

## Thyroid Diseases and Diet Control

Tan Kar Soon\* and Poh Wei Ting

Microbiology and Fish Disease Laboratory, Borneo Marine Research Institute, University Malaysia Sabah, Jalan UMS, 88400, Kota Kinabalu, Sabah, Malaysia

\*Corresponding author: Tan Kar Soon, Microbiology and Fish Disease Laboratory, Borneo Marine Research Institute, University Malaysia Sabah, Jalan UMS, 88400, Kota Kinabalu, Sabah, Malaysia, Tel: +6088-320000; Fax: +6-088-320261; E-mail: tankarsoon@ums.edu.my

Received date: February 07, 2018; Accepted date: February 09, 2018; Published date: February 16, 2018

Copyright: © 2018 Soon TK, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

Thyroid diseases are major problem of modern society and are classified as diseases of civilization. Unhealthy lifestyle, stress and exposure to chemical are believed to increase the risk of developing thyroid disorders. Medication and surgery are commonly used to address thyroid diseases. Despite the advancement in medical technology, it was unfortunate that there had not yet to be any potential cure for hypothyroidism. Treatment in the form of synthetic thyroid hormone cause patients to suffer from the symptoms of hypothyroid, despite their thyroid hormone levels being balanced. Whereas the limitation of surgery is patient might need to rely on synthetic thyroid hormone for their lifetime after the thyroid gland is removed. Approaching thyroid disease and autoimmunity from a holistic level and seeing the body as an interconnected system is the better way to address disease. Many recent studies show dietary intervention offer a promising result in treating thyroid diseases. Therefore, a strict eliminating diet to soothe gut inflammation, restore digestive health, and address autoimmune diseases from a holistic approach could be the best way to prevent or treat thyroid diseases.

**Keywords:** Thyroid diseases; Causative factors; Treatment; Diet control

### Introduction

Thyroid disease is triggered by the immune system initiating an attack on own molecules due to the deterioration of immunologic tolerance to auto-reactive immune cells [1]. Thyroid gland is commonly targeted by autoimmune diseases, where the most common dysfunctions of the thyroid gland are hypothyroidism, lymphocytic thyroiditis (Hashimoto's thyroiditis), and hyperthyroidism (Graves' disease) [2]. Among the thyroid diseases, Graves' disease is the dominant and accounts for 50 to 80% of cases of thyroid disease in different regions of the world [3].

Thyroid disease is substantially greater prevalence in old age than in those of younger age and are often covert, being masked by comorbidities. The majority of cases of thyroid diseases are diagnosed in patients aged 45 to 65 years, but they can also affect children [4]. Moreover, thyroid disease is a sex related disease where women are biologically more prone to thyroid disorders [5]. Thyroid disease is estimated to affects 2% of female and 0.2% of male worldwide [6]. In addition, tobacco smoking [7], heavy metal and toxic chemical exposure [8], and stress [9] can significantly increase the risk of developing thyroid disorders.

Diagnosis of thyroid diseases particularly hypothyroidism and Hashimoto's thyroiditis usually leads a long journey of supplementation with synthetic thyroid hormone thyroxin [10]. However, this does not address the true cause of hypothyroidism and Hashimoto's thyroiditis. In fact, despite the advancement in medical technology, it was unfortunate that there had yet to be any potential cure for hypothyroidism and Hashimoto's thyroiditis. Therefore, this paper aims to uncover some of the existing research about autoimmune disease with attempt to identify an effective way to address thyroid diseases.

### Thyroid diseases

Thyroid diseases are caused by an abnormal immune response to auto-antigens present in the thyroid gland. The three main types of autoimmune thyroid diseases are hypothyroidism, lymphocytic thyroiditis (Hashimoto's thyroiditis), and hyperthyroidism [2]. Hypothyroidism is a condition in which the thyroid gland is underactive and produces too little thyroid hormone [11]. Typical symptoms of hypothyroidism include: hoarse voice; slowed speech; puffy face; drooping eyelids; intolerance of cold conditions; constipation; weight gain; dry hair; dry skin; and depression. Patient with hypothyroidism have a greater risk of cardiovascular disease, osteoporosis, overweight, celiac disease and diabetes [12].

Hashimoto's Thyroiditis (HT) is an autoimmune disorder in which the body immune system attacks the thyroid [13]. This will cause decrease in thyroid function and eventually lead to the clinical disorder known as hypothyroid. Untreated hypothyroid can cause patients mild to severe symptoms ranging from hair loss, cold sensitivity, sleep disturbances, weight gain, depression, constipation, brain fog, fatigue, goiters (enlargement of the thyroid gland) and thyroid cancer [12]. Women are 10 to 20 times more likely to be affected by HT disease than man [14].

Hyperthyroidism also known is a condition in which the thyroid gland is overactive and produces too much thyroid hormone [3]. Typical symptoms of hyperthyroidism include: high blood pressure; fast heartbeat; moist skin; increased sweating; tremor; nervousness; increased appetite with weight loss; diarrhea and/or frequent bowel movements; weakness; eyeballs appear to be protruding; and sensitivity of the eyes to light [15]. Hyperthyroidism occurs in approximately 2 to 3% of the adult population [16]. Hyperthyroidism occurs about ten times more frequently in women than men [3]. The average age at diagnosis of hyperthyroidism is 48 years [6,17].

### Factors affecting the risk to thyroid diseases

Several factors have been identified which increases the risk of developing thyroid disorders which include gender [18], tobacco smoking [7], heavy metal and toxic chemical exposure [8], gluten and stress [9].

Most thyroid diseases are more prevalent in women than in men [5,18]. Sex specific differences in the microbiota composition are found only after puberty [19,20]. The main differences between female and male immune systems are the sex hormones, the presence of two X chromosomes versus one X and one Y chromosome [21]. To avoid double dosage of X chromosome-derived proteins, one of the X chromosomes is randomly silenced in female in the early stages of embryogenesis. However, X chromosome inactivation is not complete and about 15% of the genes are still active, which leading to over expression of some X-linked genes in females [22]. Moreover, sex hormones such as estrogens, progesterone, androgens and pro-lectin can influence different aspects of immune system function and potentially affect the risk, activity and progression of thyroid diseases. This is due to present of hormones receptors on immune cells [5]. Generally, estrogens, in particular 17- $\beta$  estradiol (E2) and prolactin, act as enhancers at least of humeral immunity, and testosterone and progesterone as natural immune-suppressants [23]. Prolactin in particular increases antibody production, regulates the development of CD4+ T cells and triggers pro-inflammatory cytokine production [24].

Tobacco cigarette smoking is a risk factor for the development of systemic lupus erthematosus, where the ratios for current smokers versus individuals who have never smoke is 1.5 [25]. Smoking causes tissue damage and increases apoptosis through high production of free radicals, release of metalloproteinase, and the induction of Fas expression on lymphocytes which associated with autoantibody production. In addition, smoking also provokes inflammation as it causes an increase in fibrinogen levels, induces leucocytosis, and elevates levels of C-reactive protein, intercellular adhesion molecule-I and E-selectin [7].

Heavy metals contamination can result in acute heavy metal intoxications in human through accumulations of metals in food chain [26]. Heavy metals such as mercury, cadmium, lead, arsenic, nickel and other metals can stimulate autoantibodies, which in turn, may result in thyroid diseases [8]. Mycotoxins produced by heavy metals are very volatile that wreak havoc on immune system. In addition, chemical toxins such as pesticides, industrial chemicals, hair dyes and some household cleaners can also be link to thyroid diseases [27].

Glutens, made up of two main fractions, gliadins and glutenins, are the main storage proteins of wheat and are comprised of about 100 different proteins in a given wheat cultivar (variety) [28]. Gluten contributes to thyroid disease in three ways. First, it is the primary cause of leaky gut because gliadin triggers the release of zonulin in intestines, a chemical that trigger the opening of gut lining [9]. Second, gluten is highly inflammatory and it stresses immune system [29]. Thirdly, the gluten protein has a similar chemical structure to some of thyroid tissues, which can lead to molecular mimicry, where body mistakes thyroid tissues for gluten and attacks it [30]. In addition, casein in milk (dairy products) also mimicks gluten hence causes inflammation [9].

Stress may affect the immune system either directly or indirectly through the nervous and endocrine systems [31,32]. Stressful situations cause body to release cortisol and activate an acute phase response, which is a part of the innate immune inflammatory response

[9]. In order to maintain homeostasis during stress, activation of the hypothalamic- pituitary- adrenal axis and of the sympathoadrenal system leads to an increased secretion of glucocorticoids and catecholamine's, respectively. The neuroendocrine hormones triggered during stress may lead to immune dysregulation or to amplify cytokine production, resulting in atopic thyroid disease (Tsatsoulis, 2006). Moreover, the stress hormones acting on antigen- presenting immune cells, which may influence differentiation of bipotential helper T-cells away from Th1 phenotype and towards a Th2 phenotype [32].

### Treatments

Medication and surgery: Hyperthyroid diseases could be addressed through medication. The main approach is to reduce the hormone via drugs, which act to stabilise the hormone level. Treatment duration is usually between one-and-half to two years, depending on cases. Once the treatment starts, the level of thyroid hormones would gradually reduce towards stabilization, and so would the dosage [33]. Nevertheless, there had been cases where the patients did not respond well to the treatment. Under such circumstances, there was another more aggressive treatment, the radiation iodine [16]. However, this treatment should consider as the last option and needed the patient's consent as it involved radioactivity. Female patient who is at child-bearing age is best to avoid undertaking the radiation iodine treatment, unless she is really in critical condition. This is because once the patient undergoes the radiation iodine treatment; she needs to postpone any plan to have children until it is completed [34]. Besides that, hyperthyroid diseases could also be addressed through surgery, in which the swelling parts of the gland are removed [15]. This could only be performed if the thyroid functions were stable.

Unlike hyperthyroidism, patients with hypothyroidism would need to depend on ongoing medication. Treatment for hypothyroidism focuses on replacing the thyroid hormone in the body, and one of the natural ways is by increasing salt-iodine in the patients' diet [11]. Treatment comes in the form of synthetic thyroid hormone thyroxin, leaving many patients of hypothyroidism and Hahimoto's thyroiditis to suffer from the symptoms of hypothyroid, despite their thyroid hormone levels being balanced [10,35]. Therefore, more studies are required to fully understand the mechanisms of hyperthyroidism, in order to come out with an effective medicine to address not just the symptom of hypothyroid, but to cure the cause of HT entirely. Although there is no medication for this condition so far, surgery would be suggested as an option should the goiter grow larger [36]. However, surgery should consider as the last option as patients will need to rely on synthetic thyroid hormone for their lifetime after the thyroid gland is removed.

**Gut healing:** Gut imbalance, or leaky gut is believed to be the root cause of most thyroid disease [30]. The leaky gut not only reduces the effectiveness of intestines in absorbing nutrients, but also allows toxins and microbes that are not supposed to be in the gut in and provoke an immune response [9]. The causative factors that can lead to a leaky gut to begin with, underlying food allergies, regular usage of antibiotics, some medications and lifestyle factors can all lead to yeast and/or bacterial overgrowths that cause lining of the gut to be disturbed and lead to autoimmune diseases down the road[37]. Childhood factors such as frequent ear infections or lack of proper bacteria from breast feeding can also lead to a pre-disposal to leaky gut [9].

In general, there are four steps to gut healing processes including; 1) removing any elements (cadmium (Cd), mercury (Hg), arsenic (As), lead (Pb) etc) that are disrupting the digestive environment, 2)

restoring good digestive enzymes into digestive system, 3) rebuilding probiotics bacterial in the gut, and 4) restoring the gut lining. Eliminating inflammatory foods such as gluten, grains, dairy, eggs, nuts, and legumes allow gut to heal [29]. Once the digestive system is healthy and able to process these foods properly, then these foods can be reintroduced.

Restoring good digestive enzymes into digestive system is important in preventing nutrients deficiency diseases. Enzymes level can be increased naturally by four ways including eat raw foods, eat low calories, chew food thoroughly and avoid chewing gum. Raw foods are enzyme-rich, and consuming them decreases your body's burden to produce its own enzymes [30]. Therefore, it is ideally to eat at least 75% of foods at raw to supply our body with the amino acids and the enzyme co-factors needed to boost our own natural enzyme production. In fact, diets heavy in cooked, processed, and sugary foods, combined with overuse of pharmaceutical drugs such as antibiotics, deplete body's ability to make enzymes. Another way to lower body's demand for enzymes is to reduce caloric intake. Reducing overall consumption will reduce the need for digestive enzymes, which allows body to put more of its energy into producing metabolic enzymes. In addition, there are important physiological reasons to chew food well. Chewing stimulates saliva production and activate digestive system by stimulates a reflex that sends a message to pancreas and other digestive organs. Increasing in chewing time caused saliva enzymes work longer in mouth which lessening the workload of stomach and small intestine. However, chewing gum fools our body into believing it is digesting something, so it wasted those enzymes by pumping out digestive enzymes unnecessarily.

Intestinal micro biome plays an important role in the function and integrity of the gastrointestinal tract, maintenance of immune homeostasis and host energy metabolism [38]. Probiotics help replenish good bacteria in the gut. Keep the harmful bacteria population in check, inhibit yeast overgrowth, support positive communication between the brain and intestinal tract, reduce inflammation, and provide an overall healthy environment for body. Probiotics particularly *Lactobacillus* strains enhance the integrity of the intestinal barrier, which may result in maintenance of immune tolerance, decreased translocation of bacteria across the intestinal mucosa, and disease phenotypes such as gastrointestinal infections, inflammatory bowel disease and irritable bowel syndrome [39]. Moreover, probiotics can modulate the intestinal immunity and alter the responsiveness of the intestinal epithelia and immune cells to microbes in the intestinal lumen [40,41].

The final step in gut healing processes is to heal the damaged intestinal lining. Gut lining restoration can be done by consuming an unprocessed diet and giving your body time to rest by providing it with substances that are known to heal the gut, like L-glutamine, omega-3 fatty acids, licorice, antioxidants (in the form of vitamins A, C, and E), quercetin, aloe vera, fish oil and turmeric. L-glutamine helps to heal and seal the gut [29], whereas omega-3, licorice and aloe can help soothe inflammation and can help to relax the gastrointestinal tract [9]. In addition, fish oil helps reduce inflammation, balance hormones, and supports the immune system. Turmeric is a potent astringent that contracts the proteins in the bowel lining, squeezing the spaces between the cells and reducing gut permeability.

### Foods that disrupting the digestive environment

**Eggs and dairy:** Egg whites contain enzymes intended to protect the yolk during embryo development. These enzymes can break up protein

chains rendering the smaller chains useless. Lysozyme has the ability to pass through the digestive system and will latch on carrying other proteins and bacteria to cross the gut-barrier, leading to a leaky gut syndrome [29].

On the other hand, dairy products contain protease inhibitors which contribute to leaky gut, and it is insulin-genic causing spikes in blood insulin levels [29]. Moreover, dairy products contain A1 casein which can cause leaky gut syndrome and increase inflammation in the thyroid gland and ultimately affect its function [9].

**Gluten:** Gluten is a protein found in wheat, barley, rye, kamut, oats, quinoa, buckwheat, and millet [30]. Gluten contains high levels of lectins, saponins, and protease inhibitors [9]. Gluten intakes by a patient with gluten sensitivity will cause the gluten go through the stomach, into the small intestine and force the body to produce a chemical called zonulin, which opens up the intestinal walls, allowing particles and liquids to flow. When this happens, over time the body becomes chronically inflamed, leaving one susceptible to developing an autoimmune disorder, such as thyroid disease and other serious conditions. In addition, gluten closely resembles many of the tissues in our body, therefore gluten that get into the bloodstream due to leaky gut will trigger body to produce antibodies to attack the gluten, but also attack our own tissues [30].

**Nightshades, nuts, seeds, grains and legumes:** Nightshades vegetables, nuts, seeds, grains and legumes contain high levels of lectins. Lectins are not broken down during the digestive process because our bodies's natural digestive enzymes are unable to digest the lectin proteins, and because they contain protease inhibitors. Lectins cause leaky gut by first tricking the gut lining enterocytes into treating it like a simple sugar, allowing it to pass from the inner-gut to the outer-gut, activating immune response and causing the immune system to attack not long the lectin but also enterocytes, creating holes in the gut lining [29].

Nightshades in particular the tomatoes have particular lectin, agglutinin, which stimulates the production of antibodies [9], and it can get into bloodstream quickly and contribute to leaky gut. In addition, nightshades contains saponins, particularly glycoalkaloids which can feed bad bacterias in the gut and destroy the red blood cell membranes when enter the bloodstream [9]. Nuts and seeds in particular contain phytic acid and amylase inhibitors which prevent the breakdown of seeds and cause inflammation, stress out the gut and active the immune system [9].

Additionally, grains and legumes are high in saponins, which can create holes in the surface membrane of the gut and cause inflammation. Protease inhibitors neutralize enzymes in an attempt to avoid digestion, so the body's response is to secrete more digestive enzymes throwing off the balance of enzymes and potentially leading to the destruction of the enterocytes creating a pathway for leaky gut and provolke an immune response.

**Sugars and sweeteners:** Natural sweeteners such as agave are pure fructose, which can tease the body into thinking because it is sweet, that it needs to release insulin to digest the glucose before realizing there is no glucose to digest [29]. Therefore, in the event of sugars are desired, it is best to gain them from natural sugar sources such as honey, maple syrup, or molasses as they all maintain glucose-fructose levels that the body is able to easily digest. It is important to consider that in case of any sort of overgrowth, bacterial or yeast, sugars should be avoided entirely, even fruit based and starchy vegetables that are



converted to glucose as these can feed the overgrowth and lead to further battles to fight them off.

**Alcohol:** Hypothyroidism and Hashimoto's patients are often developing intolerance to alcohol. This is because alcohol causes direct cellular toxicity on thyroid cells, thereby causing thyroid suppression and reducing thyroid volume [42]. Moreover, continuously high alcohol intake can inhibit thyroid hormones T3 and T4 and may reduce the activity of type II 5'-deiodinase, which resulting in reduced levels of Free T3 with ongoing symptoms.

It has also been found that alcohol creates tiny holes in the epithelial cells which can allow some endotoxins into the body [29]. Alcohol feeds on negative bacteria, and can allow them to get into the bloodstream through the holes and create an autoimmune response even in very small amounts.

## Discussion and Conclusion

The dietary intake, as well as lifestyle and environmental factors play a huge role in overall wellness. Thyroid problems seem to be more prevalent these days, in fact, thyroid cancer is the most rapidly increasing cancer in the United States [43]. This could be contributed by the less healthy lifestyle, stressful environments and higher exposure to chemicals which elevated the risk of developing thyroid disorders. Stress is a fact of modern life and it has in fact become an unavoidable part of today's fast-paced, competitive world [44]. Study showed that in stressful conditions, such as sickness or death in the family, financial problems, loss of job, and the unstable political situation caused considerable anxiety which link to autoimmune diseases in many patients [45]. Stress can prevent the body from healing itself and encourage more of an autoimmune inflammatory response. Moreover, exposure to toxins through polluted air or water can wreck the body. Although it is clear that the chemical toxins are a major cause of thyroid disease, yet synthetic compounds with estrogenic activity particularly xenoestrogens are present in cosmetics and personal care products (makeup, hair dyes, soaps, and perfume) that are more commonly used by woman [46]. In addition, caffeine-filled food such as coffee is getting popular in busy life. In fact, caffeine should be avoided because it could increase the heart rate, which might make the condition worse. However, we also do not rule out that increasing number of reported thyroid diseases cases could also be due to more people are being tested, and the tests themselves are better at detecting irregularities.

For treatment, it is important to treat the whole body as a system rather than seeing individual parts working separately. Diet and lifestyle factors formed a key component in the overall treatment of a patient with thyroid diseases. Laboratory study found that four months gluten free diet with supplements of vital minerals and vitamins was able to reverse the Hashimoto's thyroiditis [13]. A 49-year-old man presented with a typical celiac disease with malabsorption, anemia and osteoporosis. The patient received nutritional counseling and was put on a gluten-free diet. A follow-up examination after four months revealed complete remission of the abnormal clinical and laboratory findings with partial remission of endoscopic and histologic changes (reduced to Marsh stage 2 from stage 3a) [13]. Therefore, the treatment of thyroid diseases should start from practicing gluten free diet which allows the gut to heal. At the same time, adopting healthy lifestyle habits such as regular exercise and using natural products to avoid exposure toxic chemicals can facilitate the process of healing the thyroid disease. On the other hand, social factors such as the quality of

relationship between patient and his family, are useful prognostic factors in patient with thyroid disease [45,47-49]. Moreover, stress management and behavioral interventions such as weight management, adequate balanced diet, and a healthy home environment indeed will help in recovering from thyroid disease [47,48,50]. Coping strategies are important for daily routine and for physiological well-being of chronic patients. They enable the patients to adapt to problems and stressors arising from the disease, such as pain, fatigue, limitation in mobility, difficulties in daily life activities, and threats to the patient's self-esteem [50-52].

In conclusion, with this understanding, it is possible to see the positive synergic effects of healthy diet and healthy lifestyle factors in addressing thyroid disease. Although there is clear and increasing evidences that practising healthy lifestyle, gluten free diet, and use of probiotics look promising in treating thyroid diseases. However, more researches are needed before it can be used therapeutically to heal leaky gut and indirectly cure thyroid diseases. In addition, further understanding about the root causes of thyroid diseases is necessary, to find an effective solution to address not just to cure, but to prevent the cause of thyroid diseases entirely. The bottom-line is regardless of the conditions, annual health check-ups and blood tests are important for early detection [53,54].

## Acknowledgments

This work was financially supported by University Malaysia Sabah.

## References

- Invernizzi P, Gershwin ME (2009) The genetics of human autoimmune disease. *Journal of Autoimmunity* 33: 290-299.
- Przybylik-Mazurek E, Hubalewska-Dydejczyk A, Huszno B (2007) Autoimmune hypothyroidism. *Immunologia* 3-4: 64-69.
- Brent GA (2008) Clinical practice. Graves' disease. *New Eng J Med* 358: 2594-2605.
- Bjoro T, Holmen J, Kruger O, Midthjell K, Hunstad K, et al. (2000) Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trøndelag (HUNT). *European J Endocrin* 143: 639-647.
- Merrill S, Mu Y (2015) Thyroid autoimmunity as a window to autoimmunity: an explanation for sex differences in the prevalence of thyroid autoimmunity. *Journal of Theoretical Biology* 375: 95-100.
- Kahaly GJ, Grebe SK, Lupo MA, McDonald M, Sipos JA (2011) Grave's disease: diagnostic and therapeutic challenges (multimedia activity). *Am J Med* 124: S2-S3.
- Shoenfeld Y, andman-Goddard G, Stojanovich L, Cutolo M, Amital H, et al. (2008) The mosaic of autoimmunity: hormonal and environmental factors involved in autoimmune diseases 10: 12.
- Samuchiwal SK (2017) Autoimmune disease: backfiring of an otherwise unerring defence. *MOJ Autoimmune Disease* 2: 00008.
- Myers A (2015) *The autoimmune solution*. New York, New York: Harper Collins Publications.
- Baron-Faust, R, Buyon J (2003) *The autoimmune connection*. New York McGraw-Hill: New York.
- Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, et al. (2014) Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid* 24: 1670-1751.
- Rugge JB, Bougatsos C, Chou R (2015) Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive services task force. *Annals of Internal Medicine* 162: 35.

14. Schreiber F, Zolb T, Veith M, Elsbernd H (2011) A typical celiac disease in a patient with type 1 diabetes mellitus and Hashimoto's thyroiditis. *Deutsche Medizinische Wochenschrift* 136.
15. Intidhar LS, Chaabouni AM, Kralom T, Attia N, Gritli S, et al. (2006) Thyroid carcinoma and Hashimoto thyroiditis. *Ann Otolaryngol Chir Cervicofac* 123: 175-178.
16. Yi KH, Moo JH, Kim IJ, Bom HS, Lee J, et al. (2013) The diagnosis and management of hyperthyroidism consensus: report of the Korean Thyroid Association. *J Korean Thyroid Assoc* 6: 1.
17. Moon JH, Yi KH (2013) The diagnosis and management of hyperthyroidism in Korea: Consensus report of the Korean thyroid association. *Endocrinology and Metabolism* 28: 275.
18. Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, et al. (1977) The spectrum of thyroid disease in community: the Whickman survey. *Clinical Endocrinology* 7: 481-493.
19. Quintero OL, Amador-Patarroyo MJ, Montoya-Ortiz G, Rojas-Villarraga A, Anaya JM (2012) Autoimmune disease and gender: Plausible mechanisms for the female predominance of autoimmunity. *Journal of Autoimmunity* 38: 109-119.
20. Frieri M (2003) Neuroimmunology and inflammation: implications for therapy of allergic and autoimmune diseases. *Annals of Allergy, Asthma and Immunology* 90: 34-40.
21. Murphy ED, Roths JB (1979) A Y chromosome associated factor in strain BXSb producing accelerated autoimmunity and lymphoproliferation. *Arthritis and Rheumatology* 22: 1188-1194.
22. Pierdominici M, Maselli A, Colasanti T, Giammarioli AM, Delunardo F, et al. (2010) Estrogen receptor profiles in human peripheral blood lymphocytes. *Immunology Letters* 132: 79-85.
23. Selmi C, Brunetta E, Raimonda MG, Meroni PL (2012) The X chromosome and the sex ratio of autoimmunity. *Autoimmunity Reviews* 11: A531-537.
24. Zandman-Goddard G, Peeva E, Shoenfeld Y (2006) Gender and autoimmunity. *Autoimmun Rec* 6: 366-372.
25. Shelly S, Boaz M, Orbach H (2011) Prolactin and autoimmunity. *Autoimmunity Reviews* 11: A465-470.
26. Costenbader KH, Karlson EW (2006) Cigarette smoking and autoimmune disease: what can we learn from epidemiology? *Lupus* 15: 737-745.
27. Tan KS, Denil DJ, Ransangan J (2016) Temporal and spatial variability of heavy metals in Marudu Bay, Malaysia. *Oceanological and Hydrological Studies* 45.
28. Viswanath D (2013) Understanding autoimmune disease- A review. *Journal of Dental and Medical Sciences* 6: 8-15.
29. Jabri B, Kasarda DD, Green PH (2005) Innate and adaptive immunity: the yin and yang of celiac disease. *Immunol Rev* 206: 219-231.
30. Ballantyne S (2013) *The Paleo Approach: Reverse autoimmune disease and heal your body*, Victory Belt Publishing, USA.
31. Blum S (2013) *The immune system recovery plan*. New York: Scribner.
32. Tsatsoulis A (2006) The role of stress in the clinical expression of thyroid autoimmune disease. *Autoimmune Review* 7: 209-213.
33. Wu LI, El-Kaissi S, Wall JR (2004) Stress and thyroid autoimmunity. *Thyroid: Off J Am Thyroid Assoc* 14: 1047-1055.
34. Cooper DS (2005) Antithyroid drugs. *N Engl J Med* 352: 905-917.
35. Nazarpour S, Ramezani R, Simbar M, Azizi F (2016) Thyroid antibodies and the effect on pregnancy outcomes. *Journal of Obstetrics and Gynecology* 36: 3-9.
36. Vita R, Saraceno G, Trimarchi F, Benvenega S (2013) A novel formulation of L-thyroxine (L-T4) reduces the problem of L-T4 malabsorption by coffee observed with traditional tablet formulations. *Endocrine* 43: 154-160.
37. Colucci P, Yue CS, Ducharme M, Benvenega S (2013) A review of the pharmacokinetics of levothyroxine for the treatment of hypothyroidism. *European Endocrinology* 40-47.
38. Fasano A (2011) Leaky gut and autoimmune diseases. *Clinic Review Allergy and Immunology* 42: 71-78.
39. Pflughoeft K, Versalovic J (2012) Human microbiome in health and disease. *Annual Reviews Pathology* 7: 99-122.
40. Lee B, Bak Y (2011) Irritable bowel syndrome, gut microbiota and probiotics. *Journal of Neurogastroenterology and Motility* 17: 252-266.
41. Thomas C, Versalovic J (2010) Probiotics-host communication: modulation of signaling pathways in the intestine. *Gut Microbes* 1: 148-163.
42. Bron P, Van Baarlen P, AndKleerebezem M (2011) Emerging molecular insights into the interaction between probiotics and the host intestinal mucosa. *Nature Reviews Microbiology* 10: 66-78.
43. Ozsoy S, Esel E, Izqi HB, Sofuoqlu S (2006) Thyroid function in early and late alcohol withdrawal: relationship with aggression, family history, and onset age of alcoholism. *Alcohol Alcohol* 41: 515-521.
44. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM (2017) Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. *JAMA* 317: 1338.
45. Dahiya S (2015) Occupational stress and personality trait in the Indian manufacturing sector: An analytical study. *ELK Asia Pacific Journal of Human Resources Management and Organisational Behaviour* 1: 69-88.
46. Stojanovich L (2010) Stress and autoimmunity. *Autoimmunity Reviews* 9: 271-276.
47. Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F, et al. (2016) Sex-based differences in autoimmune diseases. *Annali dell' Istituto Superiore di Sanita* 52: 205-212.
48. Maefarlane GJ, Pallewatte N, Paudya P, Blyth FM, Coggon D et al. (2008) Evolution of work related psychosocial factors and regional musculoskeletal pain: results from a EUAR task force. *Annals of the Rheumatic Diseases* 68: 885-891.
49. Stojanovich L, Marisavlkevich D (2008) Stress as a trigger of autoimmune diseases. *Autoimmune Review* 7: 209-213.
50. Herrmann M, Sholmerich J, Straub RH (2000) Stress and rheumatic disease. *Rheumatic Diseases Clinics of North America* 26: 737-763.
51. Persson IO, Berglund K, Saliberg D (1999) Psychological factors in chronic rheumatic diseases- a review. The case of rheumatoid arthritis, current research and some problems. *Scandinavian Journal of Rheumatology* 28: 137-144.
52. Wilder IR (2002) Neuroimmunoendocrinology of the rheumatic diseases past, present and future. *Annals of the New York Academy of Sciences* 960: 13-19.
53. Cuolo M, Straub RH (2006) Stress as a risk factor in the pathogenesis of rheumatoid arthritis. *Neuroimmunomodulation* 13: 277-282.
54. Shoenfeld Y, Isenberg D (1989) *The mosaic of autoimmunity*. Research Monographs in Immunology Amsterdam. The Netherlands: Elsevier Science Publishers: 1989.