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Review Article

Pharmacology Section

Various Possible Toxicants Involved in Thyroid Dysfunction: A Review

JAGMINDER K. BAJAJ[1], POONAM SALWAN[2], SHALINI SALWAN[3]

ABSTRACT

About 300 million people across the world suffer from thyroid gland dysfunction. Environmental factors play an important role in causation of autoimmune thyroid diseases in susceptible individuals. Genetics contributes to 70% of the risk. In order to reduce the risk, we need to understand the association of environmental agents with thyroid dysfunction. These factors are especially relevant for those at increased risk due to positive family history. The ideal study to see the impact of a thyroid toxicant consists of directly measuring the degree of exposure to toxicant in an individual with his thyroid status. Knowledge of various factors influencing thyroid dysfunction can help in interpreting the results of such studies in a better way. This article is an attempt to highlight the various possible toxicants affecting thyroid function so that adequate measures can be undertaken to control excessive exposure in future to reduce the prevalence of thyroid disorders.

Keywords: Goiter, Hypothyroidism, Thyroid disorders, Thyroid

INTRODUCTION

Thyroid gland produces three important metabolic hormones, thyroxine, tri-iodothyronine, and calcitonin [1]. Thyroid stimulating hormone (TSH) produced by the anterior pituitary gland controls the production of these hormones. Iodine, derived mainly from sea-foods or consumed in the form of iodized salt, is utilized for producing T_3 and T_4 hormones [2]. Thyroid Disorders are the commonest amongst the various glandular disorders of the endocrine system [3]. According to a recently released report, about 300 million people in the world are suffering from this endocrine problem, out of which 42 million are Indians [4,5]. The prevalence of thyroid disorders is not distinctive in different age groups, sex as well as different areas [6]. Common thyroid disorders include hypothyroidism, hyperthyroidism, goiter and other Iodine deficiency disorders, Hashimoto's thyroiditis and thyroid cancer [7]. The untreated thyroid disease can produce serious consequences especially cardiovascular diseases. So, improved public awareness about thyroid disorders and the responsible factors for it is important to cope with thyroid illness [8].

The prevalence of hypothyroidism in 8 major cities of India is reported to be 10.95% with significantly higher proportion of females vs. males (15.86% vs. 5.02%) and older vs. younger (13.11% vs. 7.53%) adults and 21.85% patients tested positive for anti-TPO antibodies [9]. Another study however showed the prevalence of hypothyroidism to be 3.9%; out of which 53% of subjects with subclinical hypothyroidism were positive for anti-TPO antibodies. Urinary iodine status in the same population showed it to be iodine sufficient. Anti-TPO antibodies reported in more than a third of community detected hyperthyroid cases [10]. In the past, endemic goiter has been linked to iodine deficiency by several prominent researchers [11-13] but despite iodization, its prevalence has not reduced, hence thyroid auto-immunity and other goitrogens seem to play important role in causation of goiter [14].

Genetic predisposition is reported in about 70-80% of autoimmune thyroid disease [15], the rest 20-30% contributed by environmental triggers based on animal and human studies [16-19]. Thus, the knowledge of environmental factors that trigger autoimmune thyroid diseasemay help in reducing the risk [20].

Some of the factors proposed from various human and animal studies are:

DIETARY FACTORS

1. **Excess dietary iodine:** In genetically susceptible individuals, increased consumption of Iodine can act as a trigger for thyroiditis [21,22]. Iodine laden foods viz. kelp seaweed, iodinated salt, iodine additives to bread /flour, preservatives, medicines such as amiodarone, vitamins, Lugol'slodine topical antiseptics and contrast dyes may act as starting point as highly iodinated thyroglobulin is demonstrated to be more immunogenic than poorly iodinated one [23-25]. Iodine may also have a direct toxic effect on thyroid via free oxygen radicals and immune stimulation [26].
2. **Naturally occurring goitrogens:** They are found in legumes, plants, amiodarone, lithium [27], in addition to cabbage, cauliflower, broccoli, turnip, forms of root cassava. Soy or soy enriched foods can also aggravate thyroid problems reducing T4 absorption and interfering with thyroid hormone action [28] and are reported to increase auto-immune thyroid disease [29].
    a. **Role of Dietary Fat:** Nutrition can affect hypothalamo-pituitary thyroidal axis [30]. Dietary fat composition influences TSH secretion, thyroid peroxidase activity, hepatic deiodinase activities and T3 binding to nuclear receptors. In a study conducted on male Wistar rats, fed on diets differing in fat composition, total and free thyroxine levels were found to be higher in saturated fat fed group than others. Further Tri-iodothyronine and thyroid peroxidase levels were reported to decrease in rats fed on polyunsaturated fats and increased in rats fed on monounsaturated fats. However, hepatic de iodinase activity decreased irrespective of fat composition [31]. TPO activity might be stimulated by consumption of polyunsaturated n-3 FA and monounsaturated n-9 FA while it is reduced by saturated and polyunsaturated n-6 FA. Stimulating effects of n-3 PUFA have also been observed for transthyretin expression in brain [32] and thyrocyte proliferation [33]. However, other results also suggest involvement of PUFA n-6 in stimulation of thyroid activity [34]. Dietary high–fat lard intake induced significant thyroid dysfunction and abnormal morphology in rats which failed to be corrected by short-term dietary modification. Raised triglyceride levels and decreased total T4 and free T4 levels along with raised serum TSH levels

were noted [35]. In another study on rat model, the effect of thermally oxidized dietary fats was noted. Raised plasma thyroxine concentration showed that oxidized fats can also alter the morphology and function of thyroid gland [36].

b. **Role of Green Tea:** Thyroid function can be impaired by green tea extracts at high doses. A significant decrease in serum T_3 and T_4 and increase in TSH levels has been reported along with decreased TPO and deiodinase activity in response to dietary green tea extract in rats [37]. A recent study conducted to see the effect of catechins, the flavonoids in green tea on thyroid physiology in rat model concluded decreased activity of thyroid peroxide and 5'-deiodinasel enzymes. Decreased levels of serum T3 and T4 along with significant elevation of TSH was noted [38].

c. **Soy and Soybean Ppoduct:** One of the studies reported the development of goiter and hypothyroidism in a 10-month-old infant who was put on soybean product right from birth but it reversed with soybean product withdrawal and Lugol's iodine drops. In addition, thyroid showed high uptake of I^{131}after soybean product withdrawal. Studies on adults revealed significant suppression in plasma-bound I^{131} while receiving soybean product [39]. Thus soybean product seemed to contain goitrogenic agent which affects thyroid function. A review of 14 trials concluded that although soya protein and isoflavones do not affect normal thyroid function in people with sufficient iodine intake but they may interfere with absorption of synthetic thyroid hormone increasing the dose of medication in hypothyroid patients [40].

d. **Cyanogenic Plant Foods:** Raw, boiled and cooked extracts of various cyanogenic plant foods including cauliflower, cabbage, mustard, turnip, raddish, bamboo shoot and cassava have been shown to possess anti-TPO activity. Moreover, boiled exracts of these cyanogenic plant foods showed highest anti-TPO potency followed by cooked and raw extracts. Goitrin is an active goitrogen present in plants of Rutabaga, turnip and Brassicae seeds. However, cooking destroys the enzyme responsible for activation of progoitrin to goitrin thus negating its anti-thyroidal potency. Goitrogenic foods if consumed in considerable quantities may contribute to development of goiter but it is difficult to incriminate them as aetiologic factors in vast majority of goitrous patients [41].

e. **Role of Groundnut:** The effects of groundnut supplements on size and iodine content of thyroid and radioactive I^{131}uptake and its urinary excretion were studied in albino rats. Groundnuts (active principle arachidoside) were reported to be goitrogenic, however this effect was inhibited by small amounts of iodine as potassium iodide [42,43].

f. **Role of Millet:** Various studies on rats and thyroid slices of pork have shown that millet diets containing C-glycosylflavones (glycosylvitexin, glycosylorientin and vitexin) produce effects resembling small doses of anti-thyroid drug, methimazole. Maximum anti-thyroid effect and significant increase in thyroid weight along with maximum inhibition of TPO activity was seen with millet bran fraction having maximum concentration C-glycosylflavones [44].

g. Selenium deficiency and Vitamin B12 deficiency have also been implicated in autoimmune thyroiditis [45].

ENVIRONMENTAL FACTORS

a. Organochlorine compounds found in pesticides, induce hepatic enzymes leading to decreased half-life of serum thyroxine (T_4) [46].

b. Isoflavones: reduce thyroperoxidase activity [47].

c. Polychlorinated biphenyls, polybrominateddiphenylethers, bisphenol-A, and triclosan may have direct action on thyroid hormone receptor [47].

d. Perchlorates found in rocket fuels, thiocyanates and nitrates interfere with iodine uptake [47]. A study conducted on pregnant women living in an industrial area in south California showed strong association between increased urinary perchlorate and decreased total and free thyroxine levels along with increased TSH levels [48].

e. **Cosmetics:** UV filters meant to protect skin from UV irradiation can also alter thyroid homeostasis [49]. A study on Benzophenone-2 treated rats showed low T_4 levels and high TSH levels besides altered Thyroid-peroxidase activity [49]. Another chemical OMC (Octyl-methoxycinnamate)causes dose dependent decrease in serum T_3 and T_4 concentration in rats [50].

f. **Heavy metals:** Heavy metals like cadmium and lead are known to affect thyroid function. In a study on adult cows, lead exposed cows living in polluted areas showed significantly higher blood lead and T_3, T_4 concentration [51]. In a study on pregnant women, those from lead exposed town had lower mean free thyroxine (FT4), higher mean TPO antibodies along with higher lead concentration suggesting stimulation of auto-immunity by prolonged lead exposure [52].

g. Studies using genetically exposed mice have also shown bromine and bacterial lipopolysaccharides to trigger autoimmune thyroiditis [53].

h. In the third National Health and Nutrition Examination Survey (NHANESIII), relationship between smoking and thyroid abnormalities was evaluated. Smoking has been found to be inversely related to the prevalence of serum thyroid auto-antibodies. Lesser number of smokers were shown to have serum thyroid auto-antibodies (11%) and elevated TSH (2.6%) in comparison to non-smokers (18%) and (5.5%) respectively [54].

i. **Role of Age:** Thyroid diseases are reported to be more common in perimenopausal and menopausal women because of altered balance between oestrogen and progesterone [55], However, daily administration of genisteinaglycone (a known goitrogen) to post-menopausal women over a period of 3 years did not modify T_3, T_4, TSH levels and enzyme activity [56] hence proving there is no relation of age to thyroid diseases.

CONCLUSION

The goitrogenic potential of a plant or food depends upon the amount of active goitrogen present in it. Various procedures like soaking, washing, boiling and cooking can help in reducing the goitrogenic potency of these foods. These, along with the intake of iodide supplements are generally practiced in areas where goitrogenic foods are routinely consumed. How far these measures are effective in reducing anti-thyroidal activity is still unclear. Patients suffering from hypothyroidism can avoid consumption of raw cruciferous vegetables such as cabbage, Brussels sprouts, broccoli, cauliflower, mustard greens, kale, and turnip. In addition, daily diet should include thyroid boosting foods like those rich in iodine, amino acid tyrosine, minerals like selenium, zinc, copper, iron, various vitamins including, B2, B3, B6, C and E. The benefits of iodine repletion outweigh the risk of thyroid auto-immunity, hence global iodine sufficiency should be ensured. The amount of fat consumed and its composition definitely influences thyroid activity as evident from the study quoted above but more studies are required to validate the results. It is difficult to prove the role of environmental chemicals in increasing susceptibility to autoimmune thyroid disease although they have been blamed for its causation since long. Further studies on environmental toxicants can provide an indepth view of the impact of these agents.

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PARTICULARS OF CONTRIBUTORS:
1. Professor and Head, Department of Pharmacology, PIMS, Jalandhar, India.
2. Assistant Professor, Department of Pharmacology, SGT Medical College and Hospital, Gurgaon, India.
3. Associate Professor, Department of Pharmacology, PIMS, Jalandhar, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shalini Salwan,
Associate Professor, Department of Pharmacology, PIMS, Jalandhar-144001, India.
E-mail: drshalinisalwan@yahoo.co.in

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