International Journal for Pharmaceutical Research Scholars (IJPRS)

V-5, I-3, 2016 ISSN No: 2277 - 7873

REVIEW ARTICLE

Thyroid Dysfunction and its Management

Supriya Agnihotri*, Shiv Parkash Goel

Sachdeva College of Pharmacy, Gharuan, Mohali, Punjab, India.

Manuscript No: IJPRS/V5/I3/00127, Received On: 01/08/2016, Accepted On: 10/08/2016

ABSTRACT

The focus of the present review article is on thyroid dysfunctions which can be hypo or hyper thyroidism. Along with the ongoing allopathic treatment options, one can go for the alternative therapies or natural cures. Various nutritional supplements including iodine, botanicals like guggul and many more play an effective role in the management of thyroid dysfunction apart from the pharmaceuticals like synthetic T_3 and T_4 hormones and procaine thyroid. Along with these, homeopathy and yoga are equally important. The discussion suggests and emphasizes the importance of improving the lifestyle and nutritional diet; and further providing spiritual support along with natural thyroid medication.

KEYWORDS

Hyperthyroidism, Hypothyroidism, TSH, Alternative Treatment

INTRODUCTION

The thyroid hormones (TH) secreted by thyroid gland regulate a wide range of physiological functions in the body which may include growth, metabolism and energy homeostasis.[1,2] Subclinical abnormalities are more common among the population as compared to the clinical abnormalities and there is much debate over whether or not they should be actively treated.[3] With increasing age, the prevalence of thyroid dysfunction increases and the diagnosis becomes complicated due to any concomitant disease or therapy[4].

Physiology

Levothyroxine (T_4) and tri-iodothyronine (T_3) are the major hormones secreted by the thyroid gland, under the direct control of thyroid-stimulating hormone (TSH or thyrotropin), secreted from the pituitary gland, in turn under the control of thyrotropin releasing hormone (TRH), secreted by the hypothalamus[5](Figure 1).

***Address for Correspondence:**
Dr. Supriya Agnihotri
Sachdeva College of Pharmacy,
Gharuan, Mohali, Punjab, India.
E-Mail Id: asupriya149@gmail.com

Table 1: Types of thyroid dysfunction

Sr. no.	Thyroid Dysfunction	Definition
1	Hyperthyroidism	Excessive thyroid hormone production (most commonly known as Graves' disease and toxic multinodular goiter).
2	Hypothyroidism	Low secretion levels of thyroid hormone (can be overt or mild/subclinical). Most commonly seen as chronic autoimmune thyroiditis (Hashimoto's thyroiditis or autoimmune thyroid disease). It can also be caused by severe

		iodine deficiency.
3	Congenital Hyperthyroidism	Excessive thyroid hormone levels at birth, either transient (due to maternal Graves' disease) or persistent (due to genetic mutation).
4	Congenital Hypothyroidism	Infants born with an under active thyroid gland and presumed to have had hypothyroidism *in-utero*.
5	Postpartum Thyroiditis	Transient or permanent thyroid dysfunction occurring in the first year after the delivery based on an autoimmune inflammation of the thyroid. Frequently, the resolution is spontaneous.

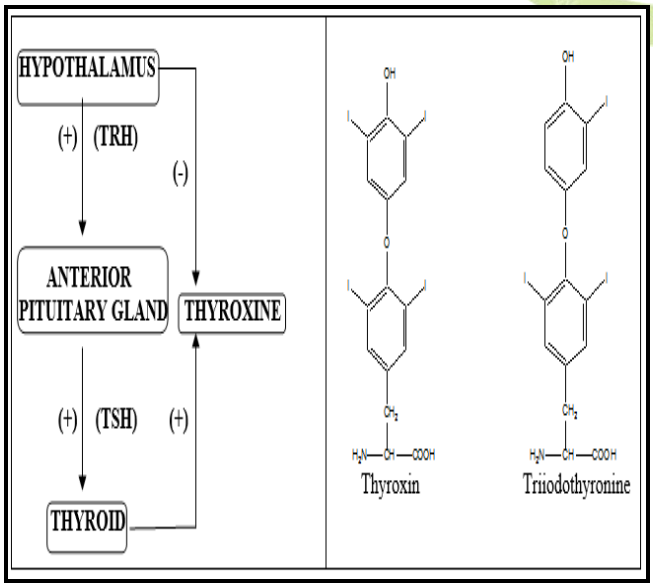


Figure 1: Physiology of thyroid gland and chemical structures of thyroid hormones

Pathogenesis

The thyroid is the main site of iodine uptake in the body, which is then incorporated into TH. The recommended daily intake of iodine for adults is 150-300 micrograms (mcg). Reduced iodine intake is the principal cause of thyroid disease worldwide[6]; intake of <50 mcg/ day is associated with the reduced thyroid function (either hypothyroidism in adults or cretinism in the presence of inadequate intake from birth) or goiter (diffused or nodular enlargement of the gland) whereby the gland size increased to compensate for the lower iodine in an effort to maintain normal TH levels.[7,8] Over the time, there is a risk that the goiter may develop 'autonomy' resulting in the production of TH, not under the control of TSH, potentially resulting in hyperthyroidism[8,9].

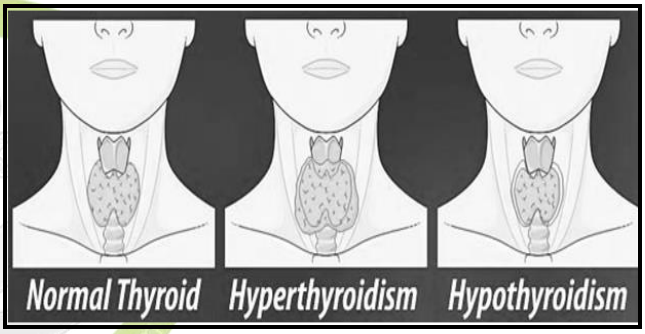


Figure 2: Thyroid gland in hyper and hypothyroidism conditions

Hyperthyroidism

Elevated secretion of TH leads to a condition of hyperthyroidism (thyrotoxicosis), which further results in increased metabolism.[5,9] It is accompanied by suppressed TSH (to undetectable levels).[9,10] If untreated, hyperthyroidism may lead to cardiovascular disorders and severe thyrotoxicosis, known as thyroid storm (very rare, precipitated by *e.g.* infection) associated with a mortality of 20-50%[11,12].

Clinical Presentation of Hyperthyroidism

The signs and symptoms of hyperthyroidism, irrespective of the cause, relate primarily to the over-stimulation of cardiovascular, gastro-intestinal, and nervous systems (Table 2).

Table 2: Clinical and Laboratory Findings of Some Forms of Hyperthyroidism

Symptoms	Physical Findings	Thyroid Function Tests
Weakness and fatigue Heat intolerance Nervousness, irritability and insomnia Weight loss or gain (increased appetite) Diarrhea Palpitations Pedal edema Tremor Amenorrhea/light menses	Thinning of hair Plummer's nails Ocular: Proptosis, lid lag, lid retraction, periorbital edema (exophthalmos in Graves' disease) Diffusely enlarge goiter Wide pulse pressure Flushed, moist skin Pretibial myxedema Brisk deep tendon reflexes	Suppressed TSH Increased TH levels including Total T_4, FreeT_4 Index, Free T_4, Total T_3, Free T_3 Index; Positive antibodies (TRAb*, TgAb$^{\Psi}$, TPOAb$^{\#}$) Radioactive Iodine Uptake (RAUI): >50% in "true" form; Decreased cholesterol; Increased Ca, AST$^{\$}$, alkaline phosphatase

***** TSH receptor antibodies, $^{\Psi}$ Thyroglobulin antibodies, $^{\#}$ Thyroid peroxidase antibodies, $^{\$}$Aspartate aminotransferase

Table 3: Treatment options in Hyperthyroidism[9,10,13]

Treatment option	Indications for use	Advantages	Disadvantages
Antithyroid drugs Carbimazole Propylthiouracil*	Newly diagnosed disease; short-term therapy before surgery or ^{131}I treatment; during pregnancy.	Non-invasive; low cost; outpatient therapy; Low risk of hypothyroidism May balance immune system.	Low cure rate; ADRs $^{\Psi}$ in 1-5%; compliance important (*e.g.* therapy for up to 18 months); regular follow-up needed.
Surgery	Presence of large goiter; serious eye disease; serious ADR $^{\Psi}$ to antithyroid drugs (including during pregnancy).	Rapid control of thyroid function; rapid relief of compression symptoms; 100% "cure".	Invasive and can be expensive (in-patient); produces permanent hypothyroidism; risk of hypo- para- thyroidism and recurrent laryngeal nerve damage; painful.
Radioactive I (^{131}I)	Newly diagnosed disease; relapsed disease; toxic nodular hyperthyroidism.	Effective "cure" i.e. definite treatment; outpatient therapy; easily administered; reduces goiter size.	Slow return to normal thyroid function; >60% develop hypo-thyroidism; adherence to radio-active guidelines needed; pregnancy must be deferred for 6 months.

* Not authorized in Ireland; $^{\Psi}$ Adverse drug reaction(s)

Younger people with thyrotoxicosis may have any of the symptoms but older patients are more likely to have cardiovascular disease such as atrial fibrillation and/or heart failure[12].

Management of Hyperthyroidism

Treatment options for the hyperthyroidism include pharmacotherapy, surgery, and radioactive iodine (^{131}I). The treatment is usually tailored to the individual patient, taking into account the likelihood of remission with medication alone, the potential (and timing) of future pregnancies, goiter size, presence of co morbidities, and the patient preference.[9,10,13] Table 3 outlines the typical uses, advantages, and disadvantages of the three treatment options.

Antithyroid drugs, known as thionamides, inhibit the production of TH in the thyroid gland, by interfering with the iodination process.[13] In addition; they may have immunosuppressive effects, which may be beneficial in promoting remission in autoimmune hyperthyroidism[10,14].

Hypothyroidism

Hypothyroidism is the commonest of all the clinical disorders of thyroid function.[15] The majority of cases are caused by the damage to, or the removal of thyroid gland, or the inhibition of its function (known as primary hypothyroidism)[16].

Autoimmune thyroiditis is the commonest cause of hypothyroidism; it is known as Hashimoto's disease when there is non-tender goiter (due to lymphocytic infiltration) or atrophic thyroiditis when the size of the thyroid gland is diminished or normal.[16] Autoimmune thyroiditis may be accompanied by vitiligo and B_{12} deficiency (due to pernicious anemia), therefore B_{12} levels should be checked regularly if clinically indicated.[17,18] Secondary hypothyroidism, due to hypothalamic and/ or pituitary disease is rare and is usually accompanied by the dysfunction of other hormones (*e.g.* adrenocorticotrophin hormone (ACTH) / gonadotropin production)[16].

Clinical Presentation of Hypothyroidism

The severity of symptoms and signs of hypothyroidism depends on the extent and duration of TH reduction[14]. Because of the insidious onset of the disease in many patients, and the fact that the symptoms are often non-specific, diagnosis may be difficult; especially when patients become passive about their symptoms as the dysfunction progresses.[19] Hypothyroidism is usually diagnosed by an elevated TSH level and a low T_4 level; the presence of specific anti-thyroid antibodies confirms autoimmune thyroiditis but they may not always be identified.

Table 4: Clinical and Laboratory Findings of Primary Hypothyroidism

Symptoms	Physical Findings	Thyroid Function Tests
Weakness, lethargy, and fatigue Muscle cramps, aches, and pains Cold intolerance, Headache Loss of taste/smell, Deafness, Hoarseness, No sweating, Modest weight gain, Dyspnea, Slow speech, Constipation, Menorrhagia, Galactorrhea	Thin, brittle nails , Thinning of skin, Pallor, Puffiness of face and eyelids, Thickening of the tongue, Effusions: peritoneal or pericardial, Decreased deep tendon reflexes, Goiter, Cardiovascular: Hypertension, bradycardia, myxedema heart"	Increased TSH, Decreased TH levels including T_4, Free T_4 Index, Free T_4, Total T_3 , Free T_3, Antibodies (Hashimoto's) Radioactive Iodine Uptake (RAIU): <10%. Increased cholesterol, creatine kinase, lactate dehydrogenase, and AST*; Decreased Sodium, hematocrit / hemoglobin

* Aspartate aminotransferase

Management of Hypothyroidism

T_4 is the replacement therapy of choice because of its long half-life, allowing once daily

administration, ease of administration and low cost.[14,20] Response to T_4 therapy should be monitored by TSH levels (taking into account the time lag in the TSH response) and the dosage increased at 25-50 mcg increments, up to a maximum daily dose of 200 mcg, until clinical evidence of normal function is present and TSH levels are restored to within the normal range.[14] In general, T_4 replacement therapy is for life (except in the case of post-viral or postpartum thyroiditis). T_4 should be taken on an empty stomach in the morning with water and nothing else should be taken at the same time as certain minerals or vitamins interfere with its absorption (*e.g.* calcium).[14,21] Side effects are usually due to excessive dosage and include gastrointestinal disorders, palpitation, and myalgia; that are reversible upon reduction of the dosage[20].

Treatment for Thyroid Dysfunction

General Principles

Ideally, the first step in the treatment is to eliminate or mitigate the effects of known or suspected causes of the thyroid dysfunction, such as medications, nutrient deficiencies, or systemic illnesses. In most of the cases, it is not required to delay the treatment of primary hypothyroidism to determine the exact cause. While the goal of therapy conventionally focuses on the restoration of objective measures of a euthyroid state (such as normalization of TSH, body temperature *etc.*), successful resolution or improvement of symptoms must also be targeted in the larger care plan.

1. Nutrition and Supplements

Iodine: Dietary iodine is an essential nutrient for the thyroid function. Iodine is concentrated in the thyroid gland and is incorporated into the thyroid hormones[22].

Iodine deficiency remains a significant cause of hypothyroidism worldwide, typically in land-locked, impoverished parts of the world. Such chronic, overt deficiency is associated with diets containing <50 mcg/day; but this is rare in industrially developed nations.[8] Iodized salt, saltwater fish, and sea vegetables are the main dietary sources of iodine[23,24,25].

Standard supplementation of dietary salt and vegetable oil has eliminated iodine deficiency in many parts of the world.[26] The Recommended Dietary Allowance (RDA) of iodine is 150 mcg per day for adults.[27] Half teaspoon of iodized salt supplies about enough iodine to satisfy this recommendation.

The Tolerable Upper Intake (TUI) level of iodine is 1,100 mcg per day for adults.[27] Excess iodine can actually cause a transient hypothyroidism that resolves with discontinuation of high doses. This can be seen in individuals or populations consuming large amounts of seafood, iodine supplements or sea vegetables.

Selenium: Adequate selenium is also required for the proper thyroid function.[28] Specifically, selenium facilitates conversion of T_4 to the active T_3 through selenium-dependent deiodinases[25].

TREATMENT

Nutrition and Supplements	Botanicals	Pharmaceuticals	Other CAM*
	Sea vegetables	Synthetic T_4	Yoga
Iodine	Guggulu	(levothyroxine)	Hydrotherapy
Selenium	Goitrogens (Restrict)	Synthetic T_3	
Vitamin A	Some other herbs	(liothyronine)	
Iron, Zinc, L-Tyrosine		Procaine thyroid	

* Complementary alternative medicine

Correcting selenium deficiency may improve concurrent thyroid dysfunction.

There is some evidence that selenium supplementation reduces thyroid peroxidase (TPO) antibody levels in the patients with autoimmune thyroiditis.[29] It has also been found to improve mood and sense of well-being in this population.[29]

Caution should be taken, as selenium can worsen thyroid function with concurrent iodine deficiency. In such cases, selenium and iodine can be supplemented simultaneously.

Other Nutrients (Vitamin A, Iron, and Zinc): A myriad of other vitamins and nutrients influences thyroid function, most notably Vitamin A, iron, and zinc. By various mechanisms, these three nutrients have been experimentally demonstrated to be supportive and necessary for the thyroid function.[25,30,31] Supplementing these nutrients in hypothyroidism is suggested, especially if deficiency states are suspected.

Recommended daily doses are Zinc 10-40 mg/day, Iron 12-45 mg/day, and Vitamin A 800-3,000 mcg/day.

L-Tyrosine: Thyroxin (T_4) is naturally produced by the iodination of tyrosine, a non-essential amino acid obtained from the dietary sources and the endogenous conversion of phenylalanine. Supplementation with L-tyrosine (one of its naturally occurring isomers) is commonly used to support thyroid function.

Given its role in thyroxin production, availability of tyrosine could theoretically affect thyroid function.[32] The usual dose is 500 mg L-tyrosine 2-3 times daily before meals.

2. Botanicals

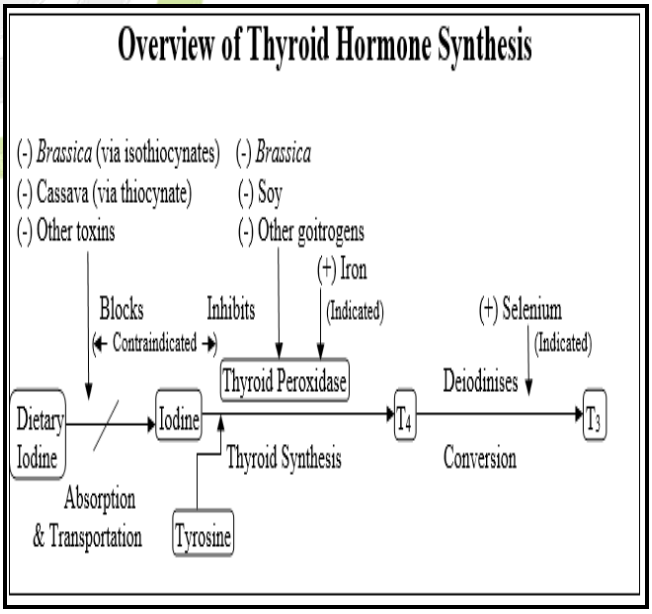
Sea Vegetables: Sea vegetables or seaweeds contain variable amounts of iodine depending on the species, local environment, and the food preparation. Including them in the diet of those suspected with iodine deficiency and reducing/ eliminating for those suspected with surplus iodine.

Guggulu: *(Commiphora wightii)* Guggulu (a common name, also known as guggal, guggul lipid *etc.*) is a gum resin of a small tree used in the Ayurvedic medicine. Its high fiber content is being used as a possible cholesterol-lowering agent.

A fraction called guggulsterone has been found to have thyroid stimulating effects,[33] but further research is needed.

Goitrogens: There are numerous foods that may contribute to the thyroid dysfunction significantly. The Intake of *Brassica* genus of vegetables (broccoli, cabbage, cauliflower, turnips, *etc.*) and soy impair thyroid function by directly inhibiting thyroid peroxidase. The other potentially important goitrogens include cassava and millet. Notably, these negative effects (specifically with *Brassica* vegetables and soy) are not seen in the absence of iodine deficiency[25,34].

Making sure of adequate iodine consumption is probably the best possible way to avoid goitrogenic effect of these otherwise generally healthy foods. Others have suggested that cooking of these goitrogenic foods helps to prevent or mitigate the negative effects.



Some more medicinal plants useful in thyroid dysfunction

Isoflavanoids from some plants have profound effect on thyroid hormones and on the hypothalamus–pituitary axis thus can be useful/ harmful in hyperthyroidism or hypothyroidism.

Sr. No.	Name of plant	Action	Ref
1	*Moringa oleifera*	The aqueous leaf extract of *Moringa oleifera* was evaluated for its ameliorative effect in the regulation of thyroidism in a rat model at the dose level of 250 and 500 mg/ kg. The result of this study suggests that the extract may have beneficial effect on the serum cholesterol concentration and a stimulant action on thyroid functions.	35
2	*Ficus carica*	Ethanolic extract of *Ficus carica* Linn. (Moraceae) leaf was evaluated for its ameliorative effect in the regulation of thyroidism in a rat model at the dose level of 125, 250 and 500 mg/ kg. The presence of tyrosine in the leaf extract may be suggestive of thyroidal activity of the herb.	36
3	Sweet corn silk	Methanolic extract of sweet corn silk was administered to rats at the dose level of 200, 300, and 400 mg/ kg for 21 days. The results show that 400 mg/ kg dose effectively revert the hypothyroid condition in rats.	37
4	Genistein and daidzein from soy (*Glycine max*)	Both inhibit thyroperoxidase that catalyses iodination and thyroid hormone biosynthesis.	38
5	Pearl millet (*Pennisetum glaucum*) and fonio millet (*Digitaria exilis*)	Hypothyroid effects	38
6	Rutabaga and turnips	Contain a thiourea like product (progoitrin), a precursor of goitrin that also interferes with thyroperoxidase	39
7	Peanuts (*Arachis hypogea*), cashew nuts (*Anacardium occidentale*), almonds (*Prunus amygdalus*), and the areca nut (*Areca catechin*).	Anthocyanins, catechins and tannins from these plants have Goiterogenic effect	40
8	*Allium cepa*	N-propyl disulphide, the major volatile constituent of common onion (*Allium cepa*), inhibited thyroid activity in the rat.	41
9	Valerian and passion flower	Insomnia associated with hyperthyroidism can be suppressed by these flowers.	42

3. Pharmaceuticals

Synthetic T_4 (levothyroxine): Synthetic T_4 is the conventional treatment of choice in most cases of hypothyroidism. Initiate at a dose of 12.5-50 mcg per day and adjust based on the blood levels of TSH every 6-8 weeks. Alternately, a dose of about 1.6 mcg/ kg/ day can be initiated for young healthy individuals. Maximum dose is ~300 mcg per day. Levothyroxine by intravenous route in the range of 75-500 mcg per day is indicated for myxedema coma.[43]

Synthetic T_3 (liothyronine): Synthetic T_3 is rarely used conventionally in combination with T_4 to treat hypothyroidism. T_3 is much more bio-active than T_4; it has a quicker onset of action and greater potential and thus can cause more instability of serum levels when administered exogenously.

In euthyroid individuals, the majority of thyroid activity in the body results from the peripheral conversion of T_4 to the more active T_3 by deiodinase enzyme. About 80% of the active T_3 form is produced by this peripheral conversion, and the remaining 20% of T_3 being produced by the thyroid gland. The variation observed in the deiodinase enzyme activity in the individuals/ organs/ tissues raises concerns for some patients with hypothyroidism; and supplemental T_4 alone may not be adequate[43].

Porcine thyroid: Ground pig thyroid (Armour Thyroid, NP Thyroid and Nature-Thyroid) is an older form of supplemental thyroid hormone that is still used by many patients. Like endogenous human thyroid secretions, porcine thyroid preparations contain a combination of about 80% T_4 and 20% T_3, in addition to other possibly active iodinated compounds. Many patients consider this to be more natural and experience better results with this form[44].

4. Other CAM to Consider: (Relatively Safe, but Speculative)

Yoga: There is a particular yoga *asana* or posture that is often purported to stimulate the thyroid gland and its function: *Sharvangasana*, or the shoulder stand. This claim has apparently not been investigated scientifically, but it is generally safe under the guidance of a qualified yoga teacher.[43]

Hydrotherapy: Hydrotherapy is a general term for therapeutic modalities that uses submersion in water for various healing purposes. This approach has extensive historical roots, spanning from ancient civilizations to a contemporary *spa*. Most often, variable temperatures of water are used. Given the central role the thyroid gland plays in regulating thermogenesis, it is possible that hydrotherapy may have some effect on thyroid function. Future research is needed[43].

CONCLUSION

From the present comprehensive review, it can be said that thyroid dysfunction, may be hypo or hyperthyroidism can be treated with medication as well as curative measures of natural origin. The complementary and alternative medicinal options can be much safer and equally effective.

REFERENCES

1. Garg, A. & Vanderpump, K. (2013). Subclinical thyroid disease. *British Medical Bulletin:, 107*, 101-116.
2. Yen, P. (2005). *Genomic and nongemomic actions of thyroid hormones* In: Werner & Ingbar's The Thyroid: a fundamental and clinical text. Braverman, L. E., & Cooper, D. (2012). *Werner & Ingbar's the thyroid: a fundamental and clinical text*. Lippincott Williams & Wilkins, 135-150.
3. Legakis, I., Manousaki, M., Detsi, S., & Nikita, D. (2013). Thyroid function and prevalence of anti-thyroperoxidase (TPO) and anti-thyroglobulin (Tg) antibodies in outpatients hospital setting in an area with sufficient iodine intake: influences of age and sex. *Acta Medica Iranica*, *51*(1), 25-34.
4. Mitrou, P., Raptis, S. A., & Dimitriadis, G. (2011). Thyroid disease in older people. *Maturitas*, *70*(1), 5-9.
5. Santisteban, P. (2005). *Development and anatomy of the hypothalamic-pituitary-thyroid axis* Braverman, L. E., & Cooper, D. (2012). *Werner & Ingbar's the thyroid: a fundamental and clinical text*. Lippincott

Williams & Wilkins. 9th Edition, Chapter 2, 8-25.

6. Vanderpump, M. P., & Tunbridge, W. M. G. (2005). The epidemiology of thyroid diseases. *Werner and Ingbar's the thyroid: a fundamental and clinical text*, 398-406.
7. Daniels, G. & Dayan, C. (Eds.) (2006). *Thyroid physiology and function tests* In: Fast Facts: Thyroid Disorders, Pub: Health Press Ltd, UK. Chapter 1, 9-25.
8. Hermus, A. & Huysmans, D. (2005). *Pathogenesis of nontoxic diffuse and nodular goiter* In: Werner & Ingbar's The Thyroid: a fundamental and clinical text. L Braverman & R Utiger (Eds.). Pus: Lippincott Williams & Wilkins. 9th Edition, Chapter 68, 874-878.
9. Franklyn, J. & Boelaert, K. (2012). Thyrotoxicosis. *Lancet, 379*, 1155-1166.
10. Brent, G. (2008). Graves' disease. *New England Journal of Medicine, 358*, 2594-2605.
11. Ross, D. S. (2011). Radioiodine therapy for hyperthyroidism. *New England Journal of Medicine*, *364*(6), 542-550.
12. Daniels, G. & Dayan, C. (Eds.) (2006). *Hyperthyroidism, oetiology and presentation* In: Fast Facts: Thyroid Disorders, Pub: Health Press Ltd, UK. Chapter 2, 26-34.
13. Cooper, D. S. (2005). Antithyroid drugs. *New England Journal of Medicine*, *352*(9), 905-917.
14. Daniels, G. & Dayan, C. (Eds.) (2006). *Hypothyroidism, diagnosis and management* In: Fast Facts: Thyroid Disorders, Pub: Health Press Ltd, UK. Chapter 5, 79-93.
15. Braverman, L. & Utiger, R. (2005). *Introduction to hypothyroidism* In: Werner & Ingbar's The Thyroid: a fundamental and clinical text. L Braverman & R Utiger. (Eds.). Pus: Lippincott Williams & Wilkins. 9th Edition, Chapter 46, 697-699.
16. Daniels, G. & Dayan, C. (Eds.) (2006). *Hypothyroidism, oetiology and presentation* In: Fast Facts: Thyroid Disorders, Pub: Health Press Ltd, UK. Chapter 4, 69-78.
17. Lahner, E., Centanni, M., Agnello, G., Gargano, L., Vannella, L., Iannoni, C., & Annibale, B. (2008). Occurrence and risk factors for autoimmune thyroid disease in patients with atrophic body gastritis. *The American Journal of Medicine*, *121*(2), 136-141.
18. Taieb, A. & Picardo, M. (2009). Vitiligo. *New England Journal of Medicine, 360*, 160-169.
19. Ladenson, P. (2005). *Diagnosis of hypothyroidism* In: Werner & Ingbar's The Thyroid: a fundamental and clinical text. L Braverman & R Utiger (Eds.). Pus: Lippincott Williams & Wilkins. 9th Edition, Chapter 66, 858-863.
20. Woeber, K. (2005). *Treatment of hypothyroidism* In: Werner &Ingbar's The Thyroid: a fundamental and clinical text. L Braverman & R Utiger (Eds.). Pus: Lippincott Williams & Wilkins. 9th Edition, Chapter 67, 864-869.
21. L-thyroxine®. Summary of Product Characteristics. Available online at: www.imb.ie. Accessed 17th May 2016.
22. Venturi, S., Donati, F. M., Venturi, A., & Venturi, M. (2000). Environmental iodine deficiency: A challenge to the evolution of terrestrial life? *Thyroid*, *10*(8), 727-729.
23. Ristic-Medic, D., Piskackova, Z., Hooper, L., Ruprich, J., Casgrain, A., Ashton, K., & Glibetic, M. (2009). Methods of assessment of iodine status in humans: a systematic review. *The American Journal of Clinical Nutrition*, ajcn-27230H.
24. König, F., Andersson, M., Hotz, K., Aeberli, I., & Zimmermann, M. B. (2011). Ten repeat collections for urinary iodine from spot samples or 24-hour samples are needed to reliably estimate individual iodine status in women. *The Journal of Nutrition*, *141*(11), 2049-2054.

25. Triggiani, V., Tafaro, E., Giagulli, V. A., Sabbà, C., Resta, F., Licchelli, B., & Guastamacchia, E. (2009). Role of iodine, selenium and other micronutrients in thyroid function and disorders. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *9*(3), 277-294.

26. Trumbo, P., Yates, A. A., Schlicker, S., & Poos, M. (2001). Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *Journal of the American Dietetic Association*, *101*(3), 294-301.

27. Guidance, D. (2011). National Agricultural Library, United States Department of Agriculture. Accessed 6th June 2016.

28. Köhrle, J., & Gärtner, R. (2009). Selenium and thyroid. *Best practice & research Clinical endocrinology & metabolism*, *23*(6), 815-827.

29. Toulis, K. A., Anastasilakis, A. D., Tzellos, T. G., Goulis, D. G., & Kouvelas, D. (2010). Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. *Thyroid*, *20*(10), 1163-1173.

30. Zimmermann, M., Adou, P., Torresani, T., Zeder, C., & Hurrell, R. (2000). Persistence of goiter despite oral iodine supplementation in goitrous children with iron deficiency anemia in Cote d'Ivoire. *The American Journal of Clinical Nutrition*, *71*(1), 88-93.

31. Zimmermann. (2007). Interactions of vitamin A and iodine deficiencies: effects on the pituitary-thyroid axis. *International Journal for Vitamin and Nutrition Research*, *77*(3), 236-240.

32. van Spronsen, F. J., van Rijn, M., Bekhof, J., Koch, R., & Smit, P. G. (2001). Phenylketonuria: tyrosine supplementation in phenylalanine-restricted diets. *The American Journal of Clinical Nutrition*, *73*(2), 153-157.

33. Panda, S., & Kar, A. (1999). Gugulu (Commiphora mukul) induces triiodothyronine production: possible involvement of lipid peroxidation. *Life Sciences*, *65*(12), PL137-PL141.

34. Messina, M., & Redmond, G. (2006). Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. *Thyroid*, *16*(3), 249-258.

35. Tabassum, W., Kullu, A. R., & Sinha, M. P. (2013). Effects of leaf extracts of Moringa oleifera on regulation of hypothyroidism and lipid profile. *The Bioscan*, *8*(2), 665-669.

36. Saxena, V., Dharamveer, G. R., & Saraf, S. A. (2012). Ficus carica leaf extract in regulation of thyroidism using ELISA technique. *Asian Journal of Pharmaceutical and Clinical Research*, *5*(2), 44-48.

37. Bhaigyabati, T., Ramya, J., & Usha, K. (2012). Effect of methanolic extract of sweet corn silk on experimentally induced hyperthyroidism in Swiss albino rats. *International Research Journal of Pharmacy*, *3*(3), 241-245.

38. Román, G. C. (2007). Autism: transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. *Journal of the Neurological Sciences*, *262*(1), 15-26.

39. Delange, F. (1989). *Cassava and the thyroid*. In: Environmental goitrogenesis. Boca Raton, Gaitan E (Eds.), Florida: CRC Press, 173–93.

40. Cody, V., Koehrle, J. & Hesch R. D. (1989). *Structure–activity relationships of flavonoids as inhibitors of iodothyronine deiodinase.* In: Environmental goitrogenesis. Boca Raton, Gaitan E. (Eds.), Florida: CRC Press, 57–69.

41. Cowan, J. W., Saghir, A. R. & Salji, J. P. (1967). Faculty of agricultural sciences, American University of Beriut, Beirut, Lebanon. *Australian Journal of Biological Sciences*, 20, 683-685.

42. Shomon, M. (2012). Retrieved from: www.ehow.com/way_5215104_herbal-treatments_thyroid.html Accessed on 23rd May 2016.
43. *Integrative Treatment of Hypothyroidism,* University of Wisconsin Integrative Medicine www.fammed.wisc.edu/integrative
44. Gaby, A. R. (2004). "Sub-laboratory" Hypothyroidism and the Empirical use of Armour® Thyroid. *Alternative Medicine Review*, *9*(2), 157-179.