



# The Thyroid PUZZLE: Hormones, Disorders and Pharmaceutical Solutions

## Corresponding Authers:

01) Sanskar Yashwant Jagtap

Sarsam College of Pharmacy, Palshiwadi, Taluka-Baramati, Dist-Pune.

02) Krupesh Anil Kate

Sarsam College of Pharmacy, Palshiwadi, Taluka-Baramati, Dist-Pune.

03) Pramod Rajendra Kale

Sarsam College of Pharmacy, Palshiwadi, Taluka-Baramati, Dist-Pune.

## Guide Name:

Prof. Charushila Bhintade

M pharm pharmacology

## ABSTRACT

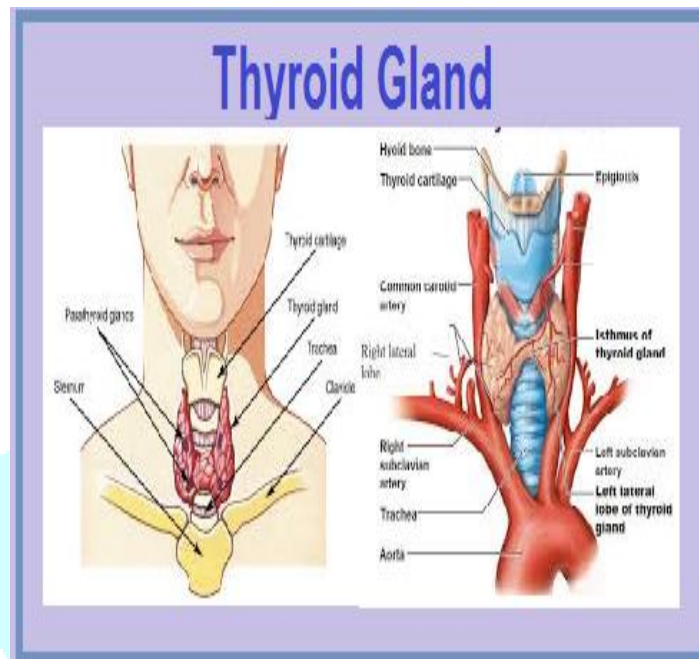
Thyroid conditions are common worldwide. In India too, there's a significant burden of thyroid conditions. According to a protuberance from colourful studies on thyroid complaint, it has been estimated that about 42 million people in India suffer from thyroid conditions. This review will concentrate on the epidemiology of five common thyroid conditions in India hypothyroidism, hyperthyroidism, thyroid cancer. (1) Endocrine diseases are common in India of which the thyroid diseases represent a major subset. Thyroid dysfunction frequencies is rising at an intimidating rate in Indian population. Hypothyroidism and hyperthyroidism constitute the maximum chance of thyroid conditions in India. Hormone relief remedy has been a standard approach to thyroid dysfunction. (2)

## Keywords: -

Hyperthyroidism, Hypothyroidism, Thyroid cancer, Endocrine, India.

## INTRODUCTION

The thyroid gland is a ductless endocrine gland positioned in the anterior/ frontal portion of the neck. It roughly resembles the shape of a butterfly. It's also one of the largest endocrine glands, importing an normal of 25 – 30 g. This gland has two lobes on either side of the trachea, with each lobe measuring 4 – 6 cm in length and 1.3 – 1.8 cm in range.(3)



**Fig:-Basic Anatomy of Thyroid Gland**

Fig-introductory deconstruction of Thyroid Gland The thyroid is an important part of the mortal endocrine system, which are responsible for regulation of oxygen use, rudimentary metabolic rate, cellular metabolism and growth and development. The thyroid gland secretes thyroxine( T4) and tri iodothyronine( T3), which are demanded for proper growth and development and which are primarily responsible for determining the rudimentary metabolic rate. The thyroid hormones are transported through the blood and act at the cellular position. Through the activation of genes, thyroid hormones stimulate protein conflation, promote development of nervous system, and increase the rate of cell respiration in apkins, therefore elevating the BMR. The variations in the situations of these hormones lead to disturbed BMR and presents with signs and symptoms which are systemic in nature. Thyroid complaint is one of the commonest endocrine diseases worldwide. According to a recent protuberance from colorful studies, it has been estimated that about 42 million people in India suffer from thyroid conditions. About 1 to 2 of the adult population is known to suffer from thyroid diseases.( 2). This review will also compactly cover the instigative work that's in progress to ascertain the normal reference range of thyroid hormones in India. Rather than being an total, in- depth review, this composition will bandy named studies from across the country and the counteraccusations and perspectives these studies bring forth, from an Indian environment.( 1)

### **HORMONES SECRETED BY THYROID GLAND:-**

Being a ductless gland the secretions of thyroid gland are directly secreted into the circulation. Secretion of thyroid gland is also known as thyroid hormones.

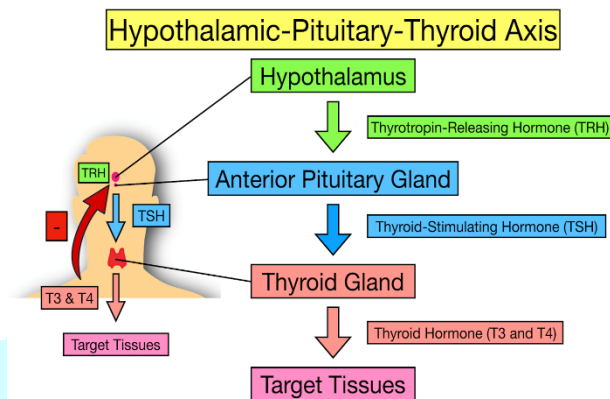
Thyroid Hormones are:-

- i. Thyroxine(T4).
- ii. Triiodothyronine(T3).
- iii. Calcitonin.

# SYNTHESIS, STORAGE AND RELEASE OF THYROID HORMONE:-

## SYNTHESIS:

conflation TSH is released into the blood and binds to the thyroid- releasing hormone receptor( TSH- R) on the basolateral aspect of the thyroid follicular cell. The TSH- R is a Gs- protein coupled receptor, and its activation leads to the activation of adenylyl cyclase and intracellular situations of cAMP. The increased cAMP activates protein kinase A( PKA). PKA phosphorylates different proteins to modify their functions. The five way of thyroid conflation are below :



- Synthesis of Thyroglobulin:** Thyrocytes in the thyroid follicles produce a protein called thyroglobulin( TG). TG doesn't contain any iodine, and it's a precursor protein stored in the lumen of follicles. It's produced in the rough endoplasmic reticulum. Golgi outfit pack it into the vesicles, and also it enters the follicular lumen through exocytosis
- Iodide uptake:** Protein kinase A phosphorylation causes increased exertion of basolateral Na- I- symporters, driven by Na- K- ATPase, to bring iodide from the rotation into the thyrocytes. Iodide also diffuses from the basolateral side to the apex of the cell, where it's transported into the colloid through the pendrin transporter.
- Iodination of thyroglobulin:** thyroglobulin Protein kinase A also phosphorylates and activates the enzyme thyroid peroxidase (TPO). TPO has three functions oxidation, organification, and coupling response.
  - Oxidation TPO uses hydrogen peroxide to oxidize iodide(I-) to iodine(I<sub>2</sub>). NADPH- oxidase, an apical enzyme, generates hydrogen peroxide for TPO.
  - Organification TPO links tyrosine remainders of thyroglobulin protein with I<sub>2</sub>. It generates monoiodotyrosin (MIT) and diiodotyrosine (DIT). MIT has a tyrosine residue with iodine, and DIT has tyrosine remainders with 2 motes of iodine.

Coupling response TPO combines iodinated tyrosine remainders to make triiodothyronine (T<sub>3</sub>) and tetraiodothyronine(T<sub>4</sub>). MIT and DIT join to form T<sub>3</sub>, and two DIT motes form T<sub>4</sub>.

## STORAGE:-

The thyroid hormones thyroxine( T<sub>4</sub>) and triiodothyronine( T<sub>3</sub>) are produced from thyroid follicular cells within the thyroid gland, a process regulated by the thyroid- stimulating hormone buried by the anterior pituitary gland. Thyroglobulin, thepre-cursor of T<sub>4</sub> and T<sub>3</sub>, is produced by the thyroid follicular cells before being buried and stored in the follicular lumen. Iodide is laboriously absorbed from the bloodstream by a process called iodide trapping. In this process, sodium isco-transported with iodide from the basolateral side of the membrane into the cell, and also

concentrated in the thyroid follicles to about thirty times its attention in the blood. Through a response with the enzyme thyroperoxidase, iodine is bound to tyrosine remainders in the thyroglobulin moles to form monoiodotyrosine( MIT) and diiodotyrosine( DIT). Linking two halves of DIT produces T4. Combining one flyspeck of MIT and one flyspeck of DIT produces T3.( 4)

## RELEASE:-

Thyroid hormones are released into the fenestrated capillary network by thyrocytes in the following steps:

1. Thyrocytes uptake iodinated thyroglobulin via endocytosis
2. Lysosome fuse with the endosome containing iodinated thyroglobulin
3. Proteolytic enzymes in the endolysosome cleave thyroglobulin into MIT, DIT, T3, and T4.
4. T3 (20%) and T4 (80%) are released into the fenestrated capillaries via MCT8 transporter.
5. Deiodinase enzymes remove iodine molecules from DIT and MIT. Iodine can be salvaged and redistributed to an intracellular iodide pool.(5)
6. Proteases digest iodinated thyroglobulin, releasing the hormones T4 and T3, the biologically-active agents central to metabolic regulation. T3 is identical to T4, but it has one less iodine atom per molecule.(4)

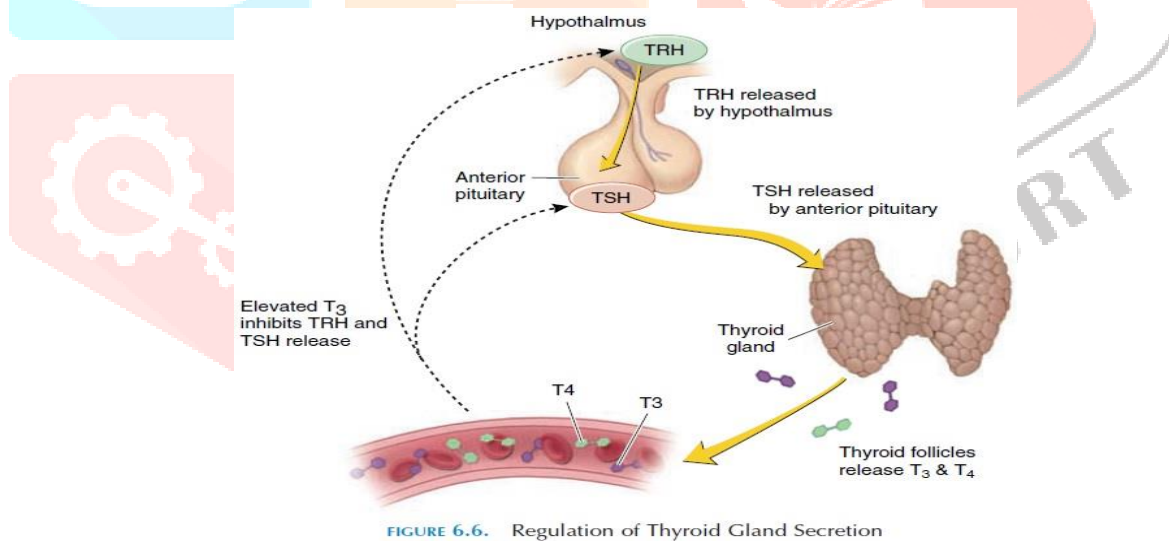


Fig: Release of hormones

## DISORDERS:

The disorders or diseases related to the thyroid gland arises due to dysfunctioning of the thyroid gland itself

Most common diseases can be enlisted as:

1. Hypothyroidism
2. Hyperthyroidism
3. Thyroid nodules

### 1.HYPOTHYROIDISM:-

Hypothyroidism refers to the common pathological condition of thyroid hormone deficiency. If untreated, it can lead to serious adverse health effects and ultimately death. Because of the large variation in clinical presentation and general absence of symptom specificity, the definition of hypothyroidism is pre-dominantly biochemical. Overt or clinical primary hypothyroidism is defined as thyroid-stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range.(6)

- Causes: Drugs such as amiodarone, thalidomide, oral tyrosine kinase inhibitors (sunitinib, imatinib) stavudine, interferon, bexarotene, perchlorate, rifampin, ethionamide, phenobarbital, phenytoin, carbamazepine, interleukin-2, and lithium,
- Thyroid radioactive iodine therapy
- Thyroid surgery
- Radiotherapy to head or neck area
- Central hypothyroidism from neoplastic, infiltrative, inflammatory, genetic, or iatrogenic disorders of the pituitary or hypothalamus.
- A new class of cancer medications such as anti-CTLA-4 and anti-PD-L1/PD-1 therapy has been associated with both primary and/or secondary hypothyroidism.(7)

All patients with overt hypothyroidism should be treated, but those with subclinical hypothyroidism do not always benefit from treatment, especially elderly patients and those with baseline TSH levels below 10 mU/L. Oral L-thyroxine is the treatment of choice because of its well-demonstrated efficacy, safety, and ease of use. (8)

### 2.HYPERTHYROIDISM:

The term "hyperthyroidism" defines a syndrome associated with excess thyroid hormone production. It is a common and hyperthyroidism are synonyms of one another. The term "thyrotoxicosis" refers to a state of excess thyroid hormone exposure to tissues. Although hyperthyroidism can lead to thyrotoxicosis and can be used interchangeably, it is important to note the difference between them.(9) The most common cause of hyperthyroidism is Graves disease, with a global prevalence of 2% in women and 0.5% in men. Other causes of hyperthyroidism and thyrotoxicosis include toxic nodules and the thyrotoxic phase of thyroiditis. Common symptoms of thyrotoxicosis include anxiety, insomnia,. palpitations, unintentional weight loss,diarrhea, and heat intolerance .(10)

### 3.THYROID NODULES:

- Thyroid nodules are most common in women and older populations
- The purpose of thyroid nodule evaluation is to determine which nodules are malignant or require surgical attention

Thyroid nodules have been defined by the American Thyroid Association (ATA) as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma."(11) Thyroid nodules can be caused by many disorders: benign (colloid nodule, Hashimoto's thyroiditis, simple or hemorrhagic cyst, follicular adenoma and subacute thyroiditis) and malignant (Papillary Cancer, Follicular Cancer, Hurthle Cell (oncocytic) Cancer, Anaplastic Cancer, Medullary Cancer, Thyroid Lymphoma and metastases –3 most common primaries are renal, lung & head-neck).(12)

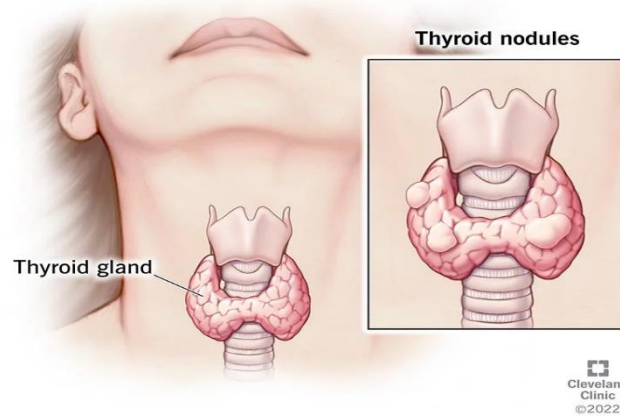


Most thyroid nodules don't cause symptoms. However, if you have several nodules or large nodules, you may be able to see them.

In rare cases, nodules can grow big enough to cause the following symptoms:

- Trouble with swallowing or breathing.
- Hoarseness or voice changes.
- Pain in the front of your neck.
- Enlargement of your thyroid gland (goiter).<sup>(13)</sup>

### Thyroid Nodules



Patients with Graves disease may have a diffusely enlarged thyroid gland, stare, or exophthalmos on examination. Patients with toxic nodules (ie, in which thyroid nodules develop autonomous function) may have symptoms from local compression of structures in the neck by the thyroid gland, such as dysphagia, orthopnea, or voice changes.<sup>(10)</sup>

### Pharmaceutical solutions:

1) Levothyroxine:-

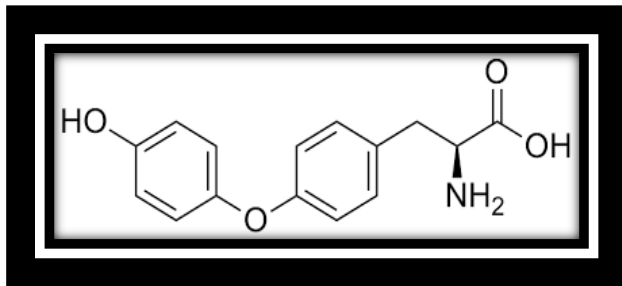


Levothyroxine is a synthetic T4 hormone that's biochemically and physiologically indistinguishable from the natural hormone

, and it's administered when the body is deficient in the natural hormone. Oral administration of levothyroxine is therefore indicated for acquired primary( thyroidal), secondary( pituitary) and tertiary( hypothalamic) hypothyroidism. It's also used to treat euthyroid goiters including thyroid nodes, subacute or habitual lymphocytic thyroiditis, multinodular goiter or for thyroid cancer cases who have experienced thyroidectomy, and as an adjunct to surgery and radioiodine remedy<sup>( 14)</sup>. The diurnal cure of LT4 is determined by the spare body mass, while age, the etiology of hypothyroidism, comorbidities, and other factors also ply goods. In general, cases are originally specified a cure of 1.6 to 1.8 µg/ kg body weight/ day and are tested for thyroid function every 6 to 8 weeks. Once thyroid hormones( THs) remain within the reference ranges, an periodic examination is recommended to cover thyroid function<sup>( 15)</sup>. Levothyroxine is substantially absorbed in the small intestine, more specifically through the duodenum, jejunum and ileum. veritably little is absorbed in the stomach. The bioavailability of levothyroxine is roughly 60 – 80 in euthyroid levies. It may be slightly advanced in hypothyroid and hyperthyroid cases, and is dropped in the presence

of food from 79 under dieted conditions to 64 under fed conditions for a 100 mcg cure. The immersion of levothyroxine appears to be told by gastric Ph( 14).

## 2)Liothyronine:-



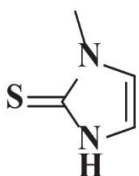
Liothyronine is the most fleetly effective thyroid hormone, a single cure giving maximum effect within 24 h and passing off over 24 – 48 h. It isn't routine treatment for hypothyroidism because its rapid-fire onset of effect can induce heart failure( 16). unforeseen pullout of L- T3 remedy isn't supported, as clinical need should come before fiscal considerations. For cases who are long established on L- T3 and are allowed to be stable, a change to L- T4 monotherapy shouldn't be enforced without careful discussion. In similar cases, change of treatment may affect in significant insecurity of thyroid status and potentially undesirable clinical issues, which may prove more precious than durability with L- T3 remedy. In cases with thyroid cancer, where L- T3 is being recommended in medication for radioiodine remedy or individual imaging, access to L- T3 is imperative and negotiation with L- T4 is unhappy( 17).

## 3)Propylthiouracil:-



Propylthiouracil is an anti-thyroid medicine used to manage Graves complaint and hyperthyroidism. This exertion will punctuate the medium of action, adverse event profile, and other crucial factors(e.g., dosing, pharmacodynamics, pharmacokinetics, monitoring, applicable relations) of propylthiouracil material for healthcare platoon members in the treatment of cases with hyperthyroidism and affiliated conditions( 18). Hyperthyroidism affects about 0.2-2.7% of all gravidity, and is generally treated with propylthiouracil( PTU). still, former studies about the goods of propylthiouracil on motherly or foetal are contentious. ideal This meta- analysis was carried out to probe the safety and efficacy of propylthiouracil during gestation( 19). Propylthiouracil inhibits the product of new thyroid hormone in the thyroid gland. It acts by inhibiting the enzyme thyroid peroxidase, which generally converts iodide to an iodine patch and incorporates the iodine patch into amino acid tyrosine. Hence, DIT( diiodotyrosine) or MIT( monoiodotyrosine) doesn't get produced, which are the main ingredients in the product of thyroxine( T4) and triiodothyronine( T3). Peripherally, it acts by inhibiting the conversion of T4 to T3. It affects the being thyroid hormones stored in the thyroid gland as well as those circulating in the blood.( 18)

## 4)Methimazole:-



### Methimazole (MET)

Methimazole, a thionamide drug, is pivotal in treating hyperthyroidism and affiliated conditions. This medicine has been the primary choice for oral remedy in treating hyperthyroidism. Hyperthyroidism is characterized by inordinate thyroid hormone product and poses substantial clinical challenges. Methimazole exerts its remedial effect by inhibiting thyroperoxidase, a pivotal enzyme in synthesizing thyroid hormones. This medium decreases the conflation of thyroid hormones, specifically thyroxine (T4) and triiodothyronine (T3), restoring normal thyroid function (20). Methimazole

use increased the odds of new-onset AP by 47 (OR1.47; 95 CI0.89 –2.43), but this association wasn't significant ( $p = 0.134$ ). This suggests that the use of methimazole might slightly increase the threat of AP. Because the substantiation for this association is limited, caution is advised for active interventions, and farther disquisition is justified (21). Methimazole is an antithyroid drug used to treat hyperthyroidism and is distributed within the thioamide medicine class. Methimazole primarily functions by inhibiting thyroid hormone product in the thyroid gland. The medicine disrupts the enzymatic process intermediated by thyroid peroxidase, which iodinates tyrosine remainders in thyroglobulin and prevents the conflation of both T4 and T3 thyroid hormones (20).

#### 5)Surgical Method:

Some croakers prefer surgical treatment of paediatric cases with Graves' complaint or cases with veritably large or nodular goitres. Implicit complications associated with surgical operation of Graves complaint include hyperparathyroidism and oral cord palsy in a small proportion of cases. Surgeons trained and endured in thyroid surgical procedures should perform this operation (22). Fine needle aspiration cytology is the dependence of the individual work-up of solitary thyroid nodes. Together with the case's history and the clinical findings, cytology determines the suggestion for surgery. The minimum intervention for a suspicious bump consists of thyroid lobectomy. However, also we recommend total thyroidectomy for all follicular lesions that are larger than 1.5 cm and for high-threat papillary tumours, If a opinion of malice is established. Near-total thyroidectomy may be applicable for low-threat cases with papillary melanoma in whom it isn't intended to use radioactive iodine ablation. Whereas ipsilateral lymphadenectomy of the central (primary) cube should routinely be performed, modified radical neck analysis is only indicated in apparent nodal complaint of the side (secondary) cube (s). Cases with apropos discovered discerned thyroid lymphomas generally don't bear complete thyroidectomy unless the tumours are larger than 1.5 cm in periphery or nodal involvement is present (23).

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Department of Endocrinology, Amrita Institute of Medical Sciences, Cochin, Kerala, India  
Corresponding Author: Dr. A. G. Unnikrishnan, Department of Endocrinology, AmritaInstitute of Medical Sciences, Cochin, Kerala, India. E-mail: [moc.liamg@gananhsirkinnu](mailto:moc.liamg@gananhsirkinnu)

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#### Affiliations

<sup>1</sup> University of New England School of Osteopathic Medicine

<sup>2</sup> Mery Fitzgerald Hospital

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#### **Affiliations**

<sup>1</sup> District Endocrine/Sentara Northern Virginia Medical Center

<sup>2</sup> VA MEDICAL CENTER, MATHER , CA

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8. Michael T. McDermott, MD

#### **Affiliations:**

University of Colorado School of Medicine, Denver, Colorado (M.T.M.)

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10. Sun Y. Lee, MD, MSc<sup>1</sup>; Elizabeth N. Pearce, MD, MSc<sup>1</sup>

#### **Author Affiliations**

- <sup>1</sup>Section of Endocrinology, Diabetes, Nutrition, and Weight Management, Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts

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Twitter: [@DrMVanderpump](https://twitter.com/DrMVanderpump)

#### 18. Authors

Fnu Amisha<sup>1</sup>; Anis Rehman<sup>2</sup>.

#### Affiliations

<sup>1</sup> University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States of America

<sup>2</sup> District Endocrine/Sentara Northern Virginia Medical Center

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19 Yiqun Miao, Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, <sup>1</sup> Yang Xu, Data curation, Formal analysis, <sup>1</sup> Ping Teng, Data curation, <sup>2</sup> Aihua Wang, Conceptualization, Methodology, Supervision, Writing – review & editing, <sup>1,\*</sup> Yuanyuan Zhang, Data curation, Supervision, Writing – review & editing, <sup>1</sup> Yun Zhou, Formal analysis, Methodology, <sup>1</sup> and Wenwen Liu, Methodology<sup>1</sup>

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#### 20. Authors

Ayoola O. Awosika<sup>1</sup>; Gauri Singh<sup>2</sup>; Ricardo Correa<sup>3</sup>.

#### Affiliations

<sup>1</sup> University of Illinois College of Medicine

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<sup>3</sup> University of Arizona

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