JOURNAL OF APPLIED BIOANALYSIS, August. 2024, p. 89-96.
https://doi.org/10.53555/jab.v10i2.149 (ISSN 2405-710X)
Vol. 10, No. 2

OPEN ACCESS

SCOPING REVIEW

Central Hypothyroidism Causing Drugs: A Scoping Review

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Received: 20 Feb 2024 **Revised: 2 March 2024** **Accepted: 4 March 2024** **Published: April 2024**

ABSTRACT

Numerous drugs can affect thyroid function. When a patient needs exogenous levothyroxine, the majority of these drugs either directly affect the thyroid or have an impact on the absorption and metabolism of thyroid hormones. Thyroid-stimulating hormone (TSH) in the hypothalamus or thyrotrope can be reduced by a certain class of drugs, which includes glucocorticoids, dopamine agonists, somatostatin analogs, and rexinoids. This can then affect thyroid function. Thankfully, most of these medications usually do not cause central hypothyroidism that is clinically noticeable. Most patients with rexinoids, a more modern class of nuclear hormone receptor agonists, experience clinically severe central hypothyroidism. Dopamine agonists may worsen "hypothyroidism" in people with nonthyroidal disorders. The main aim is to review the Central Hypothyroidism causing drugs. This systematic review aims to inventory and analyze the literature on medications associated with central hypothyroidism. The review will focus on understanding the potential causal relationship between various drugs and the emergence of central hypothyroidism. The strategy outlined below will guide the thorough search, selection, and analysis of relevant research. The discussion underscores the complexity of medication-induced central hypothyroidism and stresses the necessity of cautious assessment and treatment in a therapeutic context, taking into account the various and frequently transient effects of these drugs on thyroid function.

Keyword: Central Hypothyroidism, Drugs, Thyroid

INTRODUCTION

Central hypothyroidism (CH) is characterized by inadequate stimulation of an otherwise healthy thyroid gland, which results in a lack of thyroid hormone production due to low TSH activity [1]. This condition results from abnormalities in the pituitary or hypothalamus' structure or function, which alters TSH secretion in an unanticipated way.

TSH is a glycoprotein dimeric hormone that is made up of two subunits: TSHβ and α-GSU [2]. It is generally produced in a circadian pattern, with a nocturnal surge that happens in the early hours of the night. The negative feedback of thyroid hormone and the positive action of TRH primarily control the secretion of TSH [3, 4]. Other variables, such as the detrimental effects of glucocorticoids, dopamine, and hypothalamic somatostatin, directly affect TSH secretion [5]. Gonadal hormones, leptin, and other signals associated with feeding behavior or sleep patterns are examples of peripheral tissue signals that might indirectly influence thyrotrope secretion [6]. The pathophysiology of CH involves disruptions in various regulatory systems [7, 8, 9, 10].

While thyrotrope cell failure can occur in isolation, TSH secretion problems are more commonly associated with combined pituitary hormone deficits (CPHD) [11], which may conceal hypothyroid symptoms. Low circulating free T4 (FT4) concentrations linked to
low/normal serum TSH levels are typically used to make the biochemical diagnosis [12] consequently, CH is a significant false-negative outcome of the "reflex TSH strategy," a widely used diffuse method to assess thyroid function using the first-line TSH measurement [13]. The hypothyroid condition can have a serious negative impact

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on life quality at any age, but CH alone does not significantly shorten life expectancy. Thus, in individuals with hypothalamic-pituitary problems, the presence of minor forms of CH should always be suspected.

The primary cause of central hypothyroidism is either hypothalamic or pituitary dysfunction [14] often resulting from tumors, trauma, or other structural issues rather than medications. However, certain drugs and medical conditions affecting the pituitary and hypothalamus can potentially contribute to central hypothyroidism [15]. Here are some examples:

Glucocorticoids: A class of corticosteroids known as glucocorticoids binds to the glucocorticoid receptor [16, 17, 18]. In medicine, they are used to treat conditions including sepsis, autoimmune illnesses, allergies, and asthma that are brought on by an overactive immune system. A study found that certain drugs may have an adverse effect on the hypothalamic-pituitary-thyroid axis, leading to central hypothyroidism. Among these drugs are glucocorticoids [Fig. 1] [19, 20, 21].

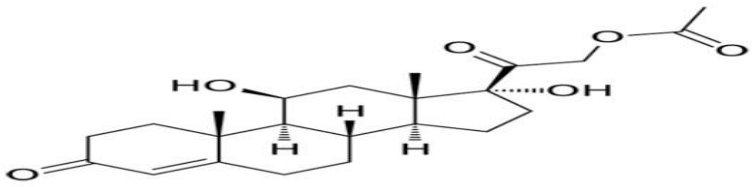

Fig. 1: Glucocorticoids

Dopamine Agonists: Patients with Parkinson disease are treated with dopamine agonists [22]. While bromocriptine is used to treat neuroleptic malignant syndrome, dopamine agonists like ropinirole are the first line of treatment for restless legs syndrome. Moreover, dopamine agonists are administered to treat hyperprolactinemia brought on by dopamine antagonists [Fig. 2] [23].

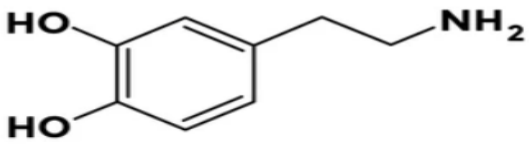

Fig. 2: Dopamine Agonists

Somatostatin Analogs: The hormone somatostatin, which is generated by the hypothalamus and some other tissues like the pancreas and gastrointestinal tract, can be mimicked or blocked by a class of medications known as somatostatin analogs. They are used to lower the body's synthesis of several hormones, especially those brought on by tumors. Tumors secreting vasoactive intestinal peptide, carcinoid tumors, glucagonomas, and other types of pituitary adenomas are treated with somatostatin analogs. Additionally, they are used to treat acromegaly, a disorder in which an adult over secretes growth hormone [Fig. 3] [24, 25, 26].

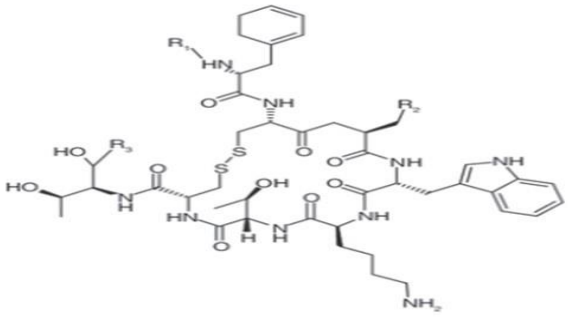

Fig. 3: Somatostatin Analogs

Rexinoids: Rexinoids are a class of pharmacological substances that bind to retinoid X receptors (RXRs) and share structural similarities with vitamin A [27]. Since they have the ability to alter genes related to inflammation, cell division, proliferation, and apoptosis, they have being investigated for possible application in cancer treatment. In numerous preclinical models, retinoid activity has demonstrated anti-neoplastic properties [Fig. 4] [28, 29, 30].

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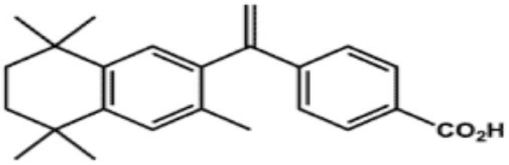


Fig. 4: Rexinoids

REVIEW

The goal of this systematic review is to examine and compile the body of research on drugs related to central hypothyroidism. The review will concentrate on comprehending the possible causal association between the onset of central hypothyroidism and different medications. The approach described here will direct the methodical search, selection, and examination of pertinent research.

Inclusion Criteria

- Human studies including randomized controlled trials, cohort studies, case-control studies, and observational studies.
- Studies investigating the association between medications and central hypothyroidism.
- Studies reporting relevant outcomes such as changes in thyroid function, TSH levels, or clinical manifestations of central hypothyroidism.

Exclusion Criteria

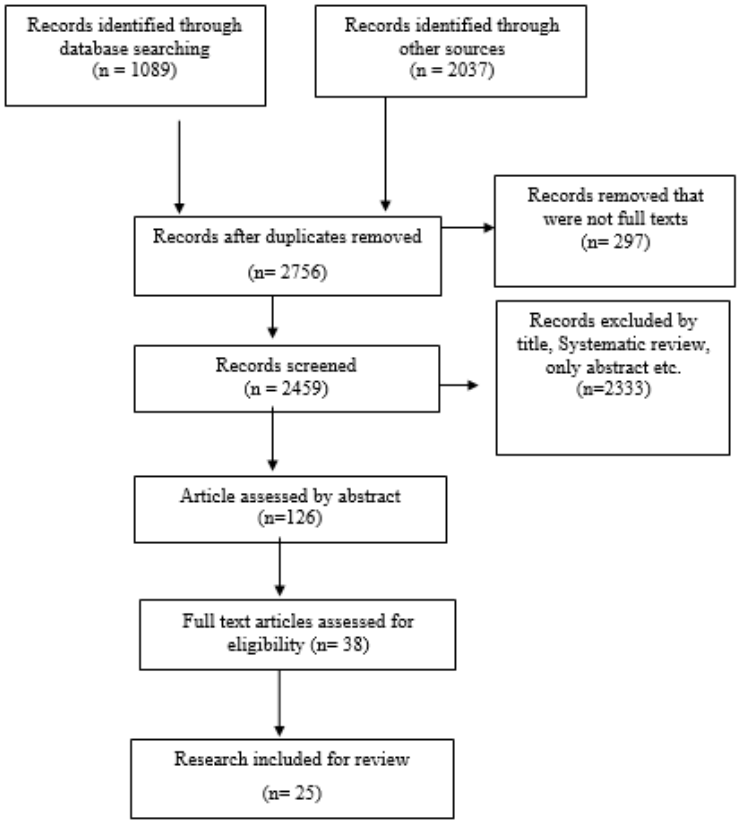
- Studies not directly addressing the association between medications and central hypothyroidism.
- Studies lacking sufficient data on the medications of interest or outcomes related to central hypothyroidism.

Search Strategy

A comprehensive exploration will be carried out in prominent electronic databases (PubMed, Embase, Scopus, Web of Science) utilizing a blend of medical subject headings (MeSH) terms and keywords associated with central hypothyroidism and drugs. An extensive search strategy will be designed to guarantee the incorporation of all pertinent studies.

The proposed methodological framework will provide clear guidance for conducting a systematic review, ensuring a thorough and transparent approach to analyzing information on drugs linked to central hypothyroidism.

PRISM chart



Glucocorticoids

Glucocorticoids are a pharmacological category commonly used for the treatment of inflammatory disorders and adrenal insufficiency [31]. They exert various impacts on thyroid function, such as inhibiting the release of TSH [11]. Thyroid-stimulating hormone (TSH) is responsible for activating the thyroid gland to generate thyroid hormones, which in turn control the body's

metabolism and growth. Hypothyroidism occurs when the thyroid gland produces less thyroid hormones due to low levels of TSH [32].

Although the exact cause of this thyroid suppression is unknown, it is thought that glucocorticoids affect the anterior pituitary gland's ability to secrete thyrotropin (TSH). Instead of acting directly on the pituitary gland, this impact acts at the suprahypophyseal level. Furthermore, it has been noted that glucocorticoids modify the pattern of thyroxine binding to plasma proteins as well as peripheral thyroxine metabolism [33]. Although the precise mechanism by which glucocorticoids induce central hypothyroidism is not entirely understood, it is thought to entail changes in thyrotropin-releasing factor (TRF) secretion as well as reduction of TSH secretion [5]. Additionally, the research indicates that, in contrast to glucocorticoid excess, glucocorticoid shortage may have an adverse effect on TSH secretion [34].

Glucocorticoid-induced central hypothyroidism typically manifests as a mild and transitory condition, often devoid of symptoms or necessitating intervention. Nevertheless, in certain instances, particularly when administering substantial quantities of glucocorticoids over an extended period, the hypothyroidism may acquire clinical significance and affect the patients' quality of life. Thyroid hormone replacement medication may be necessary in certain instances to reinstate normal thyroid function and avert the problems associated with hypothyroidism [11].

Rexinoids

Studies have demonstrated that certain ligands, such as bexarotene, which target the Retinoid X receptor (RXR), can inhibit the activity of the TSH-β promoter in the pituitary gland, resulting in central hypothyroidism. Moreover, laboratory studies conducted outside of a living organism indicate a potential ability to inhibit the generation of TRH (thyrotropin-releasing hormone) in the hypothalamus [35, 36]. Furthermore, clinical evidence indicates that retinoids can accelerate the metabolism of thyroid hormones. "These data indicate that bexarotene likely has two primary impacts on thyroid function: suppressing the generation of TSH and increasing the metabolic clearance of thyroid hormones. This is caused by the inhibition of TSH gene expression through a reversible process that is mediated by RXR and is independent of thyroid hormone. The precise method of action entails the inhibition of TSH synthesis and secretion by thyroid hormones, together with the control of TRH production in the hypothalamus [37, 38]. Furthermore, studies have demonstrated that retinoids can enhance the levels of hepatic cytochrome P450, perhaps leading to a more rapid elimination of thyroid hormones. The interactions ultimately result in central hypothyroidism in people undergoing bexarotene treatment [39].

Dopamine

The neurotransmitter dopamine is involved in a number of physiological processes, one of which is the regulation of the HPT axis. Thyroid function is significantly impacted by dopamine through the activation of D2 receptors (D2R). Intravenous dopamine infusions have been shown to lower TSH pulse amplitude in healthy individuals without appreciably changing pulse frequency [40, 41].

A dopamine agonist that is mainly used to treat conditions like hyperprolactinemia, bromocriptine, also affects the HPT axis similarly [42]. It has been shown to lower serum TSH levels, and interestingly, it acts similarly to dopamine on the amplitude of the TSH pulse. Dopamine and bromocriptine appear to elicit their effects via the same D2R pathway [43].

It's interesting to note that dopamine has a direct stimulatory effect by causing the hypothalamus to generate more thyrotropin-releasing hormone (TRH) [44]. Serum TSH levels are lowered as a result of dopamine activity on the HPT axis, though. The opposing effects on the hypothalamus and pituitary thyrotrope give rise to this paradoxical condition.

Evidence suggests that in patients with macroprolactinomas, extended bromocriptine treatment may actually help resolve central hypothyroidism brought on by the adenoma, despite worries about the medication creating central hypothyroidism [45].

There is a cumulative effect on suppression of the HPT axis in critically sick patients, especially in those with nonthyroidal illness (NTI) receiving dopamine infusions [46, 47]. These people may develop iatrogenic central hypothyroidism as a result of the combined effects of dopamine and NTI. The complex relationship that exists between thyroid function, dopamine, and severe disease raises concerns about how these cases should be managed. More specifically, the question is whether individuals with NTI who are also receiving dopamine infusions should be treated with levothyroxine [48, 49].

Somatostatin Analogs

Somatostatin analogs such as octreotide show remarkable effectiveness in lowering serum levels of TSH (thyroid-stimulating hormone) by directly inhibiting pituitary thyrotropes [50]. The therapeutic promise of these analogs is highlighted by their inhibitory function, which has been demonstrated in a variety of situations, including uncontrollably secreting pituitary tumors or pituitary resistance to thyroid hormone. Interestingly, the effect on TSH seems to be a passing phenomenon, as there is no evidence of clinically significant central hypothyroidism as a result of the reported suppression.

When somatostatin is given to healthy individuals, serum TSH pulse amplitude and frequency decrease, suggesting that somatostatin directly inhibits pituitary thyrotropes' ability to secrete TSH. Moreover, in healthy individuals, long-acting somatostatin analogs reduce serum TSH levels and attenuate TSH levels triggered by thyrotropin-releasing hormone (TRH) [51]. Nevertheless, despite the initial suppression, the majority of the research that is now available indicates that these effects are temporary and do not cause core hypothyroidism that is clinically relevant.

Research on extended octreotide therapy, especially in individuals with acromegaly, provides fascinating information. Extended treatment for six months did not appreciably affect serum thyroxine concentrations or basal TSH levels, but there is an early reduction in serum TSH levels and blunting of TRH-stimulated levels after one month of therapy [52]. Remarkably, changes in thyroid hormone metabolism are seen, including higher reverse

T3 and lower serum T3 levels, indicating a possible indirect impact on thyroid hormone pathways [53].

It is important to note that the literature consistently indicates that these changes are not linked to clinically significant central hypothyroidism, despite the documented effects on TSH and thyroid hormone levels. The fact that the suppression of TSH is only temporary and does not significantly affect baseline levels of thyroid hormone suggests that somatostatin analogs do not cause a persistent hypothyroid condition that is clinically significant. This sophisticated comprehension highlights the intricacy of the interplay between somatostatin analogs and the thyroid axis, directing the circumspect evaluation of their consequences inside the therapeutic setting.

DISCUSSION

The impact of different pharmacological drugs on Central Hypothyroidism is discussed, with a special emphasis on glucocorticoids, dopamine agonists, somatostatin analogs, and rexinoids. Glucocorticoids often prescribed to treat inflammatory conditions, glucocorticoids affect thyroid function by preventing the release of TSH. Glucocorticoid-induced central hypothyroidism is typically moderate and transient, but significant and continuous use can have a clinically significant effect and require thyroid hormone replacement. A ligand for the Retinoid X receptor (RXR), bexarotene decreases the production of TSH and raises the thyroid hormones' metabolic clearance. The reversible process regulated by RXR causes thyroid hormones to suppress TSH production and secretion, which leads to central hypothyroidism. Because of their conflicting actions on the hypothalamus and pituitary, dopamine and bromocriptine, which act on D2 receptors, reduce TSH levels but also cause a paradoxical state. Patients with macroprolactinomas may benefit from prolonged bromocriptine therapy to treat central hypothyroidism. In critically ill patients, dopamine infusions can lead to iatrogenic central hypothyroidism, particularly in those with nonthyroidal disease (NTI). The intricate correlation among dopamine, severe illness, and thyroid function prompts inquiries regarding treatment, such as the appropriateness of levothyroxine administration. Somatostatin analogs, such octreotide, directly inhibit pituitary thyrotropes, hence lowering TSH levels. Research indicates that these effects are transient and do not result in central hypothyroidism that is clinically substantial, despite the early suppression. In patients with acromegaly, extended octreotide therapy alters thyroid hormone metabolism without causing long-term hypothyroidism.

In overall, the discussion underscores the complexity of medication-induced central hypothyroidism and stresses the necessity of cautious assessment and treatment in a therapeutic context, taking into account the various and frequently transient effects of these drugs on thyroid function.

A study Done by S. C. Dogansen *et al.* [54], The results of this study lend credence to the idea that glucocorticoids, as seen in Cushing's syndrome, can cause central hypothyroidism. In order to avoid negative effects on thyroid function, including the development of hyperthyroidism from SITSH, careful management of glucocorticoid replacement is essential.

A study Done by L. Montanelli *et al.* [5], Dopamine agonists are known to reduce TSH release. Nevertheless, there is no indication of a direct connection between dopamine agonists and central hypothyroidism in the study's findings.

According to a study Done by S. A. Schneider *et al.* [55], Dopamine Agonists can cause central hypothyroidism.

A study Done by S. I. Sherman *et al.* [56], The results of the study clearly link bexarotene, one retinoid X receptor-selective ligand, to central hypothyroidism in patients with cutaneous T-cell lymphoma. This emphasizes how crucial it is to use thyroid hormone replacement treatment in conjunction with close observation when taking these drugs.

CONCLUSION

The results of the study highlight how intricately the thyroid axis interacts and how carefully the effects of pharmacological therapies must be assessed. Even if some drugs can cause central hypothyroidism, it is still important to recognize these side effects so that you can treat patients appropriately and take appropriate action as needed.

ACKNOWLEDGEMENT: NA

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article

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