A Comprehensive Review on Hypothyroidism: Pathophysiology, Diagnosis, Management and Complications

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ABSTRACT:
Hypothyroidism is a common endocrine disorder characterized by deficient production of thyroid hormones, leading to widespread metabolic and physiological disturbances. Thyroid hormones—primarily T_3 and T_4-play a crucial role in regulating growth, metabolism, cardiovascular function, neurological activity, and gastrointestinal motility. This review provides a comprehensive understanding of thyroid hormone synthesis, metabolism, transport, and physiological actions, followed by an in-depth discussion of hypothyroidism, including its types, causes, risk factors, clinical manifestations, and diagnostic criteria. Primary hypothyroidism arises from intrinsic thyroid gland dysfunction, whereas secondary hypothyroidism results from inadequate stimulation of the thyroid gland due to pituitary or hypothalamic defects. The review further summarizes the therapeutic strategies such as levothyroxine replacement therapy, management of associated pituitary deficiencies, and monitoring approaches. Additionally, the systemic complications of hypothyroidism—especially cardiovascular, metabolic, gastrointestinal, and pediatric implications—are extensively outlined. This paper aims to consolidate current knowledge and provide an updated, clear, and clinically relevant overview of hypothyroidism for healthcare professionals and learners.

KEY WORDS: Hypothyroidism, Thyroid Hormone, T3 and T4 Metabolism, Anti-Hypothyroid Drugs, Endocrine Disorder, Complications of Hypothyroidism, T3 and T4 Metabolism

INTRODUCTION [1-4]:

- **Hormone-**

Hormones are chemical messengers produced by glands in the body that travel through the bloodstream to regulate various functions. They control and coordinate processes like growth, metabolism, reproduction, and mood, affecting cells and organs throughout the body. Examples include insulin, which regulates blood sugar, and Estrogen which is a key reproductive hormone.

Various types of Hormones-

- Estrogen
- Insulin
- Thyroid Hormones
- Cortisol
- Growth Hormone
- Testosterone
- Progesterone
- Adrenaline

Thyroid

Thyroid refers to a butterfly-shaped endocrine gland at the base of the neck that produces hormones regulating your body's metabolism, growth, and temperature.

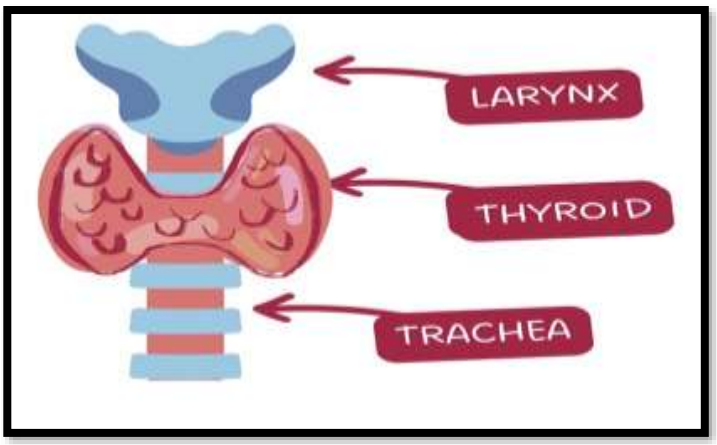


Fig.No-01 Thyroid

Thyroid Hormone-

Thyroid hormone is the hormone that's mainly responsible for controlling the speed of your body's Metabolism In infants, thyroid hormone is critical for brain development. Thyroid is a small, butterfly-shaped gland located at the front neck under skin, makes and releases thyroid hormone. It's a part of Endocrine System

There are types of Thyroid Hormone

1. T_3
2. T_4
3. TSH

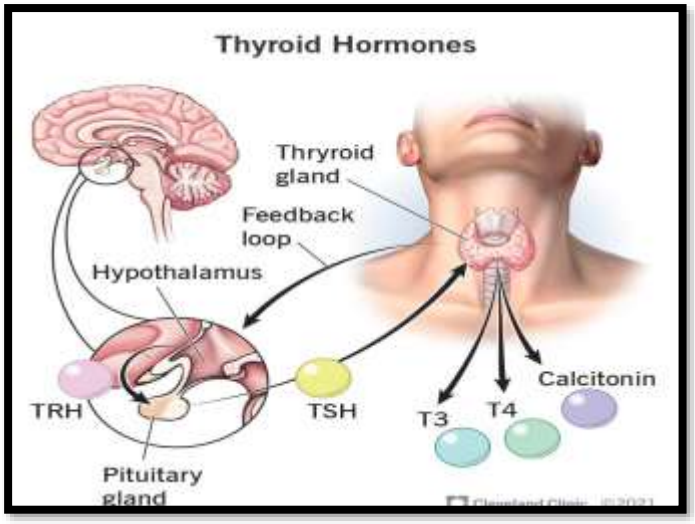


Fig No 02– Thyroid Hormone

1. **T_3 (triiodothyronine)**
   Thyroid gland produces tri-iodothyronine (T3) which is the active thyroid hormone. It is involved in most of the physiological processes in the body like growth, metabolism and heart rate. T3 is released quickly due to its lesser affinity for plasma proteins and its effect is faster than thyroxine (T4).

- **Metabolism-**

T3 is the biologically active thyroid hormone. Although some T3 is secreted directly by the thyroid gland, most of it actually comes from peripheral conversion of T4 (thyroxine). Its metabolism includes production, transport, and intracellular metabolism

1. Production of T_3

A. Direct secretion from the thyroid

A. The thyroid gland secretes ~20% of circulating T3.
B. T3 secretion is regulated by TSH (thyroid-stimulating hormone).

B. Peripheral conversion from T4

C. About 80% of circulating T3 is generated in tissues through deiodination of T4 via deiodinase enzymes:

Deiodinase	Location	Function
Type 1 (D1)	Liver, kidney, thyroid	Converts T4 → T3 (major source of plasma T3)
Type 2 (D2)	Brain, pituitary, brown fat, skeletal muscle	Converts T4 → T3 locally for cellular use
Type 3 (D3)	Brain, skin, placenta, fetal tissues	Inactivates T4 → rT3 and T3 → T2

2. Transport in the Blood

T3 is mostly bound to transport proteins:

Transport Protein	% of Binding
TBG (thyroxine-binding globulin)	~70%
Transthyretin (TTR)	~20%
Albumin	~10%

Only 0.3% of T3 is free, and free T3 is the biologically active fraction

- **Intracellular Metabolism**

Inside cells, T3 can be:

A. Activated

Not applicable—T3 is already the active form (activation applies mainly to T4).

B. Inactivated

Primarily via D3 deiodinase:

- T3 → T2 (inactive)

Storage:

1. **Most T_3 is produced** outside **the Thyroid**

- About 80–90% of circulating T_3 is formed in peripheral tissues (like liver, kidney) by deiodination of T_4.
- Because of this, the body does not store T_3 significantly in the gland.

2. **Binding in Blood**

In circulation, T_3 is loosely bound to proteins:

- Thyroxine-binding globulin (TBG)
- Transthyretin
- Albumin

2. T_4 (thyroxine)

Thyroid gland produces thyroxine (T4) in the body by the regulation of hypothalamus and the pituitary gland. Thyroxine (T4) must be converted to triiodothyronine (T3) to become active by either

type 1 (D1) or type 2 (D2) deiodinase enzyme. Iodine is the major constituent that is required for the formation of thyroxine. To synthesize
normal amount of thyroxine iodide is needed from the ingested iodine.

- **Metabolism-**
  T_4 is the major hormone produced by the thyroid gland, but it is biologically less active. Its metabolism converts it into active or inactive forms.

1. Deiodination (Most Important Pathway)

About 80–90% of T_4 metabolism occurs via deiodination in peripheral tissues (liver, kidney, muscle, and brain).
There are three types of deiodinase enzymes:

A. Type I (D1)
- Found in: liver, kidney, thyroid
- Converts:
  - $T_4 \rightarrow T_3$ (active)
  - $T_4 \rightarrow rT_3$ (reverse T_3, inactive)
- Provides major circulating T_3.

B. Type II (D2)
- Found in: brain, pituitary, brown fat, skeletal muscle
- Converts:
  - $T_4 \rightarrow T_3$ inside cells (local activation)
- Important for maintaining brain and pituitary T_3 levels (feedback regulation).

C. Type III (D3)
- Found in: placenta, brain, fetal tissues
- Converts:
  - $T_4 \rightarrow rT_3$ (inactive)
  - $T_3 \rightarrow T_2$ (inactive)
- Main inactivation pathway of thyroid hormones.

2. Minor Metabolic Pathways

Oxidative deamination
- Produces inactive metabolites

Decarboxylation
- Further inactivates thyroid hormones

Transport of T_4 in the Blood

Protein-Bound Transport (≈99.97%)

A. Thyroxine-Binding Globulin (TBG)
- Most important & highest-affinity carrier
- Carries ~70–75% of circulating T_4
- Strong binding → slow release → acts as a hormone reservoir

B. Transthyretin (TTR) / Thyroxine-Binding Prealbumin
- Carries ~15–20% of T_4
- Lower affinity than TBG but higher than albumin

- When the thyroid gland doesn't produce the right amount of hormones, it can lead to various conditions, such as:
  1. **Hyperthyroidism**: When the gland makes too much hormone.
  2. **Hypothyroidism**: When the gland doesn't make enough hormone.

3. **Goiter** : An enlargement of the thyroid gland.
4. **Thyroid nodules**: Lumps on the gland.
5. **Thyroiditis**: Inflammation of the thyroid.
6. **Thyroid Cancer**: Cancer that develops in the thyroid gland.

Hypothyroidism- [5-7]

Definition- Thyroid hormone shortage is a frequent medical disease known as hypothyroidism. It can have major negative health repercussions and eventually result in death if left untreated. The definition of hypothyroidism is mostly biochemical because to the wide range of clinical presentation and general lack of symptom specificity.

Symptoms of Hypothyroidism:

- Enlarged thyroid gland
- Weight gain
- Slowness of speech and movement
- Dry skin
- Coarse and brittle hair
- Pallor or jaundice
- Dull facial expressions
- Bradycardia
- Pericardial effusion
- Muscle weakness.
- Memory problems
- Prolonged ankle reflex relaxation time

Causes of Hypothyroidism

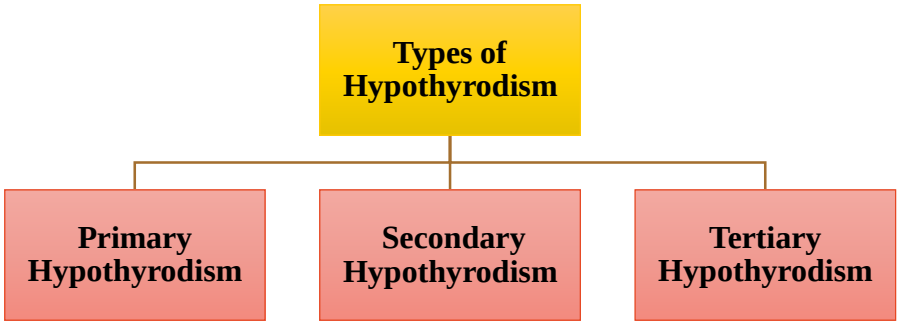
- Thyroid Destruction
- Autoimmune Disease
- Thyroiditis
- Pituitary Disorder

Risk factors

- Autoimmune diseases (e.g., Type I Diabetes)
- Family History of Thyroid Disorder
- Iodine Deficiency
- Certain Medication.
- Genetic Disorder
- Pituitary Disease
- Previous thyroiditis
- Smoking

Fig No. 03 Hypothyroidism

Types of Hypothyroidism-[4,5,6]



1. Primary Hypothyroidism[8-10]

Primary hypothyroidism is a condition where the thyroid gland itself fails to produce adequate T_4 and T_3, despite normal or high TSH from the pituitary.

- **Causes-**

Autoimmune
- Hashimoto's thyroiditis (most common)
- Postpartum thyroiditis
- Silent/painless thyroiditis

Iodine-related
- Iodine deficiency
- Excess iodine

Treatment-related
- Thyroidectomy (surgery)
- Radioactive iodine therapy (RAI)
- External radiation to neck (cancer treatments)

- **Symptoms-**

General
- Fatigue, weakness
- Weight gain (mild)
- Cold intolerance
- Dry, coarse skin
- Hair loss

Cardiovascular
- Bradycardia
- Diastolic hypertension
- Hypercholesterolemia

Neurological

- Slow speech
- Depression
- Memory impairment
- Carpal tunnel syndrome

GI

- Constipation

Reproductive

- Menorrhagia
- Irregular periods
- Infertility

Risk Factor-

- Female sex
- Increasing age
- Family history of thyroid disease
- Other autoimmune diseases
- Iodine deficiency
- Prior neck surgery or radiation
- Postpartum period
- Use of lithium
- Genetic syndromes (Down, Turner)

Diagnosis

Blood Tests

1. TSH (most sensitive)
    - ↑ High in primary hypothyroidism
2. Free T_4
    - Low
3. Anti-TPO antibodies
    - Positive in Hashimoto's
4. Lipid profile
    - ↑ cholesterol, ↑ LDL

Treatment

A. First-Line Treatment

- **Levothyroxine (T_4)**
    - Drug of choice
    - Once daily, empty stomach
    - Dose:
        1. Typical adult: 1.6 mcg/kg/day
        2. Elderly/cardiac patients: start low (25–50 mcg/day)
- **Monitoring**
        1. Check TSH every 6–8 weeks
        2. Adjust dose to keep TSH in normal range

B. Special Situations

3. Pregnancy
    1. Increase levothyroxine dose by 30–50%

2. Keep TSH lower (<2.5 mIU/L)
- Myxoedema Coma
  1. IV Levothyroxine
  2. IV Hydrocortisone
  3. Supportive Measure

Drugs-

- Levothyroxine (T_4)
- Liothyronine (T_3)
- Combination therapy (T_4 + T_3)
- IV Levothyroxine
- Liotrix

Levothyroxine Drug Pharmacology

1. Classification

- Synthetic **thyroxine (T4)** hormone analog.

2. **Mechanism of Action**

- Levothyroxine is **converted to T3** (active form) in peripheral tissues by **deiodinases**.
- T3 binds to **nuclear thyroid hormone receptors**, leading to:
  - Increased basal metabolic rate
  - Increased protein synthesis
  - Normalization of growth & neurological development
  - Regulation of cardiovascular, respiratory, and GI functions

3. Pharmacokinetics

Absorption

- Oral bioavailability: **60–80%**
- Best absorbed in **empty stomach** (30–60 min before breakfast)
- Absorption decreases with:
  - Food
  - Calcium, iron supplements
  - Antacids (aluminum, magnesium)
  - Proton pump inhibitors
  - Coffee
  - Cholestyramine

Distribution

- Highly protein-bound:
  - **Thyroxine-binding globulin (TBG)**
  - Transthyretin
  - Albumin

Metabolism

- Converted to T3 by **D1 and D2 deiodinases**
- Degraded in liver, kidney, and other tissues

Half-life

- **~7 days** (allows once-daily dosing)
- Longer in hypothyroidism
- Shorter in hyperthyroidism

Excretion

- Mostly in urine, some in bile

4. Indications

- **Primary hypothyroidism** (most common use)
- Secondary & tertiary hypothyroidism
- Goiter
- Myxedema coma (IV form)
- TSH suppression in thyroid cancer patients

5. Dosage

- Start low and titrate based on **TSH levels** (every 6–8 weeks).

Typical doses:

- Adults: **1.6 µg/kg/day**
- Elderly or cardiac disease: **12.5–25 µg/day initially**
- Myxedema coma: **IV 200–400 µg loading**, then maintenance

6. Adverse Effects

Usually due to **overdose** → hyperthyroid symptoms:

- Palpitations, tachycardia
- Tremors
- Heat intolerance
- Nervousness
- Weight loss
- Osteoporosis (long-term high dose)
- Atrial fibrillation
- Insomnia

7. Drug Interactions

Decreased absorption

- Calcium & iron supplements
- Sucralfate
- Proton pump inhibitors
- Antacids
- Cholestyramine
- Soy products
- Coffee

Increased metabolism

- Carbamazepine, phenytoin
- Rifampicin

Increased TBG levels (require higher dose)

- Pregnancy
- Oral contraceptives
- Estrogen therapy

Decreased TBG (lower dose needed)

- Androgens
- Glucocorticoids

8. Contraindications

- Untreated **adrenal insufficiency**
- Acute myocardial infarction
- Thyrotoxicosis

2. Secondary Hypothyroidism [11-13]

The underactive thyroid disease known as secondary hypothyroidism occurs when the thyroid is operating correctly but isn't getting the right signals from the hypothalamus or pituitary gland. This happens as a result of insufficient thyroid hormone production caused by the pituitary gland's inability to create enough thyroid-stimulating hormone (TSH).

Causes of Secondary Hypothyroidism

- Pituitary adenoma (non-functioning tumour)
- Pituitary surgery
- Radiation to pituitary/hypothalamus
- Pituitary infarction
- Head trauma causing pituitary damage
- Genetic defects (e.g., PIT1, PROP1 mutations)
- Pituitary infections (bacterial, fungal)
- Post-radiotherapy for brain tumours

Symptoms

- Fatigue, lethargy
- Weight gain
- Cold intolerance
- Dry skin and hair
- Constipation
- Bradycardia
- Puffy face
- Hoarse voice
- Muscle cramps
- Depression

Risk Factor

- History of pituitary tumour
- Previous cranial or pituitary surgery
- Cranial irradiation
- Major head trauma
- Long-term steroid therapy
- Family history of pituitary diseases
- Infiltrative systemic disease (e.g., sarcoidosis)

Diagnosis [14,15]

1. Laboratory Investigations

A. Thyroid Function Tests (TFTs)

- ↓ Free T4 (FT4) — *low or low-normal*
- ↓ or inappropriately normal TSH (TSH is not elevated despite low thyroid hormone → hallmark of secondary hypothyroidism)

B. Additional Hormonal Tests

Because pituitary failure often affects multiple hormones:

- ↓ ACTH and cortisol (check adrenal function before giving thyroid hormone)
- ↓ LH, FSH – may show hypogonadism
- ↓ GH, IGF-1
- ↓ Prolactin (or ↑ in case of pituitary adenoma)
- Other pituitary hormones as indicated

Treatment[15,17,18]

A. Levothyroxine (T4) – Drug of Choice

- Start Levothyroxine 1.6 mcg/kg/day (adjust as needed)
- Start lower doses in elderly or cardiac patients.

B. Secondary hypothyroidism often occurs with

- ACTH deficiency → Hydrocortisone
- Gonadotropin deficiency → Sex steroid replacement (E2/Progesterone or Testosterone)
- GH deficiency → Growth hormone therapy
- Prolactin deficiency → No specific treatment required

Drugs-

A. Thyroid Hormone Replacement

- Levothyroxine (T4) – *Drug of choice*
- Liothyronine (T3) – rarely used
- Combination T4 + T3 – not routinely recommended

B. Drugs Used to Treat Underlying Pituitary Causes

Glucocorticoids (Hydrocortisone, Prednisolone, Dexamethasone)

C. Hormone Replacement for Associated Pituitary Deficiencies

- Hydrocortisone (for secondary adrenal insufficiency)
- Prednisolone
- Fludrocortisone (rarely needed in secondary causes)
- Estrogen + Progesterone (for females with hypogonadism)
- Testosterone (for males with hypogonadism)
- Growth Hormone (Somatropin) for GH deficiency
- Desmopressin (DDAVP)

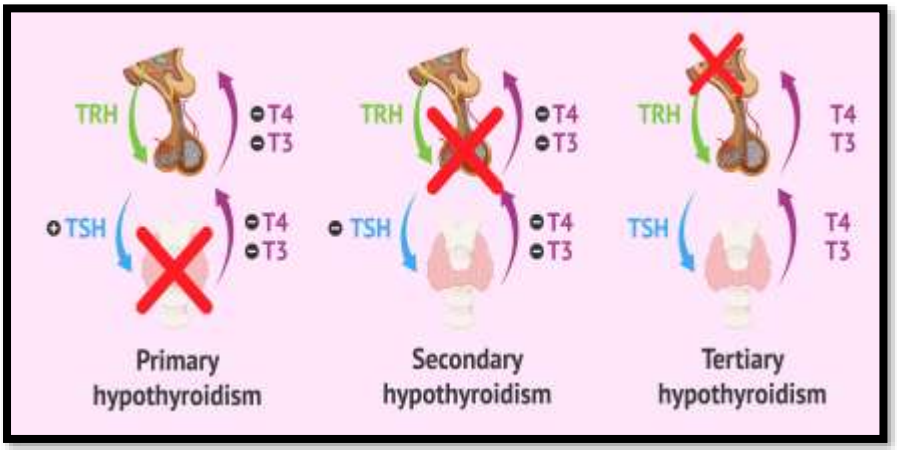


Fig.No.04 Differences between types of Hypothyroidism

Pharmacology of Secondary Hypothyroidism Drugs

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Decreased TBG (lower dose needed)

- Androgens
- Glucocorticoids

8. Contraindications

- Untreated **adrenal insufficiency**
- Acute myocardial infarction
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Complications [19-22]

1. Cardiovascular Complications

Hypothyroidism significantly affects the cardiovascular system due to reduced metabolic activity and diminished sympathetic stimulation. The heart rate becomes slow (bradycardia) as thyroid hormones normally increase chronotropy and inotropy. Cardiac output falls because of decreased stroke volume and impaired myocardial contractility. Peripheral vascular resistance increases, leading to diastolic hypertension and reduced blood flow to tissues. Patients often develop hyperlipidemia especially elevated LDL and triglycerides—due to decreased lipid metabolism, which accelerates atherosclerosis and increases the risk of coronary artery disease.

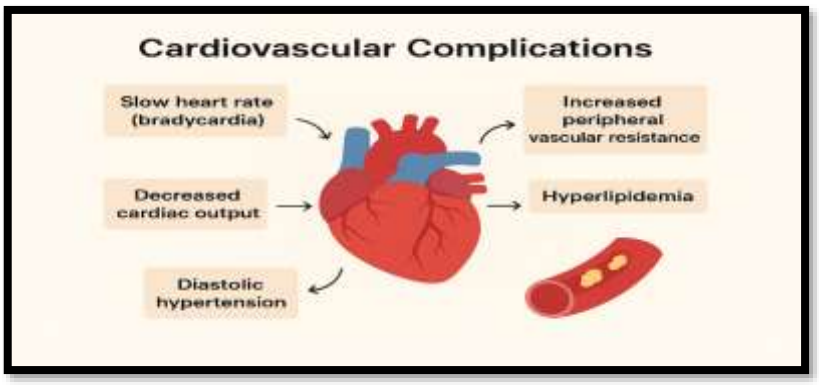

Fig.No.05. Cardiovascular Complications

2. Metabolic Complications

Hypothyroidism leads to several metabolic complications due to the reduced basal metabolic rate and impaired function of metabolic pathways regulated by thyroid hormones. Patients commonly develop weight gain because of decreased energy expenditure and accumulation of fat and fluid. Hyperlipidemia is a major complication, especially elevated LDL cholesterol and triglycerides, due to reduced LDL receptor activity and slowed lipid clearance, increasing cardiovascular risk.

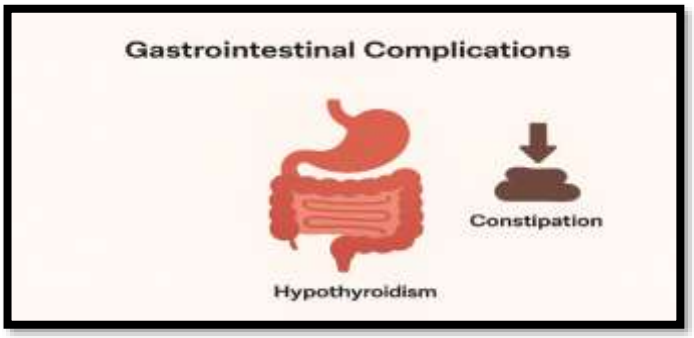

Fig.No.06. Metabolic Complications

3. Gastrointestinal Complications

Hypothyroidism significantly slows down the metabolic and gastrointestinal motility due to reduced thyroid hormone activity. This leads to constipation, which is the most common GI complaint, caused by decreased peristalsis and prolonged intestinal transit time. Patients may also experience abdominal bloating, discomfort, and flatulence. In severe cases, the slowed gut motility may progress to severe constipation, fecal impaction, or even paralytic ileus, especially in long-standing or untreated hypothyroidism

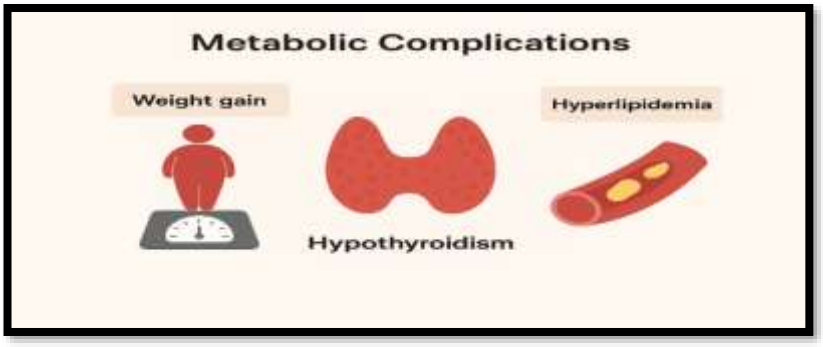

Fig.No.07. Gastrointestinal Complications

4. Complications in Children [23,24]

Hypothyroidism in children can lead to significant health complications if not diagnosed and treated early. One of the most serious consequences is impaired growth, as low thyroid hormone levels slow bone development and can result in short stature. Cognitive development may also be affected, leading to learning difficulties, poor school performance, and delayed milestones.

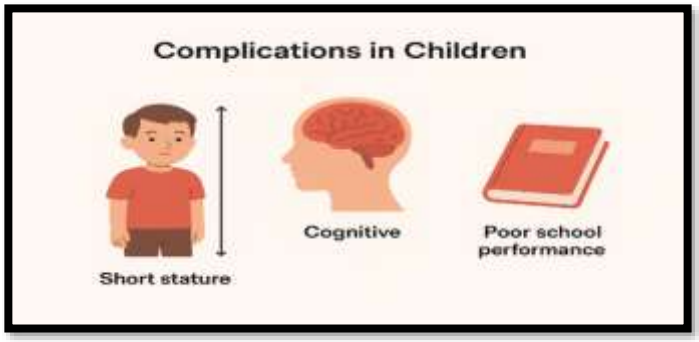

Fig.No.08 Complications in children's

REVIEW SUMMARY

This comprehensive review provides an in-depth overview of hypothyroidism, one of the most common endocrine disorders characterized by deficient production of thyroid hormones (T_3 and T_4). It begins by explaining the physiology of thyroid hormones, including their synthesis, metabolism, transport, and role in regulating metabolism, growth, cardiovascular activity, neurological processes, and gastrointestinal function.

The paper discusses the pathophysiology of hypothyroidism, noting that reduced thyroid hormone levels slow metabolic processes throughout the body. Two major types are highlighted: **primary hypothyroidism**, resulting from intrinsic thyroid gland dysfunction, and **secondary hypothyroidism**, caused by inadequate stimulation of the thyroid gland due to pituitary or hypothalamic failure.

Primary hypothyroidism is commonly associated with autoimmune causes such as Hashimoto's thyroiditis, iodine imbalance, and treatment-related thyroid damage. Secondary hypothyroidism arises from pituitary tumour's, surgery, radiation, infarction, trauma, or genetic defects. The review outlines clinical manifestations including fatigue, weight gain, cold intolerance, bradycardia, constipation, depression, and reproductive disturbances. Risk factors, especially autoimmune diseases, age, radiation exposure, genetic syndromes, and pituitary disorders, are also summarized.

Diagnosis relies on thyroid function tests, with **elevated TSH and low free T_4 in primary**, and **low TSH with low T_4 in secondary hypothyroidism**. Additional endocrine evaluations are essential for central (secondary) cases.

Management primarily involves **levothyroxine (T_4) replacement therapy**, with detailed pharmacology, dosing, contraindications, and monitoring guidelines presented. Secondary hypothyroidism requires both thyroid hormone replacement and treatment of associated pituitary hormone deficiencies, such as hydrocortisone for ACTH deficiency or sex steroids for hypogonadism. The review also describes the systemic complications of untreated hypothyroidism. Cardiovascular complications include bradycardia, reduced cardiac output, diastolic hypertension, and hyperlipidaemia. Metabolic disturbances mainly involve weight gain and elevated LDL levels. Gastrointestinal effects include constipation and reduced motility. Pediatric hypothyroidism can result in severe growth retardation and impaired cognitive development.

Overall, the paper consolidates key aspects of the physiology, classification, diagnosis, treatment, and complications of hypothyroidism, offering a clear and clinically relevant reference for healthcare professionals

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