Smoking and other goitrogens as significant risk factors of thyroid diseases

Recently, there have been many studies of smoking addiction and cessation, the influence of smoking and nicotine on thyroid diseases, and population nutrition. Novel new methods of quitting smoking have been described using vaccines and psychology. Nutritional studies of iodine replacement and need for total nutrition to maximize the benefits from iodine replacement are described. The study and treatment of thyroid diseases are becoming more multi-factorial with advances in genetic, immunology, environmental, and nutritional causes of thyroid diseases. Cigarette smoking cessation and iodine supplementation continue to be important in the health of the thyroid.

Introduction
Thyroid dysfunction is an increasing problem with great resources employed to understand its aetiology. It has been known that iodine is an important micro-nutrient for the healthy function of the thyroid, and that goitre is a common feature in iodine poor regions of the world. Even with great progress in supplementation, there still exists much to learn about thyroid dysfunctions, including other micro-nutrients that are required for proper thyroid function. The view of thyroid disease is moving into an ever more multifaceted world that includes not only iodine as the "magic bullet" that will cure all, but genetics, immunology, nutrition, the environment including common goitrogenic substances with smoking being a prime subject of study. Cigarette smoking contains thousands of chemical compounds that are hazardous to human health. The growing knowledge of the health risks has prompted implementation of new regulations in a growing number of countries to discourage smoking. The addicting nature of nicotine, and how people handle its withdrawal effects determines the success rate of long term cessation of smoking. Nicotine has physiological and immunological effects on the thyroid, and is a major risk factor in Graves' ophthalmopathy (GO), particularly when treated with radioiodine with no steroid prophylaxis [1,4].

Psychological aspects of cigarette addiction and quitting are covered, and legislation to reduce initiation of new smokers and encouraging cessation of smoking is also covered. Taking into account the negative impact that thyroid disorders have on quality of life and long term detrimental effects on the cardiovascular system, mental well being, metabolism, weight, osteoporosis, reproductive health, and economic aspects amongst others, it should be encouraged to implement screening to treat earlier, and avoid development of disease [44].

This article reviews some important studies and reviews recently published concerning thyroid diseases, smoking, goitrogenic substances, and nutrition related to thyroid diseases. It is not intended to be an exhaustive review, but to provide some important materials in one place for further thoughts and investigations.

Nutrition and Goitrogens
The awareness of nutrition importance in thyroid health is not limited to iodine, but a growing panoply of micro-nutrients, and simultaneously substances that limit the uptake and utilization of micro-nutrients. Goitrogens reduce the ability of the thyroid...
to produce thyroid hormones by reducing the bio-availability of iodine. The most commonly encountered goitrogentic foods are: soy products, cassava, millet, Lima beans, nuts, sweet potatoes, and cruciferous vegetables (cabbage, Brussels sprouts, kale, broccoli, turnips, cauliflower, rapeseed). Many drugs can also be added to this list: interferon, amiodarone, lithium, cholestyramine. On the other side there is insufficient intake of vitamins and minerals like: selenium, iron, folate, vitamins A and B. Decades after iodine supplementation and even in iodine replete regions goitre may still be encountered due to, insufficient micro-nutrients, and goitrogenic effects of substances like cigarette smoke. Large areas of the world have low selenium, iron, and iodine in their soils which play important roles in goitre even after iodine supplementation [49]. Over 2 billion people are classified as iodine deficient, defined as urine iodine concentration less than 50 µg/L, with goiter affecting 30-70% [69].

Recent studies show that even with proper urine iodine levels goitre remains in children and correlates negatively with iron levels, with cigarette smoking not an important goitrogen in iodine-replete children [17]. This suggests that thyroid health needs to be looked at in a holistic way incorporating vitamins, minerals, and managing goitrogens. Iodine alone is often just the first step in returning the thyroid to health.

People living in iodine poor regions or with poor diets are most susceptible to goitrogenic effects of drugs, foods, and cigarette smoke. Even with growing anti-smoking regulations smoking is common in developing countries and up to 50% of goitres may be due to cigarette smoke there [34]. Cyanide (CN) is a well known goitrogen present in cigarette smoke and certain foods that is quickly metabolized to thiocyanate (SCN-) an iodide transport inhibitor. Cyanogenic glucosides present in goitrogenic foods can be greatly reduced by boiling the food. Breast fed infants of smoking mothers or animal with milk based formula fed on food. Breast fed infants of smoking mothers (SCN-) an iodide transport inhibitor. Cyanide (CN) is a well known goitrogen present in cigarette smoke and certain foods that is quickly metabolized to thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits goitrogens. Iodine alone is often just the first step in returning the thyroid to health.

Table 1

<table>
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<tr>
<th>TAO subtype</th>
<th>Main clinical features</th>
<th>Candidate autoantibodies</th>
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<tbody>
<tr>
<td>Ocular myopathy</td>
<td>Diplopia</td>
<td>Calsequestrin</td>
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<tr>
<td>Congestive ophthalmopathy</td>
<td>Exophthalmos</td>
<td>Flavoprotein</td>
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<tr>
<td>Mixed congestive and myopathic ophthalmopathy</td>
<td>Congestive and myopic signs/symptoms</td>
<td>All of the above</td>
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*G2a is a fragment of the FOX-P1 transcription factor.

Abbreviations: EOM, extra ocular muscle; TSH+, thyroid-stimulating hormone receptor.

Environmental cigarette smoke from parents causes disturbances of thyroid size and function in the fetus and infants by transfer of thiocyanate [30]. Recent studies found FT4 and TPO-Abs were similar in smoking and non-smoking pregnant mothers [63]. Smoking was reported to have a weakly stimulating effect on the thyroid in healthy adults, with reduced TSH level during 1st and 3rd trimester [63]. Cigarette smoke acts on the thyroid by numerous paths, but among the thousands of compounds in cigarette smoke it is thiocyanate that has been identified as a potent goitrogen [25]. A metabolite of cyanide, thiocyanate (with a half-life > 6 days) inhibits iodide transport and organization as well as increases the release of iodide from the thyroid. Iodine deficient areas (without sufficient iodine supplementation) are the most at risk of goitrogenic compounds, including thiocyanate causing goitre, while 2,3-hydroxypridine a cigarette smoke toxin, reduces iodothyronine deiodinase activity, thereby elevating thyroxine concentration due to reduced thyroxine deiodination [56, 66].

Animal models, in this case rats, are used to study many diseases including effects of smoking in mothers on their offspring, exposed post gestationally to nicotine. The mother and offspring displayed hypothyroidism suggesting primary hypothyroidism, which was compensated by elevated T3 levels in mothers’ milk, both mother and pups became euthyroid 3 weeks after nicotine cessation [50]. Nicot ine in mothers milk leads to hypothyrroidism in pups and programs for increased weight of offspring later in life.

Further study in mother rats exposed to nicotine postnatally led offspring to develop primary hypothyroidism, with partial responsibility being reduced leptin signalling in the thyroid. The physiological effect of leptin, a hormone produced in fat tissues, is important in controlling appetite and metabolism and thereby normal body weight. Extended nicotine exposure early in life may lead to central and peripheral resistance to leptin with a permanent change in how the hypothalamus, pituitary and thyroid respond later in life [58].
Graves’ disease and Graves’ ophthalmopathy

Hyperthyroidism is a condition when the thyroid overproduces thyroid hormones (T3, and T4), with a concomitant low TSH level. It is associated with an increased risk of ischemic stroke in young adults [62]. The most common cause is an autoimmune Graves’ disease, with not uncommon ophthalmopathy especially in smokers and smokers post radiiodine treatment. Subclinical or even the toxic form of Graves’ disease, as TAO as proposed in Table I would allow better diagnosis and management of the disease. Serum concentration of IL-1, IL-15, and soluble IL-1RA (sIL-1RA) were greater in euthyroid smokers than nonsmokers with active moderate GO prior to, and 6 months post orbital radiotherapy [39]. In a large study involving over 3000 patients a correlation between autoimmune diseases and Graves’ or Hashimoto’s disease was found [7]. This correlation can be used as an indicator of autoimmune comorbidities. Thorough analysis of data was performed by Czarnecki et al. [8].

Hashimoto disease

The most common cause of hypothyroidism is Hashimoto’s thyroiditis (HT). The risk factors are advanced age, female gender, iodine intake, and positive anti-TPO antibody [16]. Cigarette smoking did not correlate with anti-TPO antibody status, but displayed a protective role for hypothyroidism with reduced subclinical hyperthyroidism in both current and former smokers [16, 21]. The case for measuring TSH levels has been growing with recent studies. Subclinical hypothyroidism (SCH) and overt hypothyroidism, TPO-Ab and/or Tg-Ab, is lower in cigarette smokers with a negative correlation with iodine consumption [16, 20]. Concentration of anti-TPO antibodies are elevated in GD and HT. Thyroid dysregulation is a slow process taking years for hypothyroidism to develop, and months for hyperthyroidism. Postpartum period is of greater risk for hypothyroidism, and greater number of pregnancies was reported to increases risk of hyperthyroidism [21]. While another study found no correlation between thyroid disease and number of pregnancies or births. Also no thyroid antibodies were present from abortions or contraceptive pills [61].

A recent study found 34% of HT patients had eye changes, without correlation with smoking, with 25% of these displaying persistent upper lid retraction, and 17% of children as of 2008 [48]. Obesity, but not a lack of physical activity, was found to be as a risk factor for thyroid cancer in both genders, with a positive correlation between BMI and thyroid cancer [31, 36]. Cigarette smoking reduces risk of thyroid cancer, while obesity, asthma, benign breast disease, and benign thyroid disease increases risk [41].

Psychological aspect of smoking cessation in thyroid patients

The psychology contributing to cigarette smoking addiction needs to studied to determine those most at risk and the most effective methods in treatment depending on the preference of patient. Doctors simply telling patients to stop smoking is frequently not effective and requires an effective program involving patient education about health and risks, counselling, nicotine replacement, a quitline [29]. Even informed smokers fail to quit smoking and require individual counsel- ling programs to reduce anxiety and increase success rates of sustained abstinence [74]. One reason other than the addictive nature of nicotine of people continue to smoke is smoking effect on appetite and weight. Nicotine was found to decrease appetite and body weight by working in the hypothalamic melanocortin system [45].

Cessation of smoking in “heavy smokers” is a great concern among they are in those with accompanying conditions. While Graves’ patients with severe nicotine addiction are difficult to treat due to emotional liability [70], it was found that mental health patients have as much motivation to quit smoking as the general population [64]. Medical comorbidities, diabetes, stroke, arthritis, and respiratory diseases, have been found to increase motivation of smoking cessation in some cases [19, 26]. Psychological distress is an important factor in initiation, continuation, and success of cessation of cigarette smoking seen in Whites but not in Blacks or Hispanics [32]. People with mental illness such as depression had a heavy cigarette consumption rate and where more difficult to treat, but an effect smoking cessation program involves the community counselling, nicotine replacement, and the use of a telephone quitline; with the depressive state of the patient was not linked to smoking cessation and it was suggested that gender specific treatment should be implemented to help depressed females quit smoking [46, 54, 59]. The risk of quitting lapsing is based on how well they manage the distress of nicotin withdrawal, and not simply nicotine tolerance [11, 55]. The rate of smoking cessation at 2 weeks is a significant prognostica- tor to longer term cessation, with nicotine patches aiding both short and long term ces- sation [24]. With the presentation of anger post cessation is a significant risk factor for relapse [52]. Smokers that were free of depression presented no increase in risk of depression upon cessation [8]. The higher rates of smoking and lower success rate of quitting smoking in depressed patients may be due to their more positive perception of smoking, regardless of gender, such as: good taste, social interaction, avoiding weight gain and cravings [71].

The cessation of smoking should be suggested to all patients with thyroid disease as a significant reduction of risk of complica- tion of their condition and treatments, but the moment of cessation should be especially approached. It was even with the presence of nicotine replacements most people (75+%) who have quit smoking in the USA, and hundreds of millions of people worldwide, have done so without any pharmacological help. This is often overlooked and not given a lot of spa- ce in the media because it is not funded by pharmaceutical companies. Prior to phar- maceutical aids to quit smoking it was not considered as difficult to quit smoking with one British in the 1980’s finding only 20% of former smokers found it very difficult to quit smoking [39].

The smoking cessation industry has funded many studies and promoted their pro- ducts to physicians and the general public. While nicotine gum, patches, and other aids help in smoking cessation, most of the world former smokers quit without any physician or pharmaceutical help. In many countries of the world the costs of the smoking cessation aids is too expensive to me used by the general population [14].

The health benefits of discouraging smoking in public places is important for the phy- sical health of bystanders is well known, but the mental health of bystanders is also af- fected. While smokers have been known to suffer from depression and addictions, it has recently become known that those who never smoked have display depressive symptoms via unknown mechanisms that needs further study [3]. Smoking cravings are reduced in those wishing to try to quite with physical exercise [23]. Psychosocial stress increases craving for cigarette smoking and even gives more satisfaction, but does not increase quantity smoked [15].

Smoking regulations and addiction

Many toxic substances in cigarette smoke including goitrogens has many effects on metabolic and biological processes of thy- roid hormones [65]. There is a growing num- ber of countries banning smoking in public places, according to the WHO as of 2008 there were 17 countries on the smoke free list, but smoking continues to be the leading cause of preventable deaths prophesied to kill 8 million people yearly by 2030. It is not of that in developing countries [2]. Even a one hour duration of environmental cigaret- te smoke significantly elevates metabolism and thyroid hormone levels [42, 44]. Ciga- rette smoke with contains many goitrogen compounds including thiocyanate, exerts a mild inhibitory effect on the thyroid which lowers serum T3 and T4 [65].

Every year more restrictions appear for smokers around the world. The first anti- tobacco laws appeared in Poland in the 1990’s, but smoking continued in public places until November 15, 2010 when Poland followed other European countries like France, Italy, Ireland, and Spain in more restric-
tive smoking legislation including bars and restaurants, but smoking areas are present in many premises. The combination of anti-smoking laws with increasing prices of cigarettes has proven to be an effective deterrent to initiation and continuation of smoking in countries that have a long history of anti-tobacco programs like Australia and where prices where not seen as an effective deterrent to initiation and continuation of smoking in Canada [10, 60, 72].

The benefits of banning public cigarette smoking has been controversial, but a recent study claims to show correlation between reduction of hospital admissions for cardiovascular and respiratory conditions associated with direct and second hand cigarette smoke after implementation of anti-smoking rules [47].

All patients have equal rights to treatment regardless of the patients’ behaviour, and if illness was self inflicted. There has been debate in difficult economic times whether to limit health care to those causing their own illnesses like smokers, obese, drug addicts, alcoholics etc. It has been suggested that the use of stigma to reduce smoking has become less effective now that the majority of remaining smokers are economically disadvantaged, and that stigma will push smokers away from regular health care [5].

While smoking is the leading preventable cause of low birth weights of babies, a study shows some correlation between baby birth weight and smoking policies, with prices affecting younger mothers (teens) while anti-smoking policies affect older mothers (25-34) [40]. The most effective anti-smoking method is visual presentation of health effects from smoking, and less so with written messages or cigarette prices, with greater effectiveness on non-smokers than smokers [73].

Conclusions

Thyroid dysfunction becomes an enraging health problem in many countries of the world. Research has made great advances in the understanding of the aetiology of thyroid diseases. Now that iodine is supplemented in most of the world there needs to be a more holistic view on the dysfunctions of the thyroid. Cigarette smoking is an important modifier of thyroid metabolism and hormone levels thus goitrogens, particularly thiocyanates from cigarette smoke can alter the size and the function of the thyroid, especially in low iodine regions or diets poor in iodine containing foods. Smoking is strongly associated with GD and particularly with GO, while protecting against the development of TPO-Ab, which may reduce the risk of HT. Smoking has been identified as an important risk factor in the development or worsening of ocular changes after 131I treatment. The anti-smoking movement would gain many in smoking cessation should improve health. Many immunological hypotheses have been put forward as to the reasons for thyroid diseases. Diagnosis and treatment will need to encompass many of these newly discovered factors.

References


