30.5%, 46.2% and 56.6%, respectively (9).
6. **Global Disability**-Foot complications in diabetes are a leading cause of the global burden of disability (10). Global prevalence of foot complications includes 131.0 million people (1.77% of the global population) with diabetes-related lower-extremity problems, incorporating 105.6 million (95% UI 85.5–128) with neuropathy only, 18.6 million (15.0–22.9) with foot ulcers, 4.3 million (3.7–4.9) with amputation without prosthesis, and 2.5 million (2.1–3.0) with amputation with prosthesis (11).
7. **Quality of Life**-Lower extremity complications also result in a reduction in quality of life (12).

INVESTIGATIONS

Specific investigations we can do to look for glycemic status of the patient like-Fasting Blood Sugar,Post Prandial Blood Sugar, oral glucose tolerance test etc, and to look for glycemic control of the patient Glycosylated hemoglobin levels can be checked.Lipid profile also done to rule out concomitant atherosclerosis.Complete blood count, ESR, CRP, Procalcitonin done to look for systemic infection or sepsis.Digital X-ray of the affected area done to look for osteomyelitis.Colour Doppler Study of the affected limb are done to check for atherosclerosis and flow patterns of peripheral arteries like triphasic or normal flow or biphasic or monophasic seen in peripheral arterial disease.

On Further work up as diabetic is a multi-system disorder, we should evaluate other system of the individual as a treating physician. Like routine eye check-up to rule out diabetic retinopathy.USG Colour Doppler of Neck Vessels to look for atherosclerotic carotid involvement which is a risk factor for CVA of such patients. 2D ECHO and colour Doppler study of heart can be done to look for any wall motion abnormalities or ischemic mitral regurgitation in case of associated underlying coronary artery disease or aortic atherosclerosis.To rule out diabetic nephropathy routine urine examination to look for urine sugar,ketone body, microalbuminuria,Urine Albumin Creatinine ratio and blood level of urea,creatinine.If kidney function is normal we can do Screening CT Coronary angiogram or conventional coronary angiogram in cath lab to rule out coronary artery disease.And Screening CT Peripheral angiogram (Fig-1) to rule out peripheral arterial involvement of such systemic metabolic disorders.

MANAGEMENT

Management of Diabetic foot ulcer includes optimal therapy for foot ulcers and prevention of amputation through identification of high-risk patients, education of the patient, and institution of measures to prevent ulceration like use of micro cellular rubber shoes.Providers should consider screening for asymptomatic PAD in individuals >50 years of age who have diabetes and other risk factors using ankle-brachial index testing in high-risk individuals. Patient education is to aware the individual about 1) careful selection of footwear, (2) daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma, (3) daily foot hygiene to keep the skin clean and moist, (4) avoidance of self-treatment of foot abnormalities and high-risk behaviour (e.g., walking barefoot), and (5) prompt consultation with a health-care provider if an abnormality arises. Patients at high risk for ulceration or amputation may benefit from

evaluation by a foot care specialist. Calluses and nail deformities should be treated by a podiatrist. Interventions directed at risk factor modification

include orthotic shoes and devices, callus management, nail care, and prophylactic measures to reduce increased skin pressure from abnormal bony architecture. Attention to other risk factors for vascular disease (smoking, dyslipidemia, hypertension) and improved glycemic control are also important. Due to the multifactorial pathogenesis of lower extremity ulcers, management of these lesions is multidisciplinary and often demands expertise in orthopaedics, vascular surgery, endocrinology, podiatry, and infectious diseases.

The plantar surface of the foot is the most common site of ulceration. Ulcers may be primarily neuropathic (no accompanying infection) or may have surrounding cellulitis or osteomyelitis. Cellulitis without ulceration should be treated with antibiotics that provide broad-spectrum coverage, including anaerobes.

An infected ulcer is a clinical diagnosis. The infection surrounding the foot ulcer is often the result of multiple organisms, with aerobic gram-positive cocci (staphylococci including MRSA, Group A and B streptococci) being most common and with aerobic gram-negative bacilli and/or obligate anaerobes as co-pathogens. Gas gangrene may develop in the absence of clostridial infection.

Cultures should be obtained from the debrided ulcer base or from purulent drainage or aspiration of the wound. A wound that probes to the bone represents clinical evidence of osteomyelitis. Plain radiographs of the foot should be performed to assess the possibility of osteomyelitis in chronic ulcers that have not responded to therapy. Magnetic resonance imaging (MRI) is the most specific modality, with nuclear medicine scans and labeled white cell studies as alternatives. Surgical debridement is often necessary.

Osteomyelitis is best treated by a combination of prolonged antibiotic and debridement of infected bone when possible. The possible contribution of vascular insufficiency should be considered in all patients. Peripheral arterial bypass procedures are often effective in promoting wound healing and in decreasing the need for amputation of the ischemic limb.

Interventions with demonstrated efficacy in diabetic foot ulcers or wounds: (1) off-loading, (2) debridement, (3) wound dressings, (4) appropriate use of antibiotics, (5) revascularization, and (6) limited amputation. Off-loading is the complete avoidance of weight bearing on the ulcer, which removes the mechanical trauma that retards wound healing. Bed rest and a variety of orthotic devices or contact casting limit weight bearing on wounds or pressure points. Surgical debridement is important and effective, but the efficacy of other modalities for wound healing (enzymes, growth factors, cellular therapy, hyperbaric oxygen) is unclear. Dressings such as hydrocolloid dressings promote wound healing by creating a moist environment, controlling the exudate, and protecting the wound. Antiseptic agents should be avoided. Topical antibiotics are of limited value.

Referral for physical therapy, orthotic evaluation, and rehabilitation should occur once the infection is controlled.

Mild or non-limb-threatening infections can be treated with oral antibiotics directed predominantly at methicillin-susceptible staphylococci and streptococci (e.g., dicloxacillin, cephalosporin, amoxicillin/clavulanate). However, in patients with a prior history of MRSA or in locations with a high prevalence of MRSA, treatment with clindamycin, doxycycline, or trimethoprim-sulfamethoxazole is preferred. Trimethoprim-sulfamethoxazole exhibits less reliable coverage of streptococci than the β -lactams, and individuals with diabetes may develop adverse effects including acute

kidney injury and hyperkalemia. Surgical debridement of necrotic tissue, local wound care (avoidance of weight bearing over the ulcer), and close surveillance for progression of infection are crucial. More severe infections require IV antibiotics as well as bed rest and local wound care. Urgent surgical debridement may be required. Optimization of glycemic control should be a goal. IV antibiotics should provide broad-spectrum coverage directed toward *Staphylococcus aureus*, including MRSA, streptococci, gram-negative



aerobes, and anaerobic bacteria. Initial antimicrobial regimens include vancomycin plus a β -lactam/ β -lactamase inhibitor or carbapenem or vancomycin plus a combination of a quinolone plus metronidazole. Daptomycin, ceftazidime, or linezolid may be substituted for vancomycin. If the infection surrounding the ulcer is not improving with IV antibiotics, reassessment of antibiotic coverage and reconsideration of the need for surgical debridement or revascularization are indicated. With clinical improvement, oral antibiotics and local wound care can be continued on an outpatient basis with close follow-up. After Debridement and dressing large ulcers (Fig-2) can be managed with skin graft or flap coverage with the help of plastic surgeons.

Other Systems also should be treated accordingly as per work up findings with the help of corresponding discipline of medical speciality.

CONCLUSION

Diabetic foot ulcer has a complicated pathology initiated by diabetic neuropathy due to nerve demyelination by sorbitol causing Charcot's motor neuropathy, deformity associated with sensory and autonomic neuropathy resulting formation of ulcer which can be complicated by infection. This may eventually result in amputation (minor or major) and increased mortality. These complications of the diabetic foot result in considerable clinical and economic burden and for these reasons, the diabetic foot remains a major public health problem. Successful management of the diabetic foot requires the expertise of a multidisciplinary care team which gives integrated care focused in a diabetic foot clinic. As diabetic is a metabolic disorder affecting multiple systems treating physician or team should also take care of other organs when treating diabetic foot ulcer.

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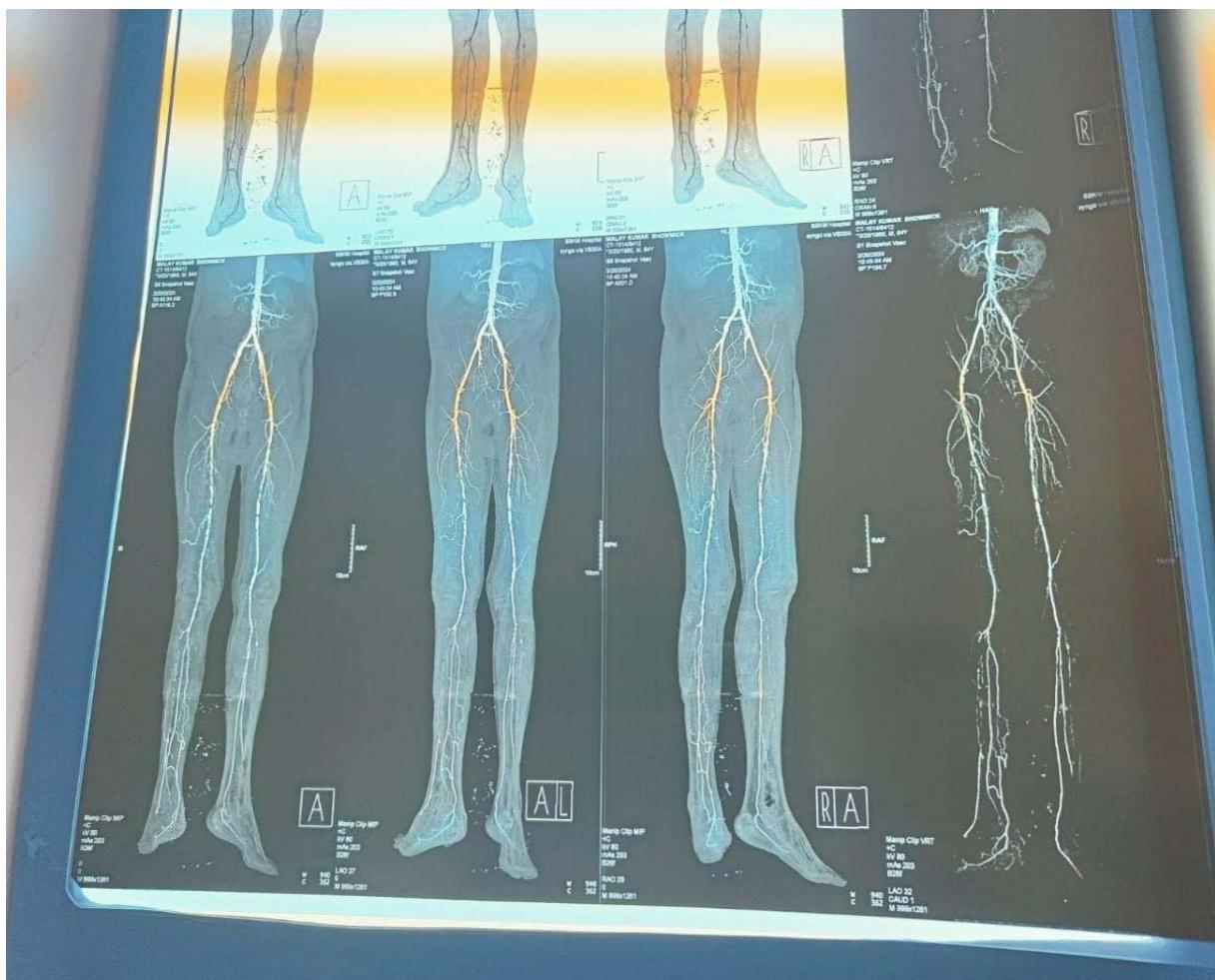


Fig-1: CT Angiogram of bilateral lower limb vessels showing peripheral arterial disease of a diabetic foot ulcer patient.



Fig-2: Picture of diabetic foot ulcer of right leg after surgical debridement. Right great toe already amputated.



Targeting Remission of Diabetes

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Diabetes is increasing worldwide with substantial increase in cases in India too. The burden in our country was previously estimated as 74.2 million and projection was 124.9 million by 2045 (1). However recent data show that the prevalence has further increased with an estimate of diabetes and prediabetes in India being 101 million and 136 million, respectively. (2)

Type 2 diabetes (T2D) has long been regarded as inevitably progressive, requiring increasing numbers of OHAs and eventually insulin. An exciting recent development is the understanding that Type 2 diabetes does not have to be a progressive condition but instead there is potential for remission with dietary intervention (3).

Obesity is associated with Type 2 Diabetes (T2D). This has been shown in studies in India too (4). Reversal of Diabetes by reducing body weight is emerging as a practical target in Diabetes care (5). There had been very few attempts at organised lifestyle based interventions for reversal of Diabetes in our country. We had proposed a simple tool to practically target achieving control of diabetes and remission with focus on good food practice. Enhancing its reach will help reverse not only Diabetes but other lifestyle diseases as well.

Twin cycle hypothesis

Insulin resistance, the prime trigger of T2D, is characterised by elevated insulin levels. The management of insulin resistance with medications typically leads to a need for "intensification of medications" to improve glycemic control. Giving medications like insulin to treat insulin resistance and/or T2D does not

cure these conditions—it perpetuates or even worsens the insulin resistance. Medication leads to weight gain, leading to worsening of insulin resistance. An alternative approach to the treatment of insulin resistance is to use strategies that *lower* insulin blood levels, including non-pharmacologic treatments (6)

The 'Twin cycle hypothesis' of Type 2 Diabetes pathophysiology, postulated by Taylor et al. states that excess carbohydrate undergo lipogenesis, promoting fat accumulation in the liver. Individuals with relative insulin resistance in muscle will accumulate liver fat more readily because of higher plasma insulin levels. Increased liver fat causes resistance to insulin suppression of hepatic glucose production. Slight increase in fasting plasma glucose level will stimulate increased basal insulin secretion rates. The resulting hyperinsulinaemia will speed the conversion of excess calories into liver fat. A vicious cycle of hyperinsulinemia and blunted suppression of hepatic glucose production becomes established. At the same time, export of VLDL triglyceride will increase fat delivery to all tissues including the islets. The increased fatty acid availability in and around pancreatic islets impairs the acute insulin secretion in response to ingested food, and at a certain point, postprandial hyperglycaemia will develop. Hyperglycaemia will further increase insulin secretion rates, resulting in increased hepatic lipogenesis, spinning the liver cycle faster and driving on the pancreas cycle.

Eventually, the fatty acid and glucose inhibitory effects on the islets reach a trigger level leading to a relatively sudden onset of clinical diabetes.

Type 2 diabetes develops as long term intake of

excess food energy leads to accumulation of liver fat, driven by a vicious cycle of hepatic insulin resistance and hyperinsulinaemia. The raised liver fat level causes increased hepatic export of very low density lipoprotein (VLDL) triglycerides. If the subcutaneous fat depot cannot accommodate this, ectopic fat will build up, including in the pancreas. In people with susceptible α cells, the acute insulin response to food becomes diminished and de novo lipogenesis from glucose is enhanced. However α Cell function can be restored if liver fat is reduced through weight loss (7)

The Counterpoint study tested in short-duration type 2 diabetes the effect of calorie restriction. It showed that liver glucose handling returned to normal within 7 days and that beta-cell function returned close to normal over 8 weeks. Major underlying factor behind normalising fasting blood

glucose within 7 days is the sudden reversal of hepatic insulin resistance. Intra-hepatic fat content decreased by 30% during the first 7 days of the 800kcal/day diet and to low normal levels after 8 weeks. In the 8-week low-calorie diet period, the level of intra-pancreatic fat decreased. In step with this, the first-phase insulin response gradually increased. 8-week time course of recovery of beta cells observed in Counterpoint is consistent with switch on of genes controlling insulin production (re-differentiation) as the underlying mechanism. (8)

Remission of Diabetes

Type 2 diabetes can be understood as a potentially reversible metabolic state precipitated by the single cause of chronic excess intra-organ fat. (9)

T2D reversal is achievable using bariatric surgery, low-calorie diets and carbohydrate restriction. (10) There could be various dietary approaches to achieve Remission including Mediterranean and low fat diets but evidence is strongest for very low energy diets and VLCDs. Reducing the intake of dietary carbohydrate, the nutrient that has the biggest impact on glycaemic control can lead to rapid improvements in blood glucose control even

before any reduction in body weight is seen. Thus carbohydrate restriction can be viewed as the most effective method for lowering blood glucose.

Low carb diet reduce A1c and weight (11).

In the PREDIMED trial Mediterranean-style vs low-fat eating pattern for prevention of type 2 diabetes onset was studied. It found that the Mediterranean- style eating pattern resulted in a 30% lower relative risk . In trials up to 6 months long, the low-carbohydrate eating pattern improved A1C more, lowered triglycerides, raised HDL-C, lowered blood pressure, and resulted in greater reductions in diabetes medication. This showed that for purposes of weight loss, the ability to sustain and maintain an eating plan that results in an energy deficit, irrespective of macronutrient composition or eating pattern, is critical for success.(12)

Remission - definition

American Diabetes Association has defined Remission of Diabetes as follows.

Partial remission - HbA1c <6.5%, fasting glucose 5.6 - 6.9mmol/l, sustained over at least one year without any diabetes medication

Complete remission - HbA1c < 6%, fasting glucose < 5.6mmol/l, sustained over at least one year without any diabetes medication

Prolonged remission - complete remission of at least 5years duration without diabetes medication

Some authors consider individuals with type 2 diabetes, who are in good control with lesser number of drugs than they were on previously to be in partial remission. Kalra et al has proposed that Type 2 diabetes remission is defined as a healthy clinical state characterized by achievement of HbA1c < 7.0%, maintained for at least 6months, with or without continued use of lifestyle modification and/or metformin, provided that this is not due to complications, comorbid conditions or concomitant therapy. (13)

Remission - determinants

Various factors can be considered as determinants

of Remission. Shorter diabetes duration, lower HbA1c, not taking insulin and a greater weight loss at 1 year were associated with greater remission. In the Look Ahead trial lower baseline HbA1c, greater level of weight loss, shorter duration of T2D diagnosis, and lack of insulin use at baseline predicted higher remission rate in intensive lifestyle intervention participants (14) Our earlier studies while concurring with most of these also found that significant majority of those who achieved remission had a weight loss of only upto five kilogram. (15)

However in western studies, It was seen that weight loss of 10–15% with very-low-calorie intervention in early stages of T2D can remit T2D. Increased odds of T2D remission after metabolic surgery in the early stages of T2D starting at a weight loss of 10–15%, which plateaus with weight loss of 20–25%. For those with more advanced T2D, including those on insulin, T2D remission was only seen with 20–25% weight loss. (16)

There is ample evidence for Remission of T2D.

8-week, low-calorie diet, with follow-up support for 6 months on diet and physical activity, to reverse type 2 diabetes was done in Barbados. 25 people, 10 men and 15 women aged 26–68 years with Diabetes upto 6 years and BMI 27–53 participated. By week 8 after intervention, average weight loss was 10 kg. Three months after finishing the 8-week diet, 17 participants had fasting plasma glucose (FPG) below the diagnostic threshold for diabetes compared to three at the start, and despite remaining off glucose-lowering medication. For nine of the 12 participants could stop taking hypertension medication by the 8th week. (17)

5145 overweight or obese patients with T2D were studied in the Look Ahead trial. The intervention group received intensive lifestyle intervention (ILI) and the control group diabetes support and education DSE. At one year, 11.5% of the participants in the ILI group achieved remission.

Remission rates achieved through ILI were 3 -6 times higher. Remission rates decreased over time (9.2% at year two and 7.3% at year four. A pilot

study in the Netherlands studied Nutrition and lifestyle intervention in type 2 diabetes. The 6-month multicomponent outpatient group-based nutrition and lifestyle intervention programme on glycaemic control and use of glucose lowering medication in motivated T2D patients with a body mass index (BMI) $> 25 \text{ kg/sq m}$ in the Netherlands (February 2015–March 2016) showed improved glucose control and reduction in glucose lowering medication . 74 T2D patients were studied. At 6 months, 49% of the participants had reduced their medication or eliminated it completely (18). In an observational study by our group, presented at IDF 2019, on the effect of lifestyle intervention on Type 2 Diabetes in 3 months, we found that 86% of patients lost weight and 72% could either reduce or stop medications for Diabetes (19)

A study in Dutch primary care setting with 15 adults, average T2D duration of 13.4 years who were treated for T2D received a diabetes subtyping (diabetotyping) lifestyle intervention (DLI) for six months. Insulin and sulphonylurea (SU) treatment could be terminated for all participants. Body weight, waist/hip ratio, triglyceride levels, HbA1c, fasting, and 2 h glucose significantly improved after three and six months of intervention. Remission and reversal were achieved in two and three participants, respectively. Indices of insulin resistance and beta cell capacity improved.

Out of 11 participants using blood pressure lowering medication at baseline, four had a decreased dosage and two completely stopped using this medication at six months of intervention. Furthermore, out of 12 participants using lipid-lowering medication at baseline, five had a decreased dosage and one completely stopped using this medication at six months of intervention. (20)

In a population-based prospective cohort study of 867 participants, 30% (257) achieved remission of Type 2 diabetes at 5 years through lifestyle changes. Positive primary care experiences increased likelihood of remission. Participants who reported higher CARE scores in the 12 months following diagnosis were more likely to achieve remission. The CARE measure quantifies

experiences in primary care with a particular focus on *relational aspects, such as empathy, compassion, under-standing, shared decision-making and whether the patient felt listened to, considered as a whole person and understood* (21)

Low carbohydrate diet (LCD) as a tool for Remission of T2D.

Various scientific bodies recommend Remission by LCD. Diabetes UK 2017 position statement supports the use of LCDs. British Dietetic Association (BDA) position statement in 2018 support carbohydrate restriction as a viable option for adults with Type 2 diabetes. Scottish Intercollegiate Guidelines Network recommend that people with Type 2 diabetes be given dietary choices for achieving weight loss that may also improve glycaemic control. The listed options for achieving this include restricting the total amount of carbohydrate that is consumed. 2018 joint position statement from the ADA and EASD promoting individualised dietary approaches for patients, with LCDs being listed as a suitable option. 2019 consensus report from the ADA states that "Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycaemia. (22)

Low carbohydrate diet can be divided into 3 categories: (11)

1. very low carbohydrate diet - 20-50 g/day carbohydrates (< 10% of the 2000 kcal/day) generally sufficient to induce ketosis
2. low carbohydrate diet - < 130 g/day or (< 26% of the 2000 kcal/day diet)
3. moderate carbohydrate diet - 130-230 g/day (26 - 45% of 2000 cal diet)

In a study of 185 participants to assess the effect of real-World Low Carbohydrate Diet on Insulin use it was seen that at 12 months (45.9%), reduced their median insulin dose from 69 to 0 units ($p < 0.0001$), HbA1c from 8 to 6.9% ($p < 0.0001$), and weight from 116 to 99 kg ($p < 0.001$). 86% percent who completed 12 months were able to

reduce or discontinue insulin with 70.6% completely discontinuing. Among all participants who completed 3, 6, or 12 months, 97.6% were able to reduce or eliminate insulin use. The authors concluded that in patients with T2DM on a LCD, it is possible to reduce and even discontinue insulin use while facilitating weight loss and achieving glycemic control. A Low Carbohydrate Diet should be offered to all patients with diabetes, especially those using insulin. (23)

Energy consumed from carbohydrate and mortality has a U-shaped association. It was seen that 50-55% energy from carbohydrate was associated with the lowest risk of mortality. Meta-analysis of all cohorts (432 179 participants), both low carbohydrate consumption (<40%) and high carbohydrate consumption (>70%) conferred greater mortality risk with a pooled hazard ratio 1.20, for low carbohydrate consumption; 1.23, for high carbohydrate consumption. Results varied by the source of macronutrients: also with mortality increased when carbohydrates exchanged for animal-derived fat or protein mortality decreased when the substitutions were plant-based (24)

In patients on LCD it is important to monitor blood glucose and blood pressure closely and decrease medications that can cause hypoglycaemia and hypotension. The most immediate and important adjustments are to insulin, sulfonylureas, SGLT2 inhibitors, blood pressure medications and diuretics. At least a 50% reduction in dose of insulins while stopping the sulfonylureas and meglitinides will be required. Further reductions in insulin may be necessary according to the blood glucose response. In individuals on a basal bolus regimen, it is advised to preferentially reduce or stop bolus insulin. As glucose levels improve, basal insulin can then be reduced. Mixed insulin should be stopped and switched to basal insulin alone and the daily dose can be reduced by 30–50% at the start of LCD. It is appropriate to stop SGLT2i's in many cases, particularly in those adhering a very low carbohydrate diet (30–50 g/day). Thiazolidinediones - Concerns exist over their long-term safety, including risks of bladder cancer, heart failure, and reduced bone mineral density. It

is recommended to stop thiazolidinediones as soon as glucose levels allow. Thiazolidinediones are also known to cause weight gain. *Metformin* is safe to continue and in some patients continues to offer favourable benefits.

Self-monitoring of blood glucose or continuous glucose monitoring (CGM) can be very helpful in providing rapid feedback. Antihypertensive medications should be titrated. (25)

The standard recommendation is to achieve and maintain 7–10% loss of initial body weight. The recommended usual proportions of macronutrients for general public is as follows:

45% of their calories from carbohydrate 36–40% of calories from fat

16–18% from protein. Recommended Daily Allowance of carbohydrate for adults without diabetes is 130 g/day minimum of 14 g of fiber per 1,000 kcal. sources. Whole intact grains, non-starchy vegetables, avocados, fruits, and berries, pulses such as beans, peas, and lentils are recommended. (26)

Physical activity for children, adolescents with type 1 or 2 diabetes or prediabetes should be 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle strengthening and bone-strengthening activities at least 3 days/ week. For adults - 150 min or more of moderate to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity is recommended along with 2–3 sessions/ week of resistance exercise on nonconsecutive days and Flexibility training and balance training 2–3 times/week. (27)

Our experience

Patients attending our Diabetes clinic from 2018 were encouraged to follow good food practice (carbohydrate and calorie restriction). A lifestyle tool was formulated with food being given using the food plate method. The specialized programme is called SLIM (Structured Lifestyle Intervention Method). It focuses on diet and

exercise. Patients are given lectures and a model breakfast based on the food plate method. Half of the plate is filled with vegetables and fruits, proteins form quarter of the plate and grains are restricted to one quarter. A model menu is given to the patients and they are encouraged to follow that. Training on exercise is given 1 month later. These patients are subsequently followed up periodically. Patients who achieved remission or reversal of Diabetes were studied to quantify the changes and to assess the impact and acceptability of lifestyle measures. It was seen that Food plate based lifestyle intervention is beneficial in controlling blood glucose and body weight in patients with type 2 Diabetes Mellitus. (19) Reversal and remission of Diabetes through lifestyle intervention is a practical target in management of Diabetes in OP clinics. This is possible in patients with any duration though chances are more in early diabetes. Any weight loss can help. This should be aimed at in every management programme. (28) Stopping Insulin and OHAs through lifestyle intervention occurred in all ages. More patients who stopped insulin were on shorter duration of therapy. OHAs were mostly stopped in early Diabetes. Even modest weight loss is helpful to stop medications for managing type 2 Diabetes. (15)

Current situation

A large study by Kaiser Permanente found a diabetes remission rate of 0.23% with standard of care. Standard of care does not lead to diabetes reversal. This raises the question of whether standard of care is really the best practice. The status quo approach will not reverse the health crisis of diabetes (10). Current situation in India shows that the standard guidelines, especially regarding following lifestyle interventions initially for the management of Diabetes is not adhered to. It was seen that 54.9% were started with antidiabetic medication on the same day of diagnosis. Most doctors, qualified as well as nonqualified, did not follow the standard guidelines for diagnosis, treatment, and patient education regarding T2DM. It was felt that it is necessary to train all medical practitioners

regarding the guidelines for managing Diabetes and that . Diabetes reversal by lifestyle modification must be prescribed as the first line of treatment in patients with T2DM. (29)

Conclusion

Type 2 diabetes is now considered as a condition of having eaten more than required over a long period. More fat than the individual's body can safely store has accumulated, leading to excess liver and pancreatic fat and subsequent loss of plasma glucose control. In the early years after diabetes onset, removal of the excess fat in these organs via intensive but achievable weight loss allows for many a normalisation of hepatic glucose production and possible beta cell re-differentiation, and the condition can be reversed to normal. As physicians, we must grasp this paradigm shift in our understanding of type 2 diabetes for the benefit of our patients. (30)

There are strong views that the potential for diet, either low energy or low carbohydrate, to dramatically improve glycaemic control and bring about remission needs to be fully embraced within dietetics and wider diabetes care. This should then be used to support people with T2DM to achieve their goals and initiate the conversation about the potential of T2DM remission, wherever it is appropriate. (31)

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Male Sexual Disorders

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INTRODUCTION:

Sexual dysfunction can be defined as any problem that prevents a person or couple from experiencing satisfaction from sexual activity. The prevalence is quite high and it can be present in both men and women. The prevalence usually increases with age. [1]

It is a poorly recognized public health problem and seriously affect the quality of life. [2],

Dysfunction can occur in various stages of the normal sexual response cycle. It can be due to a problem in desire, arousal, or orgasm. Since it has both physiologic and psychologic components and often there is significant overlap between the two, diagnosis and management can be quite complex.[3]

Various studies have looked at the prevalence of sexual dysfunction. The nature and rates of sexual dysfunction vary across age groups. The prevalence of male sexual dysfunction is greater than 40% of men aged 40 to 70 describing some degree of erectile dysfunction.[4,5]

One Indian study by Singh et al has found the prevalence in indian men to be as high as 80%[6]

Different studies have also studied the risk factors associated with sexual health disorders. Among the lifestyle factors, smoking, tobacco chewing, alcohol dependence, and opioid dependence have been implicated. Diabetes mellitus, psychiatric disorders, and coronary artery disease were common co-morbidities associated with different sexual health disorders.

TYPES OF MALE SEXUAL DYSFUNCTION

The three main categories of male sexual dysfunction include:

- **Male hypoactive sexual desire disorder.** It is characterized by lack of interest in sexual activities or thoughts. Major causes of low libido include
 - Testosterone deficiency [7],
 - Other endocrine disorders including Hyperprolactinemia, hypercortisolemia, Overt Hypothyroidism or hyperthyroidism
 - stress, relationship issues, depression [8],
 - systemic illness,
 - Some of the medications associated with low libido include selective serotonin reuptake inhibitors (SSRIs), anti-androgens, 5-alpha reductase inhibitors, and opioid analgesics[9]
- Substance abuse including Alcohol and recreational drugs

Erectile dysfunction – It can be defined as recurrent inability to initiate or maintain an erection which is hard enough for penetration

The major causes of erectile dysfunction can be grouped as

- **Vascular:** Cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, smoking, major surgery (radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)

- Neurologic: Spinal cord and brain injuries, Parkinson disease, Alzheimer disease, multiple sclerosis, stroke, major surgery (radical prostatectomy) or radiotherapy of the prostate
- Local penile factors
- Hormonal: Hypogonadism, hyperprolactinemia, thyroid disorders, cushing syndrome or adrenal insufficiency.
- drug induced: Antihypertensives, antidepressants, antipsychotics, antiandrogens, recreational drugs, alcohol
- psychogenic: Performance-related anxiety, traumatic past experiences, relationship problems, anxiety, depression, stress

Ejaculatory disorders

Ejaculatory disorders include premature ejaculation, delayed ejaculation, retrograde ejaculation, anejaculation, and painful ejaculation.[10]

Premature ejaculations are the most common sexual dysfunction in men between 18-59 years of age.[11]

- **Premature ejaculation**, defined as ejaculation associated with lack of or poor ejaculatory control that causes distress in one or both partners. The new DSM-5 definition has now added a time requirement that the ejaculation must occur within approximately 1 minute following vaginal penetration to be deemed premature.
- **Retrograde ejaculation**, instead of ejaculation through the urethral meatus, semen is propelled backward into the urinary bladder. Retrograde ejaculation can be the result of autonomic neuropathy associated with diabetes mellitus; some medications including adrenergic antagonists, certain antihypertensives, antipsychotics, or antidepressants; bladder neck incompetence; or urethral obstruction, Transurethral Resection of Prostate or open

prostatectomy. Retrograde ejaculation due to diabetes-associated autonomic neuropathy is the second most prevalent ejaculatory disorder.[12]

- **Delayed ejaculation**, it is an uncommon sexual dysfunction where it takes a person long time to ejaculate (defined as > 30 mins) and in some cases there may be a failure to ejaculate. It is usually due to discord between partners or certain medications like alpha-adrenergic antagonists and selective serotonin reuptake inhibitors (SSRIs).[9]

RARE MALE SEXUAL DISORDERS: The exact mechanisms of these disorders are unclear and the conditions could involve both physical and psychological components.[13]

- restless genital syndrome: symptoms include unwanted and unpleasant genital sensations, and a sense of restlessness in the genital area.
- post-orgasmic illness syndrome: It presents as a coming of local mucosal symptoms and systemic flu like symptoms.
- hard–flaccid syndrome: It usually occurs after penile trauma
- sleep-related painful erections
- post-retinoid sexual dysfunction, post-finasteride syndrome, post-elective serotonin reuptake inhibitor sexual dysfunction: symptoms can last even after long durations of stopping the stopping the medications.

EVALUATION OF MALE SEXUAL DYSFUNCTION

HISTORY AND PHYSICAL EXAMINATION:

Treatment of male sexual dysfunction is etiology dependent. Hence it is important to establish accurate diagnosis through a detailed history and physical examination.

A careful history can help differentiate between organic and psychogenic causes.



History should include details regarding rapidity of onset of symptoms, presence or absence of morning erections, underlying depression, anxiety and interpersonal conflicts.

Physical examination:

Besides a General Physical Examination, focussed examination should be done to rule out neurological, vascular or endocrine causes including

- Evaluation of cremasteric reflex, brief neurological examination to rule out neuropathy.
- Assessment of femoral and other vascular pulses.
- Evaluation of gynecomastia, testicular volume, varicocele, hair loss patterns
- Assessment of visual fields in case a pituitary pathology is suspected

INVESTIGATIONS:

Work up is usually indicated to diagnose associated systemic conditions that predispose to sexual dysfunction.

Initial work up: it should include a complete blood count, urinalysis, renal function, lipid profile, fasting blood sugar and thyroid function.[14]

If endocrine cause is suspected total testosterone level should be obtained. If the testosterone levels are low then a Prolactin, luteinizing hormone and follicle-stimulating hormone levels should be ordered to differentiate primary from secondary hypogonadism.[15]

Additional testing to assess erectile function

Duplex Doppler imaging

It is done to identify arterial obstruction or venous leak .

Typically, an artificial erection is induced using a vasodilating injectable agent. The peak systolic velocity and the end diastolic velocity are measured to assess for arterial insufficiency and

venous leak, respectively.

It can also help to diagnose lack of response to phosphodiesterase-5 (PDE5) inhibitors and other medications.

Nocturnal penile tumescence testing

It is performed in a hospital sleep laboratory. Monitoring devices are now available that provide accurate, reproducible information quantifying the number, tumescence, and rigidity of erectile episodes in a man during sleep.

NPT testing is generally performed when the clinician is trying to assess between psychogenic and organic ED. Typically, males with psychogenic ED will have normal NPT results.

TREATMENT:

Hypoactive sexual Disorders:

- If psychological, patient should be referred for evaluation and psychotherapy.
- The underlying systemic disease should be treated.
- In case of Testosterone deficiency, replacement with Testosterone has been shown to increase libido. It is primarily available as various injectable preparations and gel for topical application.
- Patient should be asked to decrease alcohol intake and other recreational drugs use which can be associated with low libido.
- Very commonly it is a function of partner issues and professional counseling can be helpful to resolve any discord.

Ejaculatory Disorders:

Premature Ejaculation: management depends on the etiology. The following treatment options have been found to be effective.

- Several behavioral therapies have been found effective to increase tolerance and delay ejaculation. Most commonly recommended techniques are Start and Stop

technique and Squeeze method. In Start and Stop method, patient stops all activity at the beginning of feeling of ejaculation and resumes when excitement has waned sufficiently. In Squeeze method patient is instructed to squeeze the area where glans joins the shaft at the start of feeling of ejaculation. It reduces the erection and activity can be resumed.

- Topical anesthetics : various trials have shown lidocaine, prilocaine spray/ointments when applied to glans 5 minutes before intercourse can improve ejaculatory latency, ejaculatory control, and sexual satisfaction.[16]
- Selective Serotonin Reuptake Inhibitors are considered first line agents. According to a meta-analysis of available trials, paroxetine (10-40mg/day) has been found to be most effective. [17].Other SSRI's can be used are sertraline (50 to 200 mg/day), fluoxetine (20 to 40 mg/day), citalopram (20 to 40 mg/day), and escitalopram (10 to 20 mg/day).
- An additional SSRI Dapoxetine in doses of 30 mg-60 mg/day can be taken on demand before intercourse.
- If Premature Ejaculation is coexisting with Erectile Dysfunction, then Phosphodiesterase (PDE) inhibitors may also be effective for the treatment of Premature Ejaculation. Combined therapy is more effective than only SSRI's.
- Tramadol has also been used as a second line agent if SSRI's are ineffective or not tolerated. It has activity at opioid receptors and also inhibits reuptake of serotonin and norepinephrine.
- Testosterone replacement alone has not been found to be useful.

Delayed Ejaculation or Retrograde ejaculation disorders: These are usually secondary to medications and changing the dose or switching to other medications can be tried.

Erectile Dysfunction:

Phospho-diaesterase inhibitors (PDE-5 inhibitors): Available PDE-5 inhibitors in India are sildenafil, tadalafil and vardenafil. They have proven efficacy and safety in men with erectile dysfunction and are considered as first line pharmacotherapy for management of erectile dysfunction. Among the available PDE-5 inhibitors, sildenafil and vardenafil have short half-life, whereas tadalafil have relatively longer half-life. In general PDE-5 inhibitors have been shown to be safe and have not been associated with increased risk of myocardial infarction. However, use of PDE-5 inhibitors is contraindicated in those receiving nitrates as it can cause hypotension. Use of PDE-5 inhibitors along with alpha blockers can result in orthostatic hypotension.

- Sildenafil-It can be started as an initial dose of 50 mg and can be increased to 100 mg if responds is not satisfactory. In case of adverse effects dose can be reduced to 25 mg .It should be ideally taken on an empty stomach approximately one hour before a planned sexual encounter.
- Vardenafil - It is available as a 10 mg or 20 mg dose and has similar onset and duration of action to Sildenafil. It can be taken after eating as well.
- Tadalafil -It has a longer duration of action than sildenafil or vardenafil. Recommended starting dose is 10 mg and can be adjusted to 5 mg or 20 mg as needed. Lower doses of 2.5 mg or 5 mg can be used daily instead of on demand higher doses.
- Avanafil -It is a newer PDE5 inhibitor. It has a more rapid onset of action and enhanced PDE5 selectivity. It is taken on an as-needed basis at a starting dose of 50 mg, increasing to 100 and 200 mg as needed. It is rapidly absorbed and can be taken 15 mins prior to intercourse and absorption is not affected by food.

Testosterone Therapy

In those cases where a low sex drive and low blood levels of Testosterone are documented, Testosterone replacement may be effective for libido and to achieve normal erections. Some newer studies have shown combination therapy with PDE5 Inhibitors may be more effective than only PDE5 inhibitors.[18]

Intraurethral alprostadil - Intraurethral administration of alprostadil (prostaglandin E1) can also be used in men where PDE5 inhibitors are ineffective.

After insertion of the alprostadil into the urethra, the penis is massaged for up to one minute to ensure equal distribution in the corpora cavernosa. Doses include 125, 250, 500, and 1000 mcg.

Intracavernosal injection therapy with alprostadil (prostaglandin E1) and papaverine have been used for purposes of inducing erection. The patient uses a small needle to self inject the medication at the base of the penis. It has high efficacy rate but a large proportion of patients discontinue due to pain or discomfort.

Vacuum erection pump -A plastic cylinder is placed over the penis, and an external penile pump creates vacuum suction within the cylinder, drawing blood into the penis to create an erection.

Penile Prostheses: Semi rigid or inflatable penile implants are available for patients who do not respond to medical management.

CONCLUSION:

Sexual dysfunction in men is very common but grossly undiagnosed and untreated properly both due to patients not forthcoming to seek help and unawareness amongst medical practitioners. It needs a multi disciplinary approach with involvement of Endocrinologist, Psychiatrist and Urologist. With available treatment options, the quality of life for patients can be significantly improved.

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Multiple Endocrine Noplasia (MEN syndrome) - A Clinical talk !

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MEN syndrome , as the name suggests , encompasses a group of neoplasias producing a varied symptomology unique in nature to the classification of the later , involving the endocrine glands of the body , where both tumors harboring both the benign & the malignant potential , are found .whereas the classification of MEN syndromes , according to the existing literature would be , MEN I involving the pituitary gland adenomas , the parathyroids & the pancreatic islet neoplasias along with a predilection to gastrointestinal neoplasms (Zollinger - Ellison syndrome is frequent entity), gastric carcinoids , neuro endocrine tumors in the bronchial tree & the thymus and sometimes lipomas , MEN IIA

involving the parathyroids along with two other entities such as the pheochromocytoma & the medullary carcinoma of the thyroid gland , MEN IIB (also known as MEN III) involving pheochromocytomas , medullary carcinoma of the thyroids along with a marfanoid habitus ,craniosynostosis , mucosal neuromas , intestinal neurogangliomatosis , corneal nerve neoplasias & subconjunctival neuromas.a quiddity described as the FMTC (familial medullary thyroid carcinoma) , is considered as a isolated subset of the MEN II syndrome. Also, a MEN IV , which is a rare variant , has been described which would include a frank carcinomas involving the parathyroids , the anterior pituitary with a special inclusion of the kidney , adrenals & the adnexa.

i	18.63 Multiple endocrine neoplasia (MEN) syndromes
MEN 1 (Wermer's syndrome)	<ul style="list-style-type: none">• Primary hyperparathyroidism• Pituitary tumours• Pancreatic neuro-endocrine tumours (e.g. non-functioning, insulinoma, gastrinoma)• Bronchial and thymic carcinoids• Adrenal tumours• Cutaneous lesions (e.g. lipomas, collagenomas, angiofibromas)
MEN 2 (also known as MEN 2a or Sipple's syndrome)	<ul style="list-style-type: none">• Primary hyperparathyroidism• Medullary carcinoma of thyroid• Phaeochromocytoma
MEN 3 (also known as MEN 2b)	<ul style="list-style-type: none">• As for MEN 2 above (though medullary thyroid cancer occurs earlier, even within the first year of life)• Marfanoid habitus• Skeletal abnormalities (e.g. craniosynostosis)• Abnormal dental enamel• Multiple mucosal neuromas
MEN 4	<ul style="list-style-type: none">• Primary hyperparathyroidism• Pituitary tumours• Possible tumours in the adrenals, reproductive organs, kidneys• Possible pancreatic, gastric, bronchial and cervical neuro-endocrine tumours

Fig 1- Different neoplastic lesions that are found on the MEN syndromes.

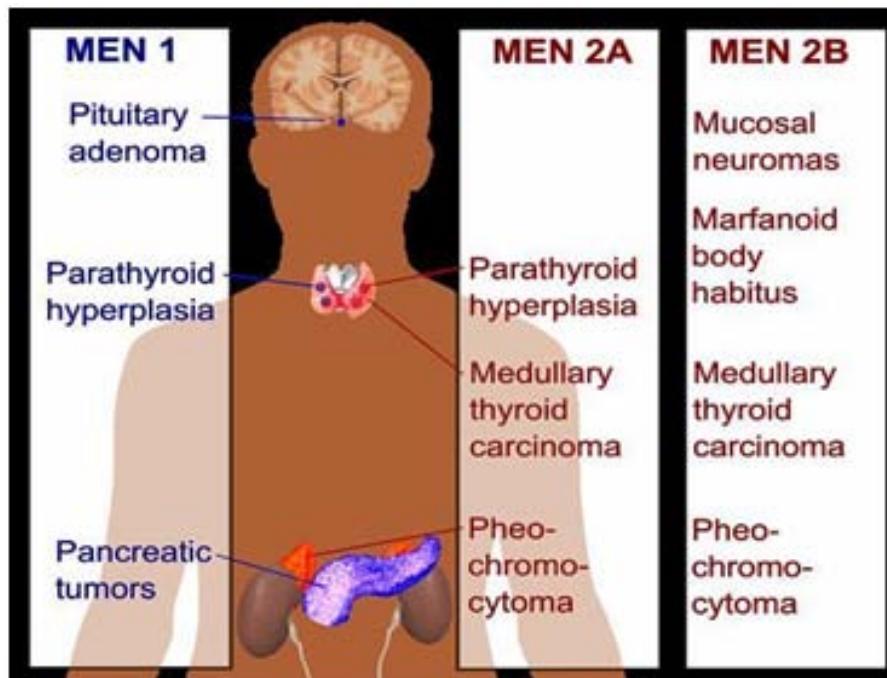


Fig 2 - A graphical depiction of the MEN syndrome .

Usually , the germ line mutations are the harbingers to develop such vivid pathologies involving the endocrine glands & would be unique to produce distinctive symptomatology. It is therefore of utmost importance to screen the genetics using cytogenetics or Fluorescent in situ hybridization (FISH) , as such entities run in families . the culprit genome is hereby known as the MEN 1 gene coding for the menin protein resulting in the MEN 1 variant , the RET oncogene for the MEN II (both II A , codon 634 mutation & II B , codon 918 mutation) & the CDKN1B genome for the MEN IV. Usually , MEN syndrome has an autosomal dominant pattern of inheritance.

Whereas it may seem that the discussion about the diagnosis of such entities encompassing such colossal endocrine pathologies would be a difficult to decipher , let us all generously focus on the cross - sectional imaging , using Computed tomography (CT)scans with/ without contrasts or a popular modality now known as the triple - phase CT which has three images which are a product of a late arterial phase, portal venous phase & a delayed phase acquisitions. the later has been a potentially sturdy radiodiagnostic tool for detecting endocrine neoplasias , along with

the Magnetic Resonance Imaging (M R I) & 18 - FDG positron emission tomograms (PET) to look out for metastasis as the tumors so described in the syndrome do harbor the property to metastasize. The needle diagnosis for histopathology & special stains using any radiological guide such as the Ultrasound (U. S .G), CT , MRI , endoscopy , colonoscopy , endoscopic ultrasounds,elastograms ,scintigrams using different isotopes , arterial secretagogue injections, naked Fine needle aspirations or Core needle biopsy along with a must clinical evaluation , a vivid history taking with special reference to the detailing of the existing pathologies of the family tree , would aid in the diagnosis as such a syndrome of our interest often overlaps with other familial neoplastic syndromes such as the Von - Hippel -Lindau syndrome & the Carney' s complex to name a few. diagnostic accuracies may be achieved using the final modality of a cytogenetic study or a FISH to stamp the etio -pathogenesis & diagnosing the disease per- se. the simple basic blood & urine parameter evaluation ,electrolytes , liver & kidney function parameters with some special tests (For example it would be the estimation of the calcium axis for parathyroid neoplasias)to aid diagnosis and to predict

prognosis alongwith the daily routine investigations , if combined with the understanding of the disease , as such syndromes are often known to occur at the younger ages , may help the clinician to furnish the exact clinical suspicion.

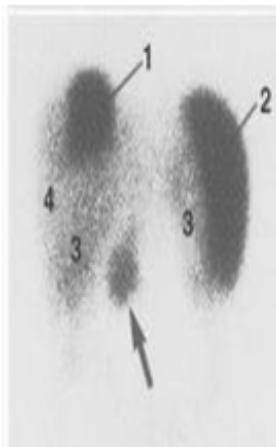
An attempt to discuss the treatment would invite an element of dyssynchrony owing to the diversity of the syndrome as described. neoadjuvant chemotherapeutics , adjuvants , radiations for debulking ,definitive exploratory surgeries based on the clinical spectrum of any of the syndrome

or its entities would possibly be a way out, though such look extremely tedious.

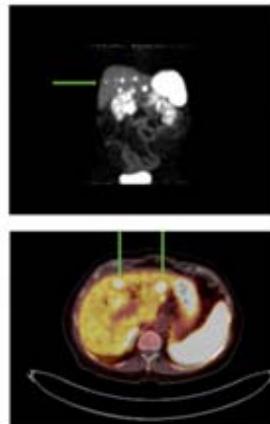
To conclude , according to my understanding what becomes of utmost importance would be the prenatal genetic screening of the fetus in utero alongwith screening of the families becomes necessary in the modern day era to terminate such pregnancies. and if , such syndromes are diagnosed later in the time, precision using the standard clinical evaluation combined with laboratory findings may help to diagnose & treat the disease early . the sooner that would be expedited , the better would that be !



(3)



(4)



(5)

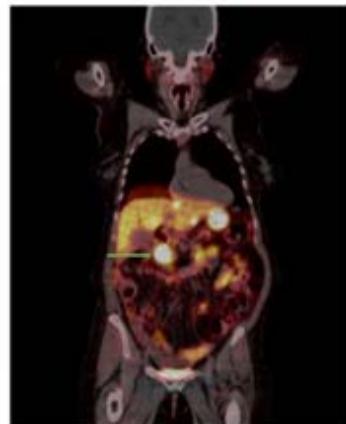
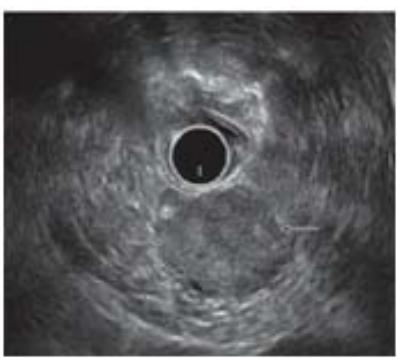


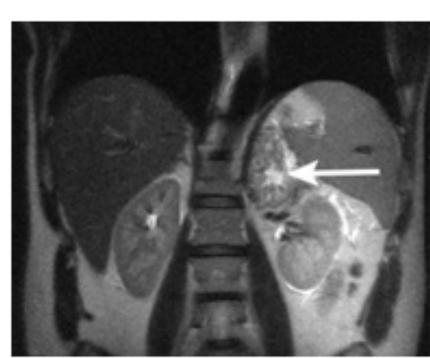
Fig 3- A MRI head with contrast depicting pituitary neoplasm in a patient of MEN 1 syndrome. Fig 4 - a somatostatin scintigram demonstrating extensive parathyroid hyperplasia especially in the region 1 & 2 in case of MEN 1 syndrome. Fig 5- PET CT using the radioisotope gallium 68 vividly demonstrates a pancreatic head mass which was later diagnosed as a neuroendocrine tumor in a case of MEN 1 syndrome.



(6)



(7)



(8)

Fig 6- a beautiful image of an endoscopic ultrasound of the pancreas demonstrating an insulinoma as the hypoechoic lesion as seen in a case of MEN 1 syndrome along with Histopathological diagnosis for confirmation. Fig 7 - A DOPA PET tomogram showing a frank medullary thyroid carcinoma (MTC) in a patient of the MEN 2 syndrome. Fig 8- A T2 sequence of the abdominal MRI demonstrating a pheochromocytoma in the left adrenal gland , a common finding in the MEN 2 syndrome.



Cushing's Syndrome

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INTRODUCTION

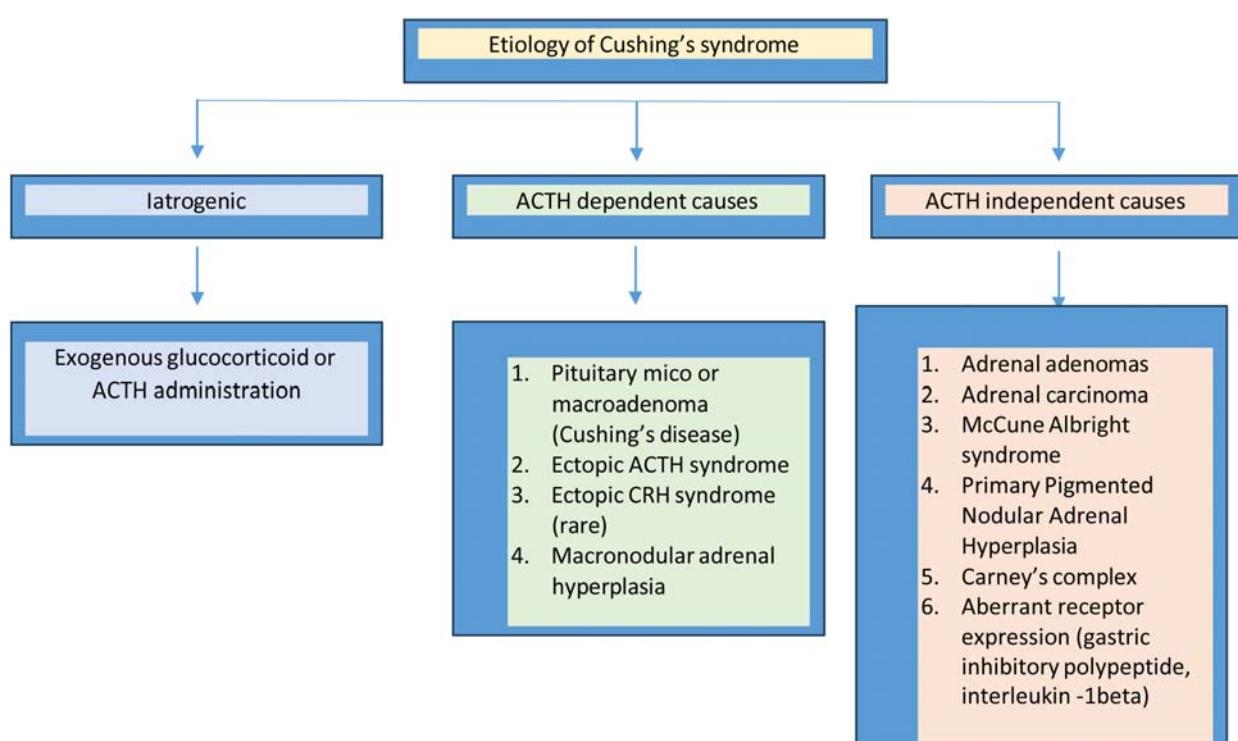
Cushing's syndrome (CS) results from exposure to high circulating levels of cortisol for a prolonged period, either from an exogenous or endogenous source. The most common source is exogenous, due to iatrogenic corticosteroid use. Harvey Cushing first described this condition, which bears his name, in 1912. CS is typically characterized by the presence of multiple symptoms and conditions that are common among the general population, such as weight gain, obesity, depression, hypertension, and diabetes. The severe and classic form may not be difficult to diagnose, but often, with associated overlapping features of other conditions (e.g., metabolic syndrome and polycystic ovary syndrome), the diagnosis can be quite challenging. This can delay the definitive diagnosis and treatment, leading to increased morbidity and mortality.

EPIDEMIOLOGY

Cushing's disease primarily affects those aged between 20 to 50 years, with a female to male ratio of 4:1. It is more common for males to have ectopic ACTH syndrome. In infancy, the most common cause of Cushing's syndrome is McCune Albright syndrome. Between the ages of 1 to 6 years, adrenal causes, predominantly adrenocortical carcinoma, are the most common cause of Cushing's syndrome. From 6 years to puberty, pituitary causes are more common than adrenal ones. For prepubertal Cushing's, the condition is more prevalent in males than females.

ETIOLOGY

The etiology of Cushing's syndrome can be categorized into:



ACTH dependent causes:

- 1) **Cushing's disease:** The term used for pituitary-dependent Cushing's syndrome is Cushing's disease. After excluding iatrogenic causes, it is the most common cause of endogenous Cushing's syndrome, accounting for 70% of the cases. The disease is caused by a pituitary adenoma of monoclonal origin. Most of these tumors are small microadenomas (<1cm size), but large macroadenomas (>1cm) can occur in 5 to 10% of the cases. Recent evidence suggests that approximately one third of Cushing's cases have a somatic missense mutation causing constitutive activation of the ubiquitin-specific protease 8 (USP8), which increases the expression of the EGF receptor on pituitary adenomas. Corticotrope adenomas may rarely be associated with familial syndromes, such as MEN1, MEN2, Carney's complex, and familial isolated pituitary adenoma syndrome. Selective surgical removal of the tumor can result in remission, but on long-term follow-up, relapse may occur in 20-30% of the cases.
- 2) **Ectopic ACTH syndrome:** In this entity, the source of ACTH is from a non-pituitary tumor (ectopic). Based on the clinical behaviour, these tumors can be of two types:

Tumors associated with Ectopic ACTH syndrome:

1. Small cell carcinoma of the lung
2. Pancreatic neuroendocrine tumors
3. Lung neuroendocrine tumors
4. Non-small cell carcinoma of the lung
5. Thymic neuroendocrine tumors
6. Medullary carcinoma of the thyroid
7. Pheochromocytoma
8. Rare carcinomas of the prostate, colon, ovary, gallbladder, and breast
- 3) **Ectopic CRH Syndrome:** This is a very rare cause of Cushing's syndrome. Cases have been reported in which tumors (bronchial carcinoid, prostate carcinoma, medullary thyroid carcinoma) have been shown to secrete CRH alone or along with ACTH. Pituitary histology will show hyperplasia rather than adenoma formation.
- 4) **Macro nodular adrenal hyperplasia (MAH):** MAH is an ACTH dependent form of Cushing's syndrome, thought to result from long standing ACTH stimulation, which results in adrenal adenoma formation. So adrenals may secrete more cortisol for a

Highly malignant tumors	More indolent, low proliferative tumors
<p><i>Examples: small cell carcinoma of the lung, highly proliferative neuroendocrine tumors.</i></p> <p>The clinical presentation of these tumors often includes weight loss, cachexia, wasting, hyperpigmentation, myopathy with hypokalemic metabolic alkalosis, and peripheral edema. These are the clinical clues for the diagnosis.</p>	<p><i>Example: bronchial carcinoid.</i></p> <p>The clinical presentation of these tumors is similar to pituitary-dependent Cushing's. However, when the imaging for a pituitary tumor is negative in a case of clinically and biochemically proven Cushing's, screening for these tumors in the chest and abdomen with appropriate imaging should be done.</p>

given ACTH level which can lead to auto suppression. Low ACTH levels with non-suppressible serum cortisol after dexamethasone can be mistaken for primary adrenal tumor.

ACTH independent causes:

- 1) **Cortisol secreting adrenal adenoma and carcinoma:** Adrenal adenomas account for 10 to 15% of Cushing's syndrome cases and carcinoma in less than 5% of cases after excluding iatrogenic causes. On the contrary, in children, adrenal causes account for 65% of the cases (50% carcinoma, 15% adenomas). Clinical features may progress rapidly in the case of carcinoma or gradually in adenoma. Features of virilization or feminization may be present due to the co-secretion of androgens or estrogens, respectively.
- 2) **McCune- Albright syndrome:** The characteristic features include fibrous dysplasia, café-au-lait pigmented macules, and endocrine hyperfunction (most commonly gonadal hyperfunction (precocity), but pituitary, thyroid, and adrenal hyperfunction can occur). This condition is due to a somatic mutation in the α subunit of the stimulatory G protein, which results in the constitutive activation of the G protein-coupled receptor at the adrenals, mimicking ACTH stimulation with resultant hypercortisolism. Bilateral adrenal nodules can be seen with low ACTH levels.
- 3) **Primary pigmented nodular adrenal hyperplasia (PPNAD) and Carney's complex:** This is also known as micronodular adrenal disease. This condition is characterized by normal-sized adrenals with dark or black-coloured cortical micronodules (2-4mm size). The internodular cortex is usually atrophic, unlike that of ACTH-dependent macronodular hyperplasia. Bilateral adrenalectomy is curative. Most cases of PPNAD occur as part of Carney's complex with characteristic

associated abnormalities, which include myxomas of the heart, breast, and skin, spotty skin pigmentation, and other endocrine disorders (sexual precocity, testicular tumors, and GH-secreting pituitary tumors). A mutation in the tumor suppressor gene type 1A regulatory subunit of protein kinase A (PRKAR1A) leads to abnormal PKA signalling, explaining the phenotype of Carney's complex in some cases. In isolated PPNAD, mutations in PRKAR1A and phosphodiesterase 11 A (PDE11A) gene have been demonstrated.

- 4) **ACTH independent Macro nodular hyperplasia (AIMAH):** AIMAH is a rare form of Cushing's syndrome, characterized by bilateral adrenal enlargement with non-pigmented nodules measuring >5mm. In most cases, aberrant receptor expression within the adrenal cortex has been demonstrated. The first described case of AIMAH was food-dependent Cushing's syndrome, in which gastric inhibitory polypeptide (GIP) receptors are aberrantly expressed in the adrenal cortex. These receptors respond to GIP released after a meal, resulting in hypercortisolaemia. Abnormal receptor expression of vasopressin V1, LH, serotonin, angiotensin (AT1), and α adrenergic receptors have also been reported. In some patients, inactivating germline mutations of the tumor suppressor gene ARMC5 (armadillo repeat containing protein 5) have been identified as a cause. Familial cases suggest a genetic cause in some patients.

Iatrogenic Cushing's syndrome

The development of Cushingoid features with exogenous corticosteroids depends on the potency, dose, and duration of use. A careful drug history can reveal the use of steroids in oral, topical, inhalation, and injectable forms. Some features, such as cataracts, increased intraocular pressure, benign intracranial hypertension, avascular necrosis of the femoral head, pancreatitis, and osteoporosis, are more common in iatrogenic

Cushing's. However, hirsutism, hypertension, and oligomenorrhoea/amenorrhoea are less common.

Pseudo Cushing's syndrome

Pseudo Cushing's syndrome refers to conditions that exhibit some of the clinical and biochemical features of Cushing's syndrome, which disappear after the resolution of the underlying condition.

- **Alcohol:** Suspected with heavy ongoing alcohol consumption and clinical evidence of liver disease. Mechanisms include increased cortisol secretion, impaired cortisol metabolism due to chronic liver disease, and increased AVP levels in decompensated liver disease. Urinary cortisol levels may be increased with non-suppressible plasma cortisol with dexamethasone. Abstinence from alcohol results in resolution of biochemical abnormalities.
- **Obesity:** Weight gain and obesity are common in Cushing's syndrome. Patients with obesity may have increased cortisol secretion and increased cortisol turnover. This may result in normal circulating levels of cortisol, mildly increased urinary free cortisol, and variable response to overnight dexamethasone suppression test. Mechanisms include reduced hepatic conversion of cortisone (inactive) to cortisol (active) and increased conversion of cortisol to 5 α reduced derivatives, thereby stimulating HPA axis due to loss of negative feedback. Patients with morbid obesity may have Cushingoid features due to increased 11beta HSD1 activity in adipose tissues which leads to increased local production of cortisol.
- **Depression:** Depression may be associated with hormonal abnormalities of Cushing's syndrome. Often patients with Cushing's are depressed, so careful clinical and hormonal assessment is required.
- **Differentiating Pseudo Cushing's states from ACTH dependent Cushing's syndrome:** Low

dose DST-CRH test can be useful to differentiate pseudo from ACTH dependent Cushing's. Based on the assumption that only ACTH dependent Cushing's show the stimulated ACTH and cortisol response with CRH after dexamethasone suppression.

PATHOPHYSIOLOGY

Cushing's syndrome is a condition characterized by biochemical cortisol excess with clinical features of protein catabolism. Cortisol, produced in the zona fasciculata of the adrenal cortex, is regulated by the adrenocorticotropin hormone (ACTH) from the anterior pituitary gland, in response to the corticotrophin-releasing hormone (CRH) and vasopressin from the hypothalamus. Cortisol exerts negative feedback control both at the level of hypothalamus and pituitary regulating normal homeostasis.

Cortisol is secreted in a circadian rhythm with the levels begins to rise at 2.00hrs peaking at 7.00-8.00hrs then gradually fall during the day reaching nadir levels at midnight. Loss of circadian rhythm with loss of feedback regulatory control of hypothalamo pituitary adrenal axis (HPA) is early manifestation, which is the basis for the diagnostic investigations.

As a catabolic hormone, cortisol affects glucose, protein, and fat metabolism, leading to glucose intolerance and possible overt diabetes mellitus in up to a third of patients.

Its catabolic effects also result in muscle weakness, thin skin, easy bruising, and characteristic cushingoid striae due to collagen breakdown. Hypercortisolism affects the bone, leading to fractures and osteonecrosis. It is also associated with hypertension and increased susceptibility to infections, including reactivation of tuberculosis.

Moreover, excess cortisol can suppress the pulsatility of GnRH, causing gonadal dysfunction and impacting mood and cognition, leading to psychiatric abnormalities such as agitated depression, paranoia, and psychosis.

Table 1: Clinical features of Cushing's syndrome

Figure 1: Schematic Representation of Thyroid Hormone Synthesis and Regulation: Primary and Secondary Hypothyroidism

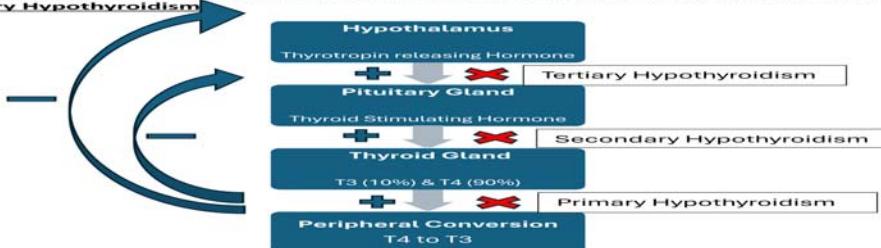


Table 2: Clinical Features of overt hypothyroidism according to the organ involvement and pathophysiology:[26]

Organ system involved	Pathology	Symptom & Signs - Manifestations
Skin & its appendages	Deposition of Hyaluronic acid	Boggy non pitting edema around eyes, dorsum of hands and feet and supraclavicular fossa. Enlargement of tongue, thickening of pharyngeal and laryngeal mucous membranes
	Cutaneous vasoconstriction	Pale and cool skin
	Reduced secretions of sweat glands and sebaceous glands	Dry and coarse skin
	Increased capillary fragility	Easy bruising
	Unclear role	Head and body hair is dry and brittle, lacks luster and hair tends to fall out.
Respiratory System	Fluid accumulation leading to Pleural effusion	Dyspnea

CLINICAL FEATURES

The clinical suspicion of Cushing's syndrome arises from the presence of certain symptoms and signs. Many of these features are nonspecific and commonly found among the general population who do not have Cushing's syndrome, while some are very pathognomonic.



Figure 1: Moon facies in a 30 years old female with exogenous glucocorticoid use



Figure 2: Buffalo hump



Figure 3: Wide(>1 cm) purplish dehiscent striae with tapering ends

WHEN TO SUSPECT? AND WHOM TO SCREEN?

1. Patients with multiple progressive features of Cushing's syndrome, especially the discriminatory features
2. Children with increasing weight and decreasing height percentile
3. Patients with unusual features for their age (e.g., osteoporosis, hypertension)
4. Patients with adrenal incidentaloma

HOW TO SCREEN? AND DIAGNOSE?

Establishing the correct diagnosis is crucial for proper management. Before evaluating for possible Cushing's syndrome, it's essential to rule

out exogenous steroid intake through a thorough history. Some patients may be unaware of their steroid use, causing a detailed history to potentially miss this information. An 8.00 am serum cortisol (basal cortisol) test can be used as an initial diagnostic measure. If the patient has been taking exogenous steroids, their basal cortisol levels will be suppressed.

Investigations of patients with suspected Cushing's syndrome

This process involves two steps:

Step 1 - Does the patient have Cushing's syndrome?

After ruling out exogenous steroid intake, any of the following first-line tests are recommended for a suspected case of Cushing's syndrome. The choice of test depends on the patient's characteristics and the availability of the test.

1. 24-hour urinary free cortisol (UFC) (requires at least two measurements)
2. Late-night salivary cortisol/midnight plasma cortisol (requires at least two measurements)
3. 1 mg overnight DST (ONDST) (dexamethasone suppression test)
4. Low dose DST (LDDST) (2mg/day for 2 days)

Note: For patients with a low index of suspicion, any single first-line test is recommended, taking into account the caveats of the test and suitability for the patient.

For patients with a high index of suspicion, two or three first-line tests might be considered.

UFC and salivary cortisol measurements should be performed at least twice, as hypercortisolism in Cushing's may fluctuate.

- **Urinary Free cortisol (UFC)**

UFC (Urinary Free Cortisol) measures the cortisol that is not bound to Cortisol Binding Globulin (CBG), which the kidney filters unchanged. Therefore, UFC measurements are not affected by conditions and medications that alter the CBG concentration. In Cushing's syndrome, cortisol production is high, resulting in increased unbound cortisol levels and elevated UFC. If UFC levels are three times above the upper limit of normal of the specified range given by the laboratory for that assay, it is considered a positive test.

False positive UFC levels-

1. Excess fluid intake (>5 liters/day) significantly increases the UFC
2. Any physiological or pathological conditions associated with increased cortisol production(Table 2)

False negative UFC levels

1. Creatinine clearance is <60ml/min
2. Cyclic Cushing's syndrome (when the urine collection is during inactive phase)

Table 2:Conditions associated with hypercortisolism in the absence of Cushing's syndrome

Some features of Cushing's may be present	No clinical features of Cushing's
Pregnancy	Physical stress (surgery, hospitalization, pain)
Depression/other psychiatric conditions	Intense chronic exercise
Obesity	Malnutrition ,anorexia nervosa
Alcohol dependence	Hypothalamic amenorrhea
Glucocorticoid resistance	CBG excess (elevated serum cortisol but not UFC)
Poorly controlled diabetes	



- **Late night salivary cortisol/Midnight serum cortisol**

In normal individuals, serum cortisol levels are at their highest in the early morning and reach a nadir (<2 μ g/dl) at midnight. This circadian rhythm is lost in Cushing's syndrome. This is the basis for the midnight serum cortisol or late-night salivary cortisol test. However, it is important to note that the circadian rhythm is blunted in most patients with depressive illness, in shift workers, and is absent in critical illness.

A midnight serum cortisol value of >7.5 μ g/dl indicates Cushing syndrome, but a false positive test can occur due to the stress of venepuncture. To avoid this, the patient should be hospitalized for 24 to 48 hours before the procedure with an indwelling heparin lock IV cannula in situ. Late-night salivary cortisol has replaced the midnight serum cortisol measurement in many centres, but if the facility is not available, a midnight cortisol test with appropriate precautions can be done.

Salivary cortisol - CBG is absent in saliva. Free cortisol in the blood is in equilibrium with cortisol in saliva. Any increase in blood cortisol levels is reflected by a change in salivary cortisol levels within a few minutes, and the concentration of salivary cortisol is not affected by the rate of saliva production. Normal subjects have late-night salivary cortisol values < 1.45ng/ml, and evidence suggests that a late-night salivary cortisol value >2.0ng/ml has a 100% sensitivity and 96% specificity for the diagnosis of Cushing's syndrome.

- **Dexamethasone suppression tests (DST)**

Dexamethasone suppresses ACTH in healthy individuals, thereby decreasing cortisol levels. A serum cortisol level of <1.8 μ g/dL after dexamethasone is given is considered a normal response.

1mg Overnight DST (ONDST)

- Procedure: Patients suspected of having Cushing's syndrome should take 1mg of dexamethasone at 11.00 pm the previous night. A cortisol measurement should be done in the 8.00 -9.00 am serum sample the following morning.
- Interpretation: A serum cortisol value of <1.8 μ g /dL is a normal response and rules out Cushing's syndrome. An abnormal test result requires further testing with other first-line tests.
- Sensitivity and Specificity: This test has high sensitivity (95%) but low specificity.

Low Dose DST (LDDST)

- Procedure: Take 0.5 mg of dexamethasone every 6 hours for 48 hours. Cortisol should be measured in the serum sample obtained 6 hours after the last dose of dexamethasone.
- Interpretation: A serum cortisol value of >1.8 μ g/dL confirms the diagnosis of Cushing's syndrome.
- True and False Positive Rate: This test has a 97%-100% true positive rate and a false positive rate of <1%.

Important Considerations:

- Drugs like phenytoin and rifampicin may increase the metabolic clearance of dexamethasone, resulting in a false positive test result. Simultaneous measurement of serum dexamethasone levels may be helpful in such cases.
- DST is not reliable (false positive result) in women taking oral contraceptive pills. This is because estrogen increases CBG levels, giving a false positive result. Hence, oral contraceptives or other forms of estrogen should be withheld for six weeks prior to testing.

- o In children, the required doses of dexamethasone for ONDST and LDDST are 15 mcg/kg/dose and 30 mcg/kg/day (in four divided doses daily for two days) respectively.

Step 2 - What is the etiology of Cushing's syndrome?

- **Morning plasma ACTH**

We measure the morning plasma ACTH levels to determine whether the cause of Cushing's syndrome is ACTH-dependent or ACTH-independent.

Precautions to be taken for blood sample collection for ACTH:

- o Blood sample should be collected into EDTA-coated, ice-cold tubes.
- o The sample should be immediately cold-centrifuged before being stored at -40

The recommended screening tests for different patient populations are as follows:

Table 3: Recommended screening tests for different patient populations

Special Population	Recommended testing
Pregnancy	24-hour UFC or late night salivary cortisol test (not the dexamethasone suppression tests)
Adrenal incidentaloma	1mg overnight DST as the first line test
Cyclic Cushing's syndrome	Condition is very rare and characterized by episodes of excessive cortisol alternating with normal cortisol secretion. Repeated measurements of late night salivary cortisol or urinary free cortisol might be required to establish the diagnosis. Scalp hair cortisol has shown potential as a novel biomarker in the diagnosis and monitoring of Cushing's syndrome. It provides a non-invasive means of assessing long-term cortisol exposure, which can be particularly useful in cases of cyclic Cushing's syndrome.
Children	If weight percentile is increasing but height percentile is decreasing, Cushing's to be suspected and evaluated. If the weight and height are increasing on the same percentile Cushing's is highly unlikely. Obesity in children with Cushing's tends to be generalized. Pubertal development can be seen with androgen /estrogen secreting tumors causing pseudo precocious puberty.
Patients with Chronic Kidney Disease	DST is the preferred test than UFC
Patients with epilepsy	UFC or midnight cortisol are the suggested tests than DST (as antiepileptics may interfere with dexamethasone metabolism)
Shift workers	UFC or DST is the suggested test than midnight cortisol/late-night salivary cortisol

degrees Celsius ahead of analysis (ACTH is heat labile and has a short half-life).

At 9.00am, ACTH levels will be elevated in cases of Cushing's disease and ectopic ACTH-secreting tumors. Conversely, in the case of adrenal tumors, ACTH will be low or undetectable. The consensus is that ACTH levels less than 5pg/ml suggest an ACTH-independent cause, while levels greater than 15 pg/ml suggest an ACTH-dependent cause of Cushing's.

- o High dose dexamethasone suppression test

Purpose: This test is designed to differentiate between Cushing's disease and the ectopic ACTH syndrome.

Rationale: In Cushing's disease, the negative feedback control of ACTH is set at a higher level than normal. As a result, cortisol levels are not suppressed with low-dose

dexamethasone but are suppressed with higher doses.

Procedure:

1. Administer a 2mg dexamethasone tablet every 6 hours for a period of 48 hours. In children, the required dose of Dexamethasone is calculated as 120 mcg/kg/day (in four divided doses daily for two days).

2. **Measure the serum cortisol level at the start and after 48 hours.**

Interpretation: A reduction of more than 50% from the initial cortisol level is considered a positive response and is suggestive of Cushing's disease. HDDST may also yield a positive result in the case of a bronchial carcinoid.

Note: With the emergence of newer ACTH assays, this test is no longer widely used. It offers no additional benefit when a greater than 50% drop in the serum cortisol level is observed with the low DST test.

- o Inferior Petrosal Sinus Sampling (IPSS)

This is a crucial test to differentiate Cushing's disease from ectopic ACTH syndrome. However, it's an invasive procedure, technically demanding, requires expertise, and may be associated with complications such as thrombosis and referred aural pain.

Rationale: Each half of the pituitary drains into the ipsilateral inferior petrosal sinus. Therefore, catheterization and simultaneous sampling of blood from both the sinuses and peripheral vein can distinguish the pituitary or ectopic source of ACTH.

Interpretation:

- o *Cushing's disease:* Ratio of ACTH in petrosal sinus to ACTH in peripheral vein $> 2:1$ or CRH stimulated ratio $> 3:1$
- o *Ectopic ACTH syndrome:* Ratio of ACTH in petrosal sinus to ACTH in peripheral vein $< 1.4:1$

IPSS may be helpful in lateralizing a pituitary tumor in a patient in whom pituitary imaging did not show any lesion.

- **Localisation of ACTH source by imaging**
 - o Magnetic Resonance Imaging (MRI) is the preferred method for detecting ACTH secreting pituitary adenomas. These tumors are identified through MRI in about 70% of cases with Cushing's disease. However, in 30% of patients, imaging results may be negative. It's important to note that tumor size does not correlate with the severity of hypercortisolism.
 - o For adrenal imaging, Computed Tomography (CT) scanning is the preferred method.
 - o To identify ectopic Adrenocorticotropic Hormone (ACTH) syndrome, Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) scans of the thorax, abdomen, and pelvis with thin sections are necessary to detect small ACTH-secreting neuroendocrine tumors.
 - o Nuclear imaging: Most neuroendocrine tumors causing ACTH syndrome have somatostatin receptors. Therefore, these tumors can be imaged using radiolabelled somatostatin analogues. Gallium 68 DOTATATE Positron Emission Tomography Computed Tomography (PET CT) can detect small tumors and should be considered for suspected ectopic Cushing's syndrome after ruling out a pituitary cause.

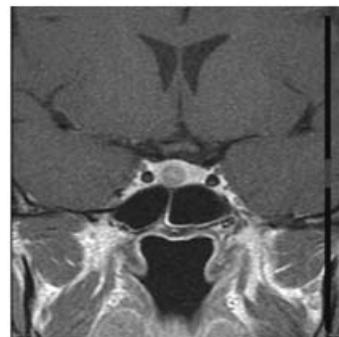
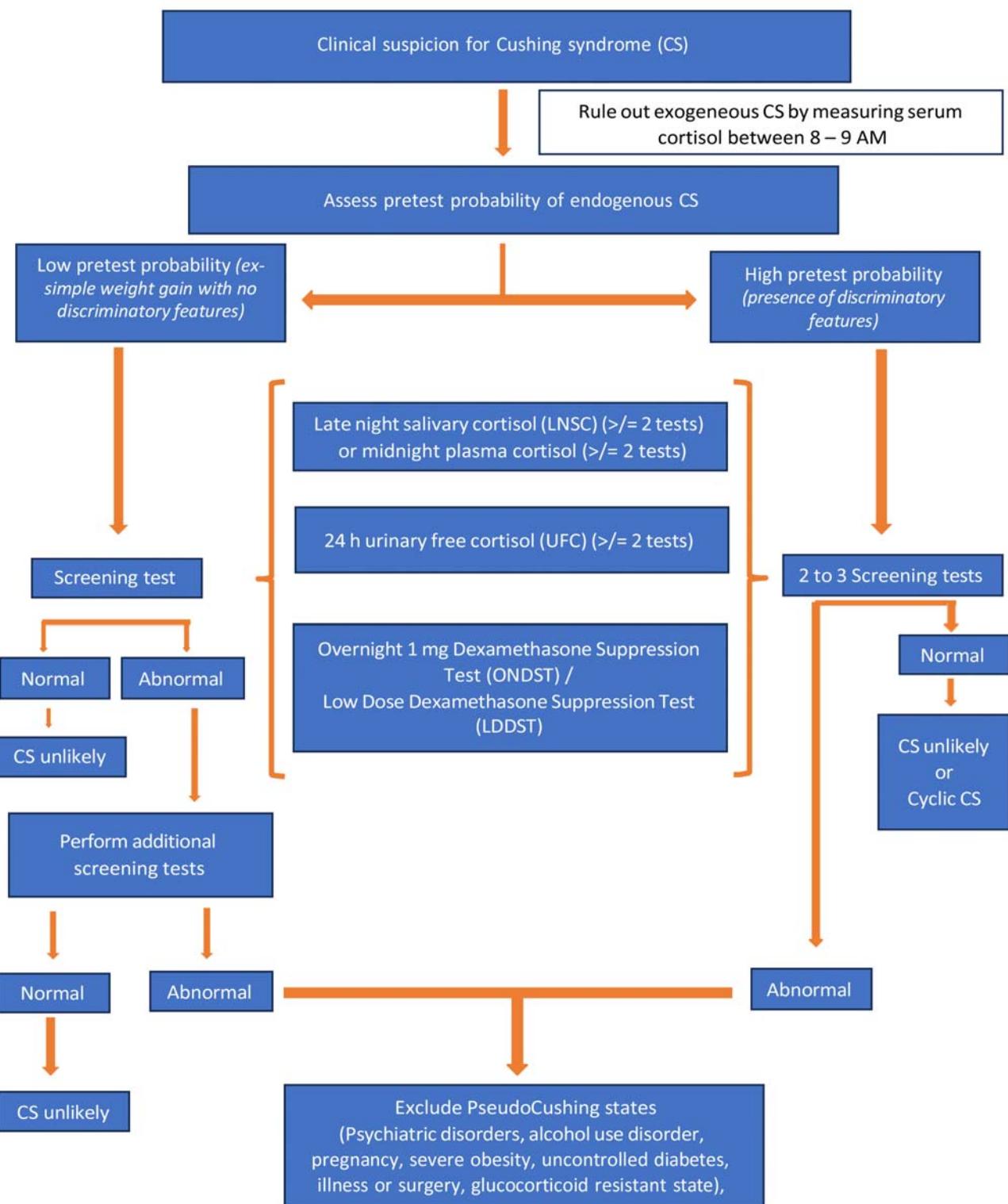
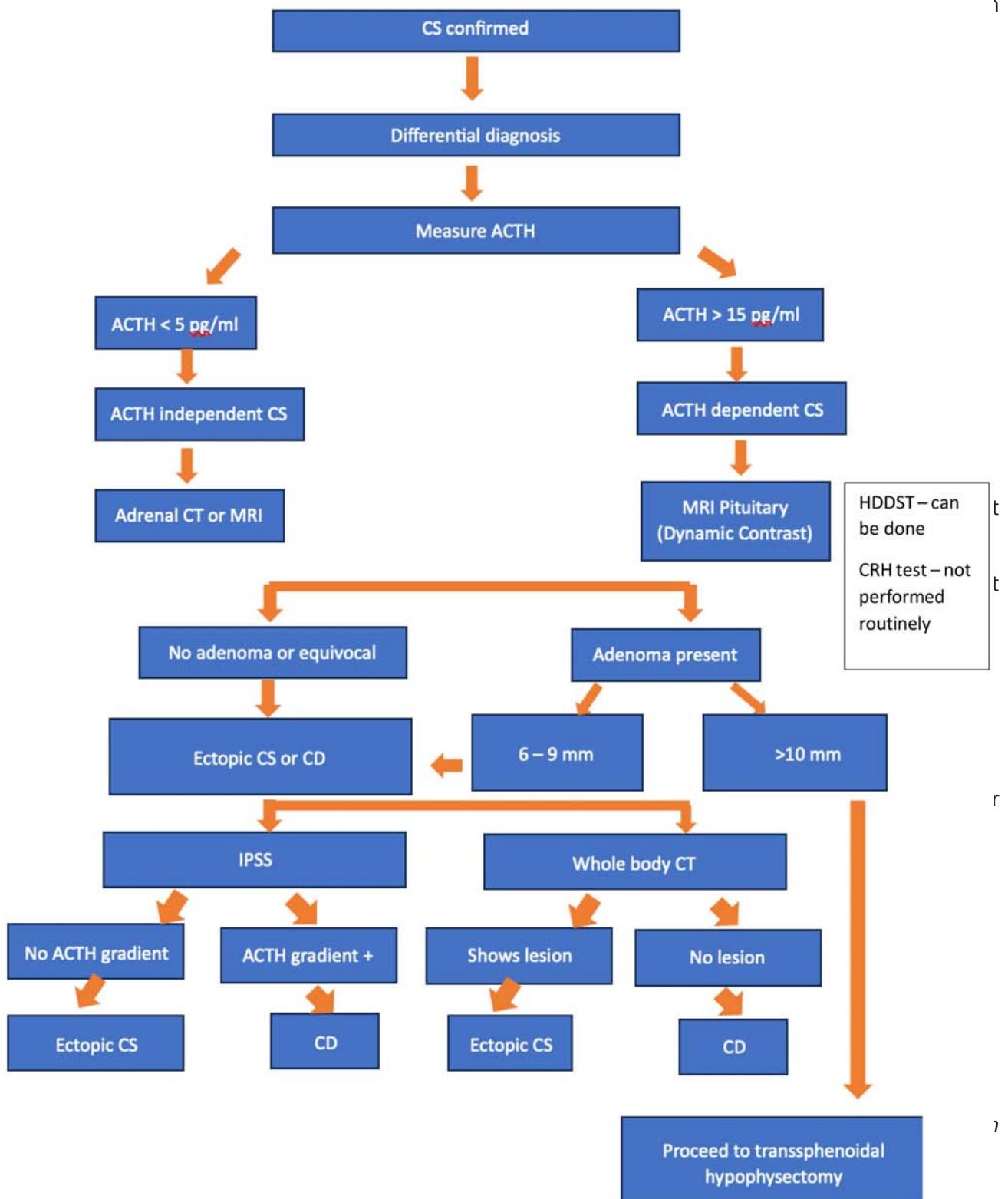


Figure 4: Centred within the right aspect of the pituitary gland is a rounded hypo-enhancing lesion measuring 8 x 6 x 6.5 mm suggestive of pituitary microadenoma. Source: Radiopedia

The various steps of diagnosis of Cushing's syndrome is summarised in the Flowcharts 1 and 2 given below.



Once Pseudo Cushing states are ruled out, the diagnosis of Cushing's syndrome is confirmed. We can then proceed with the investigation as per Flowchart 2.





Treatment

Surgical management is the first line of therapy.

- Cushing's disease - Transsphenoidal surgery is the recommended treatment.
- Adrenal adenoma/carcinoma and neuroendocrine tumors causing ectopic ACTH - these conditions require the surgical removal of the tumor.

Medical therapy

The drugs used for treatment of Cushing's disease target adrenal steroidogenesis, somatostatin and dopamine receptors in the pituitary gland, and glucocorticoid receptors.

Indications of medical therapy –

- To treat hypercortisolism in patients with persistent or recurrent Cushing's disease

- Those who are not candidates or refuse surgery
- To reduce cortisol levels in patients undergoing radiotherapy
- Patients who present with acute complications of hypercortisolism (sick enough to get operated immediately)

Radiation therapy (RT)

Most often RT is used as a second line therapy for patients with persistent or recurrent disease after the surgery, but it may also be used in high surgical risk patients, un resectable tumor or who refuse surgery. Biochemical remission with RT takes months to years, so it is important to control the cortisol excess with medical therapy. Hypopituitarism is a risk with RT.

Prognosis of Cushing's syndrome

Evidence suggests that half of the untreated Cushing's syndrome patients die within 5 years,

The drugs used in medical therapy of Cushing's disease can be broadly classified as follows:

Table 4: Classification of drugs used in the medical management of Cushing's disease

Pituitary directed agents	Adrenal directed agents	Peripheral tissue glucocorticoid receptor blocker
<i>Dopamine receptor agonist</i> – Cabergoline	<i>Inhibitors of steroidogenesis</i> – Ketoconazole, Levoketoconazole, Osilodrostat, Etomidate, Metyrapone, Mitotane	Mifepristone, Relacorilant
<i>Somatostatin receptor agonist</i> – Pasireotide	<i>ACAT inhibitor</i> – Nevanimibe	
<i>Heat shock protein 90 inhibitors</i> – Silibinin, Novobiocin, Tanespimycin		
<i>Histone deacylases (HDAC) inhibitors</i> – Trichostatin A, Vorinostat		
<i>Kinase inhibitors</i> – Roscovitine, Gefitinib, Canertinib, Binimetinib		
<i>Others</i> – Temozolomide, Retinoic acid, Triptolide		

Key details about these pharmaceutical agents are concisely presented in the following table.

Table 5: Important characteristics of drugs used in medical management of Cushing's disease

	Mechanism of action	Commonly used doses	Adverse effects
<i>Adrenal steroidogenesis inhibitors</i>			
Ketoconazole	Inhibits several key enzymes of the adrenal steroidogenesis pathway (side chain cleavage enzyme, 17 alpha hydroxylase, 11 beta hydroxylase, 18 hydroxylase, 17, 20 lyase)	400 to 1600 mg total per day, orally, given twice or thrice a day	GI disturbances, hepatotoxicity, gynecomastia, adrenal insufficiency
Levoketoconazole	Same as ketoconazole	300 to 1200 mg total per day orally given twice a day	Same as ketoconazole, lower risk for hepatotoxicity
Osilodrostat	11 beta hydroxylase inhibitor	4 to 14 mg total per day, Maximum doses: 30 mg twice a day	Hirsutism, Hypertension, Hypokalemia (due to increased androgenic and mineralocorticoid precursors), GI disturbances, adrenal insufficiency
Metyrapone	Inhibits several key enzymes of the adrenal steroidogenesis pathway (17 alpha hydroxylase, 11 beta hydroxylase, 18 hydroxylase, 17, 20 lyase)	500 mg to 6 g total per day, orally, given three or four times a day	Hirsutism, Hypertension, Hypokalemia (due to increased androgenic and mineralocorticoid precursors), GI disturbances, adrenal insufficiency
Mitotane	Inhibits several key enzymes of the adrenal steroidogenesis pathway (side chain cleavage enzyme,3 beta HSD, 11 beta hydroxylase, 18 hydroxylase)	500 mg to 4 g total per day, orally	GI disturbances, dizziness, cognitive alterations, adrenal insufficiency, hepatotoxicity
Etomidate	Inhibits several key enzymes of the adrenal steroidogenesis pathway (side chain cleavage enzyme, 17 alpha hydroxylase, 11 beta hydroxylase, 17, 20 lyase)	0.04 - 0.1 mg/kg/h intravenously for patients in the intensive care unit; 0.025 mg/kg/h for patients not in	Sedation or anaesthesia, adrenal insufficiency, myoclonus, nausea, vomiting

		the intensive care unit	
<u>Somatostatin receptor ligands</u>			
Pasireotide	The drug works by activating somatostatin receptors in the pituitary adenoma, which results in inhibiting the excessive ACTH	0.6 - 1.8 mg/ml subcutaneously total per day, given twice a day	Hyperglycaemia, diarrhoea, nausea, cholelithiasis
<u>Dopamine receptor agonists</u>			
Cabergoline	D2 is expressed in approximately 80% of corticotroph adenomas	0.5 to 7 mg total per week	orthostatic hypotension due to dopamine's vasodilatory effects, nausea, headache, and dizziness
<u>Glucocorticoid receptor blocker</u>			
Mifepristone	Inhibits glucocorticoid receptors in peripheral/target tissues	300 to 1200 mg total per day orally, given once a day	GI disturbances, headache, hypokalemia, arthralgia, peripheral edema, hypertension, vaginal bleeding, adrenal insufficiency

mainly due to vascular disease. Features of Cushing's syndrome disappear over a period of a few months after treatment. Diabetes and hypertension improve but may not resolve completely. Osteopenia improves, but vertebral fractures and osteonecrosis are irreversible. Paradoxically, some patients may experience lethargy, mood changes, skin desquamation, and development or flare-up of

autoimmune conditions (e.g., hypothyroidism, psoriasis, lupus) after surgical or medical treatment. Lifelong follow-up is recommended in Cushing's syndrome patients to monitor for recurrence, assess cardiovascular risk factors, bone

health, and psychiatric symptoms, which can be appropriately managed. Overall, the quality of health is significantly reduced in patients with Cushing's syndrome, affecting physical health and functioning. Though the quality of life improves after treatment, it does not return to normal

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Addison's Disease- an overview

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Introduction:

Primary hypoadrenalinism or primary adrenal insufficiency (AI) refers to glucocorticoid deficiency in the setting of any adrenal disease.¹ It was initially described by Thomas Addison in 1855, based on characteristic discoloration of the skin and post-mortem findings of adrenal gland involvement.²

The importance of this disease lies in the significant morbidity and mortality associated with it when not diagnosed promptly. On the other hand, once diagnosed, it can be treated easily.³

Pathogenesis:

Adrenal insufficiency can occur due to primary adrenal dysfunction or central causes affecting the pituitary and hypothalamus leading to ACTH deficiency.

Primary adrenal insufficiency affects the adrenal cortex and therefore manifests with glucocorticoid & mineralocorticoid deficiency. Normally, glucocorticoids modulate ACTH secretion (via feedback mechanism), maintain cardiac contractility^{4,5}, increase vascular responsiveness to beta 2 receptor agonists⁶, and promotes gluconeogenesis from the liver during fasting state. Mineralocorticoids are responsible for Na+ & water reabsorption and excretion of K+ & H+ ions. With decreasing cortisol levels, ACTH levels increase and this leads to hyperpigmentation possibly by stimulation of MC1R present on cutaneous melanocytes⁷. Therefore, deficiency of both of these hormones will result in orthostatic hypotension, hyponatremia, hyperkalemia & metabolic acidosis.

In secondary adrenal insufficiency, there is no mineralocorticoid deficiency as it is dependent on the Renin Angiotensin Aldosterone system (RAAS) and not on ACTH. Therefore, isolated glucocorticoid deficiency as a result of ACTH deficiency leads to hyponatremia and hypotension with normal potassium and hydrogen concentrations.

Etiology:

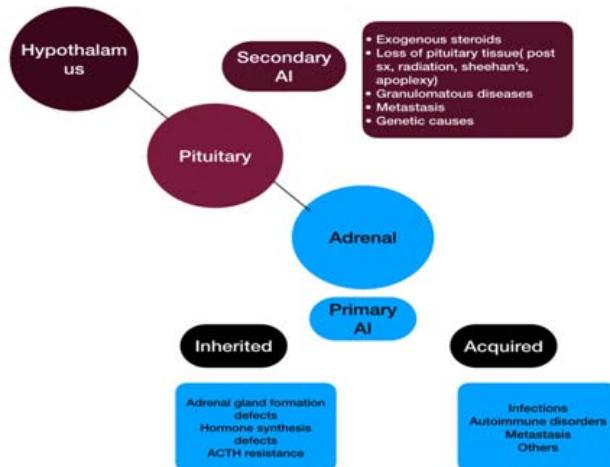


Figure 1: Types of adrenal insufficiency with causes.

(Table 1)

The major causes of primary AI can be divided into 3 categories- defects in steroidogenesis, autoimmune, and destructive causes. Out of these, autoimmune adrenalitis is reported to be the most common cause in the Western population.

In contrast, a study from north India done by Gunna et al⁹ found that the most common causes of AI were Adrenal Histoplasmosis(45%), adrenal tuberculosis(15%), autoimmunity(25%) & primary lymphoma(6%).

Table 1: Etiology of Addison's disease⁸

Inherited - primary AI	Features
1. Adrenal hypoplasia congenita(AHC): SF1 DAX1 glycerol kinase deficiency	Defects in the development of adrenal gland X-linked recessive disorder with adrenal insufficiency and central hypogonadotropic hypogonadism. SF1 - transcriptional regulation of many p450 enzymes DAX1- nuclear receptor family protein expressed in adrenals, gonads, and hypothalamus (therefore, associated with hypogonadism)
2. Adrenoleukodystrophy-ABCD1	Adrenal insufficiency +CNS demyelination Failure of beta-oxidation of fatty acids in peroxisomes. X-linked disorder - males fully express and females are carriers The most common cause of adrenal insufficiency in a male child less than 7 years of age
3. Familial Glucocorticoid Deficiency (Resistance to ACTH) Type 1: defect at the receptor - MC2R Type 2: defect in intracellular trafficking of MC2R - MRAP Others	Presents with neonatal hypoglycemia Later in life - increasing pigmentation and increased growth velocity Primary adrenal dysfunction with normal activity of the RAAS system is a very important clue.
4. Triple AAA syndrome (ALADIN) - ACTH resistance	Alacrimia, achalasia & adrenal insufficiency
5. Congenital adrenal hyperplasia	Defects in various enzymes of steroidogenesis
Acquired - Primary AI	Features
1. Infections Tuberculosis Fungal - all except candidiasis	Most common in the developing world Tuberculosis: Adrenals are initially enlarged in size due to caseating granulomas. As the disease progresses, fibrosis ensues and the gland decreases to normal or smaller. Calcification may also be present.
HIV-AIDS	Adrenalitis can occur due to CMV, atypical mycobacteria, and Kaposi's sarcoma. Drugs (Azoles- inhibit cortisol synthesis; rifampin-enzyme induction) can precipitate adrenal insufficiency High levels of circulating cytokines can inhibit the HPA axis without directly involving the adrenal



Inherited - primary AI	Features
	gland itself.
2. Autoimmune Sporadic APS type 1 APS type 2 X-linked polyendocrinopathy	More common in Western populations. Atrophic adrenal cortex with sparing of adrenal medulla. Adrenal autoantibodies were found in 75% of cases. Type 1APS includes - chronic mucocutaneous candidiasis (at 5 years of age), hypoparathyroidism(at 8 years of age), and Addison disease (at 12 years of age). Type 2 APS - Addison's disease with autoimmune thyroid illness with or without T1DM
3. Metastasis	Lymphoma can cause AI Metastasis from other cancers (most commonly bronchus & breast) does not usually cause AI perhaps because more than 90% of the adrenal cortex has to be compromised before signs and symptoms occur. ⁸
4. Others Intra-adrenal haemorrhage Waterhouse fredrichson syndrome Amyloidosis & hemochromatosis Bilateral adrenalectomy	Intra-adrenal hemorrhage is to be expected in Antiphospholipid syndrome, any sick patient with coagulopathy, trauma, or sepsis (most common organism- Pseudomonas) If this occurs due to meningococcemia, then it is known as Waterhouse-Friderichsen syndrome.

Table 2: Etiology of Secondary Adrenal Insufficiency

Secondary AI causes	Features
1. Exogenous steroids	Most common cause of AI. Suppression of CRH and ACTH synthesis at hypothalamus & pituitary respectively. On discontinuation of exogenous steroids, absolute or relative adrenal insufficiency can develop.
2. Endogenous overproduction of cortisol(as in ACTH dependent and independent Cushing's)	Treatment of glucocorticoid excess can unmask adrenal insufficiency (pituitary and hypothalamus suppressed by circulating cortisol)
3. Loss of functional pituitary tissue	Tumors in & around sella turcica Post pituitary surgery Post-radiation (usually delayed for many years) Postpartum pituitary necrosis Pituitary apoplexy Granulomatous diseases (tuberculosis, sarcoidosis) Metastatic deposits (breast, bronchus)
4. Isolated ACTH deficiency	Lymphocytic hypophysitis Genetic causes: PCSK1, POMC, T-PIT
5. Multiple pituitary hormone deficiencies	LHX4, HESX1, SOX3, PROP1 gene mutations

AI is frequently missed in HIV & tuberculosis patients because of non-specific symptoms of AI which can also be present in HIV/Tuberculosis. In a systematic review and meta-analysis on the prevalence of adrenal insufficiency in adults with tuberculosis or HIV, the pooled prevalence was found to be 33% in patients with tuberculosis and 28% in patients with HIV¹⁰.

Exogenous steroids induced adrenal insufficiency:

HPA axis suppression can occur with any dose, route, or duration of steroid use as there is

considerable inter-individual variability in response to glucocorticoids. Therefore, there are no absolute cutoffs for the type of steroid taken, dose, route of administration, duration of treatment, or time since steroid withdrawal that can predict adrenal suppression¹¹.

However, there are general guidelines that can help with diagnosis and treatment.

- Potency of steroids** - Dexamethasone causes more HPA axis suppression as a result of its long half-life & higher affinity for glucocorticoid receptors than hydrocortisone

2. **Dose & Duration:** Patients taking 7.5mg prednisolone or equivalent for longer than 3 weeks are at risk of HPA axis suppression.⁸
3. **Administration schedule:** higher doses in night blocks ACTH surge in early morning hours¹³.
4. **Effect of other drugs:** Coadministration with enzyme inhibitors can increase its potency and adrenal suppression.¹⁴
5. **Route:** In a systematic review, the frequency of AI was found to be 38-48% with oral glucocorticoid intake, 52% with intra-articular administration, 5% after topical application, 4% after nasal, and 8% with inhaled corticosteroids.¹¹

When to assess HPA axis recovery?

The ideal time to test for recovery of HPA axis after longterm glucocorticoid use is controversial because of variability in data regarding time taken for recovery of HPA axis. The HPA axis recovery may be seen as early as 4 weeks post-cessation of prolonged glucocorticoid use. It would be therefore logical to assess HPA axis around that time and then monthly until recovery is documented.¹⁵

Withdrawal of steroids:

Sudden withdrawal can result in adrenal insufficiency and if associated with any intercurrent illness, can precipitate adrenal crisis as well. Hence, the steroids are to be tapered gradually. Doses are to be reduced from pharmacological to

physiological doses (<7.5mg/day prednisone) over a few weeks. Subsequently, the dose can be reduced by 1mg every 2 weeks. Alternatively, the patient can be shifted to 20mg/day of hydrocortisone and reduced by 2.5mg/day every week to a level of 10mg/day.⁸

After 2- 3 months on hydrocortisone (10mg/day), the HPA axis can be checked using an 8 am serum cortisol and ACTH stimulation test. Good response post-stimulation (Sr. Cortisol >18mcg/dl at 1 hour after Inj. Synacthen 250 mcg intramuscular) indicates that steroids can be safely withdrawn.

Investigations:

Hyponatremia(90%), hyperkalemia(65%)

Hypercalcemia(6%) is also seen and may be markedly elevated in patients with thyrotoxicosis.⁸

Free thyroxine levels are low or normal while TSH levels may be elevated. Elevation in Tsh levels is because of glucocorticoid deficiency and reverses with replacement therapy.^{8,9}

Mineralocorticoid status:

It is assessed by plasma renin activity and plasma aldosterone which usually shows increased PRA and low or low normal aldosterone levels in cases of primary adrenal insufficiency.

Assessment of HPA axis:

Laboratory diagnosis is based on low morning cortisol concentrations(<5mcg/dl) and confirmed with low ACTH stimulated cortisol

Table 3: Effect of drugs on cortisol metabolism¹⁴

S.No	Drugs	Examples	Effect on cortisol metabolism
1.	CYP3A4 inducers	Rifampin, Topiramate, mitotane, anticonvulsants	Increased cortisol metabolism leading to decreased cortisol levels. This can precipitate acute crisis.
2.	CYP3A4 inhibitors	Ritonavir, itraconazole, voriconazole	Increased cortisol levels leading to iatrogenic cushing's

Clinical features:

Table no.4: Clinical features in acute adrenal crisis, chronic adrenal insufficiency & secondary adrenal insufficiency.⁸

Acute adrenal insufficiency	Chronic adrenal insufficiency	Secondary adrenal insufficiency
During intercurrent illness	Generalised weakness, fatigue	Associated with deficiency of other hormones
Nausea, vomiting, diarrhea, abdominal pain	Occasional abdominal pain, vomiting, diarrhea	Similar to chronic primary adrenal insufficiency except for mineralocorticoid deficiency
Fever	Postural hypotension, salt craving	No hyperpigmentation
Hypoglycemia	Hyperpigmentation (sun-exposed areas, friction areas, recent scars, mucous membranes)	Acute presentation with pituitary apoplexy
Adrenal hemorrhage: flank pain, hypotension, nausea and vomiting Suspect when features of occult bleeding, hyperkalemia, and shock occur	Loss of adrenal androgens leading to loss of axillary and pubic hair Dry & itchy skin Loss of libido	
Hypotension refractory to fluids & ionotropes	Memory impairment, depression	

levels (cutoff: 18 mcg/dl). However, basal serum cortisol levels > 14.5 mcg/dl indicate an intact HPA axis.

In case ACTH-stimulated cortisol is not available, basal cortisol and ACTH can be used as a preliminary screening tool for adrenal insufficiency. Cortisol levels < 5 mcg/dl and ACTH more than 2 times the upper limit of normal are highly suggestive of primary AI.¹⁷

Cortisol concentrations have the highest specificity when measured with mass spectrometry. However, newer immunoassays for measuring cortisol concentrations are sufficiently reliable such that

mass spectrometry is not done routinely in clinical practice. Using these methods, a lower cutoff limit has been defined as ACTH-stimulated 30-minute cortisol readings in the range of 375 to 440 nmol/L (13.5 to 15.8 mcg/dl).¹⁸

ACTH stimulated cortisol levels (SST- short synacthen test)

250 mcg of synacthen is given IM/IV & Plasma cortisol levels are checked at 0, 30, and 60 minutes after ACTH. Normal response has been said to be > 18 mcg/dl of peak plasma cortisol levels.

The test can be performed at any time of the day, even in patients on steroids except for

hydrocortisone and those on long-duration steroids.

Insulin tolerance test:

Contraindicated in patients with ischemic heart disease, epilepsy, and severe hypopituitarism (serum cortisol <6.5mcg/dl). Intravenous insulin is given at the rate of 0.1 to 0.15U/kg while measuring serum cortisol levels at 0, 30, 45, 60, 90, and 120min. Normally, the peak plasma cortisol value is more than 18mcg/dl. This test has been replaced now by the Short Synacthen test.⁸

Other tests include 1mcg ACTH test, overnight Metyrapone test, and CRH stimulation test which are not routinely done.

Other investigations:

- Autoantibodies against 21 hydroxylase in autoimmune adrenal disease. Other autoimmune illnesses associated with Addison's disease should also be looked for.
- Imaging of the chest & abdomen can show findings of adrenal involvement or any primary focus.
- Serum VLFCA (Very Long Chain Fatty Acids) can be checked when suspecting adrenoleukodystrophy.
- Pituitary MRI & assessment of anterior pituitary function are required in cases with suspected central hypoadrenalinism.

Treatment:

Chronic adrenal insufficiency:

The aim of the therapy will be to give physiological doses of hydrocortisone to mimic the normal cortisol secretion rate & avoid overtreatment. Dexamethasone is not to be given due to its long duration of action & lack of mineralocorticoid activity.

The maximum dose should be given in the morning at awakening, the next dose is given at either in the afternoon only(2 h post- lunch; two-

dose regimen) or at lunch and afternoon (three-dose regimen). Doses are to be adjusted based on blood pressure, body weight, energy levels, and signs of glucocorticoid excess.¹⁷

Mineralocorticoid replacement is given in the form of fludrocortisone (0.05mg to 0.2mg/day). Adequacy is assessed clinically by the presence of salt craving, postural hypotension, and edema and by measuring serum electrolytes.¹⁷

DHEAS replacement of 25-50mg/day is shown to improve female sexual function and well-being.⁸

Pregnancy:

Patients are to be monitored for over or under-replacement with at least one review per trimester. The dose requirement may increase modestly in the last trimester. As progesterone acts as a mineralocorticoid antagonist, an increased dose of fludrocortisone may be required.

Dexamethasone is not to be used in pregnancy for glucocorticoid replacement as it is not inactivated by the placenta.

During labor, patients are to be adequately hydrated and given intravenous hydrocortisone 50mg 6th hourly until delivery.¹⁷

Acute crisis:

Adrenal crisis is an emergency and treatment must start immediately after sending samples without waiting for reports.

Patient education: All patients should have a steroid emergency card with a diagnosis and further contact details. All patients should receive education about sick day management and how to self-administer steroid injections. They must always carry an injection kit containing a prefilled syringe of hydrocortisone 100mg or dexamethasone 4mg for emergency use.

Conclusion: As the initial symptoms of patients with adrenal insufficiency are non-specific, diagnosis is often delayed.²⁰ And hence, there is a need to improve physician awareness to avoid adrenal crisis. Also, there is a need for active and repeated patient education regarding the

Table no. 5: Dose adjustments in different levels of stress & illnesses.

Severity of illness/procedure	Examples	Management
Mild stress	Job interview, regular exercise	Stress dose not necessary
Mild illness	Common cold, temp<38C	Stress dose not necessary
Moderate stress	Hard exercise(>2hr)	Will often require extra hydrocortisone; 5 to 10 mg 1 hour prior to exercise and 10 mg at lunch or the next morning (whichever comes first)
Moderate Illness	Traffic accident planned minor surgery under local anesthesia	Normal replacement dose is doubled to tripled
Severe stress	Death in the family	Normal replacement dose is doubled
Severe illness	Acute crisis Major surgery	Explained below

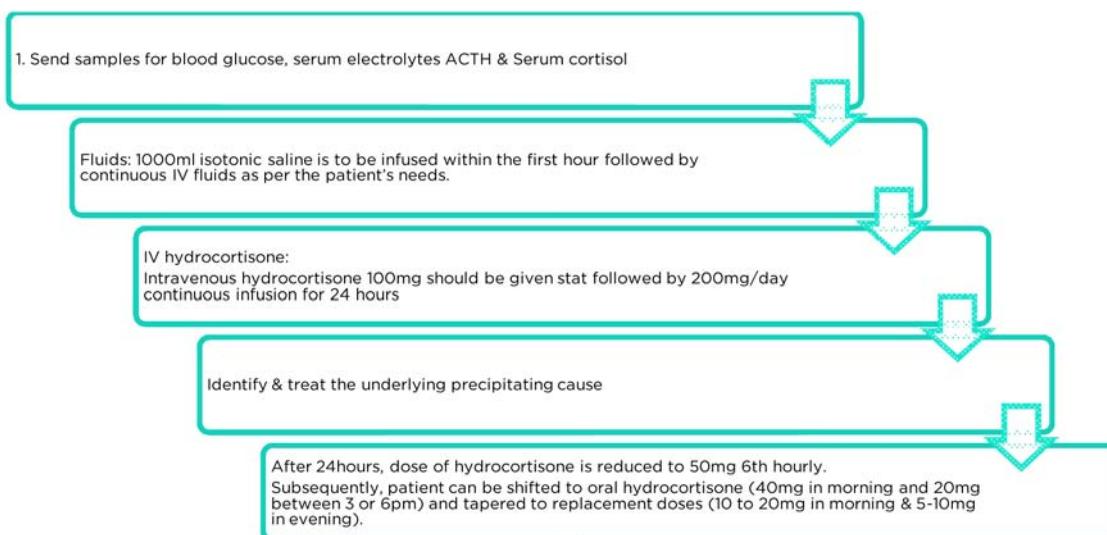


Figure 2: Management of adrenal crisis.¹⁷

management of adrenal insufficiency including dose increments during stress. This is essential to prevent adrenal crisis which occurs in more than half of the patients already diagnosed with adrenal insufficiency. Novel drug delivery methods for glucocorticoid replacement could improve the quality of life in some of these patients.²¹

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Hyperaldosteronism-An approach

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INTRODUCTION

Aldosterone is the principal mineralocorticoid hormone secreted from adrenal gland. Its functions include regulation of extracellular volume and electrolyte homeostasis through its effects on the distal convoluted tubules(DCT) of kidney. It activates the mineralocorticoid receptor in principle cells of the distal nephron, resulting in increased expression of luminal epithelial sodium channels (ENaC). Sodium is reabsorbed via ENaC resulting in a potent electronegative luminal potential that induces the efflux of cations from the principle cell, namely potassium and hydrogen ions. Thus, the net effect of this classical aldosterone action on the kidney is reabsorption of sodium (which ultimately will result in water reabsorption and intravascular volume expansion) and urinary excretion of potassium and hydrogen. In addition to these classical actions, the non-classical extra-renal actions of aldosterone, particularly on cardiovascular tissues such as the endothelium and myocardium, are now increasingly recognized in human disease.

ALDOSTERONE REGULATION AND ACTION

Aldosterone is synthesized in the zona glomerulosa of the adrenal gland. Its production is restricted to this layer of the adrenal cortex because of zonal-specific expression of aldosterone synthase (CYP11B2), which is the key enzyme for aldosterone biosynthesis. Its expression is controlled by aldosterone secretagogues. Aldosterone secretion is under the control of several factors: angiotensin II, potassium, and, to a lesser degree, adrenocorticotrophic hormone (ACTH), endothelin 1 (ET-1), estrogens, and urotensin II.

The renin-angiotensin system (RAS) is a principal regulator of aldosterone production. Renin, an enzyme produced in the juxtaglomerular apparatus of the kidney, catalyses the conversion of angiotensinogen (an inactive precursor peptide) to angiotensin I. Angiotensin I undergoes further enzymatic conversion by angiotensin-converting enzyme (ACE) to produce angiotensin II (AngII). AngII acts via the adrenal angiotensin receptor to stimulate the release of aldosterone by increasing the transcription of aldosterone synthase.

PATHOPHYSIOLOGIC IMPLICATIONS OF ALDOSTERONE

Emerging evidence has implicated aldosterone, and specifically activation of the mineralocorticoid receptor, with cardiovascular and metabolic diseases. The mineralocorticoid receptor though considered in the context of its expression in the distal nephron, yet it is now clear that this receptor is also expressed in the vasculature and heart and plays a crucial role in mediating cardiovascular pathophysiology. The non-classical effects of aldosterone have stemmed from dysregulated aldosterone physiology being linked with deleterious end-organ effects. Typically, this has been evidenced by inappropriately elevated levels of aldosterone in the setting of high dietary sodium intake (subclinical or clinical primary hyperaldosteronism). Excess aldosterone activity has been associated with cardiac fibrosis, inflammation, and remodelling, pathologic insulin secretion and/or peripheral resistance and metabolic syndrome and hence increased mortality.

CAUSES OF MINERALOCORTICOID EXCESS SYNDROME

Mineralocorticoid excess states (Figure 1) comprise of a group of disorders that can be divided into those mediated by the principal mineralocorticoid, aldosterone, and those caused by non-aldosterone etiologies. Hyperaldosteronism which result from autonomous secretion of aldosterone from one or both adrenal glands, is referred to as Primary Aldosteronism (PA). In this condition, the plasma renin activity (PRA) is suppressed (*hyporeninemic hyperaldosteronism or renin-independent aldosteronism*), and the plasma aldosterone to renin activity ratio is elevated. In Secondary hyperaldosteronism, increased activation of the RAS is the initiating event, resulting in excess aldosterone production (*hyperreninemic hyperaldosteronism or renin-dependent aldosteronism*). Therefore, secondary hyperaldosteronism can be a normal physiologic phenomenon (such as in states of systemic hypovolemia or hypoperfusion) or can manifest as a pathologic entity when activation of the RAS is inappropriate relative to the state of the systemic vasculature. The distinction between primary and

secondary causes of hyperaldosteronism is of utmost importance, as the manifestations, as well as the subsequent protocol of investigations and treatment differ entirely.

CAUSES OF MINERALOCORTICOID EXCESS WITH LOW PLASMA RENIN ACTIVITY

Primary Aldosteronism

The five established morphological subtypes of PA include: aldosterone-producing adenoma (APA), bilateral adrenal hyperplasia (BAH), unilateral adrenal hyperplasia (UAH), glucocorticoid-remediable aldosteronism (GRA), and, rarely, adrenocortical carcinoma. At present, BAH accounts for the 60% of PA cases whereas APA or UAH account for the remaining 30-40%, whereas. Definitive diagnosis of the cause of PA can be a challenge and requires a high index of clinical suspicion. However, making an early and correct diagnosis is of utmost importance, since the treatment for each underlying etiology may be different. APAs are often small tumors, usually less than 2 cm in diameter. Unilateral adrenal hyperplasia (UAH), sometimes referred to as primary adrenal hyperplasia, shares many

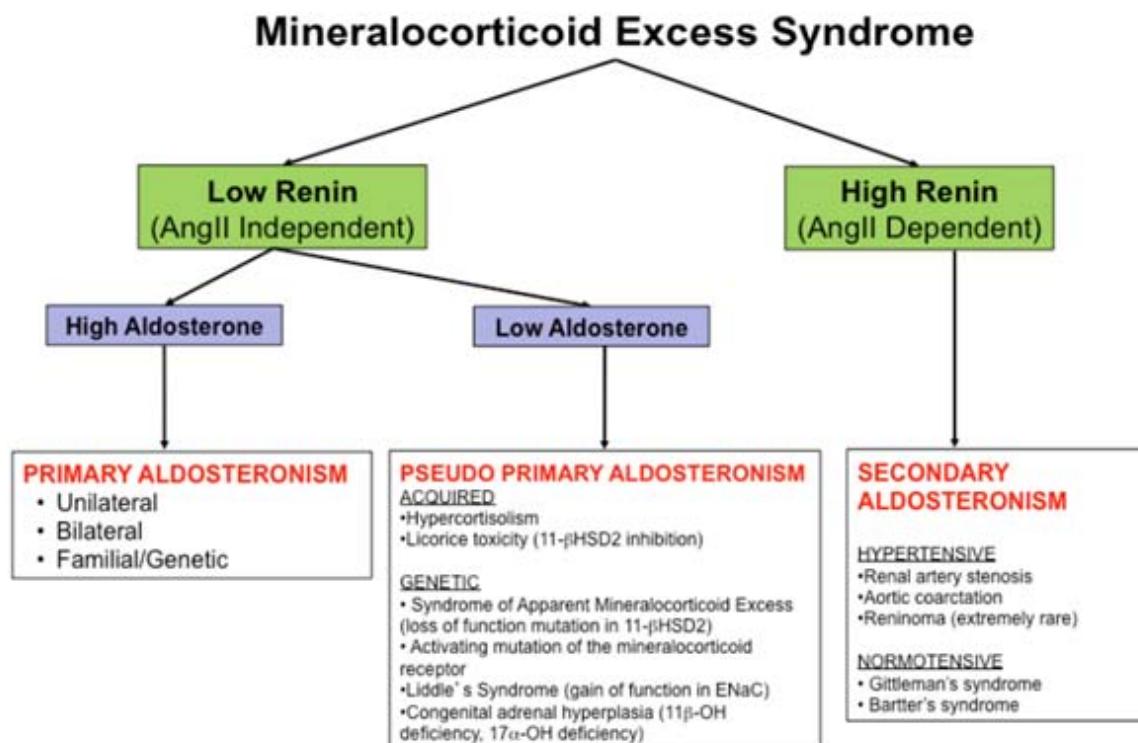


Figure 1. Approach to Mineralocorticoid Excess Syndromes

biochemical features with APA. This diagnosis is often made based on evidence of unilateral production of aldosterone in the absence of a discrete radiographic mass. Similar to APA, the hypertension and biochemical abnormalities with UAH may be cured or substantially ameliorated with unilateral adrenalectomy. The extent of hyperaldosteronism is often milder in BAH compared to APA, and consequently the severity of hypertension, hypokalemia and suppression of PRA is often less. Adrenal carcinomas are a rare cause of primary aldosteronism. At the time of diagnosis, adrenal carcinomas are generally large (>4 cm) and may be producing one or multiple adrenal cortical hormones, including cortisol, aldosterone, and adrenal androgens.

GENETIC INSIGHTS INTO THE CAUSES OF PRIMARY ALDOSTERONISM

Recent advances in the genetics of PA have provided novel insights into the pathogenesis of unilateral forms of PA. Familial types of the disease have been described as follows:

FAMILIAL HYPERALDOSTERONISM TYPE I (FH-I) OR GLUCOCORTICOID-REMEDIABLE ALDOSTERONISM (GRA)

GRA (also known as familial hyperaldosteronism type I) is an autosomal dominant disorder characterized by a chimeric duplication, whereby the 5'-promotor region of the 11 α -hydroxylase gene (regulated by ACTH) is fused to the coding sequences of the aldosterone synthase gene in a recombination event (gene defect in CYP11B1/CYPB2 -coding for 11beta-hydroxylase/aldosterone synthase). The result is that the aldosterone synthase gene (CYP11B2) is under the control of the promoter for the CYP11B1 gene, typically responsible for cortisol production under the regulation of ACTH. Aldosterone synthesis is therefore abnormally and solely regulated by ACTH. This leads to an ectopic expression of aldosterone synthase activity in the cortisol-producing zona fasciculata, making mineralocorticoid production regulated by corticotropin. The hybrid gene has been identified on chromosome 8. In GRA, urinary hybrid steroids

18-oxocortisol and 18-hydroxycortisol are approximately 20-fold higher than in sporadic aldosteronomas. Intracranial aneurysms and hemorrhagic stroke are clinical features frequently associated with familial hyperaldosteronism type I. The diagnosis is made by documenting dexamethasone suppression of serum aldosterone using the Liddle's Test (dexamethasone 0.5 mg q 6h for 48h should reduce plasma aldosterone to nearly undetectable levels (below 4 ng/dl) or by genetic testing (Southern Blot or PCR).

FAMILIAL HYPERALDOSTERONISM TYPE II (FH-II)

It consists of a familial disease without unique phenotypic features caused by mutations in the inwardly rectifying chloride channel CLCN2.

FAMILIAL HYPERALDOSTERONISM TYPE III (FH-III)

FH-III is associated with germline mutations in KCNJ5, a gene that encodes the inwardly-rectifying potassium channel GIRK4 leading to an increase in aldosterone synthase expression and production of aldosterone. This type is characterized by severe childhood-onset hypertension, hypokalemia, remarkably high aldosterone-to-renin ratio, with marked adrenal enlargement and diffuse hyperplasia of the zona fasciculata.

FAMILIAL HYPERALDOSTERONISM TYPE IV (FH IV)

Familial aldosteronism type IV results from germline mutations in the T-type calcium channel subunit gene CACNA1H. Germline mutations in CACNA1D (encoding a subunit of L-type voltage-gated calcium channel Ca_V1.3) are found in patients with primary aldosteronism sometimes associated with seizures, and other neurological abnormalities.

Pseudo Primary Aldosteronism

Congenital Adrenal Hyperplasia(CAH)

The most common cause of CAH is 21-hydroxylase deficiency, which can result in variable

insufficiencies of cortisol and aldosterone. However, much rarer forms of CAH, for example, 11 α -hydroxylase deficiency and 17 α -hydroxylase deficiency can result in monogenic hypertension due to hypermineralocorticoidism, caused by elevated deoxycortisol and deoxycorticosterone levels, and resultant excessive mineralocorticoid receptor activation.

Apparent Mineralocorticoid Excess (AME)

AME results from abnormal activation of the Type I mineralocorticoid receptor in the kidney by cortisol, secondary to an acquired (licorice ingestion or chewing tobacco) or congenital deficiency of the renal isoform of the type II isoenzyme of the corticosteroid 11-beta-dehydrogenase. This isoenzyme converts cortisol to the inactive cortisone in the renal distal convoluted tubule. However, in case of this isoenzyme's deficiency, the type I mineralocorticoid receptor is no longer protected from activation by cortisol and responds to it as if it were aldosterone.

Mutations in 11 α -hydroxysteroid dehydrogenase type 2 gene (*HSD11B2*) is a rare autosomal recessive disorder that is the main cause of AME, which is a form of low renin hypertension. The clinical manifestations are cardiovascular complications, severe hypertension, left ventricular hypertrophy, hypertensive retinopathy and nephrocalcinosis associated with hypokalemia.

Liddle's Syndrome

In Liddle's syndrome, constitutive activation of the renal epithelial sodium channel (ENaC) results from activating mutations in the ENaC gene. In both AME and Liddle's syndromes, the intrinsic renal abnormalities described lead to unregulated and excessive sodium reabsorption, and therefore a biochemical phenotype of suppressed PRA, hypokalemia, and undetectable levels of plasma aldosterone.

CLINICAL FEATURES OF HYPERALDOSTERONISM

The clinical features of hyperaldosteronism are non-specific, often resulting in or associated with hypertension. It is more important to distinguish

whether the hyperaldosteronism is primary or secondary, as this pathophysiologic designation dictates the likely clinical syndrome (Table 1). Renal potassium wasting can result in hypokalemia. The phenotype depends largely on the underlying cause, degree of the aldosterone excess, as well as the presence of other co-morbidities. The classic features of moderate-to-severe hypertension, hypokalemia, and metabolic alkalosis are highly suggestive of mineralocorticoid excess (usually primary aldosteronism). In the majority of cases, however, only subtle clues of hyperaldosteronism exist, such as the recent onset of resistant hypertension (defined as refractory to treatment with three classes of antihypertensives, including a diuretic).

Spontaneous hypokalemia in any patient with or without concurrent hypertension warrants consideration of hyperaldosteronism as the etiology. Additionally, patients that develop severe hypokalemia after institution of a potassium-wasting diuretic (such as hydrochlorothiazide or furosemide) should be investigated. In majority of cases of PA serum potassium levels are normal.

PA results in extracellular volume expansion secondary to excess sodium reabsorption. However, after the retention of several liters of isotonic saline, an escape from the renal sodium-retaining actions of aldosterone occurs in part due to the increased secretion of atrial natriuretic peptide (ANP). Therefore, peripheral edema is rarely a feature of PA if cardiac and renal functions are normal. Metabolic alkalosis occurs secondary to renal distal tubule urinary hydrogen ion secretion. Hypomagnesemia and mild hypernatremia (likely secondary to resetting of the osmostat) can also be observed.

Rarely, patients experience neuromuscular symptoms, including paresthesias or weakness, due to the electrolyte disturbances caused by the hyperaldosteronism. Nephrogenic diabetes insipidus, caused by renal tubule anti-diuretic hormone resistance due to the hypokalemia, can cause nocturia and mild polyuria and polydipsia. Atrial fibrillation and cardiac arrhythmias may occur and can be life threatening.

Table 1. CLINICAL MANIFESTATIONS OF PRIMARY ALDOSTERONISM

Classic Manifestations

- Hypertension 18-25%
- Resistant Hypertension 8%
- Hypokalemia (9 to 37%)
- Hypervolemia
- Metabolic alkalosis

Other Manifestations

Secondary to hypertension

- Headache
- Retinopathy (rare)

Due to hypokalemia

- Neuromuscular symptoms (cramps, paresthesias, weakness)
- Nephrogenic diabetes insipidus
- Cardiac arrhythmia (e.g. atrial fibrillation)
- Glucose intolerance / impaired insulin secretion

Secondary to direct actions of aldosterone on the cardiovascular system

- Cardiac Hypertrophy/Fibrosis
- Vascular smooth muscle hypertrophy

Mild hypernatremia

DIAGNOSIS OF HYPERALDOSTERONISM

Secondary causes of hypertension (including hyperaldosteronism) should be considered initially in all hypertensive individuals. A thorough medical history and meticulous physical examination can guide the clinician in deciding which patients warrants further evaluation and the necessary investigations which needs to be performed. Although the sensitivity of testing for hyperaldosteronism increases when limited to patients with moderate-to-severe hypertension, many patients with hyperaldosteronism have mild to moderate hypertension. The recent onset of refractory or accelerated hypertension, especially in a patient known to be previously normotensive, can be a valuable clinical clue. Therefore, the clinician must remain vigilant to the possibility of hyperaldosteronism, especially in the appropriate clinical setting.

Who To Screen For PA?

The Endocrine Society The task force recommends screening of the following subtypes of patients deemed to be at high risk for PA:

1. Patients with sustained blood pressure $>150/100$ mmHg on three or more measurements on different days.
2. Patients with hypertension resistant to three or more anti-hypertensive medications or patients requiring four or more anti-hypertensive medications to attain blood pressure control.
3. Patients with hypertension and sleep apnea.
4. Patients with hypertension associated with either spontaneous or diuretic-induced hypokalemia.
5. Patients with hypertension and an incidentally discovered adrenal adenoma.



6. Patients with hypertension with a family history of early-onset hypertension or cerebrovascular accident at age less than 40 years.

GRA should be considered in patients with early-onset hypertension (<20yr) in the setting of a suppressed PRA. A family history of PA or early cerebral hemorrhage (<40yr) should also raise suspicion for GRA.

How to Screen For PA?

Evaluation for PA begins with hormonal screening, specifically determination of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) with validated, sensitive assays, for calculation of a plasma aldosterone to renin ratio (ARR). The use of automated direct renin concentration (DRC) rather than PRA is increasing as automated DRC assays are becoming more available. In most studies, given that serum aldosterone is expressed ng/dL and plasma renin activity (PRA) in ng/mL per hour, an ARR > 20 is considered suspicious for PA (95% sensitivity and 75% specificity). An ARR >30, especially in the setting of a PAC > 15 ng/dL (555 pmol/L), has been shown to be 90% sensitive and 91% specific for the diagnosis of PA, whereas a ratio of >50 is virtually diagnostic of PA. Interpretation of the ARR should be made after confirming that renin is suppressed in the setting of inappropriately high endogenous aldosterone production. The absence of renin suppression should raise suspicion for secondary aldosteronism and/or the use of medications that raise renin (mineralocorticoid receptor antagonists, renin inhibitors, renin-angiotensin-aldosterone system inhibitors).

ARR is most sensitive when collected in the morning, after patients have been ambulatory for 2 hours, and have been seated for 5-15 minutes prior to blood collection. Hypokalemia should also ideally be corrected prior to screening as it directly inhibits aldosterone secretion. Furthermore, drugs that alter aldosterone or renin secretion can result in false positive or false negative results. Beta-adrenergic blockers and central alpha agonists lower PRA secretion and often produce a false

positive ARR in patients with essential hypertension. Diuretics, ACE-inhibitors (ACEI) and angiotensin receptor blockers (ARB) can increase PRA and result in false negative screening results. However, if the ARR while on any medication is high, with frankly elevated PAC and suppressed PRA, the likelihood of primary aldosteronism remains remarkably high. The mineralocorticoid receptor antagonists spironolactone and eplerenone, as well as renin inhibitors, can cause false negative ARR by virtue of raising the PRA. If a PRA is suppressed while on a mineralocorticoid receptor antagonist, the ARR may still be interpretable; however, in the context of an unsuppressed PRA, mineralocorticoid receptor antagonists should be discontinued for four to six weeks until the PRA is suppressed, before the ARR is informative. Medications with neutral effects on the ARR, such as non-dihydropyridine calcium channel blockers, hydralazine, or alpha-blockers, can be used instead to control arterial pressure during the screening evaluation.

Confirmation of Diagnosis?

In patients with a positive ARR, subsequent confirmation or exclusion of autonomous aldosterone secretion is necessary. Methods to demonstrate autonomy of aldosterone production focus on volume-expanding maneuvers. Options for volume expansion include oral sodium loading and intravenous saline infusion. Other confirmatory testing can be done by fludrocortisone suppression and captopril challenge test. (Table 2).

Identifying The Cause And Source Of PA

Once the biochemical diagnosis of primary hyperaldosteronism has been confirmed, further evaluation is necessary to determine the etiology and identify the source of excessive aldosterone production. Distinguishing between APA, BAH, and GRA, is extremely crucial to plan therapy. Unilateral adrenalectomy cures hypertension in 30-70% of patients with APA or UAH, and invariably reverses hypokalemia. In contrast, bilateral adrenalectomy in BAH cures hypertension in only <20% of

Table 2. Tests to Confirm Primary Hyperaldosteronism

Confirmation Method	Protocol	Interpretation of Results
Oral Salt Suppression Test	<ul style="list-style-type: none"> Increase sodium intake for 3-4 days via supplemental tablets or dietary sodium to >200 mmol/day Monitor blood pressure Provide potassium supplementation to ensure normal serum levels Measure 24h urinary aldosterone excretion and urinary sodium on 3rd or 4th day 	<ul style="list-style-type: none"> PA confirmed: if 24h urinary aldosterone excretion >12 mcg in setting of 24h sodium balance >200 mmol PA unlikely: if 24h urinary aldosterone excretion <10mcg
Intravenous Saline Infusion Test	<ul style="list-style-type: none"> Infusion of 2L of normal saline after patient lies supine for 1 hour. Infuse 2L of normal saline over 4 hours (500 mL/h) Monitor blood pressure, heart rate, potassium Measure plasma renin and serum aldosterone at time=0h and time=4h 	<ul style="list-style-type: none"> PA confirmed: 4h aldosterone level > 10 ng/dL PA unlikely: 4h aldosterone level < 5 ng/dL
Captopril Challenge Test	<ul style="list-style-type: none"> Administer 25-50mg of captopril in the seated position Measure renin and aldosterone at time=0h and again at time=2h Monitor blood pressure 	<ul style="list-style-type: none"> PA confirmed: serum aldosterone high and renin suppressed* PA unlikely: renin elevated, and aldosterone suppressed* <p>*varying interpretations without specific validated cut-offs</p>
Fludrocortisone Suppression Test	<ul style="list-style-type: none"> Administer 0.1 mg fludrocortisone q6h for 4 days Supplement 75-100 mmol of NaCl daily to ensure a urinary sodium excretion rate of 3 mmol/kg/body weight Monitor blood pressure Provide potassium supplementation to ensure normal serum levels Measure plasma renin and serum aldosterone in the morning of day 4 while 	<ul style="list-style-type: none"> PA confirmed: Seated serum aldosterone > 6 ng/dL on day 4 with PRA< 1ng/mL/h PA unlikely: suppressed aldosterone < 6 ng/dL
Fludrocortisone- dexamethasone	Fludrocortisone- dexamethasone	<ul style="list-style-type: none"> PA confirmed: Upright plasma

suppression test	suppression test (FDST) (61) Administration of sodium chloride (2 g 3 times daily with food) plus oral fludrocortisone (0.1 mg every 6 h for 4 days) along with potassium gluconate (4.68 g three times daily) to maintain serum potassium within the normal range (3.5–5.5 mEq/l). At midnight on the 4th day 2 mg of dexamethasone are added (2 h after dinner)(12)	aldosterone > 82 pmol/l and ARR > 26 on day 5 at 0830 h (Simultaneous cortisol measurements (< 54 nmol/l) are required to confirm patients' compliance)
Recumbent post-low dose dexamethasone suppression (LDDST)-saline infusion test	Dexamethasone administration 2 mg/day (0.5 mg/6 h) for 2 consecutive days. Maintain recumbent position early in the morning of the 3rd day (0830 h) and during the i.v. infusion of 2 l 0.9% normal saline over 4 h. Sampling for renin, aldosterone, cortisol and potassium drawn before initiation of infusion and after 4 h with continuous monitoring of BP and heart rate (12)	· PA confirmed: Post-infusion plasma aldosterone <68 pmol/l and ARR < 10 pmol/mU
Captopril-valsartan -dexamethasone test (103)	Day 1 at midnight, at least 2h after the last meal: 2mg dexamethasone, 50mg captopril, and 320mg valsartan. Day 2 morning: extra dose of 50mg captopril was given 1h before blood sampling, which was performed between 08:30 and 09:00 (cortisol, ALD, REN, ACTH, and potassium levels). All blood samples were drawn with the participants remaining seated in a non-stressful environment for at least 30 min.	· PA confirmed: Cutoff values of 0.3ng/dL/ μ U/mL (9pmol/IU) for ARR and 3.1ng/dL (85pmol/L) for aldosterone respectively

patients. Hence, the treatment of choice is surgical in APA or UAH, and medical management is generally favored in BAH and GRA.

Biochemical characteristics can assist with the diagnosis of the various causes of PA. Age (<50 years old), severe hypokalemia (<3.0 mmol/L), high plasma aldosterone concentrations (> 25 ng/dl), and high urinary aldosterone excretion (>30 ug/24hr) favors the diagnosis of APA versus BAH. The presence of a classical unilateral Conn's adenoma in addition to a serum potassium < 3.5 mmol/L or estimated glomerular filtration rate > 100 mL/min/1.73 m² is nearly 100% specific for an APA.

Patients with clinical and biochemical suspicion of PA should undergo radiological evaluation of the adrenal glands to localize the source and define the anatomy for potential surgical approaches. Computed tomography (CT) scanning with thin-slice (3mm) spiral technique is the best radiographic procedure to visualize the adrenal glands and serves primarily to exclude large masses that may represent adrenocortical carcinoma, which are usually more than 4 cm in size. Observation of a solitary hypodense adrenal nodule, usually < 2 cm in size, supports the diagnosis of APA. Adrenal adenomas typically are lipid-rich on CT scan (<10 HU) and have a greater

than 50% washout of contrast after 10-15 minutes. However, even when biochemical features suggestive of APA are present, only one-third to one-half of patients have positive CT findings for a solitary adenoma. Furthermore, it is emphasized that a radiographic abnormality does not always correlate with a functional equivalent.

Adrenal vein sampling (AVS) is a localization technique that is considered to be the 'gold standard' for distinguishing unilateral versus bilateral disease in PA. AVS involves sampling from the right and left adrenal veins, as well as from the inferior vena cava (IVC), for measurement of aldosterone and cortisol concentrations. Many favor performing AVS with adrenocorticotropin (ACTH) stimulation, which can be administered continuously or as a bolus, and may minimize stress-induced fluctuations in aldosterone secretion during the procedure as well as maximize aldosterone secretion from an APA. Multiple variables derived from AVS can be used to determine lateralization of aldosterone hypersecretion. Cortisol-corrected aldosterone ratios (A/C ratio) are determined by dividing the aldosterone concentrations from each location sampled by the cortisol concentration in the same location to correct for dilutional effects. Recent observational studies have also demonstrated that perhaps the most sensitive way to confirm contralateral suppression is when the ratio of the basal aldosterone concentration from the contralateral adrenal vein to the basal aldosterone concentration in the peripheral vein is less than 1.5. AVS has been reported to have a sensitivity of 95% and a specificity of 100% to detect unilateral disease.

TREATMENT OF PRIMARY ALDOSTERONISM

Treatment for PA depends on the underlying etiology. The goals for optimal treatment are reduction of the adverse cardiovascular effects of chronic aldosterone excess, such as increased left ventricular mass and hence increased risk of stroke, myocardial infarction, heart failure and atrial fibrillation, normalization of the serum potassium and normalization of blood pressure, which may persist even after correction of

hyperaldosteronism.

Surgery is most often the treatment of choice for APA, and is often performed with laparoscopic techniques, which reduce patient recovery time and hospital cost. A newer treatment approach, and potential alternative to surgical resection, is radiofrequency ablation of a unilateral APA. A clear advantage of radiofrequency ablation is the option to avoid surgery and instead pursue imaging guided needle placement and ablation; however, one clear disadvantage is the inability to obtain histopathology since the procedure destroys pathological tissue in situ. Resection or ablation of an APA may cure or ameliorate hypertension, and invariably reverses hypokalemia. Unilateral adrenalectomy cures hypertension in 30-70% of patients with APA or UAH. Pre-operatively, hypertension and hypokalemia should be well controlled, which may require the addition of a mineralocorticoid receptor antagonist. Post-operatively, suppression of aldosterone secretion in the contralateral adrenal gland is expected and may result in a transient hyporeninemic hypoaldosteronism state. As a result, some patients exhibit post-operative salt wasting, mild hyperkalemia, and are at increased risk of dehydration and orthostatic hypotension if sodium restricted. Potassium and mineralocorticoid receptor antagonists should be withdrawn after surgery. PAC can be measured post-operatively as an indication of surgical response. However, re-equilibration of PRA post-operatively can take several weeks to months. Blood pressure tends to show maximal improvement 1-6 months post-operatively. For patients who are not operative candidates, or choose not to undergo surgery, medical management of hyperaldosteronism should be pursued.

BAH is best treated medically with the use of a mineralocorticoid receptor (MR) antagonist. When medical therapy is planned, the available options are the mineralocorticoid receptor antagonists eplerenone or spironolactone, which prevent aldosterone from activating the MR, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in PRA. Spironolactone



doses required are usually between 50 mg and 400 mg per day, usually administered once daily. The dose can be up-titrated every two weeks, until serum potassium values of 4.5 mEq/L are achieved. However, while it is effective for controlling blood pressure and hypokalemia, the use of spironolactone is limited by its adverse effects. Gynecomastia and erectile dysfunction often occur during long-term treatment in males due to the anti-androgenic actions. In women, spironolactone may lead to menstrual dysfunction, primarily intermenstrual bleeding. Eplerenone, has no anti-androgenic activity and therefore has fewer side effects. However, it has a short half-life and is more effective if given twice daily. Its starting dose is 25 mg, twice daily. In order to achieve a sufficient response in PA, doses higher than 100 mg/day are often needed. A targeted mid- to high-normal serum potassium concentration without the aid of potassium supplements may suggest sufficient mineralocorticoid receptor blockade. A monitoring of plasma renin activity with an optimal value higher than 1 ng/mL/hour, has also been suggested to significantly reduce risk of major cardiometabolic events and mortality. However, optimization with high dosage of MR antagonists may not be ideal in cases of glomerular filtration rate decline, where there is an increased risk of hyperkalemia.

In rare situations, when blood pressure is not controlled with spironolactone/eplerenone, or side-effects limit tolerability, the addition of other antihypertensive therapies may be required. Potassium-sparing diuretics, such as the ENaC inhibitors triamterene or amiloride, have been used, although they are usually not as effective as spironolactone. The dihydropyridine calcium channel antagonists have also been shown to effectively reduce blood pressure. Dietary sodium restriction (< 100 mmol/day), regular aerobic exercise, and maintenance of ideal body weight contribute to the success of pharmacologic treatment for hypertension in BAH. Novel treatment-agents, such as finerenone, a dihydropyridine based nonsteroidal MR antagonist, are under evaluation for the treatment of PA.

Glucocorticoid-remediable aldosteronism (GRA) can be successfully treated with low doses of glucocorticoids such as dexamethasone. By inhibiting ACTH release, the abnormal production of aldosterone can be suppressed. The lowest dose of glucocorticoid that can normalize blood pressure and potassium levels should serve to minimize side effects. PRA and PAC can be measured to assess treatment effectiveness and prevent overtreatment.

CAUSES OF MINERALOCORTICOID EXCESS WITH HIGH PLASMA RENIN ACTIVITY (SECONDARY ALDOSTERONISM)

Secondary aldosteronism is the result of the hypersecretion of aldosterone because of increased activation of the renin-angiotensin system (RAS).

Usually Normotensive Or Hypotensive

The most common causes of secondary aldosteronism are medical illnesses that result from a reduction in perceived or effective circulating blood volume, such as congestive heart failure and nephrotic syndrome. Importantly, treatment and correction of the underlying medical illness and volume expansion results in reversal of the activated RAS. Secondary aldosteronism in a normotensive patient should also raise consideration for Gittelman's and Barter's syndrome

Diuretic use can also cause secondary aldosteronism. The findings can mimic those seen in renovascular hypertension, especially in a hypertensive patient. With chronic diuretic use, moderate to severe extracellular and intravascular volume depletion results in renal hypoperfusion, increased release of renin, and subsequently excessive aldosterone production.

Usually Hypertensive

It is important to distinguish renal vascular disease from renal vascular hypertension. While a large proportion of the adult population may have renal vascular disease (defined as a 50% or greater decrease in renal artery luminal diameter), only a small portion of these patients experience critical and clinically relevant renal

hypoperfusion and ischemia. Therefore, documentation of both structural and functional abnormalities is required before planning therapeutic intervention in such patients.

Renovascular hypertension is defined as hypertension associated with either unilateral or bilateral ischemia of the renal parenchyma. There are numerous causes of this disorder. Atherosclerosis of the renal arteries is the most common, accounting for 90% of cases. Fibromuscular dysplasia accounts for less than 10% of cases. In these disorders, decreased renal perfusion causes tissue hypoxia and decreased perfusion pressure, thereby stimulating renin release from the juxtaglomerular cells, resulting in secondary aldosterone secretion. Coarctation of the aorta can produce a similar pathophysiology due to renal hypoperfusion.

DIAGNOSIS OF SECONDARY ALDOSTERONISM

When there is clinical suspicion for renovascular hypertension, and initial screening has revealed a normal or elevated PRA, further testing for renovascular hypertension should be considered. Clinical features that should raise suspicion for renovascular hypertension include abrupt-onset hypertension, unexplained acute or progressive renal dysfunction, renal dysfunction induced by renin-angiotensin-aldosterone system inhibitors, asymmetric renal dimensions, or suspicion of fibromuscular disease in a young patient. Importantly screening is only recommended if intervention will be pursued if a significant lesion is detected.

The diagnosis of renovascular hypertension requires two criteria: 1) the identification of a significant arterial obstruction (*structural abnormality*), and 2) evidence of excess renin secretion by the affected kidney (*functional abnormality*). Structural abnormalities can be detected by a variety of imaging techniques. The gold standard is renal arteriography, but computed tomography (CT) scanning, duplex Doppler ultrasonography, and magnetic resonance angiography are reasonable non-invasive alternatives.

TREATMENT OF SECONDARY ALDOSTERONISM

Renal artery stenosis is managed through medical therapy alone or combined with revascularization. The goal of treatment is blood pressure control, as well as prevention of decline in renal function and secondary cardiovascular disease. For renal artery fibromuscular dysplasia, primary angioplasty is the recommended endovascular procedure. In the case of atherosclerotic renovascular disease, angioplasty with stent placement is preferred over angioplasty alone.

Aggressive medical therapy should also be instituted and may be sufficient in many patients with atherosclerotic renovascular hypertension. Given the central role of the RAS in the pathophysiology of the disease, ACE inhibitors and ARB are the agents of choice for medical management and have anti-hypertensive as well as reno-protective effects. Caution must be taken, however, as initiation of either agent can rarely be associated with precipitation of acute renal failure, particularly in patients who have critical, bilateral renal artery stenosis.

CONCLUSION

The prevalence of PA among hypertensive patients is high and patients have increased mortality rate. Cardiovascular events and mortality are markedly reduced by specific management depending on the cause. Nonetheless, the diagnosis is extremely underdiagnosed and requires a high index of clinical suspicion and expertise. Physicians must rule out Primary Hyperaldosteronism in patients presenting with moderate hypertension, or developing hypertension or stroke below forty years age, unexplained atrial fibrillation, hypertension with sleep apnoes. Screening for and diagnosis of PA should not be limited to hypertensive patients with hypokalemia, adrenal incidentaloma or resistant hypertension if we desire for a good prognosis of our patients.



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Hypothyroidism: A Comprehensive Review and Recent Updates

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Introduction:

In the realm of clinical practice, few investigations hold as much prominence as thyroid functions. These tests, pivotal in the assessment of endocrine health, serve as a cornerstone in diagnosing a wide array of conditions. Among these, hypothyroidism stands out as the most prevalent endocrine disorder encountered by primary care physicians. This chapter delves into the intricate workings of the thyroid gland, shedding light on its multifaceted nature, exploring its vital functions and the diagnostic significance of thyroid function tests. Drawing upon recent research and clinical developments, we offer a comprehensive review that encompasses the latest insights and updates in the field. Throughout this chapter, we aim to provide readers with a comprehensive synthesis of the current understanding of hypothyroidism, incorporating recent updates and advancements that shape clinical practice and inform evidence-based decision-making. By navigating the complexities of hypothyroidism with clarity and insight, we would want to empower healthcare professionals to optimize patient care and support individuals living with this thyroid disorder.

Historical Insights:

The history of hypothyroidism traces back to ancient times, with references dating back to BC era. Charaka, a revered physician, recommended a diet rich in rice, milk, barley, green grams, sugar cane juice, and cucumber as a preventive measure against hypothyroidism.[1]

In 1656, the pioneering anatomist Thomas

Wharton made a significant breakthrough by identifying the precise structure of the thyroid gland. Subsequently, in 1850, Thomas Culling provided the first clinical descriptions of hypothyroidism, highlighting its association with myxedema and cretinism.[2]

The march of scientific progress continued, and by 1927, Edward Kendall, and his colleagues at the Mayo Clinic, successfully synthesized thyroxine, a key hormone produced by the thyroid gland, marking a pivotal moment in the treatment of thyroid disorders.[3]

Epidemiology of hypothyroidism:

Hypothyroidism effects about 10% of population in India in a study conducted over eight cities, with elderly and females effected mostly.[4] A systematic review of 7 studies conducted in Europe concluded that prevalence of underdiagnosed thyroid dysfunction was 6.71% and hypothyroidism was 4.95%. [5] The prevalence of self-reported goiter or thyroid disorder in NFHS IV (2015-2016) was 2.2%, rising to 2.9% in NFHS-V (2019-2021). In NFHS IV, among individuals aged 15-49, females reported nearly 2% prevalence, while males reported less than 1%. [6] In a study of the South Indian population, 19.6% exhibited thyroid function abnormalities, with 9.4% having subclinical hypothyroidism.[7]

Definitions:

Hypothyroidism is defined and described as reduced inadequate production of thyroid hormones or a metabolic state resulting from



absence of effects of thyroid hormones over different body tissues. [8]

Hypothyroidism, a multifaceted endocrine disorder, is systematically categorized into distinct forms (Table 1a and 1b):

Primary Hypothyroidism: Within primary hypothyroidism, the root cause originates within the thyroid gland itself. Here, the gland fails to produce adequate levels of thyroid hormones, leading to a deficiency that disrupts the body's metabolic balance (Figure1).

Secondary Hypothyroidism: Contrarily, secondary hypothyroidism manifests when the thyroid gland remains structurally intact but encounters functional disruptions upstream in the intricate network of the hypothalamic-pituitary-thyroid axis. This disruption can arise from various pathologies, including central hypothyroidism, consumptive hypothyroidism, defects in peripheral conversion, and resistance to thyroid hormones within bodily tissues. These underlying pathologies underscore the complexity of secondary hypothyroidism, where the fault lies not within the thyroid itself, but in the intricate interplay of regulatory mechanisms governing hormonal balance.[9]

Tertiary Hypothyroidism: Tertiary hypothyroidism arises from hypothalamic disorders that hinder the secretion of thyrotropin-releasing hormone (TRH), thereby failing to stimulate the secretion of thyroid-stimulating hormone (TSH), consequently impeding thyroid hormone synthesis.[10]

Congenital hypothyroidism: Congenital hypothyroidism is defined as deficiency of thyroid hormones at birth. Congenital hypothyroidism is classified into two types namely – transient and permanent congenital hypothyroidism. The most common cause of congenital hypothyroidism is thyroid dysgenesis which accounts for 85% of cases, followed by dyshormonogenesis and defective thyroid hormone functioning due to genetic defects.[11]

Overt and Subclinical hypothyroidism: In

clinical practice, identifying Overt hypothyroidism from subclinical hypothyroidism is important in initiation of treatment and watchful follow up. **Overt hypothyroidism** is defined as an elevated serum TSH concentration and reduced free thyroxine and free triiodothyronine concentrations, whereas **subclinical hypothyroidism** is defined as an elevated serum Thyroid stimulating hormone (TSH) level with a normal serum triiodothyronine and tetraiodothyronine concentrations with respect to population reference range. Patients with subclinical hypothyroidism are classified into two groups: those with mildly elevated serum TSH levels (4.5–10 mIU/liter) and those with more significantly elevated serum TSH levels (>10 mIU/liter).[12]

Pathophysiology of Hypothyroidism of different etiologies:

Congenital hypothyroidism: Congenital hypothyroidism arises from thyroid dysgenesis or dyshormonogenesis. Additionally, resistance to thyroid-stimulating hormone (TSH) binding and signaling may occur due to defects in the TSH receptor or Gs protein. Various genes, including TSHB, TRHR, IGSF1, TBL1X, and IRS4, may harbor defects leading to isolated TSH deficiency, resulting in secondary failure of thyroid hormone synthesis. Furthermore, structural anomalies within the hypothalamo-pituitary region or disruptions in transcription factors can contribute to TSH deficiency. Mutations in genes such as MCT8 and thyroid hormone receptor beta also contribute to congenital hypothyroidism.[14]

Autoimmune Hypothyroidism: Hashimoto's thyroiditis, an autoimmune thyroid disorder, is a well-known cause of hypothyroidism. It can manifest as hyperthyroidism, followed by a euthyroid phase, then hypothyroidism. Major susceptibility genes include HLADR, CTLA-4, CD40, PTPN22, thyroglobulin, and

TSH receptor genes. Environmental triggers like iodine, medications, infections, smoking, and stress play significant roles.[15] Genetic susceptibility and environmental triggers prompt

antigen-presenting cells to present self-antigens to T cells, leading to specific Th cell differentiation based on cytokine production.[16]

Inflammatory thyroiditis with hypothyroidism:

Acute thyroiditis typically results from bacterial infection, primarily attributed to *Staphylococcus* and *Streptococcus* bacteria. Subacute thyroiditis arises from granulomatous viral infections. Chronic thyroiditis may stem from radiation exposure, medication-related factors, autoimmune disorders, or postpartum circumstances. Inflammation precipitates thyroid gland destruction, culminating in hypothyroidism.[17]

Iodine deficiency and Iodide excess: Excessive iodine intake can exacerbate hypothyroidism in certain patients. A subset of individuals, particularly sensitive to the inhibitory effects of iodide on its own organification, exhibit sustained activity of the sodium iodide symporter (NIS). Prolonged NIS inhibition results in diminished thyroid hormone synthesis, thereby elevating TSH levels and precipitating hypothyroid manifestations.[18] Conversely, iodine deficiency hampers thyroid hormonogenesis, prompting excessive stimulation of the thyroid gland to compensate for mild to moderate deficiencies, leading to goiter formation. Severe iodine deficiency can culminate in overt hypothyroidism accompanied by goiter.[19]

Drug induced hypothyroidism: The thyroid axis is highly susceptible to drug interactions, with hypothyroidism being the most common outcome. Primary hypothyroidism can result from inhibition of thyroid hormone synthesis/release, immune mechanisms by interferons, or drug-induced thyroiditis by tyrosine kinase inhibitors and excess iodine content in amiodarone. Central hypothyroidism may arise from thyroid-stimulating hormone inhibition (e.g., bexarotene, corticosteroids) or immunological mechanisms (e.g., anti-CTLA4, anti-PD-1 antibodies). It's crucial to identify drugs that interact with thyroid treatment, affecting levothyroxine absorption, transport, or metabolism, particularly prior to prescribing medications like amiodarone, lithium, interferon, and newer biological therapies.[20]

Postablative hypothyroidism: Radioactive iodine, employed for thyroid ablation in Graves' disease and toxic nodular goiter, results in thyroid gland destruction, leading to subsequent failure in synthesizing thyroid hormones post-procedure.[21]

Transient hypothyroidism: Transient congenital hypothyroidism can be caused due to iodine deficiency, transplacental passage of maternal TSH – binding inhibitory antibodies, and maternal exposure to radioiodine and antithyroid drugs, neonatal iodine exposure and mutations in DUOX2 and DUOXA2.

Transient hypothyroidism in adults can occur due to any inflammatory process and is difficult to differentiate from hashimotos thyroiditis.[22]

Consumptive hypothyroidism: In cases involving hemangiomas and hemangioendotheliomas, there is an upregulation of type 3 deiodinase enzyme activity. This enzyme catalyzes the deiodination reaction, resulting in the accelerated degradation of thyroid hormones, leading to their excessive depletion causing hypothyroidism.[23]

Central hypothyroidism: Central hypothyroidism occurs when there is a failure to stimulate the thyroid gland due to deficiencies in thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone (TRH), classified as secondary and tertiary hypothyroidism, respectively. [24]

Resistance to thyroid hormones: Resistance to thyroid hormone syndrome is characterized by reduced sensitivity to thyroid hormones and is primarily caused by mutations in the thyroid hormone receptor

beta gene, known as RTH α . This condition presents with elevated serum TH levels despite the absence of thyrotropin suppression.[25] (Table 1a&b)

Clinical Features of Hypothyroidism:

The clinical spectrum of hypothyroidism encompasses a diverse array of manifestations, reflecting the widespread influence of thyroid hormones on virtually every tissue in the body. From life-threatening comatose states to subtle

Table 1a: Etiologies of Primary Hypothyroidism:[13]

PRIMARY HYPOTHYROIDISM	
ACQUIRED	CONGENITAL
<ul style="list-style-type: none"> • Hashimoto's thyroiditis • Endemic goitre – Iodine Deficiency • Drugs blocking synthesis or release of T4 • Drug induced destruction of thyroid gland • Amiodarone • Goitrogens • Infiltrative disorders of thyroid • Postablatative thyroiditis • Painful or Painless thyroiditis 	<ul style="list-style-type: none"> • Defect in Transport & utilization of iodide • Iodotyrosine dehalogenase deficiency • Organification disorder • Defects in thyroglobulin synthesis • Thyroid agenesis/Dysplasia • TSH receptor defects • Idiopathic TSH unresponsiveness • Thyroidal Gs protein abnormalities

Table 1b: Etiologies of Secondary Hypothyroidism [13]

SECONDARY HYPOTHYROIDISM				
Central Hypothyroidism		Consumptive Hypothyroidism	Resistance to thyroid hormones	Impaired Conversion of thyroxine to triiodothyronine
Acquired	Congenital	T3 & T4 – metabolism increased)		
Pituitary defect Hypothalamic defect Retinoid X receptor agonist Dopamine or severe illness	TSH receptor Defect TSH deficiency TSH structural abnormality	Hepatic hemangiomas Deiodinase – Over expression	Pituitary Dominant	

signs and symptoms, the impact of hypothyroidism spans across all organs. Importantly, the severity of these manifestations correlates with the extent of hormone deficiency, rather than the specific underlying pathology responsible for hypothyroidism (Table 2).

Management and Clinical Implications of Subclinical Hypothyroidism:

As discussed earlier in this chapter, subclinical hypothyroidism is classified as those with mild elevation of TSH (<10 mIU/L) and those with significantly elevated TSH (>10 mIU/L). There is consensus that patients with TSH levels > 10mIU/L is to be treated as these patients will have high chances of turning overt hypothyroidism and this degree of subclinical hypothyroidism predisposes

to cardiovascular disease. Except in pregnant women, it is reasonable to follow-up the patients every six months with thyroid function test without starting the treatment. If TSH levels persistently are available patients can be started on treatment as minimal hypothyroidism is also a risk for atherosclerosis. [27]

Laboratory Evaluation of Thyroid functions:

In contemporary clinical practice, thyroid hormone measurement stands as one of the most common diagnostic tests conducted, with subclinical hypothyroidism emerging as a frequently encountered abnormality.

Figure1: Schematic Representation of Thyroid Hormone Synthesis and Regulation: Primary and Secondary Hypothyroidism

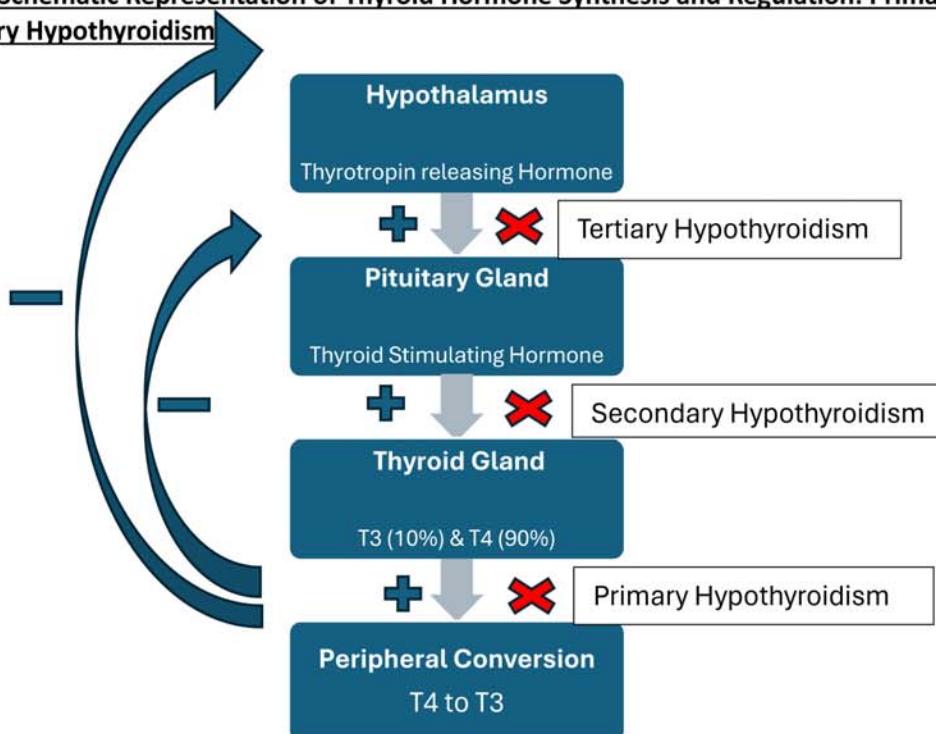


Table 2: Clinical Features of overt hypothyroidism according to the organ involvement and pathophysiology:[26]

Organ system Involved	Pathology	Symptom & Signs - Manifestations
Skin & its appendages	Deposition of Hyaluronic acid	Boggy non pitting edema around eyes, dorsum of hands and feet and supraclavicular fossa. Enlargement of tongue, thickening of pharyngeal and laryngeal mucous membranes
	Cutaneous vasoconstriction	Pale and cool skin
	Reduced secretions of sweat glands and sebaceous glands	Dry and coarse skin
	Increased capillary fragility	Easy bruising
	Unclear role	Head and body hair is dry and brittle, lacks luster and hair tends to fall out.
Respiratory System	Fluid accumulation leading to Pleural effusion	Dyspnea



	Impaired regulation of innervation of upper airway and tongue	Snoring and Obstructive sleep apnea
	In severe hypothyroidism – depression of hypoxic and hypercapnic ventilatory drives leads to alveolar hypoventilation and carbon dioxide retention.	Myxedema Coma
Gastrointestinal System	Retention of water by hydrophilic glycoprotein deposits	Weight Gain, Ascites
	Reduced peristaltic activity, gall bladder contracts sluggishly and is distended	Loss of appetite and constipation
	Impaired clearance	Aminotransaminases may be elevated
	Myxedematous infiltration of bowel wall	Gastric and intestinal mucosal atrophy
Musculo-Skeletal System	Interstitial myxedema	Muscle ache, Stiffness, muscle mass enlarged, delayed muscle contraction and relaxation with delayed tendon jerks.
	Mucinous deposits	Muscle swelling
	Impaired protein synthesis and impaired bone maturation with epiphyseal dysgenesis	Delay in development, Dwarfism – with limbs disproportionately short with respect to trunk
Cardiovascular system	Loss of inotropic and chronotropic effects of T4 – reduced stroke volume and heart rate with increased peripheral vascular resistance & reduced blood volume	Narrowing of pulse pressure, Prolonged circulation time.
	Pericardial Effusion	Muffled heart sounds, ECG – Sinus bradycardia, Low amplitude complexes
	Impaired expression of receptors over liver	Total Cholesterol and LDL is elevated
Nervous system	Thyroid hormone deficiency in fetal life and at birth leads to hypoplasia of cortical neurons, retarded myelination and reduced vascularity	Cretinism
	Reduced glucose uptake at specific areas of brains	All intellectual functions slowed, memory impaired, lethargy, somnolence, dementia, depression, agitation, headache, epileptic seizures.
	Deficient synthesis of pigment required for dark adaptation	Night Blindness
	Myxedema of 8 th cranial nerve and serous otitis media	Hearing loss
	Myxedema infiltration of tongue and larynx	Thick, slurred speech and hoarseness
	Compression of glycosamine glycan deposits around nerves	Numbness and tingling
	Decreased rate of muscle contraction and relaxation	Hung – up/delayed relaxation of reflexes

Renal System	Reduction in renal blood flow, Glomerular filtration rate, tubular reabsorption	Uric acid levels increase, urine flow is reduced, Edema
Hematopoietic System	Diminished oxygen requirement leads to decrease erythropoietin production which leads to decreased red cell mass	Mild normocytic normochromic anemia
Pituitary & Adrenocortical Function	Increased serum prolactin levels	Galactorrhea
	Subnormal response of growth hormone	Delayed growth, short stature
	Pituitary & Adrenal Function secondarily decreased	Adrenal insufficiency
Reproductive Function	Impaired sexual development	Sexual immaturity Delay in onset of puberty Anovulatory cycles
	Inadequate secretion of progesterone, persisting endometrial proliferation	Excessive – irregular break through menstrual bleeding
	In women – altered metabolism of estrogens with decreased sex hormone binding protein	Reduced fertility, diminished libido, failure of ovulation, spontaneous abortion, preterm delivery.
	In men – altered metabolism of androgens with decreased sex hormone binding protein	Diminished libido, erectile dysfunction, oligospermia
Energy Metabolism	Decreased energy metabolism	Low BMR, decreased appetite, cold intolerance, low basal body temperature
	Decreased protein synthesis	Retardation of skeletal and soft tissue growth
	Degradation of insulin is slowed	Sensitivity to exogenous insulin is increased
	Diminished degradation of Lipids	Accumulation of LDL and Triglycerides

Key components of Thyroid Function Tests include:

- 1) Thyroid Stimulating Hormone (TSH)
- 2) Total Tetraiodothyronine (Total T4) and Total Triiodothyronine (Total T3)
- 3) Free Tetraiodothyronine (FT4) and Free Triiodothyronine (FT3)
Additional tests prove valuable in discerning etiology and addressing specific clinical scenarios:
- 4) Antithyroid Peroxidase Antibodies (TPO Ab)
- 5) Antithyroglobulin Antibodies (Tg Ab)
- 6) TSH Receptor Antibodies (TR Ab)
- 7) Transthyretin (TTR)

- 8) Thyroid Binding Globulin (TBG)
- 9) Thyroxine Binding Prealbumin (TBPA)
- 10) Thyroglobulin

Evaluation of a patient with suspected hypothyroidism is done by initially doing TSH (Figure 2) and depending on the TSH values and clinical scenario either do total T3 and T4 or free hormones(pregnancy , nephrotic syndrome etc.) A high TSH suggests that the feedback mechanism due to deficiency of thyroid hormones in the circulation is increasing the levels of TSH (Figure 1) and hence we get low T4 and T3.But in cases when we get low TSH levels with low T3 and T4 hormones and suggestive symptoms one should start thinking in the lines of secondary hypothyroidism. Table 3 gives the reference range of the TSH and T3 and T4 hormones. Table 4

Figure 2: Diagnostic algorithm of Hypothyroidism:

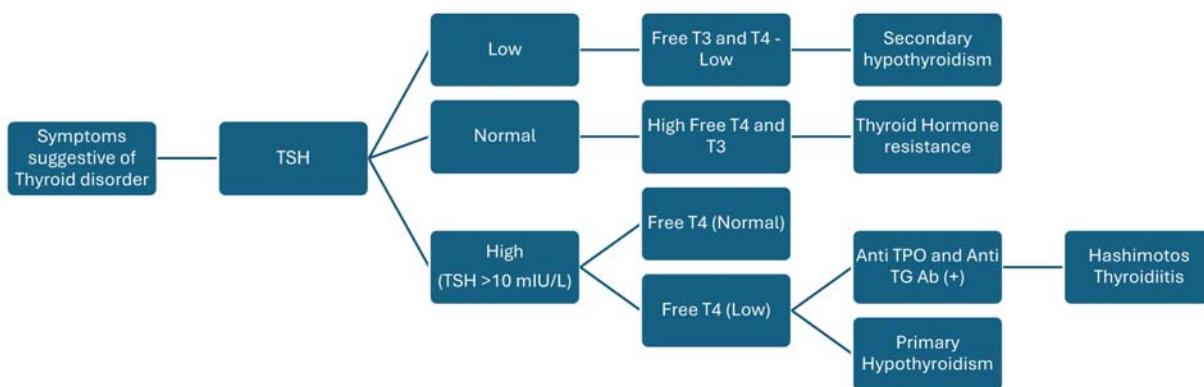


Table 3: Reference Values of Thyroid Function Tests [28]

Tests	Range
TSH	0.5 – 4.2 mU/L
FT3	0.22 – 6.78 pmol/L
Total T4	58-140 nmol/L
FT4	10.3 – 35 pmol/L
Total T3	0.92 – 2.78 nmol/L

elaborates the laboratory picture of the various types of hypothyroidism.

Even minor fluctuations in serum thyroid hormone levels trigger logarithmic amplifications in TSH secretion. The reference range for serum TSH, as determined by immunometric assays, typically falls between 0.4 to 4.2 mIU/L. However, for clinical purposes, an assay capable of detecting values ≥ 0.1 mU/L proves adequate.[29]

TSH secretion follows a diurnal pattern, peaking between midnight to 4 AM and reaching its lowest levels in the afternoon.

In asymptomatic cases with nonspecific thyroid dysfunction, measuring serum TSH levels serves as the ideal screening test, preferably conducted in the morning to capture peak levels. For follow-up assessments of suspected thyroid dysfunction cases not yet initiated on treatment, monitoring TSH levels alone suffices in clinical practice.[30]

- Indications for TSH Level Testing:
 - i. Screening asymptomatic individuals and those with nonspecific manifestations.
 - ii. Follow-up evaluations for suspected thyroid dysfunction cases not under treatment involve half-yearly screening post-exclusion of drug interference and non-thyroidal illness. Patients with positive anti-TPO antibody status require annual follow-up, while those with negative status necessitate follow-up every three years.
 - iii. Evaluation of all suspected cases of goiter.
 - iv. During pregnancy, particularly at the initial antenatal checkup.
 - v. Assessment of conditions such as delayed puberty, menstrual disturbances, and polycystic ovarian syndrome.

- Clinical Practice Guidelines:
- i. Preferred Screening Test: TSH
- ii. Optimal Testing Time: Morning

In cases where a pituitary or hypothalamic cause is under consideration, both Free T4 and TSH levels should be measured in clinical practice. Free T4 testing is indicated in pregnancy, central hypothyroidism, in hypoalbuminemia states like nephrotic syndrome, hepatic failure and severe chronic nonthyroidal illnesses.

Strategic Utilization of Thyroid Function Tests in Clinical Contexts:

- 1) Type 1 Diabetes Mellitus in Women: TSH, FT4, and TPO-Ab assessment recommended at conception.
- 2) Diabetes Patients: Initial thyroid function

testing at diagnosis with annual follow-ups thereafter.

- 3) Atrial Fibrillation, Hyperlipidemia, Osteoporosis, Infertility: TSH evaluation at diagnosis for all patients.
- 4) Postpartum Thyroiditis History: Annual thyroid function tests and prior to subsequent pregnancies.
- 5) Post-Neck Irradiation: Annual thyroid function assessment following irradiation.
- 6) After Destructive Thyrotoxicosis Treatment: Initial test at 4-8 weeks post-treatment, followed by quarterly tests for a year, then annually.
- 7) Congenital Syndromes: Annual assessment of thyroid function.

Table 4: Thyroid function tests in hypothyroidism of different etiologies:[32]

Disorder	TSH	T4	T3	FT4	Tg	TBG	Reverse T3	Anti TPO Ab	Anti TG Ab
Primary Hypothyroidism	↑	↓	N/↓	↓	N/↓	N	↓	N/↑	N/↑
Hashimoto's thyroiditis	↑	N/↓	N/↓	N/↓	N/↓	N	↓	↑	↑
TSH deficiency	N/↓	↓	↓	↓	↓	↓	↓	N	N
Thyroid Dyshormogenesis	↑	↓	↓	↓		N	↑	N	N
Thyroid hormone resistance	N/↑	↑	↑	↑	↑	N	↑	N	N
Subacute Thyroiditis	↓/↑	↓/↑	↓/↑	↓/↑	↓/↑	N	↓/↑	N	N
Nonthyroidal Illness	Variable	N/↓	↓	Variable	↓/↑	N	↓/↑	N	N

(Note: ↑ indicates increased, ↓ indicates decreased, N indicates normal)

Table 5: Pit falls in Thyroid function tests interpretation:[31]

Molecules in Interference	Mechanism of interference	Effect on Result
Heterophil Antibodies	If present in patient serum sample	False high or low TSH values
Macro – TSH	Serum contains anti TSH Ig against TSH	False High TSH levels
Drugs	If heparin present in blood	False Low T4
	If patient is on furosemide	False Low T4
Biotin	If patient is on supplements	Falsely low TSH with raised FT4 and total T3



- 8) Amiodarone and Lithium Recipients: Initial TFT at treatment onset, then biannual assessments.
- 9) Pregnancy: TFT at conception and in each trimester thereafter.

Role of imaging modalities in diagnosis of hypothyroidism:

Imaging modalities play a pivotal role in the diagnosis and management of hypothyroidism, providing valuable information on thyroid gland morphology, function, and associated complications.

Ultrasonography remains the primary imaging modality for evaluating thyroid gland morphology, while other modalities such as CT, MRI, and radionuclide imaging may be utilized in specific clinical scenarios to further characterize thyroid abnormalities and guide treatment decisions. Integration of imaging findings with clinical and laboratory data is essential for accurate diagnosis and optimal management of hypothyroidism.

Ultrasonography:

Thyroid ultrasonography is a non-invasive imaging modality widely used for assessing thyroid gland morphology and detecting structural abnormalities. Ultrasonographic features commonly observed in hypothyroidism include diffuse glandular enlargement (goiter), heterogeneous echogenicity, and the presence of thyroid nodules. Ultrasonography also facilitates the evaluation of thyroid vascularity using Doppler imaging, which may aid in distinguishing between autoimmune thyroiditis and other causes of hypothyroidism.

Computed Tomography (CT) Scan:

While not routinely indicated for the evaluation of hypothyroidism, CT imaging may be utilized in select cases to assess thyroid gland anatomy and detect extrathyroidal manifestations of thyroid disorders. CT scans can identify retrosternal extension of the thyroid gland (substernal goiter) and assess for compressive effects on adjacent

structures, such as the trachea and esophagus, which may occur in severe cases of hypothyroidism.

Magnetic Resonance Imaging (MRI):

MRI offers superior soft tissue contrast and is particularly useful for evaluating thyroid gland anatomy and detecting structural abnormalities. In hypothyroidism, MRI may reveal diffuse glandular enlargement, heterogeneous signal intensity on T1- and T2-weighted images, and the presence of cystic or solid nodules. Dynamic contrast-enhanced MRI techniques can provide additional information on thyroid vascularity and perfusion, which may aid in the differentiation of autoimmune thyroiditis from other etiologies of hypothyroidism.

Radionuclide Imaging:

Radionuclide imaging techniques, including thyroid scintigraphy with technetium-99m or iodine-123, are valuable tools for assessing thyroid function and detecting focal or diffuse abnormalities in thyroid uptake. In hypothyroidism, thyroid scintigraphy typically reveals reduced or absent radioiodine uptake, consistent with decreased thyroid hormone synthesis. Scintigraphy may also identify areas of increased or heterogeneous uptake suggestive of focal thyroid pathology, such as nodules or thyroiditis.

Hypothyroidism and Comorbidities:

Thyroid hormones exert influence on various tissues throughout the body. Consequently, deficiency in thyroid hormone action in peripheral tissues can lead to a multitude of comorbidities.

- **Hypertension and Hypothyroidism:**

Hypothyroidism contributes to increased peripheral vascular resistance and diminished endothelial-dependent vasodilation, resulting in elevated blood pressure. It's a recognized secondary cause of hypertension, with a threefold higher risk of diastolic hypertension. Masked hypertension is also more prevalent among

individuals with hypothyroidism, with a reported prevalence of 31.2% in hypertensive subjects in India.[33]

- **Diabetes Mellitus and Hypothyroidism:**
Autoimmune disorders affecting endocrine glands often coincide with hypothyroidism and type 1 diabetes mellitus. In India, hypothyroidism prevalence among type 2 diabetes mellitus patients stands at 24.8%. Elevated TSH levels correlate with increased progression from prediabetes to overt diabetes.[34]

- **Dyslipidemia and Hypothyroidism:**

Most hypothyroid patients exhibit hyperlipidemia characterized by low HDL, high LDL levels, and elevated triglycerides.[35]

- **Cardiovascular Disease and Hypothyroidism:**

The interplay between hypothyroidism and dyslipidemia, diabetes, and hypertension adversely impacts cardiovascular health. Moderate hypothyroidism induces hypercoagulability, while severe cases lead to impaired fibrinolysis. The management of subclinical hypothyroidism's impact on cardiovascular health lacks strong evidence.[36]

- **Nonalcoholic Fatty Liver Disease (NAFLD) and Hypothyroidism:**

Hypothyroidism influences dyslipidemia, weight gain, and insulin resistance, contributing to NAFLD development.[37]

- **Obesity in Hypothyroidism:**

Overt hypothyroidism, characterized by low T3, decreases resting energy expenditure, leading to weight gain. Obesity, in turn, elevates TSH levels, suggesting a bidirectional relationship between thyroid function and body weight.[38]

- **Reproductive Health in Hypothyroidism:**

Thyroid hormone regulates gonadotropin hormone secretion and its impact on ovarian function, affecting fertility, menstrual regularity, and pregnancy outcomes. Hypothyroidism increases the risk of infertility, miscarriage, low birth weight, and various complications during pregnancy and childbirth.[39]

- **Bone Health in Hypothyroidism:**

Thyroid hormones play a crucial role in bone metabolism, and their deficiency in hypothyroidism prolongs the bone remodeling cycle, resulting in poor bone quality and increased fracture risk.[40]

Management of Hypothyroidism:

Thyroid hormone replacement therapy:

Levothyroxine (T4) therapy: For non-elderly patients without cardiac comorbidities, initiate levothyroxine supplementation at 1.5–1.8 µg/kg body weight. Monitor TSH levels quarterly to adjust dosage until target levels are reached, then half-yearly to annually for stable patients. Administer levothyroxine on an empty stomach with at least a one-hour gap from any other oral intake.

Combination therapy (T4/T3):

Consider T4+T3 combo therapy for persistent symptoms despite normal TSH in LT4-treated hypothyroid patients. Further trials are required to validate its efficacy, with management of persistent symptoms focusing on exploring alternative causes. At present the combination therapy is not feasible and not cost effective in low- and middle-income countries.[41]

Management of subclinical hypothyroidism – Subclinical hypothyroidism with mild TSH elevation with TSH < 10 mIU/L is to be followed up every 6 months and if persistent elevation levothyroxine supplementation has to be started and if TSH >10 mIU/L – based on consensus it is advisable to start levothyroxine at diagnosis and to target TSH

to normal levels by testing thyroid function tests every 3 months followed by annually. [27]

Newer Clinical Guidelines and updated Recommendations:

- It is suggested to screen for thyroid dysfunction (TSH) and autoimmunity (TPOAb) in women of subfertile couples planning an assisted reproductive technology treatment. The presence of increased TgAb levels can be verified in women with TSH levels >2.5 mIU/L and no increased TPOAb levels (2021 - European Thyroid Association(ETA) – Screening/management in daily practice)
- It is recommended to screen for thyroid dysfunction (TSH) in males with erectile dysfunction and premature ejaculation or with altered semen parameters. (ETA 2021)

Approach to special populations:

Pregnancy: Target the TSH levels in pregnancy to 2-2.5 mIU/L to monitor every month till target achieved. A woman of childbearing age and planning for a pregnancy to increase the regular levothyroxine dose by 30% on missing a menstrual period.

Elderly and Cardiovascular disease patients:

The dictum should be "**start low and go slow**," with initial doses of 12.5 to 25 µg/day, gradually up titrated every 2 to 4 weeks.

Challenges and Dilemmas faced in treating hypothyroidism in day-to-day practice:

I. Refractory Hypothyroidism:[42]

Refractory hypothyroidism is characterized by persistently elevated serum TSH levels despite increasing levothyroxine dosage above the target levels. Causes include noncompliance and various factors affecting serum TSH levels and thyroid hormone resistance. Diagnosis of underlying etiologies requires a comprehensive assessment. Rapid thyroxine absorption test is useful for

differentiating between noncompliance and true refractory hypothyroidism due to malabsorption.[43]

Diagnostic Approach to Refractory Hypothyroidism:

- **Identify potential causes through detailed evaluation. Management Strategies:**
 - Increase levothyroxine dosage to achieve target TSH levels.
 - Educate patients on proper storage and administration.
 - Avoid medication interference; if necessary, advise timing adjustments.
 - Consider once-weekly dosing for noncompliant patients.
 - Alternative levothyroxine preparations, such as soft gel or liquid formulations, may be beneficial.

II. Hypothyroidism in Pregnancy:

Given the critical role of thyroid hormones in reproductive health and fetal development, hypothyroidism poses significant risks during pregnancy. Screening with thyroid function tests, including free T3 and T4 alongside TSH, is recommended. Target TSH levels 2.5 mIU/L. Levothyroxine initiation in pregnancy requires higher doses and specific administration guidelines.[44]

III. Subclinical Hypothyroidism:

Subclinical hypothyroidism presents a clinical dilemma regarding treatment necessity due to conflicting evidence. Etiologies overlap with overt hypothyroidism, and severity is classified based on TSH levels. Treatment decisions should consider patient characteristics and associated risk factors.[45]

IV. Obesity and Subclinical Hypothyroidism:

Obesity often coincides with elevated TSH levels, suggesting a bidirectional

relationship. Behavioral and dietary interventions aimed at weight reduction may normalize TSH levels.[46] Subclinical hypothyroidism is more prevalent in obese individuals, posing diagnostic challenges. Ultrasonography reveals thyroid hypoechoogenicity in excessive body fat. Euthyroid obese individuals display higher TSH, FT3, and FT3/FT4 ratios compared to non-obese individuals. Additionally, obese patients exhibit reduced TSH receptor expression and altered deiodinase function in adipose tissue.[47]

V. Hypothyroidism with Nephrotic syndrome:

Nephrotic syndrome may initiate hypothyroidism due to significant urinary protein losses, including T4 and T3 and their binding proteins. Prolonged and severe proteinuria, especially in those with low thyroid reserve, can lead to substantial urinary losses of thyroid hormones, resulting in subclinical or overt hypothyroidism. Once the underlying cause of nephrotic syndrome is corrected patients can revert to euthyroid state.[48]

VI. Myxedema Coma:

Myxedema coma, a rare and severe complication of untreated hypothyroidism, requires urgent management. Triggers include environmental exposure, infections, and various medical conditions. Clinical presentation includes characteristic features such as altered mental status, hypotension, and hypoglycemia, hypothermia, hyponatremia, hypoventilation necessitating immediate medical attention. Combination therapy of T3 (5-20 µg) and T4 (200 to 400µg) which is administered intravenously slow bolus with other supportive measures.[49]

Adverse Effects and Complications of Hypothyroidism Treatment:

Physiological levothyroxine replacement is

generally safe for treating hypothyroidism but may impact cardiovascular and skeletal health. It can exacerbate underlying conditions and drug-related issues, potentially leading to angina pectoris, myocardial infarction, osteoporosis, altered insulin needs, Addisonian crisis, and altered drug metabolism. Non-compliance may result in hypothyroidism, while excessive doses can cause iatrogenic hyperthyroidism. [50]

Emerging Research and Future Directions:

Many patients see enhanced quality of life and cognitive function by transitioning from LT4 to LT4+LT3. Slow-release LT3 formulations are undergoing testing to ensure stable serum T3 levels for such patients. Human thyroid organoids are being developed through regenerative technology, offering potential for restoring euthyroidism in hypothyroid mice upon transplantation. Patients with metabolic-associated fatty liver disease have benefited from liver-selective T3-like molecules in clinical trials.[51]

To ascertain the action of thyroid hormones several organs – tissue specific markers are being investigated.[52] As with other diseases in humans gut microbiota is thought to be influencing the

hypothyroidism. Short Chain Fatty Acid-producing bacteria like Akkermansia, Butyrivibrio, Holdemania, Anaerostipes, and Intestinimonas were pinpointed as components of the gut microbiota linked with hypothyroidism. These SCFAs are pivotal in regulating the expression of sodium/iodine symporter (NIS) in thyroid cells, thereby having an effect on hypothyroidism.[53]

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Hyperthyroidism

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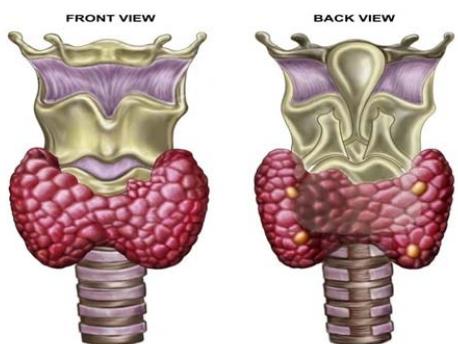
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INTRODUCTION

Hyperthyroidism is a common endocrine disorder that is characterized by excessive production of thyroid hormones by the thyroid gland. The hormones T3 and T4 play a crucial role in regulating metabolism, growth and development. When thyroid gland produces excess of these hormones, it can have a plethora of manifestations leading to a variety of symptoms and health issues some even causing morbidity and mortality.

ANATOMY AND PHYSIOLOGY OF THE THYROID GLAND



The thyroid gland is a butterfly shaped organ located at the base of the neck, just below the Adam's apple. It consists of two lobes connected by a narrow isthmus. The thyroid gland produces thyroid hormones, primarily T3 and T4, in response to thyroid stimulating hormone (TSH) produced by the pituitary gland. T3 and T4 exert a negative feedback on TSH. Hence in conditions where there is excess T3 and T4, the TSH is suppressed.

CAUSES OF HYPERHYROIDISM

There are several causes of hyperthyroidism

- **Graves' disease:** most common cause of hyperthyroidism. It's an autoimmune condition resulting from TSH-receptor antibodies.
- **Hashitoxicosis:** Autoimmune thyroiditis that causes an initial hyperthyroidism followed by hypothyroidism
- **Toxic adenoma and Toxic multinodular goiter:** focal or diffuse hyperplasia of thyroid follicular cells whose functional capacity is independent of regulation by TSH.
- **Iodine induced hyperthyroidism:** contrast agents, amiodarone in which iodine content is high, hyperthyroidism can occur
- **Trophoblastic disease and germ cell tumors:** high hCG activity can mimic TSH activity
- TSH adenomas
- **Thyroiditis:** Inflammation and destruction of thyroid tissue occurs with release of thyroid hormones and resultant hyperthyroidism. This is usually followed by a hypothyroid phase and recovery thereafter. It may occur in post viral illness which is associated with pain, fever and malaise. A similar thyroiditis can happen in the postpartum state. It is usually painless.
- **Exogenous causes:** factitious ingestion of thyroid hormone and levothyroxine overdose can show a similar hyperthyroid picture

Cause	Frequency
Graves' disease	60-80%
Thyroid nodules	10-15%
Thyroiditis	<5%
Excessive iodine intake	<5%
Excessive thyroid hormone intake	<5%
Tumors of pituitary/thyroid gland	Rare (<1%)

SIGNS AND SYMPTOMS OF HYPERTHYROIDISM

The classic symptoms:

These include heat intolerance, tremor, palpitations, anxiety, weight loss, increased frequency of bowel movements and shortness of breath

ORGAN SYSTEMS (2)

1) Skin:



- Warm skin

Pretibial myxedema



The skin is edematous and has a waxy, "orange peel" appearance. A large nodular plaque is visible on the anterior aspect of the ankle.

- Increased sweating
- Onycholysis
- Hyperpigmentation
- Pruritus
- Thinning of hair can occur
- Vitiligo and alopecia areata can occur in association with auto-immune disorders
- Infiltrative Dermopathy manifests itself as raised hyperpigmented, violaceous and orange peel textured papules. It's also called pretibial myxedema.

2) Eyes:

- ***Stare and lid lag:*** occur in almost all patients with hyperthyroidism. They are due to sympathetic activity mediated by alpha adrenergic activity in some tissues. Lid lag may be evaluated by having the patient follow the examiner's finger as it is moved up and down. Lid lag is present if sclera can be seen above the iris as the patient looks downward.
- ***Thyroid eye disease:*** is the exclusive feature of Graves' disease hyperthyroidism. It is characterized by inflammation of



extraocular muscles, orbital fat and connective tissue. Gritty eyes, pain in their eyes, diplopia occur. Proptosis and lid retraction can cause corneal ulceration. In severe cases, optic neuropathy and blindness can occur

3) Cardiovascular(5)

Increased sympathetic activity leads to:

- Increased heart rate
- Wide pulse pressure
- Systolic hypertension
- High output cardiac failure
- Atrial fibrillation in 10-20%. Even subclinical hyperthyroidism is associated with atrial fibrillation. It reverts to normal rhythm with treatment.
- Metabolic / endocrine consequences

4) Bone:

- Thyroid hormone stimulates bone resorption leading to increased calcium levels in the blood. The net effect is **osteoporosis** and increased fracture risk.
- Thyroid acropachy
- Clubbing and periosteal new bone formation in metacarpal bones and phalanges. Usually patients have severe thyroid eye disease and dermopathy
- Metabolic consequences
- Patients have low serum total cholesterol and high-density lipoprotein cholesterol.



Insulin resistance can cause impaired glucose tolerance.

5) Respiratory(6) :

- Respiratory muscle weakness leads to dyspnea.
- Tracheal obstruction may occur due to large goiter.
- Hyperthyroidism can exacerbate underlying asthma.

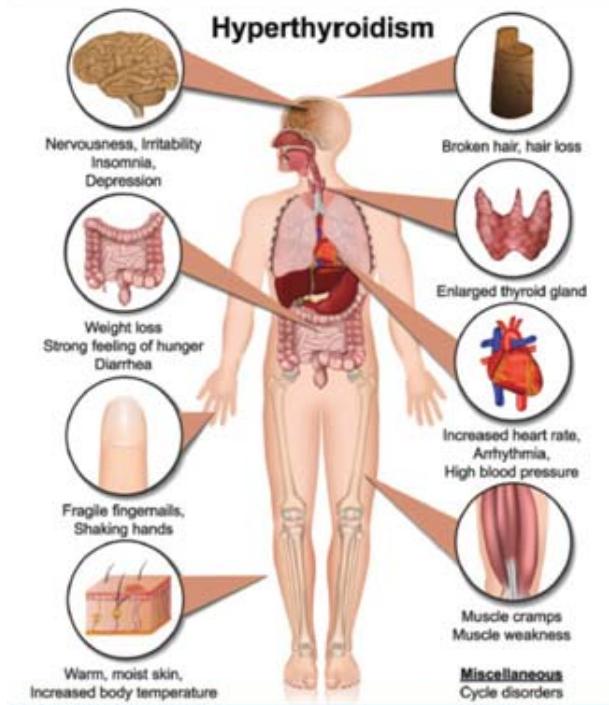
6) Gastro-intestinal:

Though high metabolic rate is the main reason for weight loss, the associated increased gut motility and malabsorption can also contribute to weight loss. Vomiting, dysphagia can occur. Raised liver enzymes are a feature of hyperthyroidism

7) Thymic enlargement

8) Genito-urinary:

- Urinary frequency is common probably due to polyuria and hypercalciuria



9) Neuropsychiatric:



Anxiety, restlessness, irritability and emotional lability are common features. In severe cases, psychosis, depression and agitation can occur. Insomnia is common

10) Thyrotoxic periodic paralysis:

Marked muscle weakness with hypokalemia which is usually precipitated by a high carbohydrate meal, fasting or exercise is seen rarely.

11) Geriatric hyperthyroidism:

In older patients(1,7), hyperthyroidism is usually apathetic.

- Weight loss
- Shortness of breath
- Atrial fibrillation
- Severe eye disease is common in this age group.
- Toxic multinodular goiter is more common.
- Constipation can occur.
- Tachycardia (>100 bpm) is absent in 40% of the cases.

DIAGNOSIS

The diagnosis of hyperthyroidism is usually evident in unequivocal clinical and biochemical manifestations of the disease.

Clinical manifestations:

Most patients have a dramatic constellation of symptoms including **weight loss, cardiovascular and neuropsychiatric symptoms and weight loss**. Older patients have predominantly cardiopulmonary symptoms such as **tachycardia, dyspnea on exertion and edema**. Decrease in appetite may be a feature. **Asthenia** is the only feature in apathetic thyrotoxicosis. Subclinical hyperthyroidism is a condition defined as **abnormal T3 and T4 levels** and a **suppressed TSH**. It is associated with a 3 fold increased risk of atrial fibrillation.

Physical examination:

- Hyperactivity, rapid speech

- Stare and lid lag
- Warm and moist skin
- Tachycardia, systolic hypertension
- Tremors, muscle weakness
- Eyes: exophthalmos, periorbital and conjunctival edema, limitation of eye movement and infiltrative dermopathy
- Goitre is a common feature of graves and toxic nodular goitre. A single nodule suggests a toxic adenoma and painful goiter in subacute thyroiditis

Laboratory tests:

Thyroid function tests

- In overt hyperthyroidism high T3 and T4 levels and a suppressed TSH is diagnostic. Graves and nodular hyperthyroidism tend to have greater T3 levels than T4.
- T3 toxicosis(8): raised T3 with a normal T4 occurs in early hyperthyroidism
- T4 toxicosis(9): raised T4 levels and a normal T3 occurs in hyperthyroidism with a non thyroidal illness. Amiodarone(10) induced hyperthyroidism also have raised T4 levels with a normal T3
- Subclinical hyperthyroidism is suppressed TSH and a normal T3 and T4 values
- TSH induced hyperthyroidism(11) occurs due to a rare TSH secreting adenoma. T3, T4 and TSH all are raised
- Critically ill patients(12)
- Hyperthyroid patients who are critically ill may have a normal T4 and even low T3 levels. This may be because of low concentrations of thyroxine binding globulin levels. The non thyroidal illness may be overshadowed by causing raised heart rate, tremors and muscle weakness. Suppressed TSH clinches the diagnosis. Anti thyroid drugs should be aggressively started in these patients.

DIFFERENTIAL DIAGNOSIS

- Euthyroid hyperthyroxinemia

- Raised thyroxine binding globulins can raise T3 and T4 levels with a normal TSH. These patients are euthyroid.
- Low TSH without hyperthyroidism
- Central hypothyroidism
- Non thyroidal illness
- Recovery from hyperthyroidism
- Pregnancy
- Biotin ingestion can cause falsely low TSH(14,15)

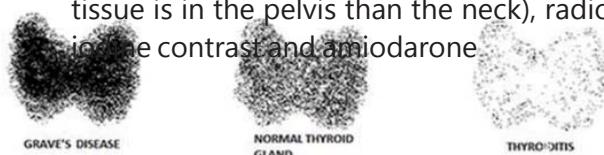
Determining the etiology(16,17)

Diagnosis is usually apparent by ophthalmopathy, goiter and symptomatology. However in non apparent cases like non nodular cases with no obvious manifestations, TSH receptor antibodies(18,19), Radio-iodine uptake and ultrasound to check thyroid blood flow may help.

1) Radio iodine uptake:

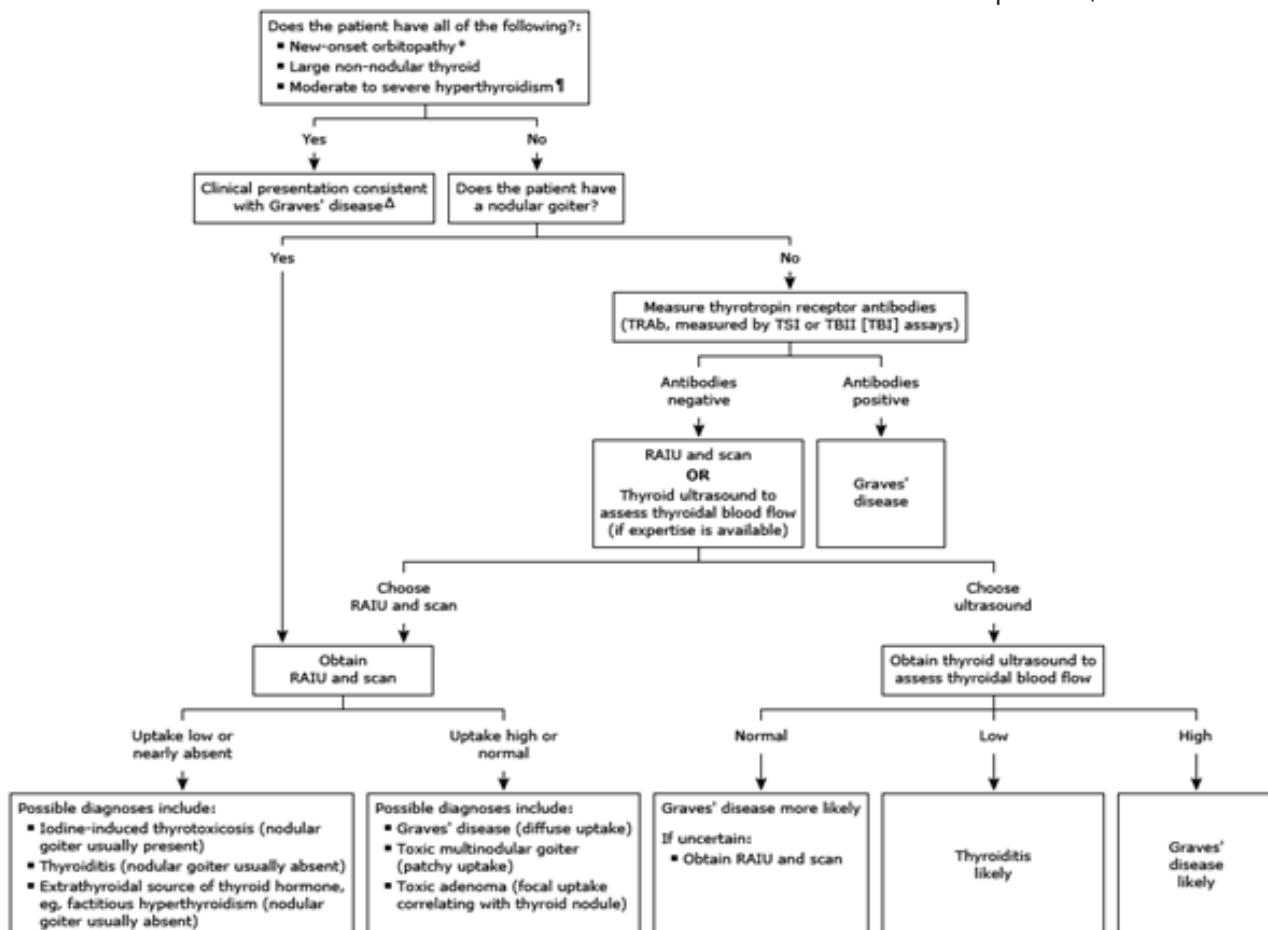
Radio uptake scan helps in distinguishing multinodular thyroid and toxic adenoma. Radio iodine uptake is suggested for hyperthyroid patients with a nodular thyroid.

- A high uptake suggests Graves/toxic multi nodular goiter or a toxic adenoma
- Low or absent intake suggests thyroiditis, struma ovarii(where the functioning thyroid tissue is in the pelvis than the neck), radio iodine contrast and amiodarone



2) TSH receptor antibodies:

TRAb must be checked in pregnancy with hyperthyroidism, hyperthyroid without nodular thyroid and no obvious clinical manifestations. If TRAb is positive, it's Graves



disease.

- 3) Thyroidal blood flow by ultrasound helps to distinguish Graves from destructive thyroiditis(20,21)

TREATMENT

The therapeutic approach consists of amelioration of symptoms by beta blockers and measures to reduce thyroid hormone secretion.

Symptom control

Beta blockers: Beta blockers(23,24) may be started as soon as the diagnosis of hyperthyroidism is made irrespective of the cause. Beta blockers (propranolol, atenolol) ameliorate palpitations, tachycardia, tremors, anxiety, and heat intolerance. Fatigability and shortness of breath also improve.

Decrease thyroid hormone synthesis has the following treatment options:

- 1) Anti thyroid drugs (thionamides)(24)
- 2) Radio iodine(25)
- 3) Surgery

Selection of therapy(26-31)

Anti thyroid drugs are the initial treatment of choice in most cases. The patient has to become euthyroid before subjecting them to radioiodine treatment or surgery.

Mild hyperthyroidism (T4 1 to 1.5 times ULN that is up to 18 mcg/dl)

- Thionamides for 1 to 2 years
- Radio iodine in those tolerating symptoms well
- Surgery, if considered, requires pretreatment with thionamides

Moderate hyperthyroidism (18-24 mcg/dl)

- Thionamides for 1 to 2 years or even more
- Radio iodine may be considered based on symptoms
- Surgery after pre treatment with

thionamides

Severe hyperthyroidism (> 24 mcg/dl)

- Thionamides plus beta blockers to achieve euthyroid status
- Definitive therapy with RAI or surgery after pretreatment with thionamides

Thyroid eye disease

- Mild disease
- Radioiodine with glucocorticoid coverage
- 1 to 2 year course of thionamides
- Moderate to severe thyroid eye disease
- Surgery with glucocorticoid coverage

Large nodules / suspicious nodules / hyperparathyroidism(38)

- Surgery is the best option

Pregnancy

- Thionamides to be used in caution owing to a minimum risk of teratogenicity

INDIVIDUAL THERAPIES

1) Thionamides

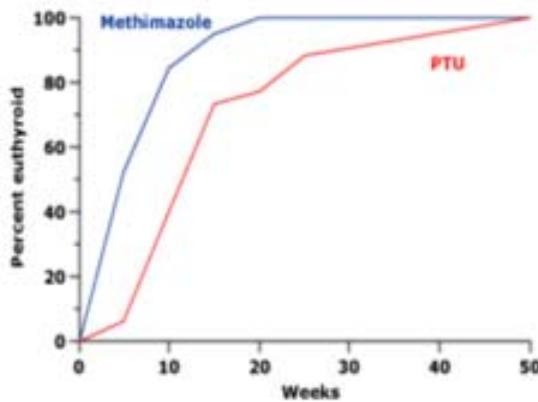
- Thionamides may be given to achieve euthyroid status in 3 to 8 weeks prior to definitive therapy with radioiodine therapy or surgery. Mild disease or small goiters may be treated with thionamides and remission rates are under 40% after 1 year of treatment. Remission means maintaining euthyroid status after 1 year without drugs. Remission rates increase to 80% after 5 years of therapy. Remission is predicted by small goitres, mild hyperthyroidism, goiters that shrink and change in TRAb.
- Pre treatment evaluation: baseline complete blood count and liver profile have to be obtained. Don't start thionamides if neutrophil count < 1000 cells/mcl or liver enzymes > 5 fold ULN

- Choice of drug: Methimazole is the drug of choice. Longer duration of action, rapid efficacy and lower side effects makes it the drug of choice. Propylthiouracil is preferred in the first trimester of pregnancy. Carbimazole is metabolized to methimazole. Its dosage is 40% higher. For eg: 10 or 20 mg carbimazole is equal to 5 to 15 mg methimazole.

Dosage :

- Mild disease: methimazole 5 to 15 mg / day
- Moderate: 10-20 mg per day of methimazole
- Severe disease: 20 to 40 mg per day methimazole
- Give in divided doses > 20 mg/d
- Taper dose to 5 to 10 mg/d once euthyroid dose is achieved
- Check T4 levels every 4 to 6 weeks till euthyroid status and then 3 to 6 monthly intervals
- Persistently low TSH and high TRAb's (41) unlikely to achieve remission
- Plan taper and stop the drug only if euthyroid for a long duration.

Methimazole acts faster than PTU in Graves'



Time required for patients with Graves' hyperthyroidism to become euthyroid (normal serum T4 and T3 concentrations) after therapy with

methimazole (10 mg three times daily, n=66) or PTU (100 mg three times daily, n=17). The euthyroid state was achieved more quickly with methimazole (5.8 versus 16.8 weeks)

2) Radioiodine ablation(32-37)

- Preferred definitive therapy in non pregnant except in patients with moderate to severe thyroid eye disease.
- Its less expensive and has less complications
- Pre treatment with thioamide should be given with significant hyperthyroidism, older patients with heart disease and other comorbidities.
- Mild or well tolerated hyperthyroidism can be treated with radioiodine alone without pretreatment
- Radioiodine treatment can cause worsening of thyroid eye disease. However, if a patient refuses surgery and has contraindications to anti thyroid drugs, it may be considered.
- Radio iodine is administered as a capsule or a solution. It is rapidly absorbed from the GI tract and concentrates in the thyroid tissue. It ablates the thyroid in 6 to 18 weeks. 10-20% of the patients require a second dose especially in patients with severe hyperthyroidism or large goiters.
- Check thyroid function tests 4 to 6 weeks after treatment till 6 months or until hypothyroidism occurs.

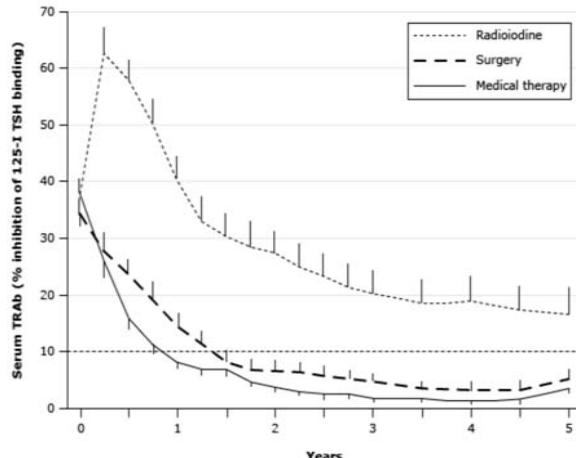
3) Surgery

- Severe hyperthyroidism with a large or an obstructive goiter
- Moderate to severe orbitopathy
- Pregnant women allergic to anti thyroid drugs
- Patients who have adverse effects and don't want to receive radioiodine therapy
- Suspicious nodule along with

hyperthyroidism

- Plan radioiodine treatment or surgery 6 to 12 months prior to planning pregnancy.

Variations in TRAbs in Graves' hyperthyroidism



Iodine

- SSKI with 50 mg iodine per drop daily for 7 to 10 days is used preoperatively to reduce gland vascularity
- Alternatively it can be used following radioiodine treatment for several weeks till the gland gets ablated.
- Smaller doses (1-2 drops per day) can be used as a primary therapy for mild hyperthyroidism or post radioiodine treatment who are still hyperthyroid

Glucocorticoids

- Glucocorticoids reduce T4 to T3 conversion and are used in thyroid storm
- They are also used to treat moderate to severe thyroid eye disease

Calcium

- Hyperthyroidism results in negative calcium balance, increased fracture risk and reduced bone density
- 1200 to 1500 mg elemental calcium is advised to diet or through supplements

- Monitoring after treatment
- Thyroid function tests: T4 levels need to be monitored. TSH remains suppressed for several weeks after the patient becomes euthyroid

Surgery

- Replace thyroid hormone prior to discharge and check TSH after 2 months to adjust dose.

Weight gain(42-46)

- 5.5 to 8 kgs weight gain happens with therapy
- Subnormal energy expenditure and inadequate thyroid hormone replacement may be the causes of the weight gain
- Dietary advice to be instituted.

Other medications infrequently used:

- Lithium
- Rituximab(39)
- Chinese herbs(40)

HYPERTHYROIDISM COMPLICATING PREGNANCY

INTRODUCTION

Overt hyperthyroidism is uncommon in pregnancy(48,49) occurring in 0.1 – 0.4 % of all pregnancies. Thyroid hormone binding globulin (TBG) excess results in high serum total T4 and total T3 concentrations but not free T4 and freeT3 concentrations. High serum hCG concentrations during early pregnancy may result in transient subclinical or rarely overt hyperthyroidism. This is even more common in hyperemesis gravidarum and multiple pregnancies.

Clinical features:

Symptoms are similar to those associated with pregnancy like **tachycardia(50)**, **heat intolerance** and **increased perspiration**. Added symptoms include **anxiety**, **tremors** and **weight loss despite**

normal or increased appetite. Goitre and ophthalmopathy suggest Graves' disease.

Pregnancy complications:

1) Overt hyperthyroidism(52-56)

It is characterized by low TSH, free T3 and free T4 levels that exceed trimester specific normal reference ranges or total T4 and total T3 levels that exceed 1.5 times non pregnant range. Pregnancy complicated by poorly controlled hyperthyroidism leads to

- Spontaneous abortion
- Premature labor
- Low birth weight(52)
- Still birth
- Preeclampsia
- Heart failure(50)

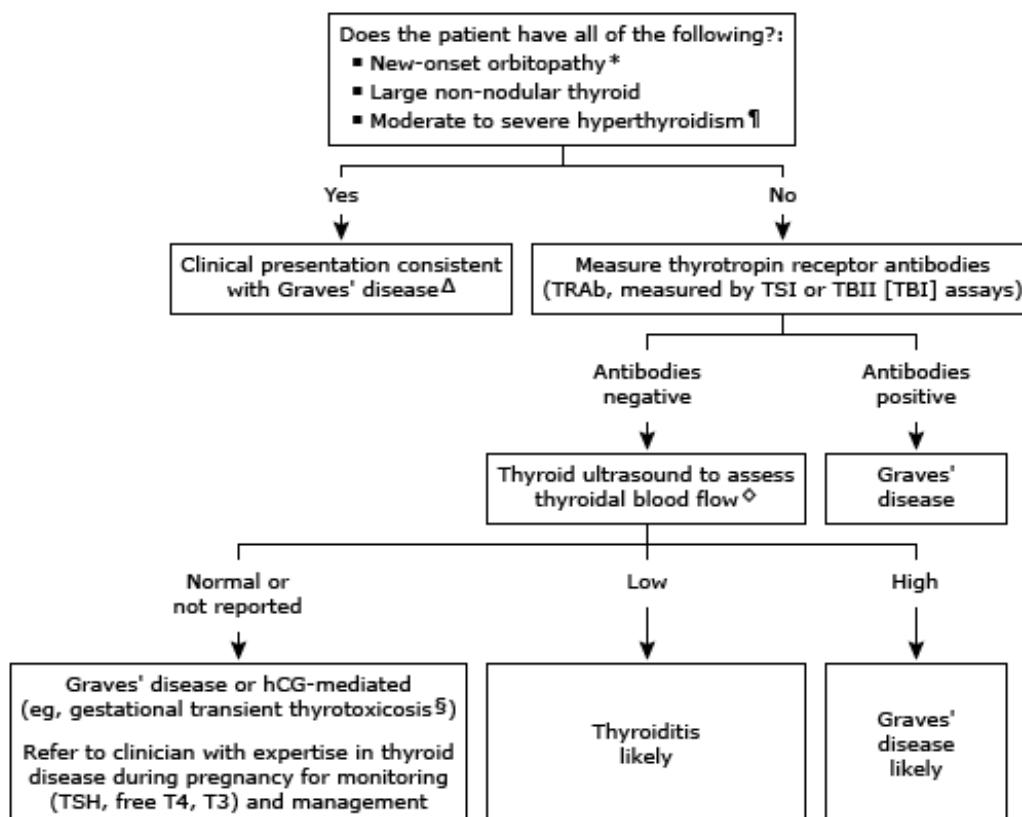
2) Subclinical hyperthyroidism

Low TSH accompanied by free T3 and free T4 levels that are normal as per trimester specific ranges or

total T4 and total T3 that are less than 1.5 times the non pregnant range. This condition is not associated with any adverse pregnancy outcomes. Free T4 in the upper normal range and a suppressed TSH are not associated with adverse pregnancy outcomes.

Laboratory findings(57-61):

Thyroid tests must be interpreted using population based trimester specific ranges(62-64). Free T4 and free T3 levels are subject to laboratory variations. Total T3 and total T4 levels are raised due to the effect of thyroid hormone binding globulin. The increase in levels is 1.5 times above non pregnant ranges. Hence total T4 and total T3 levels up to 1.5 times the non pregnant ranges can be considered normal. Any levels above these can be considered elevated. TSH concentrations are suppressed in pregnancy owing to the thyrotropic effect of hCG. First trimester TSH values are 0.08-2.99mU/L. Graves' (0.1-1%) and hCG mediated hyperthyroidism (1-3%) are the most common causes of hyperthyroidism. Treatment approaches are based on distinguishing these two



entities. Clinical features, laboratory tests and ultrasound aid differentiate these two disorders.

Clinical findings: (65)

The presence of goiter and/or ophthalmopathy favors the diagnosis of Graves' disease. Graves' disease tends to improve as the pregnancy progresses due to reduction of the TSH receptor antibody.

Laboratory evaluation(66-68):

A TSH receptor antibody (TRAb's) is measured either by a thyrotropin binding inhibitory immunoglobulin or thyrotropin stimulating immunoglobulin. It is present in 96% of the patients with Graves' and therefore the presence of TRAb's favors a diagnosis of Graves'

Imaging(69):

High blood flow in Doppler suggests Graves' disease. Blood flow is however reduced in thyroiditis. In hCG mediated hyperthyroidism, blood flow patterns are unknown.

Radionuclide imaging is contraindicated in pregnancy.

Establishing the cause

Graves' disease:

The presence of TRAb's and ophthalmopathy favors the diagnosis of Graves'. Goitre is more common.

hCG mediated hyperthyroidism(70-72)

hCG mediated hyperthyroidism includes gestational transient thyrotoxicosis, hyperemesis gravidarum and trophoblastic hyperthyroidism. Only the last needs treatment. hCG levels peak at 10-12 weeks gestation. hCG stimulates TSH and may cause hyperthyroidism.

Gestational transient thyrotoxicosis:

This condition is due to raised hCG. TSH is suppressed and free T4 is normal or mildly exceeds the range for pregnancy. Total T4 is normal or mildly increased 1.5 times the non pregnant state.

It occurs at the end of the first trimester and subsides at 14-18 weeks gestation.

Hyperemesis gravidarum(73-76):

It is a syndrome of nausea and vomiting and weight loss >5% and occurs in 0.1-0.2% of pregnancies. These women have higher hCG levels. TSH is suppressed and free T4 levels are mildly elevated. Features that distinguish it from other causes are vomiting, absence of goiter and ophthalmopathy. Other signs of hyperthyroidism are not present. Free T3 is normal and only free T4 is minimally elevated. It does not require treatment. It subsides as the hCG levels come down.

Trophoblastic hyperthyroidism:

Molar pregnancy and choriocarcinoma are associated with high hCG levels. Patients have a normal thyroid gland and few symptoms of thyroid excess. Nausea and vomiting predominate as in hyperemesis. They may need treatment based on the symptoms.

MANAGEMENT(77-79)

Goal of treatment is to maintain a mild hyperthyroidism as the fetal thyroid is sensitive to anti thyroid drugs(80). This may result in fetal goiter and fetal hypothyroidism. Free T4 must be just above the trimester specific ranges(66-68) or total T4 must be at 1.5 times the non pregnant range. TSH goal must be 0.1-0.3 mU/L. Assess thyroid function test monthly

Indications of treatment:

Overt hyperthyroidism Graves', toxic nodular goiter or adenoma and trophoblastic disease will require anti thyroid drugs. Treatment not required in

hCG mediated hyperthyroidism

- Gestational transient thyrotoxicosis, hyperemesis gravidarum come under this. Elevated hCG levels have thyrotropin properties. The levels rise at the end of the first trimester and reduce by the 18th week. Treatment is not required in these cases.

- Mild hyperthyroidism due to Graves, toxic nodular goiter, toxic adenoma.
- If total T4 is < 1.5 times non pregnant range, treatment isn't required. However if it is above 1.5 times, treatment is not required if mild and asymptomatic

Therapeutic options(82):

- Thionamides
- Thyroidectomy

Thionamides

Primary drugs due to Graves' disease, toxic adenoma and toxic multi nodular goiter

Beta blockers(81):

Propranolol may be used to treat tachycardia and tremor. They are the primary treatment for gestational trophoblastic disease. Beta Blockers shouldn't be given more than 2-6 weeks.

4) Thyroidectomy:

Its an option for women who cannot tolerate thionamides

APPROACH

Control of symptoms:

Beta Blockers may be given to ameliorate symptoms. Metoprolol 25-50 mg daily or propranolol 40 – 60 mg / day. Taper within 2-6 weeks owing to risk of growth restriction, hypoglycaemia, respiratory depression and bradycardia in the neonate. Decrease thyroid hormone synthesis: thionamides (methimazole and propylthiouracil PTU) cross placenta. Thionamides (methimazole and propylthiouracil PTU) cross placenta(83).

Women diagnosed prior to pregnancy(84):

- Elective definitive therapy like radio iodine or surgery to be opted. Women should postpone pregnancy till they have become euthyroid. This is recommended for those requiring high doses of methimazole

- Those planning pregnancy in 1-3 months and having normal cycles, switch to PTU.
- In those on methimazole for 12 to 18 months and are on low doses of methimazole, discontinue stopping the drug. In case recurrence, treat with PTU

Women diagnosed during pregnancy

- First trimester: PTU
- Later methimazole

Teratogenicity(85-101,103,104)

- Methimazole : aplasia cutis, tracheo-esophageal fistulas, choanal atresia, omphalocele, omphalomesenteric duct anomaly
- PTU: pre auricular sinuses and cysts and urinary tract abnormalities
- Gestational weeks 6 to 10 weeks is the period of highest risk for congenital anomalies from thionamides. Hence, PTU is the preferred drug during the first trimester. Reports of severe liver failure have been associated with PTU. Hence methimazole is used from 2nd trimester onwards.

Dosing

- PTU(102): 50 mg two to three times a day (100 mg TID in severe cases)
- Methimazole: 5 to 10 mg/ day (10-30 mg/d in severe cases)
- Carbimazole: 5 to 15 mg/day

MONITORING (105-107)

Thyroid function tests to be done monthly. Maintain free T4 just above trimester specific ranges and total T4 at 1.5 times the non pregnant state. Graves' usually ameliorates as pregnancy progresses due to fall in TRAb's. Toxic multinodular goiter and toxic adenoma need treatment throughout. TRAb's: check at 18-22 weeks and again at 30-34 weeks. High TRAb's are associated



with increased risk of fetal and neonatal hyperthyroidism

PTU associated liver failure:

Routine LFT not needed. Patient advised to check for malaise, nausea, vomiting, jaundice, dark urine or light colored stools. Regular monitoring of transaminases hasn't shown to reduce the incidence of liver toxicity. If LFT is monitored, stop PTU if transaminases > 3 times ULN.

Thionamide intolerance:

- Thyroidectomy is an option.
- Pre treat with beta blockers and potassium iodide (KI) 1-3 drops daily (35-50 mg per drop)
- Insufficient evidence to recommend iodine as primary therapy.(108-110)
- Radio iodine contraindicated in pregnancy(111-113)

History of treated hyperthyroidism:

Euthyroid women with a history of remission after prior treatment of Graves' have small recurrence in pregnancy or postpartum. Check thyroid function tests in early pregnancy and again in postpartum.

FETAL (OR NEONATAL) HYPERTHYROIDISM

1-5% of mothers with Graves' have fetuses or neonates with hyperthyroidism(113,114)

Manifestations:

- High fetal heart rate > 160 bpm
- Fetal goiter
- Advanced bone age
- Poor growth
- Craniosynostosis
- Cardiac failure and hydrops in severe cases.

Measurement of maternal antibodies:

Post radio iodine or surgery in those taking thyroxine as replacement, check for TSH receptor Antibodies (TRAb's) (116)in the first trimester and

if elevated at 18-22 weeks and 30-34 weeks.

In pregnant women with present hyperthyroidism TRAb's is measured at diagnosis of pregnancy, if elevated at 18-22 weeks and if still elevated at 30-34 weeks

Fetus is likely to have hyperthyroidism(117) if maternal value is 3-5 times above normal value.

Fetal monitoring(115):

Fetal heart and fetal growth rate must be monitored.

Fetal thyroid ultrasound(118) should be performed and checked for central color flow.

Fetal blood sampling(119-120): owing to potential risk of fetal loss, umbilical vein sampling is not recommended. Consider if there is a goiter on ultrasound. Perform after 20 weeks gestation.

TREATMENT

Thionamides may be given to the mother if there is fetal hyperthyroidism. Levothyroxine to be given if maternal hypothyroidism occurs.

Postpartum issues(121-125)

Methimazole is preferable owing to concerns about PTU associated liver toxicity. Administer following a feed. Infants to be checked for thyroid function test if methimazole > 20 mg /d

Relapse:

Post partum hyperthyroidism either could be a relapse of Graves' or post partum thyroiditis; differentiating features are

Clinical presentation:

- Number of months postpartum(earlier favors thyroiditis)
- TRAb's
- Women with Graves' who have been treated during pregnancy need careful monitoring during the postpartum period as an exacerbation can occur. Thyroid function tests have to be done every 6 weeks for

thionamide dose adjustment and every 4 months if thyroid status is normal. Graves' women in remission are at risk of relapse and it usually occurs 4-8 months postpartum.

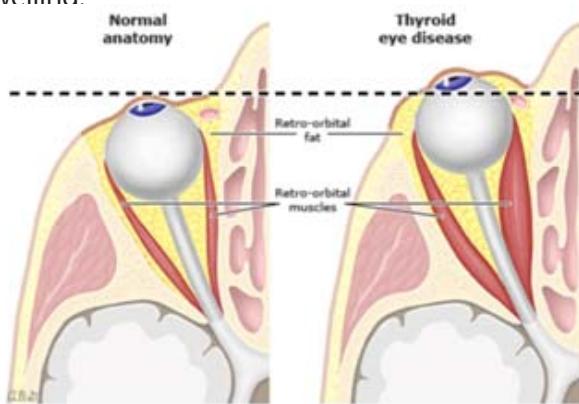
THYROID EYE DISEASE

Introduction

Thyroid eye disease, also known as Graves' orbitopathy(126-128) or ophthalmopathy is an autoimmune disease of the orbit and retro-ocular tissues.

Pathogenesis(128):

The main auto antigen is TSH receptor. The volume of the extraocular muscles and orbital connective tissue is increased due to fibroblast proliferation and accumulation of glycosaminoglycans(GAG). GAG secretion by fibroblasts is increased by thyroid stimulating antibodies and activated T cells. The hydrophilic GAG's lead to fluid accumulation, muscle swelling and increase in pressure within the orbit. This displaces the eyeball forward leading to extra ocular muscle dysfunction and impaired venous drainage causing peri-orbital swelling.



Both the retro-orbital fat and muscles are involved in the development of thyroid eye disease. Cytokine released from fibroblast and pre-adipocytes accentuate the secretion of hyaluronic acid-Inte molecules, which increase the osmotic pressure in the tissues causing fluid accumulation and, in

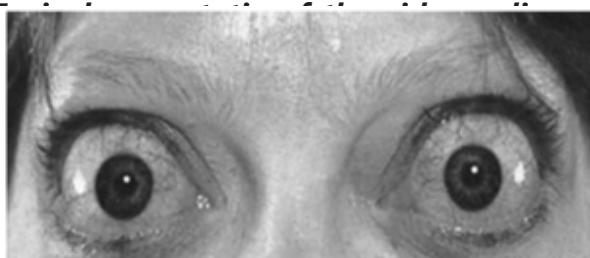
particular, disruption of the muscle bundles. This figure shows the marked swelling of the retro-orbital muscles, often well visualized on MRI or CT scanning in such patients. The consequence of retro-orbital swelling is proptosis (exophthalmos), not well illustrated here, since this may depend on both the anatomy of the orbit and the degree of swelling."

Risk factors (130-131,138)

- More common in females but severe in males
- Smoking
- Radioiodine therapy
- TRAb's high levels(142-144)

Clinical features:

- Gritty sensation
- Excessive tearing"eye pain blurring of vision
- Diplopia
- Color vision abnormalities
- Peri-orbital swelling



Signs

- Proptosis
- Conjunctival inflammation
- Peri-orbital edema

Lab findings

- Low TSH and a high T4
- In 10%, euthyroid cases
- Diagnosis
- Differentiate from lid lag and stare which disappear with treatment



ASSESSMENT OF THYROID EYE DISEASE (146-150)

Elements	Each visit	Compared to previous visit	Score
Painful feeling behind the globe over the last 4 weeks	×		1
Pain with movement last 4 weeks	×		1
Redness of eyelids	×		1
Redness of conjunctiva	×		1
Swelling of eyelids	×		1
Chemosis	×		1
Swollen caruncle	×		1
Increase in proptosis by > 2mm		×	1
Decrease In eye movement > 5° in any direction		×	1
Decreased visual acuity > 1 in snellen chart		×	1

ASSESSMENT OF SEVERITY OF THYROID EYE DISEASE

Grade*	Lid retraction	Soft tissues	Proptosis [†]	Diplopia	Corneal exposure	Optic nerve status
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	-	-	-	-	Severe	Compression
Upper limits of normal						
Black populations	F/M = 23/24 mm					
White populations	F/M = 19/21 mm					
Asian populations	F/M = 16/17 mm (Thai) or 18/19 mm (Chinese)					

Thyroid eye disease: Findings on CT scan



Imaging:

CT or MRI to assess optic nerve compression(132)

Treatment(133, 151-153):

Control of hyperthyroid status(139, 154)

- Thionamides
- Surgery as a definitive treatment
- Radio iodine can exacerbate ophthalmopathy(155)
- Smoking cessation(134,136,137,156)

Mild orbitopathy

- Local measures
- Selenium for 6 months (157)

Moderate orbitopathy

- Predominance of inflammation and less proptosis: IV glucocorticoids (159-162,174-179)
- IV methylprednisolone pulse therapy is preferred to oral dosing. It is given as 500 mg IV once weekly for 6 weeks, then 250 mg once weekly from week 7 to week 12. Cumulative dose is 4.5-5 gms over 12 weeks. Oral prednisolone if considered may be given at 60-100 mg/day
- Predominance of proptosis: Teprotumumab; Glucocorticoids alternatively.(with or

without mycophenolate)

- Teprotumumab(163-173, 181-186) is an insulin-like growth factor 1 monoclonal blocking antibody. It is the only drug for improvement of proptosis. The effect is by inducing apoptosis of retro-orbital fibroblasts and adipocytes.
- If IV glucocorticoids are contraindicated, intolerant or ineffective, secondary options include
 - Tocilizumab: targets IL-6(187, 190)
 - Rituximab: anti B-cell monoclonal antibody (188,191-197)
 - Mycophenolate mofetil (189,198-200)
 - External orbit irradiation (201-204,206-208)
 - Orbital decompression surgery (210-214)

Sight threatening orbitopathy

IV methylprednisolone 0.5-1 gm daily for 3 consecutive days and orbital decompression surgery

THYROID STORM

Definition(215,216):

It is a rare life threatening condition characterized by severe manifestations of thyrotoxicosis. It is often precipitated by acute event such as a surgery, trauma, infection, acute iodine load or parturition and untreated hyperthyroidism

Clinical features:

- Tachycardia
- Hyperpyrexia
- CNS dysfunction (agitation, delirium, psychosis, stupor and coma)
- GI symptoms (nausea, vomiting, abdominal pain)
- Goitre
- Eye signs (ophthalmopathy, lid lag)
- Tremors
- Warm moist skin

Diagnosis

- Hyperpyrexia, cardiovascular dysfunction and altered mentation
- Raised T4 and suppressed TSH
- Other lab findings: mild hyperglycemia, mild hypercalcemia, abnormal LFT, leukocytosis or leukopenia

Treatment:

Initial management

- Beta Blockers : propranolol 60-80 mg every 4-6 hrs
- Thionamides: PTU 200-250 mg every 4 hours. PTU blocks T4 to T3. Methimazole for severe non life threatening may be given at doses 20 mg every 4-6 hrs. Patients started on PTU should be transitioned to methimazole at discharge.
- Thionamide intolerance
- Surgery should be contemplated
- Pre treatment with beta blockers propranolol 60-80 mg every 4-6 hrs, glucocorticoids (dexamethasone 1-2 mg every 6 hours), and iodine every 8 hrs in doses as below.
- Glucocorticoids: IV hydrocortisone 300 mg loading dose and 100 mg every 8 hrs
- Iodine (SSKI 5 drops 20 drops/ml, 50 mg iodine per drop), Lugol's solution 10 drops (6.25 iodine per drop)

Subsequent management:

After resolution of hyperpyrexia, cardiovascular and CNS manifestations,

- Discontinue iodine therapy
- Beta Blockers after thyroid function tests have returned to normal
- Discontinue glucocorticoids
- Change from PTU to methimazole at 30-40

mg daily in divided doses

- Definitive therapy with radio iodine or surgery should be instituted later.

SUBCLINICAL HYPERTHYROIDISM

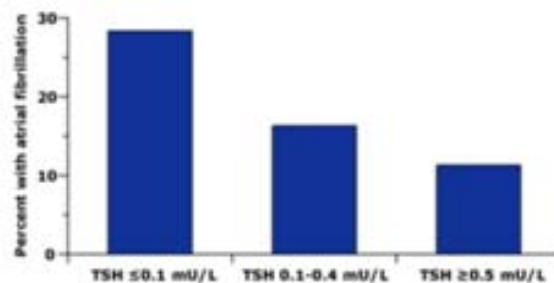
Etiology:

Prevalence varies between 0.7-12.4%. It is common in areas with mild to moderate iodine deficiency. The causes are same as with overt hyperthyroidism

Clinical findings:

Non specific symptoms, usually asymptomatic

- Increased risk of atrial fibrillation, coronary heart disease and heart failure

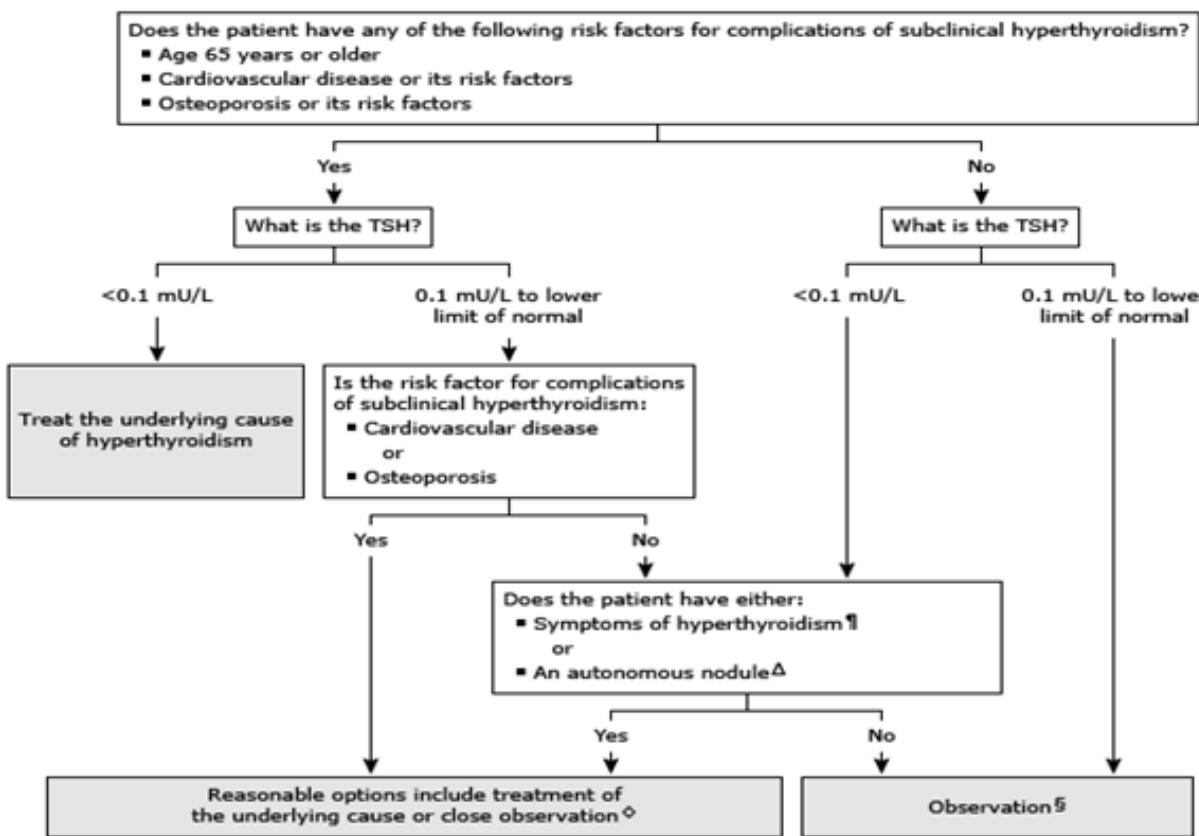


Cumulative incidence of atrial fibrillation in subjects over age 60 years according to the serum concentration of TSH. The risk of atrial fibrillation was increased almost threefold in the subjects with marked suppression of TSH (left panel) as compared with those who had normal serum TSH concentrations and were presumably euthyroid (right panel); patients with slightly low serum TSH concentrations (middle panel) had a lesser increase in risk.

Diagnosis

- Normal T4 levels and a suppressed TSH

Endogenous subclinical hyperthyroidism



Management

- Dose adjustment of levothyroxine in those with over replacement

CONCLUSION

Hyperthyroidism is a condition caused by overproduction of thyroid hormones, leading to a variety of symptoms and potential complications. It can be managed effectively with medications, radioactive iodine and surgery, depending on the underlying cause and the severity of the condition. Regular monitoring and treatment are essential to prevent complications and maintain thyroid hormone levels in the normal range. Thyroid eye disease should be graded according to severity and appropriate measures to be taken. Hyperthyroidism complicating pregnancy should be managed with a fine balance between the least medications and control of

hyperthyroidism. Thyrotoxic storm need urgent measures and treatment must be instituted on an emergent basis. Mild hyperthyroidism only needs to be treated when needed.

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Disorders of Mineral Metabolism

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Disorders of mineral metabolism include changes in serum concentrations of calcium, phosphate, and magnesium. The principal hormones regulating calcium and phosphate are parathyroid hormone (PTH), calcitriol, klotho, and fibroblast growth factor 23 (FGF23). [1] Age dependent bone density loss (osteoporosis) has significant morbidity. Perturbations in calcium concentration is the commonest form of disorder seen by far. In this chapter our primary focus will be on hypercalcemia, hypocalcemia, and osteoporosis.

Hypercalcemia

Hypercalcemia can be defined as a serum total calcium adjusted for serum albumin greater than 2 standard deviations above the normal mean in a reference laboratory. Ionized calcium (approximately 40% circulating in blood) is metabolically active and any value greater than 2 SD above normal is considered abnormal (Table 1). Approximately 45% of calcium is bound to plasma proteins (mainly albumin), and around 15% is bound to anions like phosphate and citrate. [2] Blood pH has a bearing of ionized calcium as well with acidosis reducing dissociation of calcium

from the albumin-calcium complex. The vice-versa being true during alkalotic conditions in blood. Ideally, ionized calcium should be assessed, however, if total calcium is being tested, then a concomitant serum albumin is warranted. Albumin corrected serum calcium is measured by the following formula: Albumin adjusted calcium (mg/dL) = total [Ca](mg/dL) + 0.8 (4 - [albumin])(g/dL). [3] Mild hypocalcemia may be symptomatic and present as fatigue, constipation, or cognitive dysfunction. [4] Higher serum calcium levels or acute hypercalcemia may lead to polyuria, polydipsia, and renal failure.

The prevalence of hypercalcemia varies from 1 – 2.4 %. [5, 6] About 90% of the 'apparently well' patients with hypercalcemia seen in outpatient departments have some forms of Primary Hyperparathyroidism (PHPT). [3] On the other hand, underlying malignancy is responsible in about half of the ill or hospitalised patients with moderate to severe hypercalcemia, a condition termed as malignancy associated hypercalcemia (MAHC). All possible aetiologies associated with hypercalcemia have been summarized in Table 2.

Table 1: severity of hypercalcemia in adults

	Albumin adjusted total calcium (mg/dL)	Ionized calcium (mM/L)
Normocalcemia	8.5 – 12.5	1.12 – 1.32
Mild hypercalcemia	10.5 – 11.9	1.32 – 3
Moderate hypercalcemia	12 – 13.9	3 – 3.5
Severe hypercalcemia	>14	>3.5

Table 2: Aetiology of hypercalcemia (Adapted and modified from [3])

PTH Dependent	PTH Independent
Primary Hyperparathyroidism <ul style="list-style-type: none"> a. Inherited syndromic <ul style="list-style-type: none"> a. MEN 1 * b. MEN 2 c. MEN 4 b. Inherited non-syndromic <ul style="list-style-type: none"> a. Familial Isolated Hyperparathyroidism 1(FIHP) (CDC73) b. FIHP 2 (Jaw Tumor Syndrome) (CDC73) c. FIHP 3 c. Sporadic <ul style="list-style-type: none"> a. Parathyroid adenoma b. Parathyroid hyperplasia c. Parathyroid carcinoma 	Calcitriol Mediated <ul style="list-style-type: none"> a. Excess production <ul style="list-style-type: none"> a. Granulomatous diseases b. Lymphoproliferative neoplasms c. Neonatal subcutaneous fat necrosis b. Reduced Clearance <ul style="list-style-type: none"> a. Cyp24A1 inactivating mutation c. Williams-Beuren Syndrome d. Iatrogenic <ul style="list-style-type: none"> a. Vit D toxicity
Jansen Metaphyseal Dysplasia	MAHC
McCune Albright syndrome	<ul style="list-style-type: none"> a. Metastatic dissolution of bone b. PTHrP mediated c. Multiple myeloma d. Primary bone tumours
Familial Hypocalciuric Hypercalcemia <ul style="list-style-type: none"> a. Type 1 (CASP inactivating mutation)/ Neonatal Severe Primary Hyperparathyroidism b. Type 2 (GNA11) c. Type 3 (AP2S1) 	Others <ul style="list-style-type: none"> a. Blue diaper syndrome b. Acute renal failure c. Non-parathyroid endocrine causes <ul style="list-style-type: none"> a. Hyperthyroidism b. Adrenal insufficiency c. Pheochromocytoma d. Vasointestinal polypeptide-hormone producing tumours (VIPoma) d. Immobilization e. Juvenile rheumatoid arthritis f. Recovery stage of rhabdomyolysis with acute renal failure g. Ketogenic diet h. Iatrogenic <ul style="list-style-type: none"> a. Thiazides b. Milk-Alkali Syndrome c. SGLT2 Inhibitors d. Immune Checkpoint Inhibitors e. Vitamin A toxicity f. Denosumab g. Antiestrogens h. Teriparatide/ Abaloparatide i. Theophylline j. Foscarnet k. Aluminum Intoxication
Hypocalciuric hypercalcemia secondary to CASR blocking antibodies	
Tertiary Hyperparathyroidism	
Chronic kidney disease	
Malignancy associated hypercalcemia (MAHC)	
Ectopic PTH Production	
Drugs:	
a. Lithium	<ul style="list-style-type: none"> a. Thiazides b. Milk-Alkali Syndrome c. SGLT2 Inhibitors d. Immune Checkpoint Inhibitors e. Vitamin A toxicity f. Denosumab g. Antiestrogens h. Teriparatide/ Abaloparatide i. Theophylline j. Foscarnet k. Aluminum Intoxication

* Hyperplasia

AP2S1: Adaptor related protein complex 2 subunit sigma 1, CASR: Calcium sensing receptor, CDC73: cell division cycle 73, GNA11: G protein subunit alpha 11, MEN: Multiple Endocrine Neoplasia, PTHrP: Parathyroid hormone related protein

Clinical Features

Around 80% of individuals with PHPT are asymptomatic.[7] Subtypes of PHPT are mentioned in table 3.

TABLE 3: PHPT Subtypes

PHPT subtypes
1. Classic
2. Mild PHPT
a. Normoparathyroid PHPT
b. Normocalcemic PHPT
3. Thiazide-associated PHPT
4. Hypercalciuric PHPT
5. Lithium-associated PHPT
6. Familial (genetic) PHPT
7. Recurrent PHPT
8. Persistent PHPT

The rest present with symptomatic hypercalcemia. Symptoms are diverse and include musculoskeletal, renal, gastrointestinal, neuropsychiatric, cardiovascular, ocular, and hematological system. Clinical features are mentioned in Table 4.

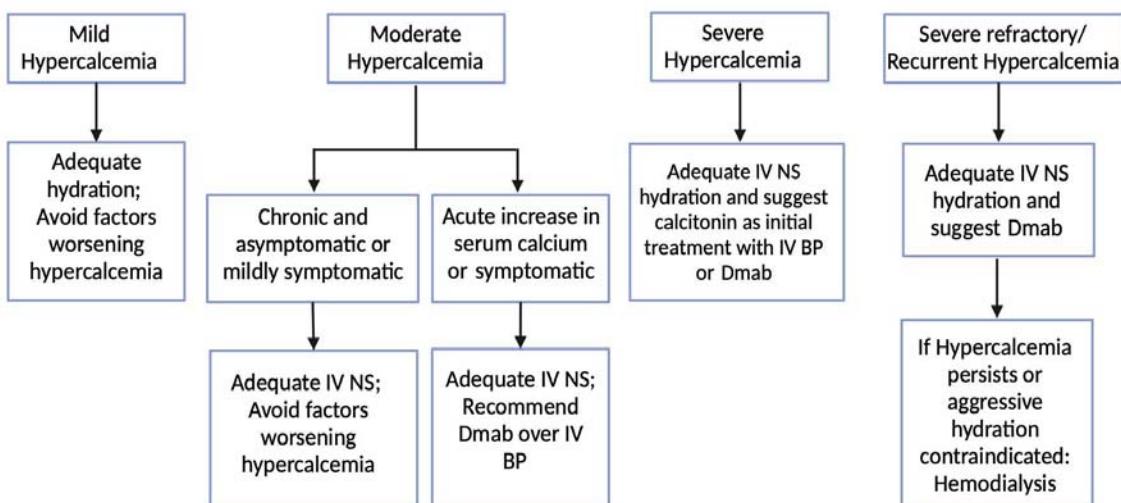
TABLE 4: Clinical manifestations of hypercalcemia

System involved	Clinical Features
Renal	Polyuria Polydipsia Nephrogenic DI Nephrolithiasis Nephrocalcinosis Acute kidney injury
Musculoskeletal	Fatigue Myopathy Bone pain Fracture Osteitis fibrosa cystica
Neurological	Confusion/altered mental status Depression Anxiety Headache Stupor/coma
Gastrointestinal	Anorexia/Nausea/vomiting/Dyspepsia Constipation Abdominal pain/discomfort Pancreatitis
Cardiovascular	Systemic Hypertension Prolonged PR/Short QT/Widened QRS Bradycardia/digitalis sensitivity
Hematological	Secondary myelofibrosis with pancytopenia
Ocular	Corneal bands Keratitis Conjunctivitis

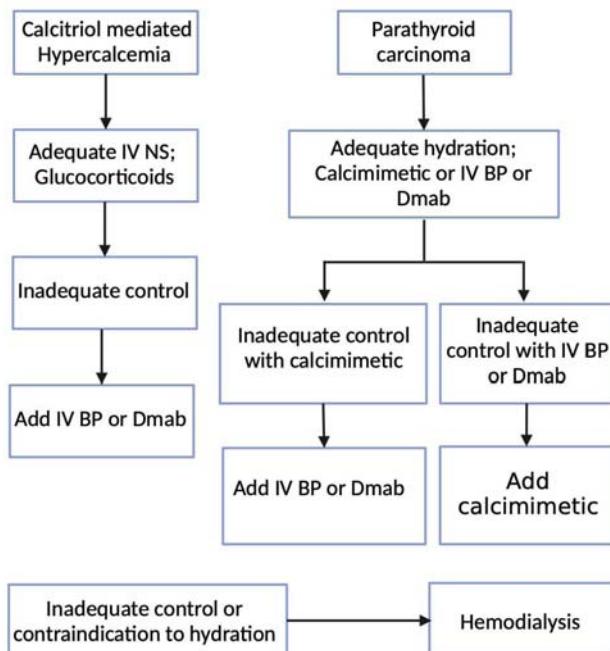
Approach to hypercalcemia

The first step in diagnosing hypercalcemia is to rule out causes of pseudo-hypercalcemia i.e. dehydration, paraproteinemia,[8] hemoconcentration secondary to a tight tourniquet application during venipuncture. Any individual presenting with hypercalcemia merits evaluation. The initial investigations include albumin, vitamin D (vit D) (25 hydroxycholecalciferol), phosphate (preferably fasting, morning sample), alkaline phosphatase, renal function tests, and intact parathyroid hormone (iPTH) (2nd generation PTH assay). Hypercalcemia is then classified as being PTH dependent or PTH independent. Concomitantly, calcium lowering measures should be initiated and the underlying pathology should be addressed.

Flowchart 1a: Approach to treatment of hypercalcemia (adapted and modified from [9, 10])



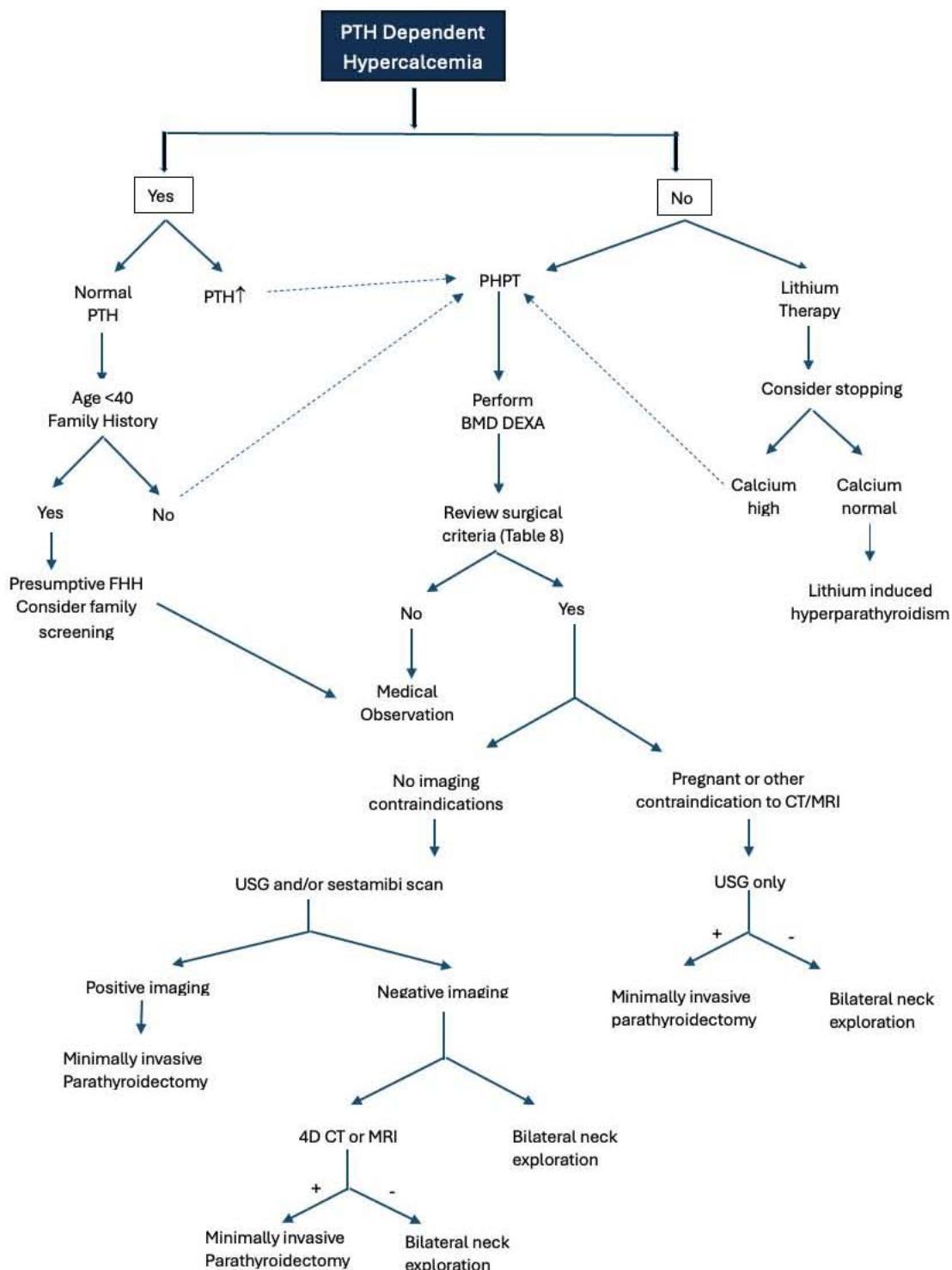
Flowchart 1b: Hypercalcemia in special populations (adapted and modified from [9, 10])



BP: Bisphosphonates; Dmab: Denosumab; IV: Intravenous; NS: 0.9% sodium chloride- Normal saline

Tests in PTH dependent hypercalcemia include urinary calcium and creatinine excretion (spot or 24-hours collection), bone mineral density (BMD DXA), and abdominal imaging (to look for nephrocalcinosis and nephrolithiasis). Another ancillary test includes serum magnesium. For PTH independent hypercalcemia, serum calcitriol levels are estimated.

FLOWCHART 2: Approach to PHPT (Adapted from [11, 12])



BMD DXA: Bone mineral density Dual X-ray absorptiometry; CT: Computed tomography; MRI: Magnetic resonance imaging; PTH: parathyroid hormone; USG: Ultrasonography

In cases of PTH dependent hypercalcemia, the next step involves localization of the lesion. Localization is usually done with high-resolution neck ultrasonography, and 99m technetium (Tc) sestamibi Single-photon emission computed tomography (SPECT) or dual-isotope Tc-99m sestamibi/I-123 sodium iodide subtraction SPECT. In equivocal cases or in individuals with scintigraphy negative results, a 4D CT neck may be done. The most sensitive imaging is 18F-fluorocholine PET/CT but it is limited to very few centres. [13]

TABLE 5: Imaging Methods to localize Parathyroid Tissue (adapted from [13, 14, 15])

Imaging Modality	Sensitivity (%)	Positive Predictive Value	Additional information
HR-USG	72 – 89	90.7 – 95.3	No radiation, simultaneous thyroid assessment. Requires operator expertise. Adenomas appear as hypoechoic lesions with peripheral vascularity. Cystic adenomas with clear aspirate are virtually pathognomonic of cystic parathyroid adenoma. Anterior echogenic capsule supports the diagnosis of parathyroid adenoma. Can't detect ectopic parathyroid adenomas
99m Tc Sestamibi SPECT	64 – 90.6	83.5 – 96	Helps with localization of parathyroid adenoma. Small adenomas may be missed. Can detect ectopic parathyroid adenomas.
4D CT neck	89.4	93.5	Cannot be used in individuals with renal impairment. Detects ectopic as well as multiple parathyroid adenomas. Useful for adenoma localization individuals with 1 st surgery failure
18 F-fluorocholine PET/CT	96 – 100	93.4 – 99.7	Choline PET radiotracer lack specificity May show false positive results Cystic parathyroid adenomas may show false negative results

TABLE 6: 99m Sestamibi SPECT Scintigraphy false negatives [16]

99m Tc Sestamibi Scintigraphy
<ol style="list-style-type: none"> 1. Calcimimetic use 2. Lithium use 3. Multigland disease or ectopic disease 4. Oxyphil-poor adenomas 5. Small sized adenoma 6. Hyperplasia 7. P-glycoprotein or MDR gene expression

Management

Management of hypercalcemia

The initial management of hypercalcemia is with IV hydration with isotonic saline. Forced alkaline diuresis with furosemide further helps lowering serum calcium. Serum calcium and magnesium should be monitored, and care should be taken to avoid diuretic induced hypomagnesemia. MAHC usually have severe hypercalcemia and require salmon calcitonin injections in conjunction with Denosumab or Bisphosphonate. [9] In refractory cases of hypercalcemia, low calcium containing dialysate hemodialysis is a viable option for lowering serum calcium. [10, 17] (Flowchart 1a, 1b, Table 7)

Table 7: Modalities for treatment of hypercalcemia [3, 9, 18]

Intervention	Dose and frequency	Mode of action	Onset of action	Median duration of action	Adverse effects
IV Fluids- 0.9% Sodium chloride saline	Bolus of 1 to 2 L then 200 to 500 mL/hour to maintain urine output at 100 to 150 mL/hour.	Restores depleted intravascular volume. Enhances urinary calcium excretion.	Immediately	During infusion. Lowers calcium by 1 to 1.5 mg/dL (0.25 to 0.375 mmol/L) over first 24 hours	Carefully assess for volume overload
Loop diuretics- Furosemide	Furosemide 160 mg/d to 100 mg/h intravenously, or 40 to 60 mg/d orally only to be administered after volume repletion.	Increase urinary calcium excretion by inhibiting renal calcium reabsorption in the thick ascending loop of Henle, and proximal and distal renal tubules. Interferes with the chloride cotransport system	Within 3 to 60 minutes	2 hours if bolus. During therapy if IV drip. Lowers calcium by 0.5 to 1.0 mg/dL (0.125 to 0.25 mmol/L) after resolution of volume depletion.	Volume depletion, and worsening hypercalcemia May be useful in patients at risk for volume overload/congestive heart failure Dyselectrolytemia
Salmon Calcitonin	4 to 8 units/kg Intramuscular or SQ every 6 to 12 hours for 48 to 72 hours.	Inhibits bone resorption by interfering with osteoclast function. Promotes urinary calcium excretion, as well as that of magnesium, sodium, potassium and phosphate.	4 to 6 hours	6 to 8 hours. Rapidly lowers calcium by 1 to 2 mg/dL (0.25 to 0.50 mmol/L).	Tachyphylaxis may occur after 48 to 72 hours
BP- Zoledronate	4 mg IV over 15 to 30 minutes. Can be repeated in 7 days, if desirable calcium level not achieved, and every 3 to 4 weeks thereafter.	Pamidronate and zoledronic acid are nitrogen-containing BPs that inhibit bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS) within osteoclasts to cause osteoclast apoptosis. They also interfere with osteoclast recruitment and function.	48 to 72 hours	4 to 6 weeks. Normalizes calcium in 80% to 90% of patients.	May cause kidney damage especially if glomerular filtration rate <30 to 35 mL/ minute. Dose adjustment required if glomerular filtration rate <60 mL/min, and administer over 30 to 60 minutes.
BP- Pamidronate	60 to 90 mg IV over 2 to 24 hours. Can be repeated every 2 to 3 weeks.	Pamidronate and zoledronic acid are nitrogen-containing BPs that inhibit bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS) within osteoclasts to cause osteoclast apoptosis. They also interfere with osteoclast recruitment and function.	48 to 72 hours	7 to 14 days; may last 2 to 4 weeks. Normalizes calcium in 60% to 70% of patients.	May cause kidney damage especially if glomerular filtration rate is <30-35ml/min Acute-phase response relatively common; hypocalcemia; renal insufficiency possible if

					decreased glomerular filtration rate; Atypical femoral fractures are rare and ONJ occurs infrequently.
Glucocorticoids	200 to 400 mg hydrocortisone IV/day for 3 to 5 days. 60 mg/day of prednisone for 10 days, or 10 to 20 mg/day for 7 days	Decrease intestinal calcium absorption. Inhibits 1 α -hydroxylase and limits 1,25-dihydroxyvitamin D production by mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	As long as on therapy.	Hyperglycemia, altered mental status, and hypertension
Ketoconazole	200 mg up to 800 mg oral in 2 divided doses	imidazole antifungal agent, that inhibits CYP27B1			CYP3A4 inhibitor, may potentiate toxicity of certain drugs Hepatotoxicity Adrenocortical hormone inhibitor at doses >400 mg/day QT prolongation
Denosumab	120 mg SQ. Repeat 1, 2 and 4 weeks later, then monthly thereafter.	Inhibits bone resorption via inhibition of RANKL. Dmab is an antibody to RANKL. Upon binding to RANKL, Dmab blocks the interaction between RANKL and RANK (receptor on osteoclast surfaces) and prevents osteoclast formation and thus bone resorption	3 to 10 days	Time to complete response 23 days. Median duration of effect 104 days. Normalizes calcium in at least 70% of patients	Acute-phase response rare; Atypical femoral fractures are rare and ONJ occurs infrequently. Rebound osteoclastogenesis may occur with discontinuation. Patients with GFR < 30 mL/min have a higher risk of hypocalcemia, and a lower dose should be considered.
Calcimimetics- Cinacalcet	Initial: 30 mg twice daily; increase dose incrementally every 2 to 4 weeks (to 60 mg twice daily, 90 mg twice daily, and 90 mg 3 to 4 times daily) as necessary to normalize calcium levels.	Calcium-sensing receptor agonist, reduces parathyroid hormone secretion, and may decrease renal calcium reabsorption	2 to 3 days	During therapy. Reduces calcium by at least 1 mg/dL (0.25 mmol/L) in approximately 60% of patients	Nausea, vomiting, headache, and fractures. Case reports indicate reduction of calcium levels in patients with refractory HCM related to non-small-cell lung, neuroendocrine, breast, or renal cancer.
Hemodialysis		Removes calcium, a low or no calcium dialysate should be used	Hours	During therapy	May cause hypotension, dyselectrolytemia

BP: Bisphosphonates; CYP27B1: 1 α hydroxylase; Dmab: Denosumab

Management of primary hyperparathyroidism

All symptomatic PHPTs require definitive treatment i.e. surgical resection. There are certain criteria for surgical resection of asymptomatic PHPT (Table 8). [19] Only a small subset of individuals with mild PHPT who have mild asymptomatic hypercalcemia may be treated with calcimimetic and bisphosphonates.



Such individuals require annual biochemistries (serum creatinine, serum calcium, urinary calcium) and BMD-DXA on follow-up. [19]

Table 8: Indications of surgery in asymptomatic PHPT [19]

Indications for surgery in individuals with asymptomatic PHPT
1. Serum calcium > 1 mg/dL above upper limit of normal
2. Osteoporotic fracture on X-Ray, CT, MRI, or VFA Reduced BMD by DXA to a T-score of -2.5 at any site (lumbar spine, hip, or distal one-third radius)
3. Renal impairment secondary to hypercalcemia. eGFR < 60 mL/min/1.72 m ² Nephrocalcinosis or nephrolithiasis on imaging
4. Hypercalciuria: 24 hour urinary calcium a. > 300 mg/24 hours in men b. > 250 mg/24 hours in women
5. Age < 50 years of age

BMD DXA: Bone mineral density- Dual Xray absorptiometry; CT: Computed tomography; MRI: Magnetic Resonance Imaging; VFA: Vertebral fracture analysis

Surgery is the cornerstone of management of parathyroid adenoma, parathyroid carcinoma. For individuals with tertiary hyperparathyroidism 3 and a half gland resection or four gland resection auto-transplantation of remainder of parathyroid gland is done. [20] For parathyroid hyperplasia associated with MEN1 syndrome, the surgery done is 4 gland or 3 ½ gland parathyroid resection with thymectomy. [21 – 23]

Success of surgery in PHPT is considered if the iPTH levels drop by more than 50% of pre-surgery levels 10 minutes after resection of lesion, also known as the Miami criteria. [24]

Post-operative period most of PHPT patients develop hypocalcemia which may be due to hungry bone syndrome (HBS) or hypoparathyroidism. Both conditions require intensive management with calcium supplementation, cholecalciferol, and calcitriol supplementation. Serum phosphate concentration usually differentiates between the two. [25, 26] Management of hypocalcemia will be discussed in the section below on hypocalcemia.

Management of persistent hypercalcemia after surgery

Surgical cure rates after the first parathyroid excision are usually about 95 %. [27, 28] Factors leading to surgical failure include inadequate localization studies, surgical inexperience, failure to recognize and adequately treat multiple-gland disease, presence and persistence of supernumerary glands; errors on frozen-section examination, incomplete excision of invasive parathyroid carcinoma, and parathyromatosis. Repeat surgery in such cases has a success rate of up to 87 – 95%. Usually these individuals are discharged with a calcimimetic and an oral bisphosphonate. Prior to the next scintigraphy study, calcimimetics are stopped 2 weeks before the scan. Keep in mind that the predictive value of 99m Tc Sestamibi SPECT/CT falls from 80% before the 1st surgery to about 50%. [28] Ideally, a 4D CT scan should be carried out which should be corroborated with a HR-USG neck. USG guided FNA iPTH levels are an invaluable source of localizing the PTH producing lesion. PTH levels from FNA increase the localization of parathyroid adenomas. [29] (Table 5)

Hypocalcemia

Hypocalcemia is defined as a total serum calcium concentration $< 8.8 \text{ mg/dL} (< 2.20 \text{ mmol/L})$ in the presence of normal plasma protein concentrations or as a serum ionized calcium concentration $< 4.7 \text{ mg/dL} (< 1.17 \text{ mmol/L})$.

TABLE 9: Aetiology of hypocalcemia [30]

Disorders of PTH	Disorders of Vit D Metabolism	Others
<p>1. Low PTH</p> <ul style="list-style-type: none"> a. Absence of the Parathyroid Glands or of PTH <ul style="list-style-type: none"> Postsurgical hypoparathyroidism Congenital DiGeorge syndrome X-linked or autosomally inherited hypoparathyroidism Other Congenital causes of hypoparathyroidism Autoimmune polyglandular syndrome type I Infiltrative disorders <ul style="list-style-type: none"> Hemochromatosis Wilson disease Metastases Hypoparathyroidism post radioactive iodine thyroid ablation b. Impaired Secretion of PTH <ul style="list-style-type: none"> Hypomagnesemia Hypermagnesemia Respiratory alkalosis Activating mutations of the calcium sensor or GNA11 <p>2. Elevated PTH</p> <ul style="list-style-type: none"> a. Vitamin D Deficiency b. Hypomagnesemia c. Pseudohypoparathyroidism Type I d. Pseudohypoparathyroidism Type II 	<p>1. Vitamin D deficiency</p> <ul style="list-style-type: none"> • Dietary absence • Malabsorption <p>2. Accelerated loss</p> <ul style="list-style-type: none"> • Impaired enterohepatic recirculation • Anticonvulsant medications • CYP3A4 mutation <p>3. Impaired 25 hydroxylation</p> <ul style="list-style-type: none"> • Liver disease • Isoniazid • CYP2R1 mutation <p>4. Impaired 1α-hydroxylation</p> <ul style="list-style-type: none"> • Renal failure • Vitamin D-dependent rickets, type I • Oncogenic osteomalacia <p>5. Target organ resistance</p> <ul style="list-style-type: none"> • Vitamin D-dependent rickets, type II • Phenytoin 	<p>1. Excessive deposition into the skeleton</p> <ul style="list-style-type: none"> • Osteoblastic malignancies • Hungry bone syndrome <p>2. Impaired bone resorption</p> <ul style="list-style-type: none"> • Vitamin D deficiency • Bisphosphonates • RANKL inhibition <p>3. Chelation</p> <ul style="list-style-type: none"> • Foscarnet • Phosphate infusion • Infusion of citrated blood products • Infusion of EDTA containing contrast reagents • Fluoride <p>4. Neonatal hypocalcemia</p> <ul style="list-style-type: none"> • Prematurity • Asphyxia • Diabetic mother • Hyperparathyroid mother • Vitamin D-deficient mother • Infantile malignant osteopetrosis <p>5. HIV</p> <ul style="list-style-type: none"> • Drug therapy • Vitamin D deficiency • Hypomagnesemia • Impaired PTH responsiveness <p>6. Critical illness</p> <ul style="list-style-type: none"> • Pancreatitis • Toxic shock syndrome • Intensive care unit patients

Clinical features

Clinical features of hypocalcemia depend on the chronicity and level of serum calcium.

Table 10: Clinical Manifestations of Hypocalcemia

Neuromuscular	Tetany(muscle spasms/cramps) Paresthesias(tingling/numbness) Chvostek's sign(facial muscle/twitching) Trousseau's sign(carpal spasm with BP cuff)
Neuropsychiatric	Seizures Calcifications Parkinsonism or dystonia Confusion/irritability Anxiety and depression Hallucinations
Cardiovascular	Prolonged QT Hypotension Hypocalcemia-associated dilated cardiomyopathy Heart failure/cardiac arrest
Respiratory system	Laryngospasm Bronchospasm and wheezing
Gastrointestinal	Abdominal cramps/pain Diarrhoea Increased bowel sounds
Musculoskeletal	Myopathy Spondyloarthropathy Osteoporosis/osteomalacia* Bone pain/fractures* Low bone turnover and increased bone mineral density#
Ophthalmological	Corneal calcification Cataract Papilledema
Dental	Altered tooth morphology
Dermatological	Dry skin/hair Alopecia Onycholysis Pustular psoriasis
Other Manifestations	Fatigue/weakness Impaired clotting Easy bruising/bleeding

*Vitamin D deficiency, osteomalacia

#Chronic hypoparathyroidism

Approach to hypocalcemia

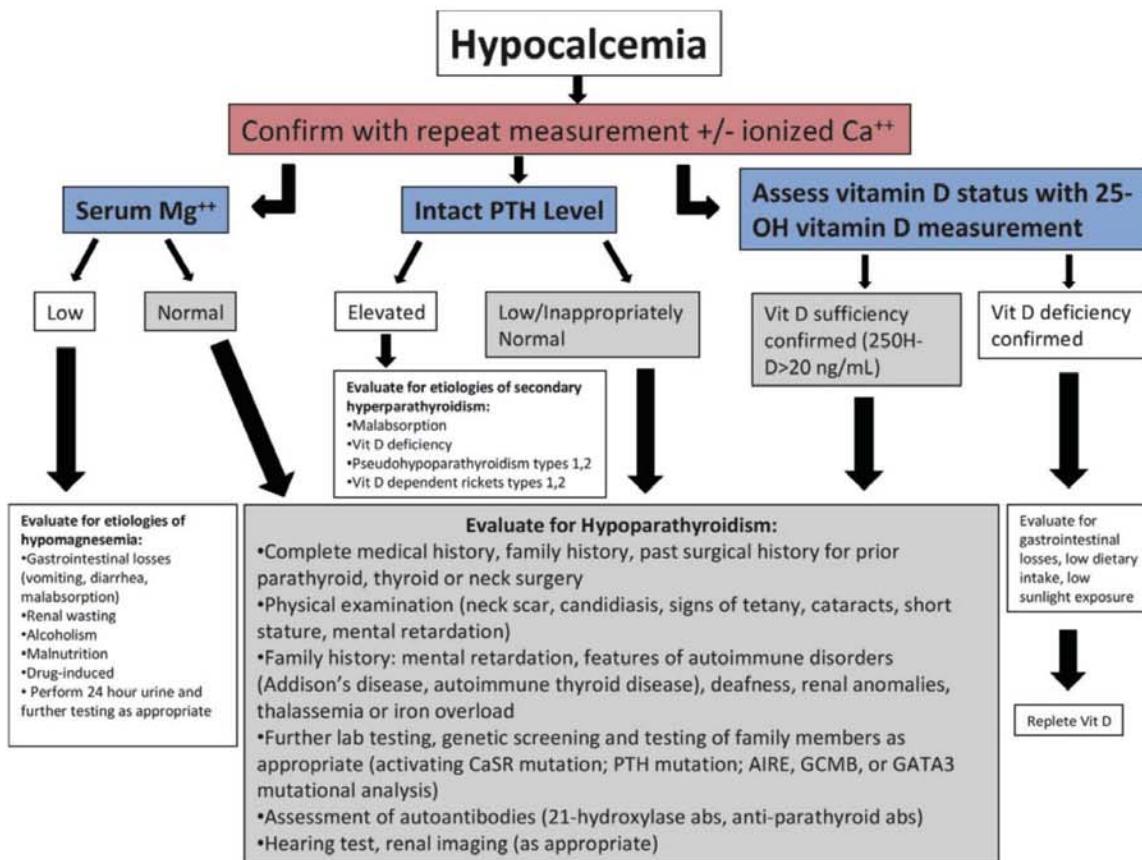
The initial step in the management of hypocalcemia is sending serum phosphate (preferably fasting, early morning sample), albumin, Vit D, iPTH, serum magnesium. The commonest cause of hypocalcemia is due to vit d deficiency and secondary hyperparathyroidism. [31] The commonest cause of hypoparathyroidism (hypoPT) is post-surgical hypoPT. Hypocalcemia should be anticipated and evaluated in individuals who undergo neck surgery, especially thyroidectomy. Hypocalcemia after thyroidectomy occurs in 30 – 60% of patients and initially manifests within 24 ours after surgery. About 2/3rds of these cases have transient hypoPT which resolves within 4 to 6 weeks after surgery. PTH concentration on post-op day 1 greater than 10 pg/mL (>1.06 pmol/L) predicts normal parathyroid function 6 months following surgery (32, 33).

The number of parathyroid glands excised directly correlates with risk of permanent hypoPT.[33]

Permanent hypoPT is defined as low iPTH and serum albumin adjusted calcium after 12 months of surgery

in individuals who underwent neck surgery. [34] Elevated serum phosphate may also be considered as part of the diagnostic criteria. Rates of permanent hypoPT range from 1 – 12.5%. [35, 36] A rare scenario may arise wherein there may be biochemical features of hypoparathyroidism, however, the iPTH concentration is abnormally within normal range or elevated. This scenario may point towards Inactivating PTH/PTHrP signaling disorders (iPPSD). Mantovai et al have published an excellent practical tool which covers iPPSD. [37]

Flowchart 3: Approach to hypocalcemia (from Hypoparathyroidism in the Adult: Epidemiology, Diagnosis, Pathophysiology, Target Organ Involvement, Treatment, and Challenges for Future Research [38])



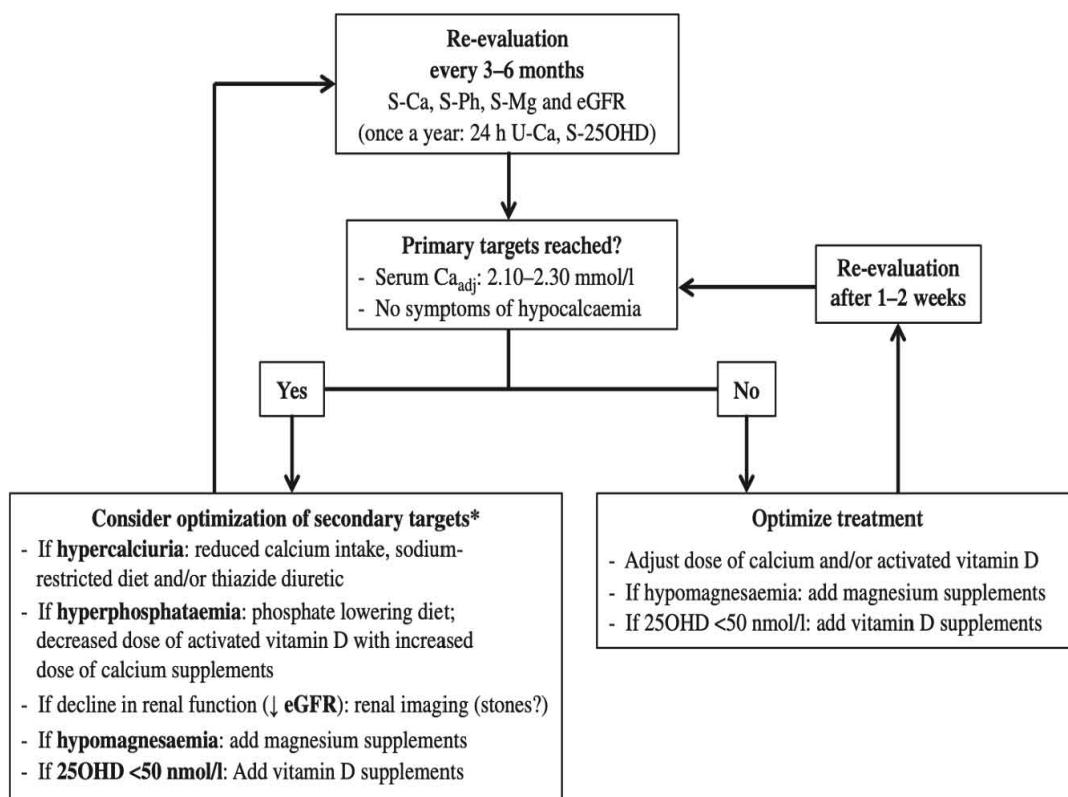
Treatment of hypocalcemia

All individuals with hypocalcemia should be treated when they are symptomatic, or if albumin adjusted calcium is <8.0 mg/dL (ionized calcium < 4mg/dL). Management of acute symptomatic hypocalcemia involves prompt IV access and administration of 2 ampules of a 10% calcium gluconate (which contains 90 mg of elemental calcium in each ampoule) in 50 mL of 5% dextrose, over 10 to 20 minutes followed by a slower infusion of calcium gluconate at a rate of 0.5 to 1.5 mg/kg/h over an 8- to 10-hour period. [39]

Serum calcium and magnesium should be monitored at baseline and thereafter serum calcium. An initial serum phosphate and iPTH level may indicate the aetiology of hypocalcemia.

In individuals with chronic hypoparathyroidism, activated vitamin D analogue (Calcitriol 0.25 to 2 mg given in divided doses; Alfacalcidol 0.5 – 4 mg given in divided doses) plus calcium supplements in divided doses is the primary therapy. Vitamin D supplementation should be given with a daily dose of 400 – 800 IU per day. In individuals with hypomagnesemia, cause of hypomagnesemia should be sought, and magnesium supplementation should be given. [40]

Flowchart 4: Monitoring and treatment of chronic hypoPT



*If dose of calcium or activated vitamin D is changed, re-evaluation of serum calcium levels is recommended after 1–2 weeks. (Adapted from Bollerslev et al. [40])

Table 11: Goals of therapy in chronic hypoparathyroidism [40]

1. To maintain serum albumin adjusted calcium level in the lower part or slightly below the lower limit of normal (target range) with patients being free of symptoms or signs of hypocalcaemia
2. 24-hours urinary calcium excretion should be within reference range
3. Serum phosphate levels should be within the reference range.
4. Serum calcium–phosphate product should be below $55 \text{ mg}^2/\text{dL}^2$
5. Serum magnesium levels should be within the reference range
6. Adequate vit D status
7. Treatment be personalized and focused on the overall well-being and quality of life of the patient when implementing different therapeutic efforts

In individuals with hard-to-treat chronic hypoPT, recombinant human PTH may be given (table 12). Teriparatide in doses of 20 mcg subcutaneous twice a day reduce the requirement of calcitriol and calcium. [41]

TABLE 12: Indications for considering use of recombinant human PTH therapy [39]

- | |
|--|
| 1. Inadequate control of serum calcium with hypocalcaemia, or erratic swings to hypocalcaemia or hypercalcaemia on conventional therapy |
| 2. Doses of supplemental calcium of $>2.5\text{g}$, or of activated vitamin D of $>1.5\mu\text{g}$ calcitriol or $>3.0\mu\text{g}$ alpacacladol daily |
| 3. Evidence for renal involvement with hypercalciuria, nephrocalcinosis, nephrolithiasis or reduced creatinine clearance on conventional therapy |
| 4. Hyperphosphataemia or a calcium-phosphate product of $>55\text{mg}^2/\text{dl}^2$ on conventional therapy |
| 5. A gastrointestinal disorder or post-bariatric surgery, associated with malabsorption |
| 6. Reduced quality of life on conventional therapy |

In individuals with vit d deficiency, treatment with calcium supplements and vit D. The Endocrine Society of India recommends 400 international units (IU) of vitamin D per day for infants, 600-1000 IU for children, 1000 IU for adolescents and pregnant women after 12 weeks' gestation, and 1000-2000 IU for adults. [42] The Indian Council of Medical Research (ICMR) has recommended a lower dose of Vit D as RDA of Vit D; Vit D supplementation in case of minimal sun exposure in infants is 400 IU, and rest of the population it is 600 IU. [43]

The recommended daily dose of elemental calcium required for attaining calcium replete status in mentioned in table 13.

Table 13: Recommended calcium dose in Indian population [43]

	EAR (mg/day)	RDA (mg/day)
Adult Women (18 years – Premenopausal), and pregnant women	800	1000
Lactating, and post-menopausal women	1000	1200
Men	800	1000
Infants	-	300 (AI)
Children (1 – 3 years)	400	500
Children (4 – 6 years)	450	550
Children (7 – 9 years)	500	650
Adolescents (10 – 12 years)	650	850
Adolescents (3 – 15 years)	800	100
Adolescents (16 – 18 years)	850	1050

EAR- Estimated average requirement; RDA- Recommended dietary intake

Calcium preparations and calcium-foods are mentioned in table 14.

Table 14: Calcium preparations [44, 45]

Calcium-rich foods	Calcium (mg)
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250 ml of milk and curd	300	
50 g of pulses	50	
15 g of til seeds	170	
15 g of green leafy vegetables	250	
50 g of millets especially ragi	180	
<hr/>		
Elemental calcium in calcium preparations	Calcium (%)	Calcium (mg/g)
Calcium carbonate	40	400
Calcium phosphate	38	383
Calcium citrate	21	210
Calcium acetate	25	253
Calcium lactate	13	130
Calcium gluconate	9	93

Osteoporosis

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and micro architectural deterioration of the bone tissue with a consequent increase in bone fragility and susceptibility to fractures, involving the wrist, spine, hip, pelvis, ribs, or humerus. [46, 47] The prevalence of osteoporosis in India for women and men (older than 50 years of age) ranges between, 8 to 62% and 8.5 to 24.6%, respectively. [48] The presence of previous osteoporotic fracture raises the risk for subsequent fracture and mortality.[49] The presence of one vertebral fracture increases the risk of another vertebral fracture by 20% within 1 year. There is a five-time increase risk of vertebral fractures thereafter. Individuals with hip fracture have a 20% risk of mortality within next two years. [50]

Osteoporosis may be classified as primary or secondary. Primary osteoporosis is seen in postmenopausal women and with old age in whom there is no specific pathogen mechanism, other than age and lack of oestrogen, Secondary osteoporosis has a defined underlying pathology for impaired bone architecture (Table 15)

Table 15: Classification of osteoporosis [47, 51]

Osteoporosis is classified as primary and secondary

1. Primary osteoporosis
 - a. Type I or PMO:
 - Mainly affects trabecular bone occurring in the early part of menopause transition
 - Accelerated bone loss: 1%–2% /year (range 1%–5% yearly)
 - Seen in the first 5–7 years after menopause
 - b. Type II or senile osteoporosis
 - Age related
 - Bone loss occurs at a rate of 1% per year in both sexes
 - Affects cortical and trabecular bone
 - Secondary osteoporosis is due to specific causes
2. Secondary Osteoporosis

- a. Drug induced osteoporosis
 - Hormones and Drugs with Actions on the Endocrine System
 - Glucocorticoids
 - Thyroid Hormone
 - Hypogonadism-inducing agents
 - Aromatase Inhibitors
 - Medroxyprogesterone Acetate
 - GnRH Agonists
 - Thiazolidinediones
 - Drugs with Actions on the Central Nervous System
 - Antidepressants
 - Anticonvulsants
 - Drugs with Actions on the Immune System
 - Calcineurin Inhibitors
 - Antiretroviral Therapy Anticoagulants; heparin
 - Diuretics: Loop diuretics
 - Drugs with Actions on the Gastrointestinal Tract
 - Proton Pump Inhibitors
- b. Endocrine Disorders
 - Glucocorticoid-induced osteoporosis
 - Hyperthyroidism
 - Hypogonadism
 - Hyperparathyroidism
 - Diabetes mellitus
 - Growth hormone deficiency
 - Acromegaly
- c. Gastrointestinal, Hepatic and Nutritional Disorders
 - Celiac disease
 - Inflammatory bowel disease
 - Gastric bypass surgery
 - Anorexia nervosa
 - Hemochromatosis and chronic liver diseases
- d. Hematological disorders
 - Monoclonal gammopathy of uncertain significance
 - Multiple myeloma
 - Systemic mastocytosis
 - Beta thalassemia major
- e. Renal Disorders
 - Idiopathic hypercalciuria
 - Renal tubular acidosis
 - Chronic kidney disease
- f. Autoimmune Disorders
 - Rheumatoid arthritis
 - Systemic lupus erythematosus
 - Ankylosing spondylitis

- Multiple sclerosis

Major risk factors for developing osteoporosis are advancing age, low body mass index, prior history of fracture, parental history of hip fracture, smoking, alcohol consumption, use of glucocorticoids, and rheumatoid arthritis. Modifiable risk factors include nutrition (adequate calcium, vit D, and protein intake), physical activity and sunlight exposure, and decrease the risk of falls.

Some guidelines use fracture-risk thresholds (US, Canada, and UK) whereas other guidelines use T-score based thresholds (Austria, Belgium, India, and Brazil).[57]

Severity of osteoporosis may be defined by 10 year fracture risk (FRAX) or by T-score at neck of femur and spine (Figure 16)

Table 16: Severity of osteoporosis [53, 54]

WHO Risk Categories

WHO Risk Categories	Hip Or Spine Fracture	BMD T-Score At The Hip And Spine	10-Year Fracture Risk Assessment tool (FRAX)	
			Hip Fracture	Major Osteoporotic Fracture
Low fracture risk	No prior fracture	both above -1.0	<3%	<20%
Moderate fracture risk	No prior fracture	Both above -2.5	<3%	<20%
High fracture risk	Prior fracture	≤-2.5	≥3%	≥20%
Very high fracture risk	Multiple spine fractures	≤-2.5		
AACE Risk categories				
AACE Risk categories	Hip Or Spine Fracture	BMD T-Score At The Hip And Spine	10-Year Fracture Risk	
			≥3	≥20
High fracture risk	Prior fracture	≤-2.5		
Very high fracture risk	Fracture within 1 year Fracture while on approved osteoporosis therapy Multiple fractures while on drugs causing skeletal harm (eg. long term glucocorticoids)	≤-3.0	≥4.5	≥30



AACE: American Association of Clinical Endocrinology; BMD: Bone mineral density; WHO: World Health Organization

Figure 1: FRAX-India [55]

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth

Age: Date of Birth:

 Y: M: D:

2. Sex

Male Female

3. Weight (kg)

Clear Calculate

4. Height (cm)

5. Previous Fracture

No Yes

6. Parent Fractured Hip

No Yes

7. Current Smoking

No Yes

8. Glucocorticoids

No Yes

9. Rheumatoid arthritis

No Yes

10. Secondary osteoporosis

No Yes

11. Alcohol 3 or more units/day

No Yes

12. Femoral neck BMD (g/cm²)

Select BMD

Approach to Osteoporosis

Any adult with a fragility fracture (defined as fractures resulting from “low energy trauma”, i.e. often from a fall from standing height or less, that would not normally result in a fracture) should be evaluated for underlying osteoporosis (primary or secondary). Height loss of more than 4 cm or persistent back pain may be due to an asymptomatic vertebral fracture. [48]

It would be prudent to differentiate osteoporosis from vitamin D deficiency osteomalacia, the latter is a treatable cause of low bone mineral density. Treatment of osteomalacia leads to improvement of BMD. [56] Initial investigations include serum albumin adjusted calcium, phosphate, creatinine, alkaline phosphatase, vit D, iPTH, serum protein electrophoresis, and X-ray (lumbosacral spine, bilateral hip). [47, 48, 52, 54] Detailed evaluation for aetiologies for secondary osteoporosis are mentioned in table 18.

Imaging for bone mineral density includes the following modalities.

1. BMD-DXA

BMD-DXA is the most commonly used technique for measuring BMD. DXA measures areal bone density (two-dimensional measurement). BMD is reported as grams/cm². [57] BMD-DXA values are represented with a “T” score and a “Z score”. “T” Score of an individual is the number of standard deviation (SD) their BMD deviates from the mean BMD of 20 – 29 years-old reference population. “Z” Score of an individual is the number of SD their BMD deviates from the mean BMD of the same age, gender, and ethnic group reference population. [58] Another tool that is implemented in DXA is the Trabecular Bone score which is pixel gray-level texture estimation. TBS below 1.2 is considered as degraded bone, 1.2 to 1.35 as partially degraded bone, and greater than 1.5 as normal trabecular bone. [59]

treatment of osteoporosis. QCT has some disadvantages such as higher cost and greater amount of radiation exposure.

Bone turnover markers [47]

Bone turnover markers (BTMs) are dynamic parameters that reflect short-term, acute changes in bone remodeling status that are not measured by BMD and hence, are complementary to BMD measurement. They have no role in the diagnosis of osteoporosis. BTMs may be used in the follow-up of patients who are on anti-osteoporotic treatments as a surrogate to check compliance on therapy.

Table 18: Evaluating causes of secondary osteoporosis [51]

Initial workup

- Detailed history to identify risk factors for osteoporosis
- Evaluation of nutritional status, calcium, and vitamin D intake
- Bone mineral density X-ray lumbar and thoracic spine (if height loss >1.5 inches)
- Complete blood count with differential
- Serum calcium, phosphate, creatinine, albumin and 25 hydroxy-vitamin D
- Serum protein electrophoresis
- Serum total, FSH, LH, prolactin
- Bone resorption and formation markers
- 24-hour urine calcium, creatinine, and sodium

Further workup

- Serum parathyroid hormone
- Serum thyroid stimulating hormone
- Serum tissue transglutaminase antibodies
- Serum ferritin, Iron, Total iron binding capacity, and liver function tests
- Serum electrolytes
- Serum tryptase levels
- 24-hour urinary cortisol or dexamethasone suppression test
- Nuclear bone scan (if high bone turnover)

Role of other screening tools

Scoring tools other than FRAX which have been studied in Indian population include

1. SCORE (Simple Calculated Osteoporosis Risk Estimation) [63]
2. OSTA (Osteoporosis self-assessment tool for Asians) [64]
3. MORES (Male osteoporosis risk estimation score) [65]

Another scoring system for osteoporosis risk estimation is the GARVAN score, however this has not been validated in Indian population.

Indications for treatment

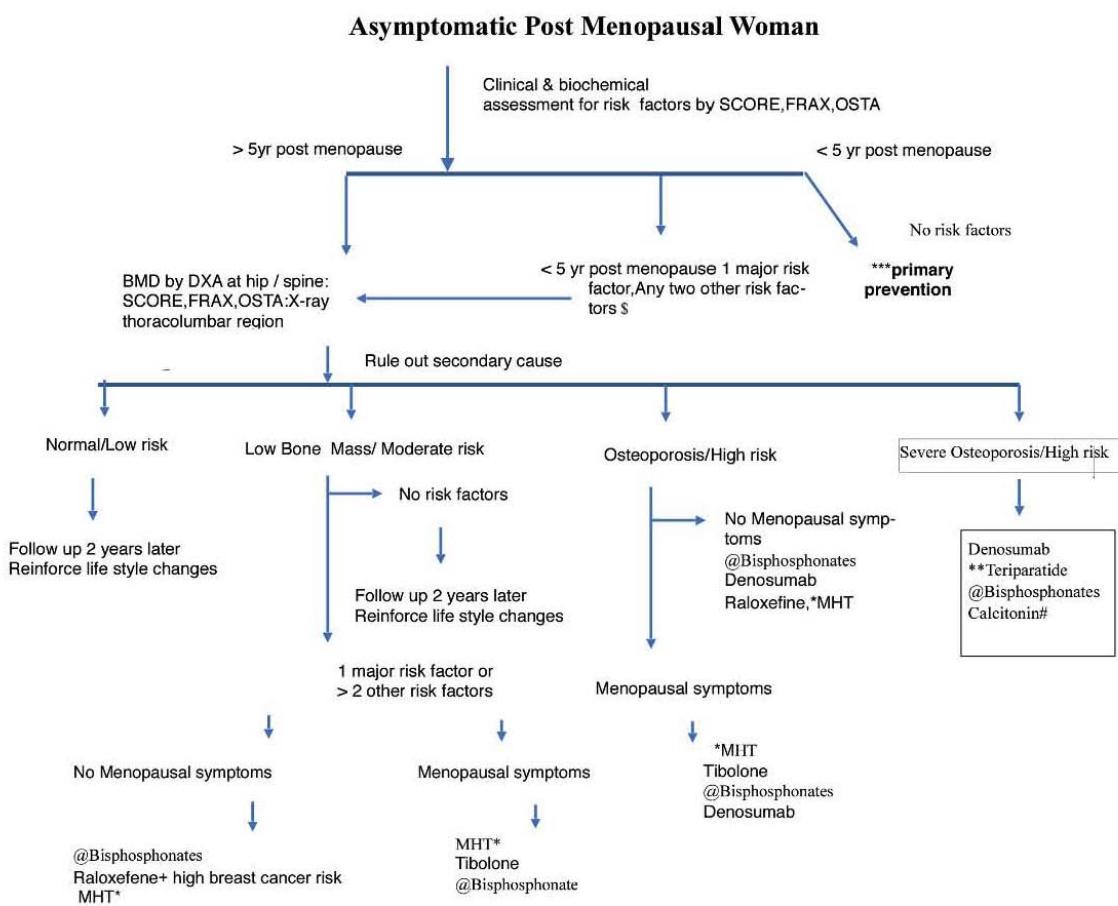
After diagnosis osteoporosis and stratifying severity of osteoporosis, individuals with osteoporosis should be initiated on osteoporosis therapy. All women with post-menopausal osteoporosis should be initiated on

calcium and vit D supplementation. If the individual is not adequately exposed to sunlight (sunlight by exposing 15%–30% of body surface area (face, neck, and both arms and forearms) without sunscreen for at least 30 min between 10 am and 3 pm per day) then they should consume vit D of at least 600 – 1200 IU per day. The RDA for calcium is 1200 mg/dL. Preparations for calcium are mentioned in table 14.

The proven efficacy of all osteoporosis medications has been elucidated with supplementation of calcium and Vit D supplementation. Apart from calcium and Vit D supplementation, all individuals with osteoporosis should receive adequate nutrition, lifestyle and behavioral modifications, limb strengthening exercises, education on avoidance of falls, and avoidance of bone depleting agents. [47]

The management of symptomatic and asymptomatic post-menopausal osteoporosis are shown in flowcharts 5, 6.

Flowchart 5: Treatment of asymptomatic Postmenopausal women [47]



@Bisphosphonates: Drug holiday after 3 yrs for IV, 5 years for oral (at low risk) - Consider continuation after a drug holiday

***Hormone therapy:** To be used within 10 years of menopause, Pre-initiation workup to assess malignancy risk; Review annually; Individualize therapy

**** Teriparatide - can be used for up to 2 years**

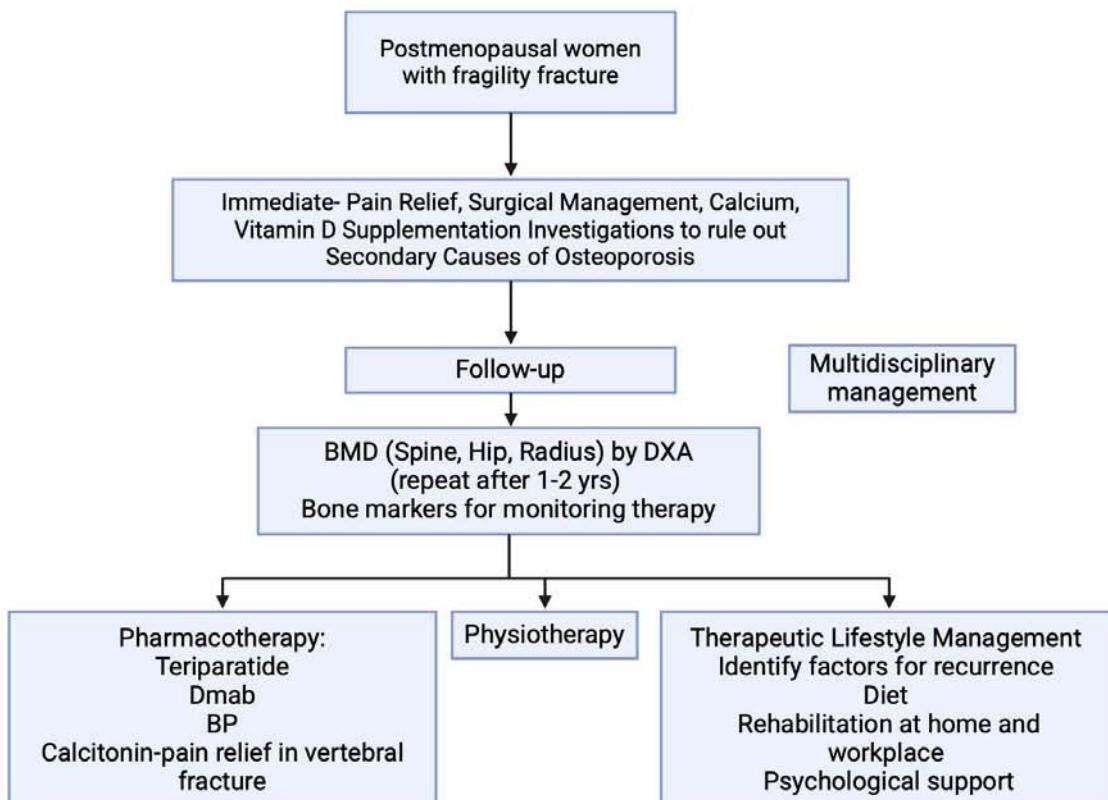
***** Primary Prevention for all -**Nutrition Lifestyle Modification, Adequate Vitamin D and Calcium, Exercise, Avoid bone depleting agents

Calcitonin – Used as an analgesic, short term for three months in vertebral fractures

\$ Low body mass index (BMI); Prior history of a fracture; Parental history of hip fracture; Smoking; Alcohol; Use of glucocorticoids; Rheumatoid arthritis

FRAX: Fracture Risk Assessment Tool; MHT: Menopausal Hormone Therapy; OSTA: The Osteoporosis Self-Assessment Tool for Asians; SCORE: Simple Calculated Osteoporosis Risk Estimation)

Flowchart 6: Management of postmenopausal woman with a fragility fracture (Modified and illustrated from [47])



Apart from hormone replacement therapy, anti-osteoporosis medications can loosely be divided into two categories: -

1. Anti-resorptive medications
 - a. Bisphosphonates- Alendronate, Risedronate, Ibandronate, Zoledronate
 - b. Monoclonal antibodies inhibiting receptor activator of nuclear factor kB ligand (RANKL)- Denosumab
2. Osteoformer medications
 - a. Recombinant PTH: Teriparatide, Abaloparatide
 - b. Monoclonal antibodies inhibiting binding of Sclerostin: Romosozumab

In India, anti-resorptive medications and teriparatide are available and hence used in the management of osteoporosis (Table 19).

Drug	Calcitonin	Tibolone	Raloxifene	Menopausal hormone therapy	Denosumab	Teriparatide	Zoledronate	Risedronate	Alendronate
Dose	200 IU	1.5 mg	60 mg	Various regimens	60 mg	20 mcg	5 mg	5 mg daily 35 mg weekly 150 mg monthly	5/10 mg daily 35 mg weekly 150 mg monthly
Route	Nasal spray	Oral	Oral	Various regimens	Subcutaneous	Intravenous	Oral	Oral	Oral
Position in therapy	2 nd line	1 st Line < 10 years menopause	At risk of breast cancer, without vasomotor symptoms, < 10 years of menopause	1 st Line with menopausal symptoms (< 10 years of menopause)	1 st Line	For severe osteoporosis	1 st Line	1 st Line	1 st Line
Incident VF reduction	Yes, 21 %	Yes, 50 %	Yes, 40 %	Yes, 30 – 70 %	Yes, 68 %	Yes, 65 %	Yes, 70 %	Yes, 41 – 49 %	Yes, 50 %
Incident HF reduction	No	Yes, 26 %	No	Yes, 40 %	Yes, 40 %	Insufficiency date	Yes, 41 %	Yes, 3.0 %	Yes, 51 – 56 %
Incident NVF reduction	No	Yes, 36 %	No	Yes, 27 %	Yes, 20 %	Yes, 33 %	Yes, 25 \$	Yes, 3.6 %	Yes, 49 %
Precautions	Serious hypersensitivity reactions-fatal anaphylaxis reported; consider skin testing prior to treatment	To stop fibrolone a few weeks before any operation to reduce the risk of a blood clot, drug interaction with warfarin	With a low risk of DVT and for whom BP or Dmab are not appropriate, or with a high risk of breast cancer	Blood clots, Cancer (breast, uterine, or endometrial), Heart or liver disease, pregnancy, Stroke	Hypocalcemia, Vit D status, pregnancy, lactation, pediatric	Hypocalcemia, Vit D status, Hypersensitivity, local tissue damage, pregnancy, lactation, pediatric	Hypocalcemia, Vit D status, Hypersensitivity, local tissue damage, pregnancy, lactation, pediatric	Hypocalcemia, Vit D status, Hypersensitivity, local tissue damage, pregnancy, lactation, pediatric	Hypocalcemia, Vit D status, Hypersensitivity, local tissue damage, pregnancy, lactation, pediatric
Advantages	Effect of administration	↑ BMD, ↑ TFC and TG similar to conventional MHT	↓ incidence of invasive E-receptor-positive ca breast both during tx and for at least 5 yrs after cessation	Less musculoskeletal symptoms of aches and pains and possibly sarcopenia (or muscle wasting)	↑ BMD reported over 10 years at spine, hip and nonvertebral sites, can be used in patients in eGFR 1.5-30 ml/min.	Potent bone-forming activity, Large ↑ spine BMD over 2 years	Proven efficacy in the prevention of vertebral and nonvertebral fractures, including hip fractures	Most commonly used drug	Most commonly used drug
Disadvantages	Circulating antibodies to calcitonin-salmon may develop, and may cause loss of response to treatment	Reduction of HDL levels and its high cost	Daily oral administration	Loss of effect and drop in BMD after discontinuation (should be continued on bisphosphonates)	Reserved line drug, 2 years usage, daily injections required.	Anaphylaxis, including fatal events,	Inconvenient administration - Stay upright for 30 min on intake, drink lots of water, no food before taking the drug, drug holiday may be needed after 3-5 years anaphylaxis, including fatal events,		
Contraindications	Hypersensitivity to calcitonin-salmon	Pregnancy and lactation, Active history of thromboembolic disorders	Active endometrial and E-dependent cancers, abdominal vaginal bleeding, Moderate and high risk for breast cancer, Established CVD and at severe increased risk of ASCVD, SLE, DM with end organ disease, Severe active liver disease, serious personal or family history of VTE, Known or	Hypocalcemia, Hypersensitivity	Hypocalcemia, hypersensitivity	Hypocalcemia, hypersensitivity, compromised renal function	Hypocalcemia, hypersensitivity, compromised renal function	Hypocalcemia, hypersensitivity, compromised renal function	Hypocalcemia, hypersensitivity, compromised renal function
Adverse effects	Rhinitis, epistaxis, and allergic reactions	May ↑ stroke acts in women > 60 yrs, Weight gain, Unscheduled bleeding	Venous thromboembolism, stroke	Bloating, Breast swelling or tenderness, Headaches, Mood changes, Nausea, Vaginal bleeding	Dermatitis, rash, mild bone/muscle pain, UTIs	Headache, hypercalcemia (high-quality); hypocalcemia, renal adverse effects, mastitis, rhinitis, arthralgia	Rash, abdominal pain, dyspepsia, diarrhea, arthralgia	Dyspepsia, esophagitis, abdominal pain, musculoskeletal pain	Dyspepsia, esophagitis, abdominal pain, arthralgia

Table 19: Drugs used in management of osteoporosis [47]



ASCVD: Atherosclerotic cardiovascular disease; BP: Bisphosphonate; Dmab: Denosumab; DM: Diabetes mellitus; DVT: Deep vein thrombosis; E-receptor: Estrogen Receptor; HF: Hip fracture; ONJ: Osteonecrosis of jaw; MHT: Menopausal hormonal therapy; NVF: Non-vertebral fracture; PMS: Premenstrual syndrome; SLE: Systemic lupus erythematosus; TC: Total cholesterol; TG: Triglycerides; Tx: treatment; UTI: Urinary tract infection; VF: Vertebral fracture; Vit D: Vitamin D (25-hydroxycholecalciferol); VTE: Venous thromboembolism

Bisphosphonate Drug Holidays

The role of drug holiday is controversial and therefore stopping of anti-osteoporotic medications needs a thorough evaluation and discussion with the patient as well. Studies demonstrating benefits of drug holiday (prevention of atypical femur fracture) and demerits (diminishing antiresorptive effects after drug cessation) are lacking. However, it may be planned for patients who have been on bisphosphonates without persistently high fracture risk who have completed 3 years on parenteral bisphosphonate, or 5 years or oral bisphosphonate. [66]

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Prediabetes Biomarkers- Do they have role in predicting disease progression?



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Abstract

Increasing prevalence of prediabetes is a major public health concern globally. Prevalence of prediabetes vary widely depending on the definition. According to International Diabetes Federation(IDF) 10th ed ,prevalence of IGT worldwide in 2021 was 10.6% or 541million,where as prevalence of IFG worldwide was 6.2% or 319million. In India,according to National urban Diabetes survey estimated prevalence of prediabetes is 14%. The recently published results of ICMR INDIAB study showed a prevalence of 15.3% with an estimated number of 136 million. The annual progression rates of prediabetes to diabetes is reported as 5-18% among different ethnicities.These rates are significantly greater in Indian population. Conventional markers are inconclusive to predict the progression of prediabetes to T2DM. Novel biomarkers have been identified as predictive of T2D development; however, none of them have been validated for clinical practice. Combining biomarkers in a clinical scenario may provide better sensitivity and specificity in predicting and preventing the disease. However, long-term prospective studies are needed to further to establish the utility of these biomarkers. This review article describes the novel biomarkers of the 21st century that can predict progression of prediabetes and their present potential for assessing risk stratification.

Introduction

Increasing prevalence of prediabetes is a major public health concern globally. "Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism(1) . People

with prediabetes are defined by the presence of IFG100 to 125 mg/dL (5.6 to 6.9 mmol/L)and/or IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (7.8 to 11.0 mmol/L) and/or A1C 5.7–6.4% (39–47 mmol/mol)⁽¹⁾.

Prevalence of prediabetes vary widely depending on the definition. Currently there are varied cut-offs as suggested by ADA and WHO,IEC. Global prevalence data on prediabetes are lacking. According to International Diabetes Federation(IDF) 10th ed⁽²⁾,prevalence of IGT worldwide in 2021 was 10.6% or 541million,where as prevalence of IFG worldwide was 6.2% or 319million. Prevalence of prediabetes was reported at 10.3% using WHO criteria in the ICMR-INDIAB study among 15states in India^(3,4).According to National urban Diabetes survey estimated prevalence of prediabetes is 14%⁽⁵⁾ in India. A recent study by Kumar et al. stated a prevalence of prediabetes/diabetes as 8.4 and 12.3% among adolescent girls and boys in India⁽⁶⁾. The recently published results of ICMR INDIAB study showed a prevalence of 15.3% with an estimated number of 136 million.

The progression rates of prediabetes to diabetes is varied among different ethnicities. Those with an A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25%to 50% and a relative risk 20 times higher compared with A1C of 5.0% (31 mmol/mol)⁽⁷⁾.As per study by Anjana et al, incidence of diabetes in prediabetes individuals was 78.9 per 1000 person years among Indians⁽⁸⁾.These are much higher than Caucasians ,which was reported as 35-40 per 1000person years⁽⁹⁾.In terms of annual progression rates, it is about 15-19% which is higher than in

Diabetes Prevention Program(DPP) study⁽¹⁰⁾where the progression rate was 2.5%. Estimated annual progression rate as suggested in LEADR study⁽¹¹⁾ was 5.3%.Overall the progression rates of prediabetes to diabetes annually is significantly greater in Indian population.

There are various identified conventional risk factors for progression like age, sex, family history of diabetes, high HbA1C, low HDL levels, obesity etc. Identifying high-risk pre-diabetes people who progress to diabetes can help us carry out effective interventions to prevent diabetes, and better control of these risk factors can increase the reversion to normoglycemia. Therefore, it is essential to find more accurate and sensitive biomarkers that can predict the onset of diabetes prior to significant loss of α -cell function⁽¹²⁾.

Novel biomarkers have been identified as predictive of T2D development; however, none of them have been validated for routine clinical practice. This review article focuses on potential biomarkers and their significance in disease progression.

Fetuin-A

Auberger et al. provided the first evidence of fetuin-A in insulin signalling. Human fetuin-A or alpha-2 Heremans Schmid glycoprotein is an endogenous glycoprotein secreted by the liver. Fetuin-A is an endogenous inhibitor of the insulin receptor and causes insulin resistance by inhibiting phosphorylation of tyrosine kinase predominantly (Figure 1).

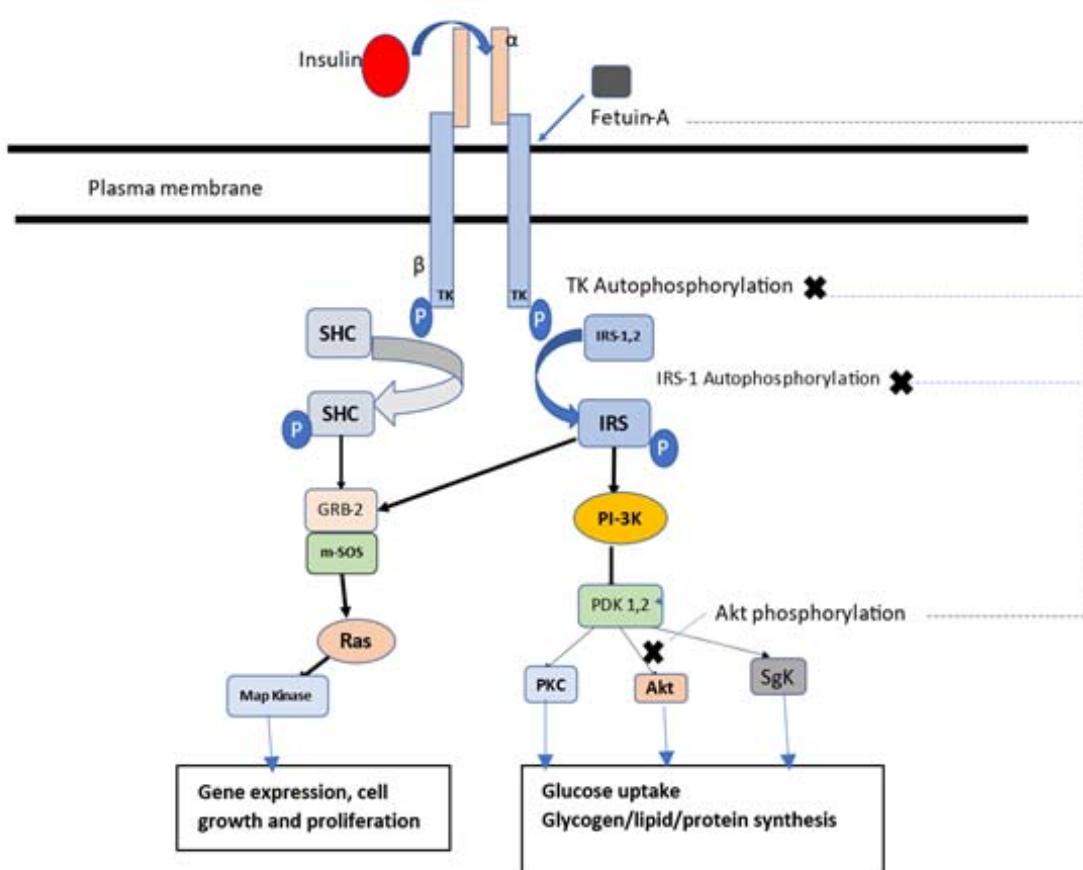


Figure 1:showing mechanism of action of fetuin-A on insulin signaling. Fetuin-A interacts with the extracellular domain of the transmembrane subunit of the tyrosine kinase receptor. Fetuin-A inhibits the intracellular insulin signaling pathway by impairing the autophosphorylation of tyrosine kinase and IRS-1 and also by inhibiting phosphorylation of AKT (as shown in dotted lines). Abbreviations; IRS-1, insulin receptor substrate-1; MAPK, Mitogen-activated protein kinase; PI-3k, Phosphoinositide 3-kinase; TK, Tyrosine kinase,SHC-Src homology domain containing protein,GRB-2Growth factor receptor binding protein ,PDK-Phosphoinositide dependent kinases,PKC protein kinase C,SgK Serum induced and glucocorticoid induced protein kinase

Fetuin A administered to rodents caused the inhibition of tyrosine phosphorylation of the insulin receptor. Also the inhibition of insulin substrate 1 in skeletal muscles and liver of rat. Insulin sensitivity was experienced in Fetuin A knockout mice and there was resistance to the adipogenic effect of a high fat diet.⁽¹³⁾ Stefan et al, in 2008 showed high levels of circulating Fetuin-A is connected with resistance of insulin in humans⁽¹⁴⁾. Other researchers also showed that Fetuin-A may represent a novel risk marker for T2D in non-diabetic populations⁽¹⁵⁻¹⁷⁾.

Meta-analysis done by Chaterina Sujana et al.,⁽¹⁸⁾ included a total of 3106 cases of T2D during a mean/median follow-up time of 2.7–14.3 years. suggests that higher fetuin-A levels increase the risk of T2D independently from subclinical inflammation, adiponectin and liver fat content.

Study done by Dutta et al.,⁽¹⁹⁾ in Eastern India suggested People with prediabetes in the highest fetuin-A quartile had the highest risk of progression to diabetes (relative risk 2.68, 95% CI 0.95–7.55; P = 0.06) and the lowest rate of reversion to normoglycaemia (relative risk 0.27, 95% CI 0.08–0.85; P = 0.03).

High fetuin-A levels in prediabetes were associated with a higher risk of progression to diabetes. Though fetuin A has been widely studied and related to diabetes progression, further prospective studies in large population are needed to understand its significance and to depict cutoffs in prediabetes population.

FABP4

Fatty acid binding protein 4 (FABP4), an intracellular lipid chaperone, is secreted from adipocytes (during lipolysis) and macrophages. FABP4 has been shown to contribute to the development of insulin resistance, type 2 diabetes mellitus, atherosclerosis, hypertension⁽²⁰⁾. Various studies showed that levels of FABP4 significantly correlated with increase in body mass index, insulin resistance, plasma insulin and glucose levels⁽²¹⁾. However its exact role in the pathogenesis of T2DM is unclear. Fabkin, the hormonal complex of FABP4 with ADK (Adenosine Kinase) and NDPK

(Nucleoside Diphosphate Kinase) is suggested in the pathogenesis of T2DM⁽²²⁾. (Figure 2) This complex act mainly by: i) inhibition of Glucose-Stimulated Insulin Signalling (GSIS) by decreasing ADP/ATP ratio ii) regulating intracellular calcium dynamics, and iii) by increasing Endoplasmic Reticulum (ER) stress⁽²²⁾.

Previous studies have demonstrated association between serum FABP4 levels and various cardiometabolic risk factors⁽²³⁾. In a case cohort study ,within the sample of EPIC-POSTDAM study higher plasma FABP4 concentrations were associated with a higher risk of incident T2D⁽²⁴⁾ which was statistically significant. In a 10-year prospective study, done in a Chinese cohort of 322 prediabetes,⁽²⁵⁾ the serum FABP4 level was predictive of the progression to type 2 diabetes, independent of the influence of conventional risk factors of type 2 diabetes (RR-1.87[1.12–3.15](P-0.018). In a recently done retrospective cohort study in China among 398 prediabetes patients,⁽²⁶⁾ baseline FABP4 concentrations were higher in participants with AGM than in those with NGT, and the baseline level of FABP4 positively correlated with age, BMI, WC, 2hBG, TG, TC and LDL at the 2-year follow-up. Furthermore, they found that high baseline FABP4 [OR 0.960, 95% CI (0.928–0.993)] was associated with decreased reversion from prediabetes to NGT(26). There is a need for further prospective studies in our population, in evaluating the role of this potential biomarker.

Galectin

Galectin-3, encoded by LGALS3 gene, is a member of α -galactoside-binding lectin family⁽²⁸⁾. Human Galectin-3 is a 26 kDa size lectin, it mainly has a C-terminal carbohydrate recognition binding domain (CRD) and N-terminal domain⁽²⁹⁻³¹⁾. Recent evidence has shown that levels of circulating Galectin-3 are elevated in chronic inflammatory diseases including obesity, diabetes and its complications, suggesting that Galectin-3 is related to those disease states⁽³²⁾.

Galectin-3 contributes to pathogenesis of T2D by disturbing the insulin signalling pathway. Atalar et al.⁽³³⁾ in a cross-sectional study of 41 controls,

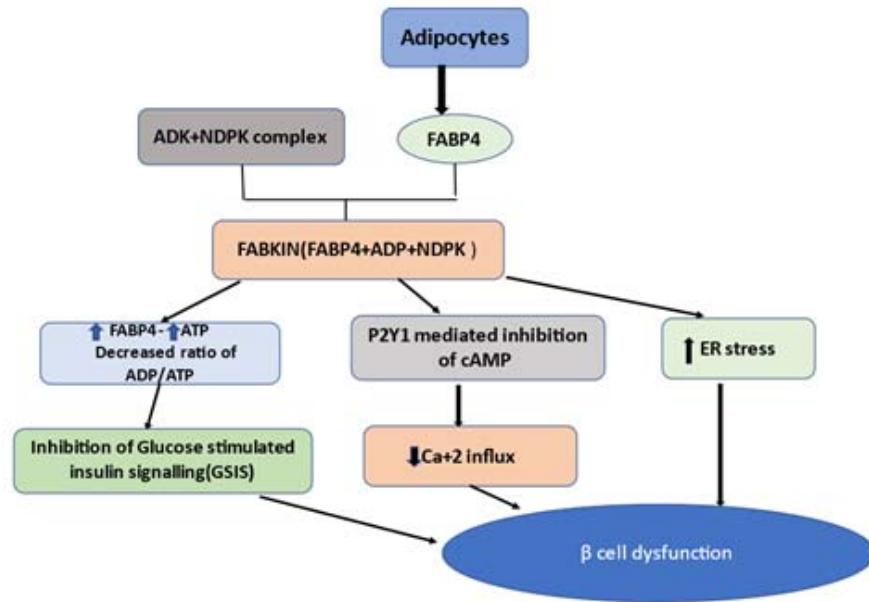


Figure 2: depicting action of FABP4 and FABKIN complex. Abbreviations: FABP4: Fatty acid binding protein 4, ADK: Adenosine Kinase, NDPK: Nucleoside Diphosphate Kinase, GSIS: Glucose stimulated insulin secretion, ER: Endoplasmic Reticulum, cAMP: Cyclic AMP

34 prediabetes, 84 T2D patients suggested that Galectin-3 was increased in T2D and had a positive correlation with FPG and HbA1c, as well as hs-CRP. In a study done by Nabila et al⁽³⁴⁾ where T2DM and their first degree relatives (FDR) were included, In FDR, mean Gal3 levels increased stepwise with worsening glucose tolerance - normal (7.6ng/ml); prediabetes (8.1ng/ml) and diabetes (9.1 ng/ml) and subjects with HOMA-IR > 2 had significantly higher mean Gal 3 than subjects with HOMA-IR < 2 (10.2 vs. 9.3 ng/ml). Further, prospective studies in large cohorts are needed to confirm these findings.

Ferritin

Ferritin is an intracellular protein that stores and releases iron. High serum ferritin has been associated with increased risk of prediabetes and diabetes.^(35,36) Iron contributes to insulin resistance by increasing production of free radicals, damaging DNA causing α -cell oxidative stress resulting in decreased insulin secretory capacity⁽³⁷⁾. It also interferes with glucose uptake in skeletal muscles and adipocytes⁽³⁷⁾. In addition to production of reactive oxygen species, iron also causes hepatic dysfunction, and α -cell apoptosis IR. In Kuopio Ischemic Heart Disease

Risk Factor Study⁽³⁸⁾ after multivariable adjustments, a weak and direct association was observed between serum ferritin quartiles and HOMA-IR in normoglycaemia (P -trend = 0.001) but a direct association in prediabetes (P -trend = 0.007) and in T2D (P -trend = 0.078)⁽³⁹⁾. The threshold levels of ferritin that correlate with IR may vary with sex and age⁽⁴⁰⁾.

Inflammatory biomarkers

There is increasing evidence suggesting the role of inflammation in the development of type 2 diabetes mellitus (DM)⁽⁴¹⁻⁴³⁾. Previous studies reported inflammatory markers to associate with the risk of type 2 DM.

CRP

C-Reactive Protein (CRP), a sensitive marker of systemic inflammation, has been shown to be increased in patients with type 2 diabetes mellitus. CRP is primarily derived from IL-6 dependent hepatic biosynthesis and is an acute phase reactant. A meta-analysis of 22 prospective studies suggests a significant association of elevated levels of CRP with type 2 diabetes risk and the overall RR of type 2 diabetes was 1.26 (95% CI 1.16–1.37; P = 0.000) per 1 log mg/L increment in CRP

levels⁽⁴⁴⁾. In the Gutenberg Health Study⁽⁴⁵⁾ a prospective cohort study that included 15,010 adults, 1,425 of whom had prediabetes and 1,299 had diabetes CRP was shown to increase incrementally from normoglycemia to prediabetes (1.4 vs. 2.3 mg/L), a small increase was observed between subjects with prediabetes and diabetes (2.3 vs. 2.4 mg/L), suggesting that early immune activation plays a role in the onset of diabetes.

Adiponectin

Adiponectin, a 30-kDa complement C1-related protein, is the most abundant protein expressed in adipose tissue, and it plays a crucial role in the regulation of insulin sensitivity⁽⁴⁶⁾. Previous studies showed that adiponectin improves insulin sensitivity by stimulating glucose utilization and fatty acid oxidation in the skeletal muscle and liver through AMP-activated protein kinase⁽⁴⁷⁾. Lower adiponectin levels are associated with obesity and negatively correlated with insulin resistance⁽⁴⁸⁾. A meta-analysis of 14,598 participants and 2,623 incident T2DM cases showed that lower adiponectin levels were associated with a higher incidence of insulin resistance and type 2 diabetes in humans.⁽⁴⁹⁾ In a large prospective study⁽⁵⁰⁾ among Japanese population which included prediabetes also, baseline serum adiponectin concentrations were inversely associated with risk of type 2 diabetes during 3 years. This association persisted even after adjusting for conventional risk factors of type 2 diabetes (age, sex, family history of diabetes, smoking, alcohol drinking, physical activity, BMI). Higher adiponectin levels at baseline⁽⁵¹⁾ were significantly associated with lower risk of type 2 diabetes.

IL-6

IL-6, a pleiotropic proinflammatory cytokine, is produced by a variety of cells, including activated leukocytes, endothelial cells, and adipocytes⁽⁵²⁾. IL-6 contributes to the pathophysiology of type 2 diabetes by interacting with insulin-signalling pathways and α -cell function⁽⁵³⁾. In addition, IL-6 also stimulates production of CRP⁽⁵⁴⁾. In a meta-analysis including 10 prospective studies⁽⁵⁵⁾, the overall RR of type 2 diabetes was 1.31 (95% CI

1.17–1.46; $P = 0.000$) per 1 log pg/mL increment in IL-6 levels.

ENRAGE

EN-RAGE, also known as S100A12 or Calgranulin C, is a calcium-binding proinflammatory protein which is mainly secreted by granulocytes. Binding of EN-RAGE with RAGE or TLR4, activates inflammatory pathways, including the NF- κ B pathway and JNK (c-Jun NH₂-terminal kinase) which are involved in the pathogenesis of insulin resistance and type 2 DM⁽⁵⁶⁾. A cross-sectional study in Italian population found that prediabetic patients exhibited lower RAGE plasma levels as well as increased levels of ENRAGE in both prediabetic and diabetic patients⁽⁵⁷⁾. Based on Rotterdam study higher EN-RAGE levels were associated with an increased risk of incident prediabetes, and T2DM. EN-RAGE was significantly associated with both HOMA-IR and HOMA-B⁽⁵⁸⁾, suggesting that proinflammatory EN-RAGE can lead to incident type 2 DM by causing chronic inflammation leading to insulin resistance as well as via B-cell dysfunction.

IL-13

Interleukin 13 (IL13) is a cytokine mainly produced by the T-helper (Th)-2 lymphocytes^(59,60). IL13 down-regulates the inflammatory diabetogenic pathways⁽⁶¹⁾. Stanya et al.⁽⁶²⁾ suggested that IL13 inhibits proinflammatory response in mice and regulates glucose homeostasis via the IL-13r α 1-STAT3 signalling pathway in the liver, and that this pathway might provide a therapeutic target for glycemic control in type 2 DM. IL13 was also associated with HOMA-IR and HOMA-B suggesting a protective role against insulin resistance and B-cell dysfunction⁽⁵⁸⁾.

IL-17A

IL17A was produced mainly in T cells. The role of IL17 on the risk for type 2 DM remains unclear. Somarac et al⁽⁶⁴⁾ found that therapeutic improvement of glycemic status in newly diagnosed type 2 DM patients is associated with a reduction of IL-17 levels. Roohi A et al⁽⁴³⁾ reported no significant association between serum IL17 and

T2DM. Rotterdam study⁽⁵⁸⁾ suggests a protective role of IL17 cytokine against the risk for type 2 DM (HR = 0.76).The exact role of IL-17A should be further studied.

IL-18

IL-18 is a cytokine belonging to IL-1 superfamily⁽⁶⁵⁾.In vivo studies showed elevated IL-18 levels in response to acute hyperglycemia in healthy volunteers and subjects with impaired glucose tolerance⁽⁶⁶⁾.Patients with newly diagnosed T2D have been shown to have a significantly higher IL-18 levels when compared to non-diabetic subjects.^(67,68). Increased IL-18 levels are shown to be predictive of the risk of prediabetes⁽⁵⁸⁾and T2D^(58,69) independent of other markers of chronic inflammation . Increased IL-18 significantly correlated with progression of prediabetes to diabetes⁽⁷⁰⁾.

IL-1RA

IL-1RA is an anti-inflammatory cytokine that acts by inhibiting the effect of the proinflammatory IL-1 α , an important cytokine in the pathogenesis of type 2 diabetes due to its relation to insulin resistance and β -cell dysfunction.⁽⁷¹⁾ There was a continuous increase in IL-18 levels with worsening of glycemic control in the Gutenberg Health Study (45) suggesting the role of IL-1RA in predicting progression of prediabetes to T2DM.

Retinol Binding protein 4(RBP-4)

RBP4 is an adipokine, and multiple studies suggested that elevated serum RBP4 levels play a significant role in the development of metabolic diseases, including insulin resistance and type 2 diabetes⁽⁷²⁻⁷⁵⁾. Retinol-binding protein 4 (RBP4) is primarily a vitamin A transport protein⁽⁷⁶⁾. RBP4 is produced from hepatocytes and, to a lesser extent, from adipocytes and other cell types⁽⁷⁷⁾. RBP4 increased insulin resistance by inducing the hepatic expression of phosphoenolpyruvate kinase, suppressing muscle insulin signalling, activating antigen-presenting cells, and stimulating inflammatory state in adipose tissue⁽⁷⁸⁻⁸⁰⁾.Sun L et al., reported an association between higher circulating RBP4 levels and incident diabetes⁽⁸¹⁾.

In a prospective study conducted among 1,011 Chinese prediabetes participants a U-shaped association was noted between RBP4 and incident type 2 diabetes, with both higher and lower RBP4 levels being associated with a high risk for incident type 2 diabetes⁽⁸²⁾.

Metabolomic biomarkers

Novel metabolomic biomarkers can predict the incidence, or complications associated with T2DM usually with non-targeted metabolomic analyses⁽⁸³⁾. Various cross-sectional analyses have suggested associations of metabolite levels with insulin resistance, prediabetes and overt diabetes⁽⁸⁴⁻⁸⁶⁾. Branched chain aminoacids (BCAA) were associated with insulin resistance⁽⁸⁷⁾ and T2DM⁽⁸⁸⁾.A prospective study in Chinese prediabetes individuals⁽⁸⁸⁾ suggested that inosine, carvacrol and carnitine were all associated with increased risk of developing diabetes from prediabetes, and the associations were independent of conventional risk factors. Although these three metabolites have been well-studied, the mechanisms by which they cause increased diabetes risk is not clear. In the above study the levels of amino acids phenylalanine and tyrosine were decreased in diabetes group compared with the prediabetes group. Besides, the BCAA valine was increased and isoleucine was decreased in diabetes group based on the univariate analysis⁽⁸⁸⁾. Phenylalanyl phenylalanine, was significantly up-regulated in diabetes group and was associated with an increased risk of diabetes⁽⁸⁸⁾. In the METSIM study⁽⁸⁹⁾ branch-chain amino acids (leucine, isoleucine) and aromatic amino acids (phenylalanine, tyrosine) were shown to be associated with increased risk of T2D and hyperglycemia, whereas glutamine was associated with decreased risk of T2D.

Micro RNAs

MicroRNAs are small, 20–25.nt long noncoding RNA molecules which binds to the 3' end of its target mRNAs and acts by inhibiting its translation, leading to reduced gene expression⁽⁸⁹⁾. Many studies have demonstrated that miRNAs are related to the occurrence and development of

T2DM. miR-375 and miR-9 were found to be increased in individuals with pre-diabetes and T2DM and positively correlated with blood glucose levels⁽⁹⁰⁾. miR-192 and miR-194 were also shown to be related to the development of T2DM.⁽⁹¹⁾ In a cross sectional study, by Yan LN et al.⁽⁹²⁾, which included individuals with prediabetes and T2DM four micro RNAs miR-148b, miR-223, miR-148b, and miR-148b were studied, miR-223 had the best diagnostic value, in discriminating prediabetes and T2DM.

Conclusion and future perspectives

Inspite of our advanced understanding of pathogenesis of prediabetes and the factors predicting progression, there has been continuous rise in incidence of diabetes. Early identification of individuals at risk⁽⁹³⁾ is important for initiating effective prevention strategies and delaying onset of disease. Conventional markers are inconclusive in predicting the progression of prediabetes to T2DM, which eventually leads to severe complications. Thus, there is a need for novel biomarkers which are more specific, noninvasive and accurate in predicting progression to T2DM. Many prediabetes biomarkers can also be used as potential therapeutic targets. The various biomarkers described in this review require further research to be clinically validated and useful. Further research can show if these novel biomarkers can replace conventional markers. There is a need for large prospective studies in prediabetes cohorts to understand the importance of these novel biomarkers. Various omics platforms—genomics, metabolomics, proteomics, and microbiomics—and RNA sequencing-based studies have now revolutionized biomarker development. Future efforts should be oriented to understand the relationship between various biomarkers with metabolic profile of these individuals and in development of a risk-stratifying tool. A risk stratifying model using biomarkers may represent a powerful asset that could help in reversing or preventing the progression of prediabetes to diabetes.

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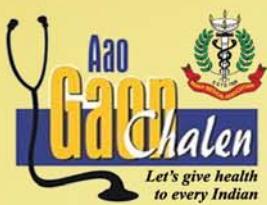


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