PharmacologyOnLine

Archives • 2021 • vol.3 • 902-907

A COMPREHENSIVE REVIEW ON COMORBIDITIES ASSOCIATED WITH HYPOTHYROIDISM

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Abstract

Hypothyroidism is an endocrine disease that is caused by the depletion of thyroid hormones in our bodies. There is a high prevalence of hypothyroidism worldwide and in India too. There is a strong link between hypothyroidism and a number of other medical disorders, including diabetes. It has been shown that hypothyroidism is connected with high mortality and impaired quality of life, particularly if there are comorbidities. This review provides a short summary of the comorbidities that are impacted by hypothyroidism.

Key Words: Hypothyroidism, Comorbidities, Thyroid gland.

Introduction

Hypothyroidism is an endocrine condition in which the thyroid gland produces insufficient thyroid hormones (1). Hypothyroidism was found to be present in 3.9 percent of adults in India. Females between the ages of 15 and 49 are more likely to develop hypothyroidism. Since it runs in families, it also tends to have a genetic aspect. It was reported that the thyroid disorder affects about 42 million people in India.(2). Hypothyroidism may be caused by a wide variety of chronic or temporary disorders that suppress thyroid hormone secretion. Around 95% of hypothyroidism cases are caused by issues with the thyroid gland and the condition is known as primary hypothyroidism. Disorders of the pituitary gland and hypothalamus cause secondary and tertiary hypothyroidism (3) respectively. 5% of hypothyroid patients were affected by Primary and tertiary hypothyroidism. Many research work reported that hypothyroidism can lead to other comorbid diseases. The emphasis of this article will be on a few of the comorbid diseases that are linked to hypothyroidism (4).

Hypothyroidism

Hypothyroidism is a condition under which the thyroid gland fails to deliver enough thyroid hormones to meet the body's demands. Thyroid hormone impacts essentially every organ in the body and regulates metabolism, or how the body uses energy. Many of the body's functions slow down when there isn't enough thyroid hormone (5). Clinical symptoms may differ from mild unspecific symptoms including tiredness, cold intolerance, loss of vitality, and constipation to life-threatening myxedema, Hypothyroidism is divided into three types: Primary hypothyroidism, Secondary hypothyroidism and Tertiary hypothyroidism.

Hypothyroidism and calorigenesis

Nearly all metabolically active tissues experience an increase in oxygen consumption as a result of thyroid hormone stimulation. Activation of membrane-bound Na-ATPase is increased by thyroid hormones in a variety of tissues. Activating cellular metabolism and resetting the energy balance, thyroid hormones increase the basal metabolic rate (BMR), with surplus energy discharged as heat as a result of the increased metabolic rate. Decreased thermogenesis is caused by a reduction in thyroid hormone production. Cold intolerance develops as a result of the patient's medical history. As a result of the patient's slowed metabolism, his or her energy intake would be reduced, causing weariness (6).

Hypothyroidism affects growth and development

There are numerous processes through which thyroid hormones control growth and development. Besides having a negative feedback impact on the stimulatory hormones thyrotropin-releasing hormone (TRH) and thyrotropin-releasing hormone (TRH), thyroid hormones also regulate their receptors in a variety of physiological and pathological contexts (TSH). Through the up- and down-regulation of thyroid receptors, the biological effects of thyroid hormones can be fine-tuned (7). When it comes to child development, thyroid hormones (TH) are critical for healthy brain development, somatic growth, bone formation, and pubertal maturation. Due to a lack of thyroid hormone, the body's development is retarded, and bone growth is reduced linearly. This results in hypothyroid cretinism (delayed bone maturation(8).

Hypothyroidism and intermediary metabolism

Thyroid hormones have effects on carbohydrate, protein, and lipid,metabolism.

Carbohydrate metabolism

Glucose metabolism is a metabolic process that occurs in the body that involves the breakdown of carbohydrates. As a result of impaired glucose absorption from the digestive tract, hypothyroidism is characterised by extended peripheral glucose buildup, gluconeogenesis, decreased hepatic glucose intake, and decreased glucose elimination. Whether the hypothyroidism is overt or subclinical, insulin resistance leads to glucose-stimulated insulin secretion. A decrease in the rate of insulin-stimulated glucose transport can occur in subclinical hypothyroidism due to a disruption in the expression of the glucose transporter type 2 gene (GLUT 2) translocation. Insulin resistance can develop as a result of this disruption in the rate of insulin-stimulated glucose transport. Type 2

diabetes is the consequence of the entire process(12).

Protein metabolism

An underactive thyroid is frequently connected with weight gain because an individual suffering from hypothyroidism has a reduced basal metabolic rate (BMR). In persons who have more severe hypothyroidism, the tendency to gain weight is greater. The exact cause of weight gain in hypothyroid persons is frequently unclear, and it is not always attributable to an increase in body fat content. Salt and water in excess are responsible for the majority of weight gain in hypothyroid individuals. Large weight gain is connected with hypothyroidism only very rarely. If you have hypothyroidism, the thyroid can be responsible for anything from 5-10 pounds of extra body weight. Final point: If hypothyroidism is manifested solely by weight increase, the weight gain is less likely to be attributed solely to the thyroid gland. Protein catabolism is reduced in hypothyroid patients, resulting in the buildup of an osmotically active protein, which results in the conjugation of proteins under the skin or subcutaneous tissue, which results in a puffy face (11).

Lipid metabolism

The thyroid hormones triiodothyronine (T3) and thyroxine (T4) increase lipolysis indirectly by activating catecholamines and other lipolytic hormones, which in turn increases fat burning. When there is a thyroid hormone imbalance, there is a rise in plasma cholesterol levels and a decrease in cholesterol elimination from circulation. This results in an increase in serum total cholesterol, low-density ldl (LDL), apolipoprotein B, lipoprotein (α), and possibly triglyceride levels. Overall, dyslipidemia is the outcome (9). Obesity develops in hypothyroid people as a result of an excessive accumulation of fat in adipose tissue. Hypothyroidism has been associated to reduced thermogenesis and metabolic rate, as well as a higher body mass index (BMI) and a higher prevalence of obesity in the general population (10).

Hypothyroidism affecting the cardiovascular system

When a person has hypothyroidism, his or her cardiac output decreases as a result of poor vascular smooth muscle relaxation and decreased endothelial nitric oxide production. A cascade effect occurs, with increased arterial stiffness leading to increased systemic vascular resistance, which in turn leads to reduced arterial filling and activation of the renin-angiotensin-aldosterone system (RAAS), which is followed by increased reabsorption of sodium and water, ultimately resulting in high blood pressure (hypertension)(13).

Blood vessel dilation, development of vasodilatory molecules, inhibition of angiotensin II receptor expression and signal transduction are the direct anti-atherosclerotic effects of thyroid hormone. Decreased expression of hepatic LDL receptors and reduced activity of cholesterol-α-monooxygenase, which breaks down cholesterol, resulting in decreased LDL clearance, which will lead to deposition of cholesterol and fats in the lumen of blood vessels and causes atherosclerosis(14).

Because of this, hypothyroidism can impair cardiac contractility and decrease cardiac muscle relaxation, resulting in diastolic dysfunction due to a lack of relaxation in the heart. Heart output, heart rate, and stroke volume are all lowered as a result of this phenomenon. Heart failure would become more likely as a result of these changes. Low thyroid hormone levels induce a hypodynamic state of circulation, which reduces peripheral demand and ultimately results in diminished performance, contraction power, and bradycardia

Hypothyroidism can impair cardiac contractility and decrease cardiac muscle relaxation, indicating diastolic dysfunction due to a lack of relaxation. As a result, cardiac output, heart rate, and stroke volume are all reduced. As a result, heart failure would become more likely. Hypothyroidism causes a hypodynamic condition of circulation, which reduces peripheral demand and leads to decreased performance, contraction power, and eventually bradycardia (15).

Hypothyroidism and nervous system

Inadequate thyroid hormones have an effect on the central nervous system, causing defective myelination of axons in the cortical region, which results in reduced vascularity in the brain, which causes an uncontrolled discharge of nerve signals

from the brain, causing epilepsy. Low thyroid hormone levels in hypothyroid people cause memory loss, intellectual impairment, delayed responses, and finally psychosis (myxedema madness) (16).

Hypothyroidism can have an effect on the peripheral nervous system, increasing the likelihood of developing peripheral polyneuropathy and entrapment neuropathies such as carpal tunnel and Guyon canal syndromes. Importantly, autoimmune thyroid dysfunction has been connected to other autoimmune disorders that can cause neurological symptoms, such as myasthenia gravis and Guillain-Barre syndrome(17).

Hypothyroidism and musculoskeletal system

Thyroid hormones have anabolic effects on bone during growth and catabolic effects on bone in adults. Chondrocytes, osteoblasts, and osteoclasts experience diminished proliferation and differentiation when their thyroid hormone levels are low. Even while it appears that there is an increase in bone density in adult subjects with hypothyroidism, the bone quality in these people is poor, which may explain why there is a likely rise in fractures in these patients (18). Hypothyroidism has an effect on the muscles as well. Hypothyroid myopathy is a prevalent clinical characteristic in patients with hypothyroidism, affecting around 79 percent of those who are diagnosed with the condition. Both congenital and acquired hypothyroidism are characterised by generalised myalgias and muscular weakness. Patients suffering from severe or untreated hypothyroidism can develop considerable muscle disease, which can result in severe functional restrictions and even death(19).

Hypothyroidism and Haemopoietic system

In contrast, iron deficiency anaemia has a detrimental impact on thyroid hormone status, as evidenced by increased erythropoietin production as well as direct stimulation of erythrocyte precursor proliferation. As a result, several types of anaemia can develop as a result. Normocytic anaemia is the most prevalent type of anaemia, with macrocytic and microcytic anaemia being less common. Anaemia in hypothyroidism individuals can be caused by bone marrow depression, decreased erythropoietin activity, concomitant illnesses, or iron, vitamin B12, or folate insufficiency (20).

Hypothyroidism and respiratory system

Hypothyroidism reduces respiratory drive and cause obstructive sleep apnoea or pleural effusion. Patients with hypothyroidism may have a greater risk for developing obstructive sleep apnoea due to multiple factors involving respiration such as damage to the nerves/muscles involved in breathing. It also occur due to the enlargement of the tongue(macroglossia) and disruption of muscles that control the upper airway (21). Hypothyroidism can also lead to bronchial asthma as a result of respiratory muscle weakness and impaired pulmonary function, which results in a reduction in respiratory drive, this in turn leads to pleural diffusion.

Skin and hypothyroidism

Thyroid hormone deficiency causes skin changes such as thickening, hyperkeratosis, diffuse loss of scalp hair, and nail atrophy. With widespread xerosis, the skin is cold, dry, and pale, particularly on the extensor surfaces of the muscles (22). When specific T3 and T4 levels were impaired, it affects other body processes such as hair growth and leads to hairfall. Hair loss or alopecia occurs when hair falls out and is not replaced by new growth, resulting in thinning around scalp and other areas such as eyebrows. The smooth appearance of alopecia areata distinguishes it from other nondiffuse hair-loss disorders such as pathognomonic exclamation point hairs (23).

Reproduction and hypothyroidism

Thyroid hormones are required for effective functioning of the female reproductive system because they govern the growth and metabolism of ovarian, uterine, and placental tissue. As a result, hypo- and hyperthyroidism can cause subfertility or infertility in both humans and animals (24). It was reported that the progesterone and total testosterone levels in hypothyroid males were shown to be significantly lower. Hypothyroidism was much lower in men with normal sperm

morphology compared to controls. After treatment with levothyroxine, although, morphology improved dramatically. Hypothyroid males' sperm motility was similarly reduced, albeit not to the same degree as controls. Subclinical hypothyroidism has little effect on sperm quality or quantity in adult males (25).

Myxoedema coma

The loss of brain function caused by an extreme, long-term low level of thyroid hormone in the blood is known as myxoedema (crisis) coma (hypothyroidism). Myxoedema coma is a severe, life-threatening complication of hypothyroidism and one of the disease's more serious aspects. Hypothermia, hallucinations, disorientation, seizures, deep coma, edema, swollen pupils, thickening of the tongue, sparse, dry hair, trouble breathing, pleural effusions, and pericardial effusions are only a few of the symptoms.(26).

Conclusion

Hypothyroidism, a common condition especially in aged women, is frequently associated with other health problems. This review explains the complications of hypothyroidism's comorbidities, which encompass conditions affecting almost every organ system. Comorbidity has an impact on clinical outcomes and quality of life, as well as patient care, as a result of drug-disease, disease-disease, and drug-drug interactions. These findings show that hypothyroidism necessitates periodic control visits, which raises the likelihood of diagnosing related chronic illnesses. A greater understanding of hypothyroidism comorbidity could be beneficial in providing more personalised and better attention. It could assist clinicians in taking into consideration expected related disorders. Treatment with levothyroxine may interact with a variety of drugs, and dosage modifications may be necessary in some cases. Therefore, a good knowledge of possible comorbidities and prescription is required.

Acknowledgments

The authors are thankful to the authorities of Vinayaka Mission's Research Foundation (Deemed to be University), Salem for providing the facilities for carrying out this research.

References

1. Garber JR, Cobin RH, Gharib H, Hennessey J V, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2012;18(6):988–1028.
2. Unnikrishnan AG, Menon U V. Thyroid disorders in India: An epidemiological perspective. Indian J Endocrinol Metab [Internet]. 2011 Jul;15(Suppl 2):S78–81. 3. Lania A, Persani L, Beck-Peccoz P. Central hypothyroidism. Pituitary. 2008;11(2):181–6.
4. R. G. A. Ahmed, RG., 2017. Maternal Hypothyroidism and Lung Dysfunction. International Journal of Research Studies in Medical and Health Sciences Volume 2, Issue 11, 2017, PP 8-11. Int J Res Stud Med Heal Sci Vol 2, Issue 11, 2017, PP 8-11. 2017 Dec;2.
5. Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Clinical review: Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. J Clin Endocrinol Metab. 2009 Jun;94(6):1853–78.
6. Izmail-Beigi F, Edelman IS. Mechanism of thyroid calorigenesis: role of active sodium transport. Proc Natl Acad Sci U S A. 1970 Oct;67(2):1071–8.
7. Tarım Ö. Thyroid hormones and growth in health and disease. J Clin Res Pediatr Endocrinol. 2011/06/08. 2011;3(2):51–5.
8. Salisbury S. Cretinism: The past, present and future of diagnosis and cure. Paediatr Child Health. 2003 Feb;8(2):105–6.
9. Pearce EN. Hypothyroidism and dyslipidemia: modern concepts and approaches. Curr Cardiol Rep. 2004 Nov;6(6):451–6.
10. Sanyal D, Raychaudhuri M. Hypothyroidism and obesity: An intriguing link. Indian J Endocrinol Metab [Internet]. 2016;20(4):554–7.
11. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet (London, England). 2017/03/20. 2017 Sep;390(10101):1550–62.

12. Wang C. The Relationship between Type 2 Diabetes Mellitus and Related Thyroid Diseases. J Diabetes Res [Internet]. 2013/04/04. 2013;2013:390534.
13. Cai P, Peng Y, Chen Y, Wang Y, Wang X. Blood pressure characteristics of subclinical hypothyroidism: an observation study combined with office blood pressure and 24-h ambulatory blood pressure. J Hypertens. 2021 Mar;39(3):453–60.
14. Ichiki T. Thyroid hormone and atherosclerosis. Vascul Pharmacol. 2010;52(3–4):151–6.
15. Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the Heart. Methodist Debakey Cardiovasc J. 2017;13(2):55–9.
16. Feldman AZ, Shrestha RT, Hennessey J V. Neuropsychiatric manifestations of thyroid disease. Endocrinol Metab Clin North Am. 2013 Sep;42(3):453–76.
17. Stasiolek M. Neurological symptoms and signs in thyroid disease. Thyroid Res. 2015 Jun;8(Suppl 1):A25–A25.
18. Dhanwal DK. Thyroid disorders and bone mineral metabolism. Indian J Endocrinol Metab. 2011 Jul;15(Suppl 2):S107–12.
19. Fariduddin MM, Bansal N. Hypothyroid Myopathy. In Treasure Island (FL); 2021.
20. Szczepanek-Parulska E, Hernik A, Ruchała M. Anemia in thyroid diseases. Polish Arch Intern Med. 2017 May;127(5):352–60.
21. Grunstein RR, Sullivan CE. Sleep apnea and hypothyroidism: mechanisms and management. Am J Med. 1988 Dec;85(6):775–9.
22. Puri N. A study on cutaneous manifestations of thyroid disease. Indian J Dermatol. 2012 May;57(3):247–8.
23. Vincent M, Yogiraj K. A Descriptive Study of Alopecia Patterns and their Relation to Thyroid Dysfunction. Int J Trichology [Internet]. 2013 Jan;5(1):57–60. 24. Silva JF, Ocarino NM, Serakides R. Thyroid hormones and female reproduction. Biol Reprod. 2018 Nov;99(5):907–21.
25. Kumar A, Shekhar S, Dhole B. Thyroid and male reproduction. Indian J Endocrinol Metab. 2014;18(1):23–31.
26. Mathew V, Misgar RA, Ghosh S, Mukhopadhyay P, Roychowdhury P, Pandit K, et al. Myxedema coma: a new look into an old crisis. J Thyroid Res [Internet]. 2011/09/15. 2011;2011:493462.