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Review Article

Impact of tobacco on thyroid function

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ABSTRACT

A psychoactive substance is any chemical that, upon consumption, leads to a state of intoxication and alteration of physiological functions. Tobacco is the most common licit psychoactive substances being used globally and is the biggest contributors to mortality and morbidity. Tobacco has multiple effects on the hypothalamic-pituitary-thyroid axis and the functioning of the thyroid gland. This article presents a review of the clinically relevant effects of tobacco on the hypothalamic-pituitary-thyroid axis. This review mainly focuses on clinical issues. Tobacco smoking modifies almost all functions of the thyroid gland.

Key words: Thyroid, tobacco, hypothalamic-pituitary-thyroid axis

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INTRODUCTION

Cigarettes are considered as the commonest source of toxic chemical exposure and chemically mediated illness in humans. Globally, tobacco use is one of the commonest licit substances of abuse and is projected to kill 50% more people than HIV/AIDS by 2015, and to be responsible for 10% of all deaths by 2030. Of great concern is the fact that more than 80% of these deaths are expected to occur in low- and middle-income countries including India.[1] The first Global Adult Tobacco Survey of 2010 reports that currently 34.6% of adults (47.9% males and 20.3% females) in India are users of tobacco products.[2] Additionally, prevalence of tobacco use is high among people seeking help for use of other psychoactive substances as well.[3] In view of the magnitude of the problem, it becomes necessary for us to understand the effect of tobacco on various body systems.

Recent advances in addiction biology suggest that craving and withdrawal are not only psychological but are often biological and result from the neuroendocrine changes that these psychoactive substances cause. Dopamine, serotonin, and the hypothalamic-pituitary axis are intricately linked to development and continuation of dependence of chemical substances.[4] It is, therefore. not surprising to find that most substances of abuse in return have multiple effects on the hypothalamic-pituitary-thyroid axis. Indeed, ample evidence now documents the effect of nicotine and tobacco smoke on human endocrine system. Of the multitude of drug-endocrine interactions reported, this review focuses on the effect of tobacco on the hypothalamo-pituitary-thyroid axis. A major shortcoming of the current literature is that most of the information is in context of smokable forms of tobacco. The impact on hypothalamic-pituitary-thyroid (HPT) axis of smokeless tobacco, the commoner form of abuse in India, largely remains unexplored. The paper is presented as a critical overview for readers and is by no means an exhaustive systematic review because of wide scope of the subject.

METHODOLOGY

Databases of Medline (PubMed), PsycINFO, and Scopus were searched from inception till July 2012. The initial decision of the authors was to limit all searches to English language original articles on human subjects; excluding all reviews, systematic reviews, and meta-analysis. The MeSH terms: "Tobacco Use Disorder", "Smoking", "Thyroid Diseases", "Thyroid Gland", and "Thyroid Function Tests" were used to build primary search queries. Currently, the term "Nicotine Use Disorder" is subsumed under "Tobacco Use

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Disorder", while "Cigarette smoking" is under the MeSH heading of "Smoking."[5]

To supplement the data gathered from the first round of searches, we searched with specific terms in all the above databases and Google Scholar. Such secondary search terms for thyroid functions were: Thyroid, neuroendocrine, endocrine, thyroid stimulating hormone (TSH), Thyrotropin-releasing hormone (TRH), T3, T4, thyroid-stimulating hormone, thyrotropin-releasing hormone, thyrotropin, thyroxine, triiodothyronine, hypothalamic-pituitary axis, hypothalamo-pituitary axis (HPA), and hormone. Each of these secondary terms was combined with terms for tobacco to generate search results.

We also identified previous reviews and systematic reviews on the topic, and manually searched all cross-references for further studies [Table 1]. Only one meta-analysis on the topic by Vestergaard in 2002 was identified. All abstracts were individually considered by both the reviewers for inclusion into the study. For included abstracts, full texts were subsequently procured. Figure 1 depicts the search strategy and the studies included.

A majority of the selected studies were descriptive and often contradictory, suggesting a complex interrelation of tobacco smoke with the thyroid function. Randomized control trials were rare, although comparison groups were often used. Lack of consensus in clinical findings also hampered the development of theoretical models of causation. Theoretical constructs for how these changes in thyroid functioning are brought about by tobacco are mostly presented as assumptions by authors. Despite these limitations, clinically important patterns of interaction between tobacco use and thyroid axis emerged from these studies, which this review tries to summarize.

CHEMICAL AGENTS IN TOBACCO SMOKE AFFECTING THYROID

Tobacco smoke contains around 7000 chemical compounds of which at least 158 compounds have been reviewed in scientific literature as harmful, carcinogenic, and/or potentially affecting physiological functions.[34] Of these combustion products, nitroso compounds, polycyclic hydrocarbons, aromatic amines, and aldehydes are most commonly implicated for toxicity.[35] The effect of cigarette smoke on thyroid is believed mostly to be due to the compound "Thiocyanate," a derivative of hydrogen cyanide with a half-life >6 days.[36-40] Thiocyanate hampers thyroid functioning by at least three distinct pathways. Thiocyanate inhibits iodine uptake by the thyroid, thereby

Table 1: Reviews and systematic reviews on effect of tobacco on thyroid function

Principle author	Year	Topic of review	Reference no.
Galor A	2011	Effects of smoking on ocular health.	[6]
Duntas LH	2011	Environmental factors and thyroid autoimmunity.	[7]
Czarnywojtek A	2010	Smoking and thyroid diseases--what is new?	[8]
Czarnywojtek A	2009	Smoking and thyroid disease--review of literature	[9]
Lois N	2008	Environmental tobacco smoke exposure and eye disease.	[10]
Thornton J	2007	Cigarette smoking and thyroid eye disease: A systematic review.	[11]
Mallampalli A	2006	Smoking and systemic disease.	[12]
Costenbader KH	2006	Cigarette smoking and autoimmune disease: What can we learn from epidemiology?	[13]
Krassas GE	2006	Smoking and autoimmune thyroid disease: The plot thickens. *(Commentary)*	[14]
Kapoor D	2005	Smoking and hormones in health and endocrine disorders.	[15]
Mallampalli A	2004	Smoking and systemic disease.	[16]
Prummel MF	2004	The environment and autoimmune thyroid diseases.	[17]
Dorea JG	2004	Maternal thiocyanate and thyroid status during breast-feeding.	[18]
Hegediüs L	2004	Relationship between cigarette smoking and Graves' ophthalmopathy.	[19]
Erdogan MF	2003	Thiocyanate overload and thyroid disease.	[20]
Vestergaard P	2002	Smoking and thyroid disorders--a meta-analysis.	[21]
Cheng AC	2000	The association between cigarette smoking and ocular diseases	[22]
Mann K.	1999	Risk of smoking in thyroid-associated orbitopathy.	[23]
Wiersinga WM	1999	Environmental factors in autoimmune thyroid disease.	[24]
Utiger RD	1998	Effects of smoking on thyroid function.	[25]
Bartalena L	1995	Cigarette smoking and the thyroid.	[26]
Bertelsen JB	1994	Cigarette smoking and the thyroid.	[27]
Hegedüs L	1990	Thyroid size determined by ultrasound. Influence of physiological factors and nonthyroidal disease.	[28]

Search Result: 176, Rejected for relevance of content: 149, Rejected for non-English language: 5,[29-33] Selected: 22

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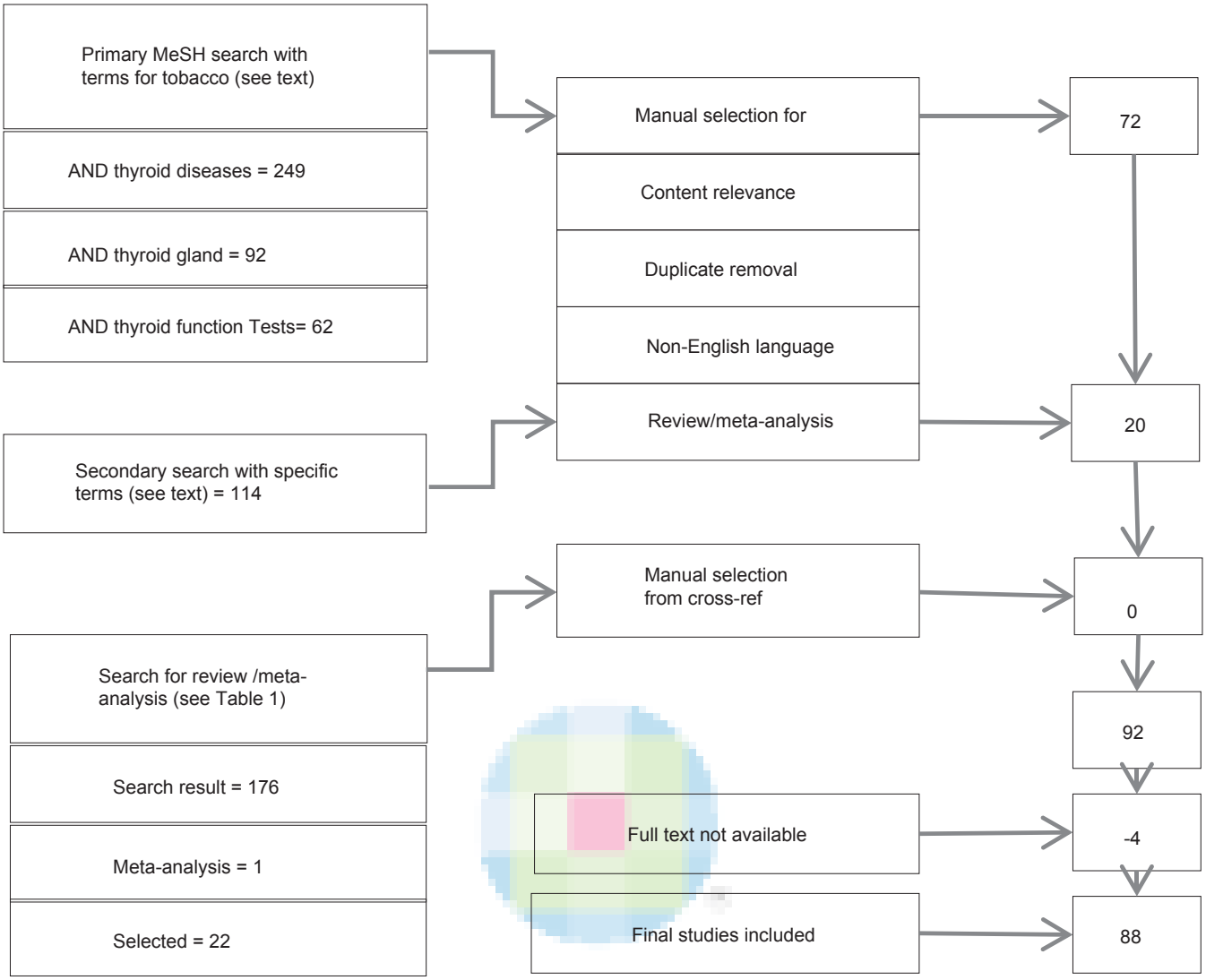

Figure 1: Search methodology

producing a relative iodine deficient state. Thiocyanate also competes with iodide in the organification process,[36] thereby inhibiting thyroid hormone synthesis[37] and finally, it also leads to increased excretion of iodine in kidney.

Inhibition of iodide transport by thiocyanate is independent of TSH concentration but competitive with iodine concentration.[37] Because of this competitive inhibition, iodine deficiency enhances the antithyroid action of thiocyanate, whereas iodide excess diminishes its harmful effect. Thereby, thiocyanate may be responsible for the goitrogenic effect of cigarette smoking seen at least in iodine deficient areas.[41] Variations in iodine intake might also modulate the response to smoking, the predominant action of smoking being antithyroid when iodine intake is low and immunogenic when it is adequate.[38] Whether thiocyanate affects the peripheral action of T3 or T4 is currently not known.

Studies show that nicotine and cotinine, the major psychoactive compounds of cigarette do not have any direct detrimental effect on the thyroid gland.[38] However, nicotine has been implicated to be a thyroid stimulant by its action through the HPA. As early as in 1989, Balfour showed that nicotine was a potent activator of the HPA. Nicotine mimics the effects of acetylcholine at selected central nicotinic acetylcholinergic receptors,[42,43] thereby causing sympathetic activation, which can increase thyroid secretion.[25] Thus, tobacco smoke might have a dual mode of action on the thyroid gland, one of direct suppression by thiocyanate along with indirect activation through the HPA.

The activation-suppression model might be an oversimplification of the effects of tobacco smoke, as tobacco smoke is known to contain thousands of active chemicals. Though evidence currently favors to the role of thiocyanate as the predominant thyroid suppressor, multiple other components of smoke, like hydroxypyridine

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metabolites and benzpyrenes, are also being researched for their potential to interfere with thyroid function.[25,44] 2,3-hydroxypyridine have been found to inhibits thyroxin deiodination by reducing iodothyronine deiodinase activity.[44]

Several other mechanisms have been forwarded to explain the effect of tobacco smoke on thyroid. Tobacco smoke can cause hypoxia and formation of oxygen-free radicals which may result in free radical injury.[26,27,45] In addition, tobacco glycoprotein promotes formation of interleukin (IL)-1 in *in vitro* experiments. Thus, smoking may promote inflammatory processes via an increase in IL-1[46] in humans which may contribute to autoimmune thyroid diseases. In support of this theory, higher concentration of IL-1a, IL-1ß, and soluble IL-1RA (sIL-1RA) have been demonstrated in serum of smokers compared to nonsmokers with active autoimmune thyroid disease.[47]

SMOKING AND THYROID HORMONE LEVELS

Due to multiple contrasting pathways in which tobacco smoke can affect the functioning of thyroid gland, individual cross-sectional studies have reported a decrease, an increase, or no effect[41,44,48,49] of smoking on the peripheral thyroid hormones [Table 2]. In studies that show alteration, T4 and reverse T3 (rT3) have been found to be increased along with normal T3 levels in some studies,[50-53] whereas others report an increase of T3 only without accompanying rise of T4.[36,54,55] One study reported higher levels of free T3 (fT3) and free T4 (fT4) in smokers.[56] A decrease in the levels of both T4 and T3 has also been reported by some.[57-59] Accompanying TSH levels were found to be low in most[44,48-53,56,60-63] and normal in some studies.[36,54,55,57]

Interpreting all these results, smoking seems to have either no effect on thyroid function or a weak thyroid-stimulating effect in normal adults, causing small, thyrotrophin independent increases in T4, and more commonly in T3 levels.[25,61] Indeed in a Norwegian population survey of 20,479 women and 10,355 men without previously known thyroid disease, the authors reported the prevalence of overt hypothyroidism to be lower in current smokers compared with never smokers (odds ratio, 0.60), whereas the prevalence of overt hyperthyroidism was higher among current smokers (odds ratio, 2.37) than never smokers.[61] A Korean study similarly reports smoking to be associated with a lower prevalence of subclinical hypothyroidism in noniodine deficient normal population.[64]

In contrast to the thyroid-stimulating effect in healthy subjects, tobacco smoke has been implicated to have an antithyroid effect in Iodine deficient areas. In healthy euthyroid patients, the pool of circulating thyroid hormones may be sufficient to compensate for the noxious effect of tobacco smoke. The injurious effect of smoking becomes more apparent when thyroid function is slightly compromised.[65] Thus, smoking has been found to contribute toward development of overt hypothyroidism[58] and subclinical hypothyroidism, as much as 10% in some studies,[66] particularly in areas of iodine deficiency.

In addition to causing hypothyroidism, smoking can also worsen its clinical effects in a dose-dependent manner. Studies on women with subclinical hypothyroidism report that smoking results in exacerbation of the hypothyroid state (↑TSH and ↓fT4 in smokers compared to nonsmokers) and affect consequences of hypothyroidism like lipid profile abnormalities and cardiovascular risk in an adverse manner. In women with overt hypothyroidism, though the biochemical differences in hormonal levels become indistinguishable between smokers and nonsmokers, probably due to the gross abnormality of the hormones themselves, smoking still affects the consequences of hypothyroidism, as smokers have more lipid abnormalities and cardiovascular risk compared to nonsmokers.[65]

SMOKING, GRAVES' DISEASE, AND GRAVES' ORBITOPATHY

Smoking has been strongly related to graves hyperthyroidism and the evidence is growing.[44,67-73] The evidence is even more robust for Graves' orbitopathy (GO), an autoimmune inflammatory condition characterized by upper eyelid retraction, edema, erythema, and proptosis.[74] The association was first described in 1987[75] and multiple recent studies and reviews now conclude that there indeed is a causal association.[6,12,20,22,72,73,76-78] In patients with Graves' hypothyroidism, smoking increased the relative risk of orbitopathy by a factor of 1·9, and the RR rises up to 7·7 for orbitopathy among those with Graves' hyperthyroidism. Not only the relative risk, but also the severity of the orbitopathy was more in patients who smoked compared to those who did not.[67]

Multiple studies investigating for dose-response effect report a positive association of the severity of the GO with the duration and number of cigarettes smoked.[67,68,79-83] In a comprehensive analysis, Pfeilschifter and Ziegler,[81] reported a linear trend of increase in RR for orbitopathy in Graves' disease with increasing dose of smoking. Compared with never-smokers, there was a significant increase in RR for the development of total symptoms and proptosis ($P = 0.05$) and for diplopia ($P = 0.01$) as smoking dose increased.

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Table 2: Thyroid parameters in smokers in relation to comparison groups

Studies	Type	Cases	T4	T3	fT4	fT3	rT3	TSH	Others
Melander *et al*., 1981	Follow-up	Subjects tested before and after quitting tobacco	↑	N	-	-	↑	↓	Changes reverse with quitting
Edén *et al*., 1984	Cross-sectional	181 men of age 70, divided based on past/present smoker	↑	N	-	-	↑	↓	-
Sepkovic *et al*., 1984	Comparison between groups	Four groups: Nonsmokers, light, moderate, and heavy smokers	↓	↓	N	N	-	N	-
Christensen *et al*., 1984	Cross-sectional	441 women, divided into nonsmokers (192), smokers (169) and exsmokers (80)	N	↑	-	-	↓	↓	↑Goiter, ↑Tg
Hegedüs *et al*., 1985	Cross-sectional	215, healthy sample in relation to smoking habits	N	N	N	N	N	-	Tg-Ab↑Thyroid volume↑I-131 uptake ↑
Joffe RT and Levitt AJ, 1988	Cross-sectional	89 patients in relation to smoking habits	-	-	-	-	-	↓	All patients had major depression
Karakaya *et al*., 1987	Comparison	Smokers vs nonsmokers	N	↑	-	-	-	N	-
Lio *et al*., 1989	Comparison between groups	Three groups of women: Goitrous nonsmokers; goitrous moderate smokers; goitrous heavy-smokers	N	↑	-	-	-	N	↑Goiter
Ericsson and Lindgärde, 1991	Birth cohort follow-up	1555 smokers Vs. 1048 exsmokers vs 1497 nonsmokers	-	N	-	-	-	↓	Goiter ↑
Petersen *et al*., 1991	Random population survey	1154 women	N	N	N	N	-	↓	No difference in thyroid in smokers vs nonsmokers
Georgiadis *et al*.,1997	Cross-sectional (in hospital employees)	189 healthy smokers and nonsmokers (111 females and 78 males)	-	-	-	-	-	↓	Thyroid volume higher in smokers
Fisher *et al*., 1997	Vietnam-era male US Army veterans aged 31-49 years	4462 subjects (1962 current smokers and 2406 current nonsmokers)	↑	-	-	-	-	↓	Heavy smokers had a smaller increase in thyroxine levels than did light smokers
Belin *et al*., 2004	Cross-sectional	15,592 subjects	-	-	-	-	-	↓	↓ thyroid autoantibidies
Jorde and Sundsfjord, 2006	Cross-sectional	6,085 subjects (1,744 smokers) at baseline. 460 subjects (114 smokers) at follow-up	-	-	↑	↑	-	↓	no association to number of cigarettes smoked
Asvold *et al*., 2007	Cross-sectional	20,479 women and 10,355 men	-	-	-	-	-	↓	Cessation may reverse of smoking.
Vejbjerg *et al*., 2008	Pooled result from 2 cross-sectional studies	4,649 cases before and 3,570 cases after mandatory salt iodination programme	-	-	↑	↑	-	↓	↑ thyroid volume
Soldin *et al*., 2009	Comparison between groups	Women (18-44 years of age) divided into active smokers, passive smokers, and nonsmokers	↑	↑	-	-	-	↓	-
Mehran *et al*., 2012	Cross-sectional	1,581 subjects	-	-	-	-	-	↓	↓ TPO-Ab

TPO-Ab: Thyroid peroxidase antibodies

Multiple theories to explain this association have been forwarded. Smoking may make the thyrotrophin more immunogenic in susceptible persons by chemically altering the receptor structure. This would subsequently result in formation of antithyrotropin-receptor-antibodies which are known to react with retroorbital tissue. Furthermore, smoking may suppress development of tolerance toward thyroid autoantigens.[25] Smoking may also create a proinflammatory environment, where immune responses are exacerbated due to reduced inhibition of IL-1 receptor antagonist (IL-1Ra) on IL-1 stimulation,[47,84] although some authors do report no effect of cigarette smoking on serum IL-1/IL-1Ra concentrations in patients of thyroid-associated orbitopathy.[85]

Though cigarette smoke have been found to enhances adipogenesis in cultured human orbital fibroblasts, clinical studies generally find smoking associated with an increase

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in muscle volume rather than fat volume in GO.[86] Cigarette smoke also alters the chemical composition of tear in patients with GO,[87] but the clinical significance of this finding is currently unknown.

HASHIMOTO'S THYROIDITIS AND SMOKING

In contrast to Graves' disease; smoking might confer some protection against Hashimoto's thyroiditis, another autoimmune thyroid disorder.[9,10] Studies report that smoking suppresses the formation of thyroid peroxidase antibodies (TPO-Ab), an antibody considered crucial for the development of Hashimoto's thyroiditis. Current smokers were found to have lower plasma TPO-Ab levels when compared to exsmokers in some studies,[60,62,88,89] although a few did not find such association.[64] Even studies on patients of Graves' hyperthyroidism report a lower level of TPO-Ab in current smokers compared to nonsmokers,[90] prompting authors to postulates that smoking may protect against Hashimoto's hypothyroidism by reducing TPO-Abs, while at the same time elevating the risk for Grave's hyperthyroidism.[15] The protection against autoimmune hypothyroidism may not be complete, an increase in serum thiocyanate concentration from smoking may also contribute to the development of hypothyroidism in patients with Hashimoto's thyroiditis, rather than protecting against it.[91]

Smoking has been found to affect other autoimmune thyroiditis in inconsistent manner. Smoking suppresses the formation of thyroglobulin antibodies, an autoantibody commonly seen in autoimmune thyroidal illness[60,89] and therefore may confer some protective effect. In contrast, smoking has also been found to increase the risk of postpartum thyroiditis and influence the severity of other thyroiditis, especially when occurring as part of a polymorphic autoimmune disease.[92]

SMOKING AND THYROID NODULARITY AND GOITER

The association between smoking and thyroid nodularity is less clear. Most studies reporting association, report an increase in multinodular goiter, at least in women.[44,54,55,93-96] Ericsson *et al*.,[44] reported that diffuse goiter more common in younger women, while predominantly multinodular was found in the elderly. Lio *et al*.,[55] found a similar increase in frequency of multinodular goiter among women heavy smokers, but found no correlation between goiter size and the number of cigarettes smoked. Supplementing the studies in women, two recent studies; a Turkish population survey and a German population-based study, found correlation between smoking and multinodular goiter in both sexes.[97,98] The association seems to be specific for thyroid multinodularity as smoking has not been associated with solitary thyroid nodules.[99] In contrast, almost an equal number of studies[26,49,67,100-102] report no relation of goiter frequency with smoking habits. Similar to other noxious effects of tobacco, the association of thyroid multinodularity also seems to exist predominantly in areas with more pronounced iodine deficiency suggesting that tobacco smoke may be more toxic for a compromised thyroid gland.[94,103] The best evidence for the role of iodine intake comes from an interesting study from Denmark, which followed 8,219 individuals before and after the mandatory salt iodization program in year 2000.[52] The authors found a reduction in the overall difference in thyroid volume between heavy smokers and nonsmokers across the age groups after iodization of salt was introduced. However, even after iodization, the odds ratio for having thyroid enlargement was increased for smokers and smokers still had a lower mean thyroid stimulating hormone and a higher free thyroxine in serum than nonsmokers.[52]

The two most common hypotheses to explain this phenomenon involve the role of thiocyanate and thyroglobulin. Thiocyanate, which inhibits iodide transport into the thyroid gland, may cause a relative iodide deficiency state in the gland. This may be responsible for the goitrogenic effect of cigarette smoking,[93] especially in areas with iodine deficiency[104] and may in part explain the diverging results and the regional differences in the goitrogenic effect of cigarette smoking. The other theory postulates that tobacco smoke directly stimulates the thyroid gland and increases the level of thyroglobulin, a precursor of thyroid hormones. Serum thyroglobulin positively correlates with the volume of the thyroid gland and has been implicated in development of goiter in even nonsmoking population.[105] In support of this theory clinical studies[20,54] do report significantly higher levels of serum thyroglobulin in smokers as compared to nonsmokers and exsmokers.

SMOKING AND THYROID CANCER

Cigarette consumption has been associated with a decrease in the risk for thyroid cancer in most[45,106-111] but not all[110] epidemiological studies. The association is stronger in women, where a reduced risk for all histological groups of thyroid cancer was found. On the contrary, in men this effect is not so clear; with evidence for the protective effect[45] and evidences for no effect,[112] both available in literature. Few large studies have tried to find a consensus on this interesting finding. A recent pooled analysis of

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2,725 thyroid cancer cases[113] suggests that cigarette smoking is associated with a moderately reduced risk of thyroid cancer in both sexes. Smoking decreased the risk of both papillary and follicular cancers and was valid in all geographical regions (Asia, Europe, and United States). The protective effect was also correlated with greater duration and frequency of smoking.[113] Similarly, in a large cohort study that followed 1,59,340 women over a 12.7 years period, the authors found that current smokers had reduced risk for all types of thyroid cancer. No associations or trends were seen for amount smoked, age of starting smoking, or age at quitting. However, significant dose relationship was found with smokers of ≥40 pack-years having a significantly reduced risk of papillary thyroid cancer compared to those who smoked less.[111]

Four possible biological pathways explain the protective effect of tobacco on thyroid cancer. First, smoking may confer its protective effect by decreasing the body weight of the smoker, as increased body weight have been associated with increased risk thyroid cancer. Second, TSH, by its effect of proliferation of the thyroid follicular cells has been long implicated in formation of thyroid carcinoma. The protective effect of smoking may result from the smoking induced reduction of TSH secretion. Third, a genetic pathway involving the CYP1A1 genotype might be associated with reduced risk for carcinomas among smokers. Germline inheritance of a wild-type CYP1A1 gene is associated with decreased susceptibility for thyroid cancer and CYP1A1 has been associated with smoking.[114] Fourth, oestrogen has been implicated in the etiology of thyroid cancer, to explain the higher incidence of this cancer in females relative to males. The potential anti-oestrogenic effect of cigarette smoke may be the reason of the decrease in thyroid cancer at least in females.[106,113]

EFFECT OF SMOKING ON NEONATAL THYROID PROFILE

Smoking habits of parents affect the thyroid status in infants. Maternal smoking during pregnancy is generally believed to have a weak stimulating effect on the infant thyroid. Studies have reported a decreased serum TSH level in mother as well as decreased TSH and increased T4 level in newborn babies of smoking compared to nonsmoking mothers.[115-120] Only one study currently reports no such correlation.[121]

Placental transfer of thiocyanate is believed to be the cause of this effect. In pregnant women who smoke, a nearly complete equilibrium is achieved between thiocyanate level in the mother and umbilical cord blood thiocyanate level.[121] Even in infants whose fathers alone smoked, cord serum thyroglobulin levels were elevated, suggesting passive transfer of compounds of tobacco smoke (probably thiocyanate) from the environment. Increased thyroglobulin in cord blood from newborn suggests neonatal thyroid stimulation by parental cigarette smoking. Higher levels of serum thyroglobulin have been reported at birth and at 1 year of age.[122] Additionally, thyroid gland volume in such babies was found to be high, a finding which lends further support to this theory. Thus, smoking seems to induce similar changes in the fetal thyroid function as in the adult.[16,120,123]

The rapid placental and breast milk transfer of thiocyanate to the fetus/neonate has raised the controversy on role of passive smoking and environmental thiocyanate[39,59] and perchlorate in alternation of maternal and neonatal thyroid state. Studies till date, however, suggest no effect of environmental thiocyanate or perchlorate on maternal or neonatal thyroid systems.[40,124]

EFFECT OF CESSATION OF SMOKING ON THYROID ABNORMALITIES

Abstinence from smoking generally results in reversibility of most smoking-induced changes with perhaps the exception to GO. Such reversibility of smoking induced changes can be inferred indirectly from studies that compare smokers with exsmokers and directly from follow-up studies of quit programs. As early as in 1981, Melander *et al.*,[50] demonstrated a small decrease in serum T4 and rT3 levels, and an increase in serum TSH level after 3-77 days of abstinence from smoking. Smoking-induced goiter and thyroid nodularity also seems to be reversible as one study reported goiter in only in 4% of exsmokers compared to 15% in current smokers.[54] In contrast, cases of autoimmune thyroid disorders might experience a sharp but transient rise in thyroid antibodies with resultant autoimmune hypothyroidism with the cessation of smoking.[125,126]

In smokers suffering from Graves' disease, the response to treatment has been reported to be poorer[83] and smoking has been found to increases the likelihood of Graves' disease recurrence in males treated with antithyroid drugs.[127] Studies looking into GO[68,128] similarly suggests that giving up smoking neither reduces a preexisting orbitopathy nor decrease the risk of development or deterioration of orbitopathy. Even after discontinuation of anti-thyroid drugs smoking increases the chance of relapse of GO.[129] In contrast, only one cohort study,[81] examining the effect of quitting on GO found no difference in the risk for orbitopathy between exsmokers and never-smokers. The development of other types autoimmune thyroiditis

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also seems to be related to previous, rather than present smoking habits.[19]

TREATMENT OF NICOTINE DEPENDENCE AND THE THYROID AXIS

Treatment of nicotine dependence involves either use of nicotine replacement therapy, which uses medical nicotine gums, patches, and sprays to tide over craving. These agents are mostly considered safe, though presumably they may result in activation of the thyroid by the central pathway, like the nicotine in cigarettes. Studies, however, are sparse on the topic. Bupropion and varenicline have also been used additionally to decrease craving for nicotine. Bupropion, an atypical antidepressant, functions by increasing the levels of norepinephrine, while varenicline is a nicotinic receptor partial agonist. Therefore, both have the theoretical potential to cause thyroid stimulation. Current literature data, however, seem to be lacking for both these drugs.

CONCLUSION

Tobacco smoking modifies almost all functions of the thyroid gland. Currently, studies point toward a robust association between smoking and Graves' disease and in particular GO. Additionally, two interesting findings of decrease risk of Hashimoto's thyroiditis and thyroid cancer require further elaboration and clinical judgment, if the benefits can out weigh the numerous toxic and detrimental effect of tobacco smoke on the human physiological system.

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