Extra-Thyroidal Factors Impacting Thyroid Hormone Homeostasis: A Review

Brock McGregor, BSc, ND[a]

ABSTRACT

Peripheral metabolism plays a significant role in maintaining thyroid hormone expression in local tissues. The thyroid secretes thyroxine (T4) at substantially greater levels than triiodothyronine (T3), relying on peripheral mechanisms to convert T4 to T3. Peripheral control is exerted through a number of pathways. These pathways include deiodination, facilitated by deiodinase enzymes, as well as conjugation and lipid peroxidation. Factors influencing any or all of the peripherally active pathways continue to be explored and may help explain why many patients continue to experience symptoms consistent with hypothyroidism, including low body temperature, even when their thyroid blood tests are normal. These factors include liver and kidney function as well as seasonal changes. Although non-thyroidal illness syndrome was originally defined as a condition occurring without direct thyroid function impact, there is evidence that the thyroid itself may alter T3 and T4 during illness via modified gene regulation in the presence of pro-inflammatory cytokines. There are also a number of lifestyle behaviors, including fasting, alcohol dependence, and smoking that have been shown to affect peripheral metabolism of thyroid hormones. Zinc affects both the synthesis and mode of action of action of thyroid hormones. For example, thyroid transcription factors, which are essential for modulation of gene expression, contain zinc at cysteine residues. Selenium is required for the selenocysteine moieties that confer the function of the deiodinase enzymes. Selenium supplementation has been shown to reduce anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies in patients with autoimmune thyroiditis. Selenium has been shown to increase the level of glutathione peroxidase, which contains selenocysteine. Both *Withania somnifera* and *Commiphora mukul* have been shown to improve hypothyroidism by elevating T3 levels and increasing T3:T4 ratios through peripheral metabolic pathways.

Keywords: Selenium; Thyroid; Peripheral thyroid metabolism; Hypothyroidism

[a]Corresponding author: 220 St Clair St, Chatham, ON, N7M 1G4, Canada, Tel.: +1 519 354 6600;

Fax: +1 519 354 3300; E-mail: info@mcgregornd.com

INTRODUCTION

Thyroid hormones play an important role in determining metabolic function. Disruption in thyroid hormone homeostasis via under-functioning of the thyroid gland in hypothyroidism is a common endocrine disorder characterized by clinical symptoms such as fatigue, weight gain, decreased memory, and dry skin. Regulating thermogenesis is one of the major tasks of thyroid hormone in adult humans.[1] Body temperature homeostasis is under tight control and hypothermia can result when thyroid hormone expression is too low and hyperthermia can result when thyroid hormone expression is too high.[2] Indeed, a recent study suggests that normalizing low body temperature be used as a therapeutic target in the treatment of obesity.[3]

Inadequate thyroid hormone supply from either endogenous or exogenous sources is confirmed with the resultant feedback response leading to increased thyroid stimulating hormone (TSH) production by the pituitary gland and elevated serum TSH.[4]

The mechanisms and outcomes of both primary and secondary hypothyroidism are well understood, but the effects of extra-thyroidal peripheral metabolism of thyroid hormones remains less clear. While the thyroid is solely responsible for thyroxine (T4) production, enzymes in peripheral or target tissues metabolize T4 to triiodothyronine (T3), or T3 to reverse T3 (rT3).[5] Thyroid production of T4 and T3 occurs at a ratio of 17:1, with 80% of T3 being produced through extra-thyroidal conversion, indicating that peripheral metabolism has a significant influence on thyroid hormone availability at target tissues.[6]

T4 to T3 conversion in the target tissues occurs intracellularly, and thus is unable to be evaluated by serum thyroid testing. It may be that many patients are experiencing low thyroid hormone expression, low body temperatures, and hypometabolic symptoms even when they have adequate thyroid hormone supply and normal thyroid hormone blood tests. The focus on altered thyroid hormone homeostasis has broadened from a central, thyroid-associated model to include peripheral influences on thyroid hormone levels. This has far reaching clinical implications. The medical research demonstrates a clear connection between hypothyroidism and headaches,[7,8] premenstrual syndrome,[9] insomnia,[10] anxiety,[11] obesity,[12] fluid retention,[13,14] hair loss,[15] carpal tunnel syndrome,[16] irritable bowel syndrome,[17] depression,[18,19] low sex drive,[20] infertility,[21] and many other physical and mental complaints. The magnitude and variety of effects of hypothyroidism result from the integral role the thyroid system plays in DNA transcription. Thyroid hormone activity affects every cell and function dependent on DNA. The experience of individuals presenting with low body temperature and low thyroid expression in the presence of normal laboratory thyroid values suggests serum TSH levels may be incorrectly ruling out hypothyroidism.

NON-THYROIDAL ILLNESS SYNDROME

The findings of non-thyroidal illness syndrome (NTIS) are encountered most frequently in the emergency room or intensive care unit settings. NTIS, or sick euthyroid syndrome, is considered to be an adaptive, asymptomatic abnormality in thyroid blood tests that does not benefit from treatment and that resolves with resolution of the non-thyroid illness.[22] Laboratory hallmarks include lowered T3 and T4 levels, with elevated rT3, and normal or slightly decreased TSH.[23] Initially, elevated rT3 measurements were thought to be useful in differentiating between NTIS and secondary hypothyroidism, but recent studies have demonstrated this strategy inaccurate.[5] NTIS is an adaptive response, slowing metabolism to counter excessive illness associated catabolism.[4] While generally considered a protective adaptation early in disease, if it persists, it may be considered clinically detrimental later in the course of chronic illness.[4,6]

Physiologically, NTIS is caused by changes in thyroid hormone metabolism in hepatic, muscle, and adipose tissues, including decreased T4 to T3 conversion and reduced liver clearance of rT3.[4,22] Alteration in thyroid hormone (TH) binding to protein carriers, TH entry into cells, expression

of TH receptors, and iodothyronine deiodinase activity all contribute to the totality of altered tests in the NTIS state.[6] Rodent models suggest that the main mechanism influencing NTIS is likely a cytokine-mediated response.[24] Cytokines released during illness affect gene expression throughout the hypothalamus-pituitary-thyroid (HPT) axis and target tissues, contributing to the complexity of findings in NTIS.[25] While many of the molecular mechanisms involved in NTIS are well understood through animal and cellular models, gaps remain in understanding the comprehensive etiology of NTIS.[22]

Interestingly, post mortem studies comparing individuals who suffered from prolonged illness versus acute cardiac disease demonstrated a reduction in TRH gene expression in the hypothalamus of those in the prolonged disease group.[26] This finding demonstrates that the down-regulation of the HPT axis occurs in chronic disease but not from acute pathological changes.

Although NTIS was originally defined as a condition occurring without direct thyroid function impact, there is evidence that the thyroid itself may alter T3 and T4 during illness via modified gene regulation in the presence of pro-inflammatory cytokines.[27]

PERIPHERAL THYROID METABOLISM OVERVIEW

The pituitary gland releases TSH in response to thyrotropin releasing hormone (TRH) secreted from the hypothalamus.[28] TSH leads to increased cAMP in the thyroid cell which increases iodine pumping by sodium/iodide symporter (NIS), thyroglobulin synthesis, iodination, thyroid peroxidase activity, endocytosis, and hormone release (primarily in the pro-hormone form T4 with a small amount of active T3 produced as well).[29,30] Thyroid hormones negatively feedback to both the hypothalamus and pituitary to regulate thyroid hormone homeostasis.[31]

T4 is converted to the active T3 form by deiodination, removal of an iodide from the outer phenolic benzene ring by selenium-containing enzymes, deiodinase enzymes D1 or D2.[32] T4 is deactivated to the inactive rT3 by deiodination of the inner tyrosyl benzene ring by the deiodinase D3 (and to a lesser extent, D1).[33] The three types of deiodinases have variable tissue distribution. D1 has been found in the liver, kidneys, thyroid, and pituitary; D2 in the central nervous system (CNS), thyroid, pituitary, brown adipose tissues, and skeletal muscles; and D3 has been found in the CNS, skin, gravid uterus, placenta, and fetal liver.[34,35] D1 and D2 both produce T3, and D3 degrades both T4 and T3 to inactive forms.[33] The particular levels of deiodinases found in cells in a tissue control local exposure to T3 in that tissue, providing peripheral control over thyroid hormone action.[22]

Although deiodination is generally considered the primary pathway of peripheral thyroid metabolism, two alternate pathways have been identified as contributors to thyroid hormone homeostasis.[35] Conjugation occurs primarily in the liver, with some activity in renal tissue as well. Conjugation involves addition of sulfate or glucuronic acid to the hydroxyl group of thyroid hormones.[34,36,37] The products of this process are inactive and easily eliminated. Antioxidant enzyme systems including lipid peroxidation (LPO) have garnered attention as possible pathways regulating T3 and T4 balance.[35] Several nutrient and botanical interventions are thought to work via this system and are discussed below.

FACTORS AFFECTING PERIPHERAL METABOLISM

LIVER FUNCTION

Thyroid hormones regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function; the liver in turn metabolizes the thyroid hormones and helps regulate their systemic endocrine effects. Thyroid dysfunction may perturb liver function, and liver disease can affect thyroid hormone metabolism.[38]

In cases of severe hepatitis with impending liver failure, free T3:T4 ratio correlates negatively with the severity of the liver disease and has prognostic value.[39]

KIDNEY FUNCTION

Peripheral metabolism of thyroid hormones occurs to a significant degree in hepatic and renal tissues.[40] It is unsurprising that reduced kidney function and chronic kidney disease (CKD) impact thyroid hormone homeostasis. Subclinical hypothyroidism with low serum T3 can occur in individuals with CKD.[41,42] Centrally, the pituitary has an altered, decreased response to TRH in the presence of uremia occurring in CKD.[41] Peripherally, T3 and T4 are displaced from protein binding sites by competitive inhibitors present during uremia.[41] Due to reduced glomerular filtration rate, inflammatory cytokines are more slowly cleared in CKD and act to inhibit T4 to T3 conversion in peripheral tissues.[43] Selenium levels have been shown to be regularly decreased in patients undergoing hemodialysis, but supplementation with selenium in this patient population has not shown any significant impact on thyroid markers.[44]

ALCOHOL

Alcohol dependence (AD) has been linked to hypothalamus-pituitary-thyroid axis disruption in several studies.[45] AD is correlated with decreased T3, T4, and TSH. In a study exploring the link between alcohol craving in alcohol-dependent individuals and thyroid function, it was demonstrated that elevated T3 levels were correlated with alcohol craving, and low TSH levels were correlated with aggression and anxiety.[45] Individuals who remained in treatment and abstained from alcohol for 12 weeks saw a normalization of T3 and TSH levels.[45] While there remains no established mechanism for the relationship between thyroid function and alcohol dependence, the effects of alcohol dependence on dopamine levels offer a plausible explanation for study findings. Dopamine has an established modulatory effect on TSH and TRH through binding to D2 receptors.[45] Alcohol exposure itself may influence thyroid hormone levels independent of AD, as animal models have demonstrated that exposure to alcohol blunts the response to TRH, leading to lowered TSH and subsequent decreases in T3 and T4.[46] A population study of Danish individuals correlated higher than average alcohol consumption with reduced risk of goiter and thyroid nodularity. It is unclear whether alcohol may have a direct

protective effect on thyroid tissue, or if alcohol's inhibitory effect on thyroid hormones through peripheral metabolism may reduce the need for thyroid hormone production, subsequently preventing thyroid enlargement.[47]

FLAVONOIDS

Kaempferol is a flavonoid found in apples, grapes, tomatoes, green tea, potatoes, onions, broccoli, brussels sprouts, green beans, squash, spinach, blackberries, and raspberries that has been shown to increase D2 activity. D2, an intracellular enzyme that activates thyroid hormone (T3) for the nucleus is upregulated three-fold by kaempferol. Kaempferol also dramatically increases the half-life of D2. The net effect is an approximately 10-fold stimulation of D2 activity, which increases the rate of T3 production by 2.6-fold.[48]

HYPOXIA

Hypoxia-induced D3 activation leads to reduction of T3 and oxygen consumption, suggesting that D3 activation is a component of cellular responses to hypoxia and supports the idea of cell-specific regulation of thyroid hormone levels by deiodinases.[49] This also supports the importance of good breathing habits and proper exercise.

FASTING AND CALORIC RESTRICTION

Fasting alters HPT axis functioning at multiple levels, including decreasing TSH production by the pituitary, decreased production of thyroid hormones by the thyroid, and altered peripheral metabolism.[50] This adaptive response slows metabolism to conserve energy during times of food scarcity. While occurring in both human and rodents, alterations in thyroid hormone homeostasis in response to fasting is more pronounced in rodents, as they have much smaller energy stores and are more susceptible to the impacts of food scarcity.[50]

Studies have demonstrated an association between fasting and both reduced serum T3 and elevated serum rT3 in rodent and human models.[50,51] One of the primary drivers of this alteration of peripheral thyroid hormone homeostasis is a reduction of T4 converting to T3 in peripheral tissues, most notably

hepatic and renal tissues.[50,51] Re-feeding, either with a balanced or carbohydrate-heavy meal following a fasting period has been shown to restore pre-fasting T3 and rT3 levels by reducing rT3 production.[52]

Individuals observing prolonged fasting offer a unique opportunity to explore the effects of intermittent fasting on thyroid metabolism. Studies have shown that cycles of intermittent fasting associated with prolonged fasting do not significantly alter thyroid function, with only slight alterations in thyroid hormones noted in the final days of prolonged fasting in female subjects.[52] It is well known that TSH values fluctuate throughout the day, and recent studies have demonstrated that TSH is significantly reduced in the fed state, with no significant variation in T4 levels between the fasted and fed states.[53]

SEASONAL CHANGES

Thyroid hormone homeostasis shows seasonal variation related to cold exposure, with studies demonstrating a small elevation in TSH, T3, and thyroglobulin in healthy adults when exposed to long periods of cold.[54] An increased need for thyroid hormones in peripheral tissues is thought to be the primary driver of this endocrine change.[55]

Along with changes in the average ambient temperatures, seasonal change in photoperiod has been hypothesized as a possible contributor to variation in thyroid metabolism.[55,56] Melatonin is known to affect a number of neuroendocrine pathways in mammals.[57] Recent rodent studies have demonstrated that the timing of melatonin administration affects type 2 and type 3 deiodinase expression in the hypothalamus, suggesting a possible mechanism for light exposure affecting thyroid hormone homeostasis.[57] Despite this finding in animal models, recent human studies have reported no light exposure associated seasonal variation in thyroid hormones in individuals with subclinical hypothyroidism.[55]

Interestingly, seasonal affective disorder (SAD) has been linked to symptoms closely related to hypothyroidism. A number of small studies have attempted to investigate a possible link between SAD and thyroid function but have not conclusively established a statistically significant correlation.[58,59] However, an intervention trial did demonstrate that individuals suffering from SAD undergoing light therapy for 1 week had reduced TSH levels as well as significant reduction in depressive symptoms.[60] Those individuals with the most significant response in depression scoring to light therapy also had the largest decreases in TSH during treatment.[60]

SMOKING

Smoking has significant impacts on a variety of health parameters, and should be discouraged in all patient populations. The known impact of smoking on risk reduction in ulcerative colitis and increased risk of Crohn's disease demonstrates an immune modulatory impact of smoking behavior.[61] This behavior is similar to the impact of smoking on thyroid conditions, with smoking increasing the risk of Grave's disease and Grave's opthalmopathy, and decreasing risk of Hashimoto's thyroiditis and both papillary and follicular thyroid cancer.[62,63]

In population-based studies a correlation between smoking and both lower serum TSH levels and elevated free thyroxine (FT4) levels was demonstrated.[64,65] Following cessation, TSH levels recover to pre-smoking levels by 5–10 years in women, and over 18 years in men.[65] There appears to be a dose-related response to smoking behavior, with heavier smokers (8–12 cigarettes per day) having a larger TSH reduction than light smokers (<4 cigarettes per day).[65] While it is clear that smoking behavior impacts thyroid hormone homeostasis, variables associated with both smoking behavior and thyroid function, including body mass index (BMI), alcohol consumption, and iodine sufficiency may confound population-based results.[63]

While the mechanism of thyroid disruption due to smoking has not been clearly established, short exposure to cigarette smoke (1 hour) has been shown to increase FT3 and FT4, without an impact on TSH.[66] It is possible that this short exposure period was not long enough to note a resultant reduction in TSH. Although more study is needed, this finding indicates the possibility that long-term smoking may decrease TSH levels by increasing thyroid hormone production in a TSH-independent pathway.[63]

HEAVY METAL EXPOSURE

Exposure to a variety of metals, primarily mercury, lead, and cadmium, has been shown to have possible effects on thyroid function and thyroid hormone metabolism.[67] There are multiple challenges in assessing the impact of environmental exposure on thyroid hormone pathways. Challenges in assessing exposure to metals, including standardization and applicability of urinary or serum testing, remain problematic. Population-based studies have established a correlation between heavy metal exposure and thyroid function, and animal studies have established possible mechanisms for interaction.

Occupational and environmental mercury exposure has demonstrated a correlation with altered thyroid hormone metabolism. T4 to T3 conversion mediated by deiodinases may be adversely affected by methyl mercury as it can sequester selenium.[68] Mercury levels have been associated with lowered T3 and T4 levels with no impact on TSH levels, suggesting a reduction in deiodinase activity.[69] Mercury also may centrally affect thyroid hormone production by accumulating in thyroid tissues and binding directly to iodine, reducing iodine availability for hormone synthesis.[70]

Cadmium levels in animal studies have been correlated with decreased T4 levels. It is hypothesized that cadmium may reduce deiodination, leading to this alteration in thyroid hormone balance.[71,72] Rodent models assessing thyroid hormone response to cadmium exposure demonstrated that rats injected with cadmium experienced significant reduction in T4 to T3 conversion, and no change in TSH levels, suggesting a mechanism for extra-thyroidal impact of cadmium on thyroid hormone homeostasis.[73]

Along with well-established deleterious neurologic, hematologic, and gastrointestinal effects, lead exposure has garnered interest for its possible effects on thyroid metabolism. While studies investigating correlations between lead levels and thyroid hormone alteration have been mixed, some studies have demonstrated a relationship between high lead exposure (blood levels above 20 μg/dL) and low T4, FT4, and T3.[74–77] At a lower level, lead has been shown to be associated with reduced FT4 in adolescents, and inversely associated with TSH in adult men. Unlike with cadmium or mercury, there is no proposed mechanism for lead interfering in peripheral metabolism of thyroid hormones. Rodent models suggest lead interferes with thyroid hormone metabolism via direct reduction in thyroid hormone production from thyroid tissues.[78]

MINERALS

SELENIUM

Selenium is an important mineral in thyroid function and thyroid hormone homeostasis through integration in a number of selenoproteins involved in thyroid hormone production, conversion of T4 to T3, protection from oxidative damage, and immune modulation.[24]

Although not discussed fully in this review, selenium has been shown to play a complex role in autoimmune thyroid diseases. Selenium supplementation has demonstrated benefit in reducing and reversing Grave's associated opthalmopathy, and reduces autoimmune thyroid markers in Hashimotos.[79–81] The protective mechanism in autoimmune thyroid diseases is complex, and likely involves selenium's role in immune regulation and protection from oxidation in thyroid tissues.[79–81]

Studies investigating the role of selenium in NTIS have demonstrated that selenium deficiency is not the main cause of thyroid hormone alteration in NTIS, rather it is cytokine-induced inhibition of deiodinases that impacts thyroid hormone levels.[82] Despite selenium deficiency not being the primary driver of altered thyroid metabolism, there is evidence that selenium demand increases in the sick state.[24] Selenium supplementation in critical illness has shown benefit in both mortality reduction and clinical outcomes.[24] Although important in various mechanisms involved in thyroid function, the benefit of selenium supplementation in illness is due to altered cytokine release not just seleno-enzyme functioning.

ZINC

Zinc is an important component in a wide variety of enzymes and receptors involved in physiological processes, including thyroid-related metabolic function. The role of zinc in the body is remarkably complex, and its impact on thyroid function includes thyroid hormone production, T4 to T3 conversion, and T3 receptor function.[83]

Zinc deficiency has been shown to decrease thyroid hormone availability, with correction of hormone levels noted with zinc supplementation.[72] A recent study demonstrated that 12 weeks of 30 mg zinc supplementation alone or in combination with selenium in overweight or obese female hypothyroid patients significantly increased FT3 levels, and increased the FT3:FT4 ratio.[83] These findings confirm zinc's integral role in T4 to T3 conversion. Interestingly, serum zinc levels did not change throughout the study, consistent with previous studies,[84] suggesting zinc concentrations remain in a normal range during sub-clinical deficiency.[83] At initiation of the study, participants did not have baseline zinc levels in the deficiency range.[83]

BOTANICALS

Despite their common use in complementary therapies to treat thyroid conditions, there remains limited human research into the effects of botanical therapies on thyroid hormone homeostasis. A number of plants including *Lithospermum officinale, Lycopus europeaus, Withania somnifera, Bauhinia purpurea,* and *Commiphora mukul,* have demonstrated potential in impacting the HPT axis and peripheral conversion of thyroid hormones in rodent and animal models.[35]

WITHANIA SOMNIFERA

Withania somnifera (Ashwaghanda) is an Ayurvedic herb traditionally used to treat stress, and has been shown to have immunomodulatory, antioxidant, and anti-inflammatory functions.[85] Along with a case report of *Withania*-induced thyrotoxicosis, rodent studies have demonstrated increase in thyroid hormone levels following administration of *Withania.*[86–88] A very small human study in bipolar patients treated with levothyroxine confirmed findings from animal models, demonstrating a significant increase in T4 levels, as well as normalization of TSH levels in subclinical hypothyroid patients.[89] Mechanistically, it was postulated that this effect was likely due to direct effect on the thyroid gland.[89] Adding to this possible central effect on the thyroid, animal evidence of the impact of *Withania* extract demonstrated increases in both T3 and T4, and reduced hepatic lipid peroxidation and increased antioxidant activity.[87] In a similar study, an extract from *Bauhinia purpurea* showed similar effects in lowering hepatic lipid peroxidation and increasing antioxidant activity.[88]

COMMIPHORA MUKUL (GUGGUL)

Commiphora mukul (guggul), a traditional Ayurvedic medicinal herb, has shown thyroid-stimulating effects in animals and is used to treat high cholesterol, obesity, and a lowered metabolism.[90,91]

In a rodent study of hypothyroid-induced mice, administration of guggul was shown to increase T3 levels.[92] Along with an increase in T3, guggul administration decreased lipid peroxidation, and increased superoxide dismutase and catalase, markers used to assess tissue toxicity. This trend demonstrated a tissue-protective effect of *Commiphora.*[92] Hepatic deiodinase activity increased with guggul use, suggesting the major contributor to T3 increase is conversation of T4 to T3.[92] A previous study demonstrated similar results, with an increase in T3 and T3/T4 ratio with administration of guggul extract.[93] Again, lipid peroxidation was noted in the liver, suggesting that guggul's effects occur via alteration in peripheral hormone metabolism.[93]

CONCLUSION

Peripheral thyroid metabolism is a complex process involving deiodination, conjugation, and lipid peroxidation pathways. It is clear that adequate, symptom-free thyroid hormone expression depends not only on adequate thyroid hormone supply as evidenced by normal thyroid hormone blood tests but also upon healthy peripheral thyroid metabolism. Lifestyle practices, nutrient intake, and botanical interventions can support thyroid hormone physiology and expression via peripheral mechanisms. Assessment and intervention in suspected cases of normal thyroid hormone supply and low thyroid hormone expression should involve lifestyle investigation and warrants the consideration of nutrient and botanical intervention.

DISCLOSURE

The author has no conflict of interest to disclose.

REFERENCES

1. Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid.* 2008;18(2):141–4.

2. Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. *Ann Intern Med.* 2003;139(3):205–13.

3. Grimaldi D, Provini F, Pierangeli G, *et al.* Evidence of a diurnal thermogenic handicap in obesity. *Chronobiol Int.* 2014;32:299–302.

4. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. *Endocr Rev*. 2011;32(5):670–93.

5. Economidou F, Douka E, Tzanela M, Nanas S, Kotanidou A. Thyroid function during critical illness. *Hormones (Athens)*. 2011;10(2):117–24.

6. Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. *J Endocrinol*. 2010;205(1):1–13.

7. Moreau T, Manceau E. Headache in hypothyroidism. Prevalence and outcome under thyroid hormone therapy. *Cephalalgia*. 1998;18(10):687–9.

8. Fallah R, Mirouliaei M. Frequency of subclinical hypothyroidism in 5- to 15-year-old children with migraine headache. *J Ped End Met.* 2012;25(9–10):859–62.

9. Moline M, Zendall S. Evaluating and managing premenstrual syndrome. *Medscape Womens Health,* 2000;5(2):1.

10. Kales A. Sleep disorders: recent findings in the diagnosis and treatment of disturbed sleep. *N Engl J Med*. 1974;290(9):487–99.

11. Simon N, Blacker D. Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review. *J Affect Disord*. 2002;69(1):209–17.

12. Kokkoris P, Pi-Sunyer F. Obesity and endocrine disease. *Endocrinol Metab Clin North Am.* 2003;32(4):895–914.

13. Wheatley T, Edwards O. Mild hypothyroidism and oedema: evidence for increased capillary permeability to protein. *Clin Endocrinol.* 1983;18(6):627–35.

14. Deodhar A, Fisher A. Fluid retention syndrome and fibromyalgia. *Rheumatology*. 1994;33(6):576–82.

15. Harrison S. Diffuse hair loss: its triggers and management. *Cleve Clin J Med*. 2009;76(6):361–7.

16. Cakir M, Samanci N. Musculoskeletal manifestations in patients; with thyroid disease. *Clin Endocrinol*. 2003;59(2):162–7.

17. Olden K. Diagnosis of irritable bowel syndrome. *Gastroenterology*. 2002;122(6):1701–14.

18. Sintzel F, Mallaret M, Bougerol T. Potentializing of tricyclics and serotoninergics by thyroid hormones in resistant depressive disorders. *Encephale*. 2004;30(3):267–75.

19. Jackson I. The thyroid axis and depression. *Thyroid*. 1998;8(10):951–6.

20. Viera A. Managing hypoactive sexual desire in women. *Medical Aspects Hum Sex.* 2001;1:7–13.

21. Verma I, Sood R, Juneja S, Kaur S. Prevalence of hypothyroidism in infertile women and evaluation of response of treatment for hypothyroidism on infertility. *Int J Appl Basic Med Res.* 2012;2(1):17–9.

22. De Vries EM, Fliers E, Boelen A. The molecular basis of the non-thyroidal illness syndrome. *J Endocrinol*. 2015;225(3):R67–81.

23. Docter R, Ep K, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. *Clin Endocrinol (Oxf)*. 1993;39:499–518.

24. Gärtner R. Selenium and thyroid hormone axis in critical ill states: an overview of conflicting view points. *J Trace Elem Med Biol*. 2009;23(2):71–4.

25. Boelan A, Kwakkel J, Thijssen-Timmer D, Alkemade A, Fliers E, Wiersinga W. Simultaneous changes in central and peripheral components of the hypothalamus-pituitary-thyroid axis in lipopolysaccharide induced acute illness in mice. *J Endocrinol.* 2004;182:315–23.

26. Fliers E, Guldenaar S, Wiersinga W, Swaab D. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. *J Clin Endocrinol Metab*. 1997;82:4032–36.

27. Bartalena L, Bogazzi F, Brogioni S, Grasso L, Martino E. Role of cytokines in the pathogenesis of the euthyroid sick syndrome. *Eur J Endocrinol*. 1998;138:603–14.

28. Scanlon M, Toft A. Regulation of thyrotropin secretion. In: Braverman L, Utiger R, eds. *The Thyroid 8th Ed*. 2005. pp. 234–53.

29. Maia A, Kim B, Huang S, Harney J, Larsen P. Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. *J Clin Invest.* 2005;15(9):2524–33.

30. Farid NR, Szkudlinski MW. Minireview: structural and functional evolution of the thyrotropin receptor. *Endocrinology.* 2004;145(9): 4048–57.

31. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev*. 2002;23(l):38–89.

32. Kohrle J. The deiodinase family: selenoenzymes regulating thyroid hormone availability and action. *Cell Mol Life Sci*. 2000;57:1853–63.

33. Kwakkel J, Fliers E, Boelen A. Illness-induced changes in thyroid hormone metabolism: focus on the tissue level. *Neth J Med*. 2011;69(5):224–8.

34. Robbins J. Factors altering thyroid hormone metabolism. *Env Heal Perspect*. 1981;38:65–70.

35. Kelly G. Peripheral metabolism of thyroid hormones: a review. *Altern Med Rev*. 2000;5(4):306–33.

36. Kohrle J, Spanka M, Irmscher K, Hesch R. Flavonoid effects on transport, metabolism and action of thyroid hormones. *Prog Clin Biol Res*. 1988;280:323–40.

37. Visser T. Pathways of thyroid hormone metabolism. *Acta Med Austriaca*. 1996;23:10–6.

38. Malik R, Hodgson H. The relationship between the thyroid gland and the liver. *Q J Med*. 2002;95(9):559–69.

39. Kano T, Kojima T, Takahashi T, Muto Y. Serum thyroid hormone levels in patients with fulminant hepatitis: usefulness of rT3 and the rT3/T3 ratio as prognostic indices. *Gastroenterol Jpn*. 1987;22:344–53

40. Ohnhaus E, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol*. 1983;15:71–6.

41. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. *Indian J Endocrinol*. 2012;16(2):204–13.

42. Mohamedali M, Reddy Maddika S, Vyas A, Iyer V, Cheriyath P. Thyroid disorders and chronic kidney disease. *Int J Nephrol*. 2014;2014:520281.

43. Lim V, Fang V, Katz A, Refetoff S. Thyroid dysfunction in chronic renal failure. A study of the pituitary thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. *J Clin Invest*. 1977;60(3):522–34.

44. Omrani HR, Rahimi M, Nikseresht K. The effect of selenium supplementation on acute phase reactants and thyroid function tests in hemodialysis patients. *Nephrourol Mon*. 2015;7(2):e24781.

45. Aoun EG, Lee MR, Haass-Koffler CL, *et al.* Relationship between the thyroid axis and alcohol craving. *Alcohol Alcohol*. 2014;50(1):24–9.

46. Zoeller R, Fletcher D, Simonyl A, Rudeen P. Chronic ethanol treatment reduces the responsiveness of the hypothalamic-pituitary-thyroid axis to central stimulation. *Alcohol Clin Exp Res*. 1996;20(5):954–60.

47. Knudsen N, Bülow I, Laurberg P, Perrild H, Ovesen L, Jørgensen T. Alcohol consumption is associated with reduced prevalence of goitre and solitary thyroid nodules. *Clin Endocrinol (Oxf)*. 2001;55(1):41–6.

48. da-Silva WS, Harney JW, Kim BW, *et al.* The small polyphenolic molecule kaempferol increases cellular energy expenditure and thyroid hormone activation. *Diabetes*. 2007;56(3):767l76.

49. Simonides WS, Mulcahey MA, Redout EM, Muller A, Zuidwijk MJ, Visser TJ. Hypoxia-inducible factor induces local thyroid hormone inactivation during hypoxic-ischemic disease in rats. *J Clin Invest*. 2008;118(3):975–83.

50. Boelen A, Wiersinga W, Fliers E. Fasting-induced changes in the hypothalamus-pituitary-thyroid axis. *Thyroid*. 2008;18(2):123–9.

51. De Vries EM, van Beeren HC, Ackermans MT, Kalsbeek A, Fliers E, Boelen A. Differential effects of fasting vs. food restriction on liver thyroid hormone metabolism in male rats. *J Endocrinol*. 2015;224(1):25–35.

52. Azizi F. Islamic fasting and thyroid hormones. *Int J Endocrinol Metab*. 2015;13(2):14–6.

53. Nair R, Mahadevan S, Muralidharan RS, Madhavan S. Does fasting or postprandial state affect thyroid function testing? *Indian J Endocrinol Metab*. 2014;18(5):705–7.

54. Do NV, Mino L, Merriam GR, *et al.* Elevation in serum thyroglobulin during prolonged Antarctic residence: effect of thyroxine supplement in the polar 3,5,3-triiodothyronine syndrome. *J Clin Endocrinol Metab*. 2004;89:1529–33.

55. Kim TH, Kim KW, Ahn HY, *et al.* Effect of seasonal changes on the transition between subclinical hypothyroid and euthyroid status. *J Clin Endocrinol Metab*. 2013;98(8):3420–9.

56. Dardente H, Hazlerigg DG, Ebling FJP. Thyroid hormone and seasonal rhythmicity. *Front Endocrinol (Lausanne)*. 2014;5:1–11.

57. Goto M, Matsuo H, Iigo M, Furuse M, Korf HW, Yasuo S. Melatonin-induced changes in the expression of thyroid hormone-converting enzymes in hypothalamus depend on the timing of melatonin injections and genetic background in mice. *Gen Comp Endocrinol*. 2013;186:33–40.

58. Bauer M, Kurtz J, Winokur A, Phillips J, Rubin L, Marcus J. Thyroid function before and after 4-weeks light treatment in winter depressives and controls. *Psychoneuroendocrinology*. 1993;18:437–43.

59. Lingjaerde O, Reichborn-Kjennerud T, Haug E. Thyroid function in seasonal affective disorder. *J Affect Disord*. 1995;33(1):39–45.

60. Martiny K, Simonsen C, Lunde M, Clemmensen L, Bech P. Decreasing TSH levels in patients with Seasonal Affective Disorder (SAD) responding to 1 week of bright light therapy. *J Affect Disord*. 2004;79(1–3):253–7.

61. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun*. 2010;34:J258–65.

62. Vestergaard P. Smoking and thyroid disorders–a meta-analysis. *Eur J Endocrinol*. 2002;146:153–61.

63. Wiersinga WM. Smoking and thyroid. *Clin Endocrinol (Oxf)*. 2013;79(2):145–51.

64. Jorde R, Sundsfjord J. Serum TSH levels in smokers and non-smokers. The 5th Tromso study. *Exp Clin Endocrinol Diabetes*. 2006;114:343–7.

65. Asvold B, Bioro T, Nilsen T, Vatten LJ. Tobacco smoking and thyroid function: a population-based study. *Arch Intern Med*. 2007;167:1428–32.

66. Metsios G, Flouris A, Jamurtas A, *et al.* A brief exposure to moderate passive smoke increases metabolism and thyroid hormone secretion. *J Clin Endocrinol Metab*. 2007;92:208–11.

67. Yorita Christensen KL. Metals in blood and urine, and thyroid function among adults in the United States 2007–2008. *Int J Hyg Environ Health*. 2013;216(6):624–32.

68. Soldin O, O'Mara DM, Aschner M. Thyroid hormones and methylmercury toxicity. *Biol Trace Elem Res*. 2008;126(1–3):1–12.

69. Holt R, Handley N. *Essential Endocrinology and Diabetes*. Malden, MA: John Wiley & Sons; 2012.

70. Nishida M, Yamamoto T, Yoshimura Y, Kawada J. Subacute toxicity of methylmercuric chloride and mercuric chloride on mouse thyroid. *J Pharmacobiodyn*. 1986;9(4):331–8.

71. Mori K, Yoshida K, Hoshikawa S, *et al.* Effects of perinatal exposure to low doses of cadmium or methylmercury on thyroid hormone metabolism in metallothionein-deficient mouse neonates. *Toxicology*. 2006;228(1):77–84.

72. Hammouda F, Messaoudi I, El Hani J, Baati T, Said K, Kerkeni A. Reversal of cadmium-induced thyroid dysfunction by selenium, zinc, or their combination in rat. *Biol Trace Elem Res*. 2008;126(1–3):194–203.

73. Pavia Junior M, Paier B, Noli M, Hagmuller K, Zaninovich A. Evidence suggesting that cadmium induces a non-thyroidal illness syndrome in the rat. *J Endocrinol*. 1997;154(1):113–7.

74. Lopez C, Pineiro A, Nunez N, Avagnina A, Villaamil E, Rose O. Thyroid hormone changes in males exposed to lead in the Buenos Aires area (Argentina). *Pharmacol Res*. 2000;42(6):599–602.

75. Robins J, Cullen M, Connors B, Kayne R. Depressed thyroid indexes associated with occupational exposure to inorganic lead. *Arch Intern Med*. 1983;143(2):220–4.

76. Singh B, Chandran V, Bandhu HK, *et al.* Impact of lead exposure on pituitary-thyroid axis in humans. *Biometals*. 2000;13(2):187–92.

77. Tuppurainen M, Wagar G, Kurppa K, *et al.* Thyroid function as assessed by routine laboratory tests of workers with long-term lead exposure. *Scand J Work Env Heal*. 1988;14(3):175–80.

78. Wu CY, Liu B, Wang HL, Ruan DY. Levothyroxine rescues the lead-induced hypothyroidism and impairment of long-term potentiation in hippocampal CA1 region of the developmental rats. *Toxicol Appl Pharmacol*. 2011;256(2):191–7.

79. Duntas LH. The evolving role of selenium in the treatment of Graves' disease and ophthalmopathy. *J Thyroid Res*. 2012;2012:736161.

80. Eskes SA, Endert E, Fliers E, *et al.* Selenite supplementation in euthyroid subjects with thyroid peroxidase antibodies. *Clin Endocrinol (Oxf)*. 2014;80(3):444–51.

81. Turker O, Kumanlioglu K, Karapolat I, Dogan I. Selenium treatment in autoimmune thyroiditis: 9-month follow-up with variable doses. *J Endocrinol*. 2006;190(1):151–6.

82. Boelen A, Platvoetter-Schiphorst M, Bakker O, Wiersinga W. The role of cytokines in the lipopoly-saccharide-induced sick euthyroid syndrome in mice. *J Endocrinol*. 1995;146:475–83.

83. Mahmoodianfard S, Vafa M, Golgiri F, *et al.* Effects of zinc and selenium supplementation on thyroid function in overweight and obese hypothyroid female patients: a randomized double-blind controlled trial. *J Am Coll Nutr*. 2015;(July):1–9.

84. Bonham M, O'Connor J, Alexander HD, *et al.* Zinc supplementation has no effect on circulating levels of peripheral blood leucocytes and lymphocyte subsets in healthy adult men. *Br J Nutr*. 2003;89:695–703.

85. Gupta G, Rana A. Withania somnifera (Ashwagandha): a review. *Pharmacogn Rev*. 2007;1:129–36.

86. Van der Hooft C, Hoekstra A, Winter A, de Smet P, Stricker B. Thyrotoxicosis following the use of Ashwagandha. *Ned Tijdschr Geneeskd*. 2005;149:2637–8.

87. Panda S, Kar A. Changes in thyroid hormone concentrations after administration of ashwagandha root extract to adult male mice. *J Pharm Pharmacol*. 1998;50(9):1065–8.

88. Panda S, Kar A. Withania somnifera and bauhinia purpurea in the regulation of circulating thyroid hormone concentrations in female mice. *J Ethnopharmacol*. 1999;67:233–9.

89. Roy Chengappa K, Gannon J, Forrest P. Subtle changes in thyroid indices during a placebo-controlled study of an extract of Withania somnifera in persons with bipolar disorder. *J Ayurveda Integr Med*. 2014;5(4):241.

90. Tripathi YB, Malhotra OP, Tripathi SN. Thyroid stimulating action of Z-guggulsterone obtained from Commiphora mukul. *Planta Med*. 1984;50(l):78–80.

91. Singh AK, Tripathi SN, Prasad GC. Response of Commiphora mukul (guggulu) on melatonin induced hypothyroidism. *Anc Sci Life*. 1983;3:85–90.

92. Panda S, Kar A. Guggulu (Commiphora mukul) potentially ameliorates hypothyroidism in female mice. *Phyther Res*. 2005;19(1):78–80.

93. Panda S, Kar A. Gugulu (Commiphora mukul) induces triiodothyronine production: possible involvement of lipid peroxidation. *Life Sci*. 1999;65(12):137–41.