

Review

Hypothesis: Dietary Iodine Intake in the Etiology of Cardiovascular Disease

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This paper reviews evidence suggesting that iodine deficiency can have deleterious effects on the cardiovascular system, and correspondingly, that a higher iodine intake may benefit cardiovascular function.

In recent years, public health bodies have aggressively promoted sodium restriction as a means of reducing hypertension and the risk of cardiovascular disease. These inducements have led to a general decline in iodine intake in many developed countries. For example, a United States national health survey conducted in the early 1970s observed that 1 in 40 individuals had urinary iodine levels suggestive of moderate or greater iodine deficiency; twenty years later, moderate to severe iodine deficiency was observed in 1 in 9 participants.

Regional iodine intake has been shown to be associated with the prevalence of hypothyroidism and hyperthyroidism, where autoimmune hypothyroidism is the more common of the two in regions with moderate to high iodine intake. Both of these thyroid abnormalities have been shown to negatively affect cardiovascular function. Selenium, an important antioxidant in the thyroid and involved in the metabolism of iodine-containing thyroid hormones, may play an interactive role in the development of these thyroid irregularities, and in turn, cardiovascular disease. Iodine and iodine-rich foods have long been used as a treatment for hypertension and cardiovascular disease; yet, modern randomized studies examining the effects of iodine on cardiovascular disease have not been carried out.

The time has come for investigations of sodium, hypertension, and cardiovascular disease to also consider the adverse effects that may result from mild or greater iodine deficiency.

Key teaching points:

- Iodine deficiency can cause thyroid dysfunction including hypothyroidism, impaired mental and physical development, loss of energy, and increased prenatal and infant mortality.
- In recent years, the prevalence of iodine deficiency has increased in many countries that use iodized salt as a dietary source of iodine.
- The prevalence and incidence of hypothyroidism and hyperthyroidism has been shown to vary with regional iodine intake. Both thyroid diseases are known to adversely affect cardiovascular function.
- Selenium interacts uniquely with iodine: selenium-containing antioxidants protect the thyroid against oxidative damage during thyroid hormone synthesis; whereas selenium-containing deiodinases are involved in both activation and inactivation of thyroid hormones.

INTRODUCTION

Few public health interventions have produced the degree of benefit as the addition of iodine to table salt. It is a well-recognized intervention for the prevention of iodine deficiency disorders such as thyroid dysfunction, impaired mental and

physical development, loss of energy, and prenatal and infant mortality [1]. It is of concern that this successful intervention may be compromised by the suggested link between cardiovascular disease and sodium, if emphasis is not placed on the beneficial role iodine plays in human health, particularly with respect to cardiovascular function [2].

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This manuscript reviews animal and human data on the association between iodine and cardiovascular disease, including: (1) recent trends in iodine intake; (2) the association between iodine intake and cardiovascular disease in Finland; (3) the association between iodine intake and thyroid disease; (4) how hypothyroidism and hyperthyroidism affect the cardiovascular system; (5) animal and human studies examining the influence of iodine and thyroid hormones on cardiovascular disease; (6) the physiological interactions between iodine and selenium and its relevance to cardiovascular health; and (7) finally, some potential mechanisms through which iodine may affect the cardiovascular system.

Current Trends in Iodine Intake

In the general United States (US) population, a declining trend in urinary iodine levels has been observed as estimated through the large National Health and Nutrition Examination Surveys (NHANES I, 1971–74; and NHANES III, 1988–94) [3]. The proportion of the US population with moderate to severe iodine deficiency ($<50 \mu\text{g}$ iodine/L in urine) has more than quadrupled in the last 20 years, 2.6% in NHANES I vs 11.7% in NHANES III [3]. This decline may be due to a reduced intake of iodized salt. For example, Enstrom *et al.* [4] compared data from nationally representative samples of the American population from two time periods, 1980–1982 vs 1990–1992. Based on dietary intake studies from over 10,000 individuals, no change was observed in sodium intake from food, while there was a 65% decline in sodium intake from discretionary (iodized) salt. Adventitious sources of iodine have also declined with reductions in the use of iodine in the dairy industry and in commercial bread production [5]. Comparable trends have been observed in other countries that iodize salt. For example, public health recommendations to reduce salt intake have been implicated in the decreasing iodine status in Australia and New Zealand [6]. Similarly, a recent decline in median urinary iodine levels in Austria may be due to lower salt intake as well as the availability of noniodized salt in Austria after joining the European Union in 1995 [7]. In Greenland, as imported foods have replaced consumption of traditional foods such as fish and sea mammals, there has been a gradual decline in iodine status. Andersen *et al.* [8] found that median urinary iodine excretion declined with the degree of decrease in the traditional lifestyle. Evidence of iodine deficiency was seen in non-inuit subjects, who had the lowest levels. Thus, in countries where there are changing dietary patterns, including those long established iodization programs, significant declines in iodine intake may occur.

A segment of the population that may often experience a decline in iodine intake includes individuals with hypertension or other cardiovascular diseases. Sodium restriction has been associated with improvement in intermediate physiological variables such as reduced blood pressure. For example, a recent

meta-analysis reviewed randomised studies examining the effects of a low sodium vs high sodium diet in normotensive individuals [9]. A small but significant decrease in systolic -1.27 mm Hg ($p < 0.0001$) and diastolic -0.54 mm Hg ($p = 0.009$) blood pressure was observed; however, there was a simultaneous and significant increase in plasma lipids: cholesterol, 5.4% ($p < 0.0001$), LDL cholesterol, 4.6% ($p < 0.004$), and triglycerides, 5.9% ($p = 0.03$) [9]. Whether some of these effects were due to concomitant changes in iodine intake (from iodized salt) was not considered in these studies. Overall iodine intake has been shown to decline in subjects on sodium-reduced diets for cardiovascular disease. Simpson *et al.* [10] conducted a one-year randomized study of hypertensive subjects on sodium-restricted vs control (unrestricted) diets. Despite other dietary sources of iodine, urinary iodine excretion was strongly correlated with sodium excretion ($r = 0.69$, $p < 0.001$) and was significantly lower in the sodium-restricted group at one year ($p < 0.01$). Grzesiuk *et al.* [11] monitored the adequacy of a newly implemented iodization program in Poland. Thirty-six months after implementation of the program, an overall rise in iodine status in the study cohort was observed; yet for subjects placed on sodium-restricted diets due to cardiovascular disease, their iodine status was half that of pre-implementation values and indicative of mild to moderate iodine deficiency. Fruhwald *et al.* [12] has recommended that patients with cardiovascular disease on sodium-reduced diets should be screened for the presence of thyroid disorders. They investigated the prevalence of thyroid disorders in 61 patients with idiopathic dilated cardiomyopathy. Only two patients (3%) showed completely normal thyroid morphology and function. Moreover, the duration of cardiomyopathy was significantly correlated with thyroid gland volume ($r = 0.44$, $p < 0.001$). Iodine intake was not determined, however, the authors suggested that iodine deficiency (the most common cause of goiter) secondary to sodium restriction was the underlying cause. Although subjects with hypertension or other cardiovascular conditions may benefit from a reduction in sodium intake, a concomitant reduction in iodine intake may counter some of these benefits. This latter point is a particular concern in light of the increasing prevalence and incidence of chronic heart failure. Improved treatment of acute coronary events resulting in prolonged survival, an increased awareness of and ability to diagnose heart failure, and the aging of the population, account for the continuing increase in the incidence and prevalence of this condition [13,14]. The burden of prolonged iodine deficiency in such individuals placed on sodium-reduced diets is unknown.

At what level of iodine deficiency one would observe negative effects on cardiovascular function is not known. A one year study conducted by Andersen *et al.* [15] examined the relationship between thyroid hormone production and iodine intake in subjects with mild to moderate iodine deficiency.

Clear signs of substrate deficiency for thyroid hormone synthesis were observed in subjects with moderate iodine deficiency (20–49 μg iodine/L in urine) [15]. Thus, there has been a declining intake of iodine in many developed countries and declines have been observed in subjects with cardiovascular disease on sodium-reduced diets. The costs of concurrently reducing iodine intake with respect to the development of cardiovascular disease or its adverse effects in subjects with pre-existing cardiovascular disease need to be determined.

Cardiovascular disease in Finland

Before the establishment of an iodization program in Finland in 1963, some early investigations suggested an inverse association between iodine intake and cardiovascular disease. Epidemiological studies in the 1950s revealed that Finland had the highest rate of coronary heart disease mortality in Europe [16]. These findings led to a series of studies examining possible causative factors. Keys *et al.* [16] demonstrated that serum cholesterol levels in Finland were unusually high, particularly in the eastern part. This paralleled the fact that cardiovascular disease was significantly more prevalent in eastern than western Finland [16].

Roine *et al.* [17] comprehensively examined the dietary differences between western and eastern Finland. A wide variety of dietary components were examined in the summer and winter, including: major foodstuffs, proteins, fats, carbohydrates, lipids, amino acids, vitamins and minerals. Among the 47 macro and micronutrients considered, iodine showed the greatest difference statistically, being higher in the west in both winter and summer. There was no significant difference in cholesterol or saturated and unsaturated fat intake.

Uotila *et al.* [18] made the observation that subjects who died from coronary sclerosis often had goitre. In order to further examine this phenomenon, 250 Finnish subjects who had died from coronary heart disease were age and sex-matched to controls who died from other causes [19]. The risk of death from coronary heart disease was found to be significantly higher in individuals with goiter (odds ratio (OR) = 3.53, 95% confidence interval (CI) 2.43–4.99). It was noted that the average thyroid weight was higher in those dying from coronary disease. Moreover, among the coronary disease cases with goiter, there was a lower average age of death and a higher average heart weight. Due to the low iodine content of foods and lack of an iodization program at the time, endemic goiter was common in Finland, particularly in the east.

In 1971, Hasanen [19] carried out a correlational study comparing the levels of a variety of trace elements in drinking water (*i.e.* calcium, chlorine, fluorine, bromine, and iodine) to the prevalence of cardiovascular diseases in 21 Finnish cities. The prevalence of such diseases for each city was estimated from disability pensions, which included a spectrum of cardiovascular conditions, primarily: angina pectoris (26%), coronary

thrombosis (20%), hypertensive diseases (19%) and arteriosclerosis (7%). The strongest correlation was noted for iodine ($r = -0.83$), where the highest iodine levels were associated with the lowest rates of cardiovascular disease. It was estimated that up to 23% of the average daily intake of iodine in Finland could be obtained from drinking water [19]. Overall, while not definitive, these studies were suggestive of a protective role for iodine against the development of cardiovascular disease.

Geographical Variations in Hypothyroidism and Hyperthyroidism

Population-based studies of adults have shown that the prevalence and incidence of thyroid diseases differ from one region to the next, varying with regional iodine intake [20,21]. In developing countries with moderate or greater iodine deficiency, hypothyroidism due to iodine substrate insufficiency is the more common of the two [22,23], and more common in individuals from a lower socio-economic status [23]. In these developing countries, human studies have demonstrated that inadequate nutrition has been shown to exacerbate the adverse effects of iodine deficiency [24–28].

In developed nations with moderate iodine deficiency, prevalence of hyperthyroidism tends to be higher than hypothyroidism [29]; whereas in regions where iodine intake is sufficient or high, hypothyroidism predominates [30,31]. In support of these findings, it has been observed that in areas of moderate deficiency, as regional iodine intake increases, the incidence of hyperthyroidism gradually declines while hypothyroidism increases [32–35]. For example, following the initiation of iodine supplementation in deficient regions, there is a marked rise in the incidence of thyroglobulin and thyroperoxidase autoantibodies [33,34]—autoantibodies that are found in a form hypothyroidism called autoimmune thyroiditis. The overall prevalence of hypothyroidism and hyperthyroidism, however, is similar in regions of adequate iodine intake such as the USA [31] and in regions where iodine intake may be excessive such as Japan [30].

In addition to the variable prevalence of hyperthyroidism and hypothyroidism, the underlying causes of these conditions appear to vary with regional iodine intake. For example, in regions of moderate iodine deficiency, such as Denmark and Spain, toxic nodular goiter is the main cause of hyperthyroidism [36,37]; whereas in regions of adequate or greater iodine intake such as Iceland, USA or Japan, autoimmune Graves' hyperthyroidism prevails [30,38,39]. In regions where iodine intake is high such as Japan, an autoantibody-negative form of hypothyroidism is also observed, which is largely reversible following iodine restriction [30,40]. What remains undetermined is how an individual's underlying iodine intake in these conditions may influence its effects on the cardiovascular system.

Thyroid Disease and the Cardiovascular System

Iodine-containing thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are important metabolic regulators of cardiovascular activity with the ability to exert action on cardiac myocytes, vascular smooth muscle, and endothelial cells [41,42]. Numerous studies of patients with spontaneously occurring hypothyroidism and hyperthyroidism have demonstrated that thyroid hormones can have profound effects on the heart and cardiovascular system [43,44].

Clinical cardiovascular features of *hypothyroidism* include: bradycardia, reduced cardiac output, increased pericardial and pleural effusions, increased diastolic blood pressure and peripheral vasoconstriction [43,44]. In addition, cardiovascular disease risk factors known to be more prevalent in hypothyroid subjects include: elevated C-reactive protein (CRP), elevated total cholesterol and LDL cholesterol, and reduced HDL cholesterol [45]. T4 therapy generally leads to the normalization of these parameters in hypothyroid subjects [46], with more modest effects in subjects with subclinical hypothyroidism (normal serum T3 or T4 with elevated thyroid stimulating hormone (TSH)) [47,48]. A population-based cross-sectional study of 1149 randomly selected women by Hak *et al.* [49] found that women with subclinical hypothyroidism were at an increased risk of for atherosclerosis (OR = 1.9, 95% CI 1.1–3.6) and myocardial infarction (OR = 3.1, 95% CI 1.5–6.3).

Cardiovascular abnormalities seen in subjects with *hyperthyroidism* include: increased systolic blood pressure, venous resistance, cardiac output and cardiac mass; tachycardia and atrial arrhythmias such as atrial fibrillation; as well as symptoms such as palpitations, dyspnea and chest pain [43,44]. Most cardiac abnormalities return to normal once a euthyroid state has been achieved, although atrial fibrillation may persist in a minority [51,52]. Long-term followup studies have demonstrated an increased mortality (primarily from cardiovascular disease) in those with past history of hyperthyroidism or overt hyperthyroidism [53–55], as well as those with subclinical hyperthyroidism [56,57]. Thus, many cardiovascular features of hypothyroidism are in diametric opposition to those of hyperthyroidism.

Amongst the subtypes of hypothyroidism and hyperthyroidism, there are often subtle differences in the prevalence of cardiovascular signs and symptoms. For example, atrial fibrillation is more common in toxic nodular goiter than in Graves' disease [51,58], however, Graves' disease tends to present at a much younger age and therefore increasing age may increase the frequency of disease manifestations.

Animal Studies of Iodine, Thyroid Hormones and Cardiovascular Disease

In 1918, Murata and Kataoke [59] first demonstrated that the feeding of iodine compounds could prevent the deposition of cholesterol in the arteries, when the latter substance was fed

to rabbits. Further studies in rabbits elaborated upon and confirmed their findings [60–64]. In 1933, Turner [62] conducted the only study to compare the relative efficacy of T4, iodine, and desiccated thyroid (a source of both iodine and thyroid hormones) in preventing the development of atherosclerosis in rabbits. Control rabbits fed a cholesterol-rich diet for over three months exhibited moderate to marked aortic atherosclerosis. Rabbits fed a cholesterol-rich diet and T4 showed slight to moderate aortic atherosclerosis. Yet, rabbits fed cholesterol and either desiccated thyroid or iodine similarly showed an absence of atherosclerotic lesions. Average blood cholesterol levels of animals on the three diets were: cholesterol (13.45 mmol/L), cholesterol + T4 (10.32 mmol/L), cholesterol + desiccated thyroid (4.60 mmol/L), and cholesterol + iodine (4.73 mmol/L). Thus, iodine appeared to have an effect independent of or possibly synergistically with thyroid hormones.

Studies in rats [65,66] have suggested that a higher relative dietary cholesterol intake may further exacerbate iodine deficiency by enhancing thyroid hyperplasia. This was demonstrated by Girard *et al.* [66] who examined the interaction between iodine intake and cholesterol on the development of goiter over a four and a half month period. Relative to rats on a basal (iodine-reduced) diet, iodine supplementation was found to lead to a lower average thyroid weight (43.4 vs 10.3 mg, respectively). In contrast, dietary cholesterol supplementation led to a significant increase in average thyroid weights compared to combined cholesterol/iodine supplementation (133.6 vs 12.1 mg, respectively). Using injections of I¹³¹-labeled T4, increased fecal excretion of I¹³¹ was observed in the cholesterol supplemented group relative to the group on the basal diet; hence suggesting that cholesterol feeding enhanced iodine depletion either by increasing biliary excretion of T4 or interfering with intestinal reabsorption of T4.

Morreale de Escobar *et al.* [67] studied the effects of an iodine-reduced diet on thyroid hormone levels in rats. The iodine deficiency led to a condition analogous to subclinical hypothyroidism—that is while there was a rise in plasma TSH levels, T3 and T4 levels remained unchanged. Yet despite normal plasma thyroid hormone levels, T3 concentrations were particularly reduced in cardiac tissue. A follow-up study by Morreale de Escobar *et al.* [68] in thyroidectomized rats demonstrated that the administration of T4 at a dose that normalized plasma T4 levels was insufficient to normalize cardiac T3 levels. Therefore, even for subjects with normal thyroid hormone levels, as in subclinical hypothyroidism, there may be insufficient cardiac tissue levels of thyroid hormones when iodine intake is low [69].

Human Studies on Iodine and Cardiovascular Disease

Iodine regimens have long been used in Europe [70–74], and iodine-rich seaweed in China and Japan [75,76], as traditional treatments for cardiovascular disease and control of high

blood pressure. Similarly, numerous texts from the middle of the last century [77–79] and earlier [80] advocated the use of iodides for the treatment of various cardiovascular diseases on an empirical basis. For example, Sollmann [77] stated that iodides should be employed in arteriosclerosis, coronary sclerosis, angina pectoris, and aortic aneurysm. Bastedo [78] recommended iodides for arteriosclerosis, atherosclerosis, and arterial hypertension. McGuigan [79] commented that iodides are beneficial in premature arteriosclerosis, essential arterial hypertension, aneurysm of the aorta, and angina pectoris.

A number of clinical case series from the 1920s to 1950s also reported on the beneficial effects of iodine in subjects with cardiovascular disease [81–84]. Guggenheimer and Fisher [81] stated that iodine was the most effective treatment for producing vasodilatation. They reported beneficial results with cerebrovascular disease patients in treating headaches, dizziness and insomnia; and for patients with cardiovascular disease in treating angina pectoris, reducing blood pressure, and over a more prolonged period, improving the general condition of the patient. No improvement was seen in patients with renal disease. In a case series by Stevens [82], he observed beneficial effects in patients with vascular disease for symptoms including: angina, giddiness, lack of energy, poor memory, and difficulty concentrating. Feinblatt *et al.* [83], in a series of 59 arteriosclerosis patients, reported a reduction in dizziness (71%), headache (61%), disturbed orientation (50%), and fatigue (41%). Subjects were given both iodine and niacinamide. Wieters [84] who used intramuscular and intravenous injections of iodine in patients with arteriosclerosis reported relief of symptoms including: headaches, dizziness, leg cramps, asthenia, amnesia, disorientation, and hypertension due to arteriosclerosis. Although these studies suggested a benefit, no randomised studies using iodine have been conducted for the treatment of cardiovascular disease.

More recently, Ronnefarth *et al.* [85] examined the association between iodine intake and lipid parameters in 136 adolescents with euthyroid goitre in Germany. Compared to non-goiterous controls, iodine-deficient goiterous subjects had higher average total cholesterol ($p < 0.001$) and LDL cholesterol ($p < 0.001$) levels. In a corresponding study, Ronnefarth *et al.* [86] investigated the effects of iodine (300 $\mu\text{g}/\text{day}$, $n = 50$) or combined iodine and T4 supplementation (100 μg iodine and 100 μg T4 per day, $n = 56$) on lipid parameters in adolescents with euthyroid goiter. Following nearly six months of therapy, the initially elevated levels of cholesterol and LDL cholesterol decreased significantly in both treatment groups relative to pre-treatment values ($p < 0.001$ for both groups). These results suggest that, even in subjects who are clinically “euthyroid”, deficient iodine intake could over the long term increase cardiovascular disease risk, and as animal studies have suggested [65,66], such an effect may be exacerbated when cholesterol intake is high.

Human Studies on Thyroid Hormones and Cardiovascular Disease

In 1883, Kocher [87] observed that atherosclerosis frequently appeared following thyroid extirpation and suggested that hypothyroidism may be causally associated with atherosclerosis. By the 1940s and 1950s, human intervention studies appeared examining the effects of thyroid hormones (initially desiccated thyroid and later T4) on atherosclerosis and serum cholesterol levels in hypothyroid and euthyroid subjects [53–55]. Eventually T4 predominated as some formulations of desiccated thyroid were considered to be inconsistent in hormone content [53]. The results of T4 treatment were consistent with respect to lowering cholesterol levels and improving cardiovascular function in hypothyroid subjects [45,46]. In the 1960s, the Coronary Drug Project was developed to evaluate whether similar benefits could be obtained in euthyroid subjects [91]. This collaborative study assessed the long-term effects of T4 therapy ($n = 1,083$) vs placebo ($n = 2,715$) on cardiovascular disease morbidity and mortality. After an average follow-up of three years of treatment, both morbidity and mortality rates (primarily from cardiovascular causes) were higher in the group receiving T4. Thus, treatment of dyslipidemia with T4 has been limited to hypothyroid and subclinical hypothyroid subjects.

In contrast to the results with T4, a number of case studies from the 1950s to 1970s concluded that desiccated thyroid showed some beneficial cardiovascular effects in euthyroid subjects [92–96]. All subjects in these studies were maintained within the euthyroid range. Moses *et al.* [92] conducted a 10-month study of desiccated thyroid in elderly euthyroid diabetics and nondiabetics institutionalized for custodial care. Total cholesterol was reported to have declined in the majority of subjects, although the relative decline in diabetics as compared to nondiabetics was not reported. Menof [93–95] used desiccated thyroid to treat euthyroid subjects with hypertension. In a series of 334 subjects, he reported a decline in blood pressure to normal in 14% of subjects, to an intermediate range in 55% of subjects, and no change in 31% [93,94]. Most subjects in the latter group had evidence of renal hypertension, a condition Menof stated was not responsive to thyroid therapy [94]. Furthermore, Menof was careful to emphasize that there was considerable variation in the activity of different thyroid preparations and that a biochemical assay was necessary to ensure potency [93]. Wren [96] used desiccated thyroid to treat 347 patients with atherosclerosis, 91% of whom were euthyroid. In the 132 patients with symptomatic atherosclerosis, subjective improvements (increased sense of well-being, improved exercise tolerance, greater motivation and alertness) were noted in 76%. In subjects with elevated cholesterol, the mean reduction in serum cholesterol was 22.4% in hypothyroid subjects and 22% in euthyroid subjects. The five-year mortality rate was 58% of the expected rate for a matched population drawn from regional life tables and 44% of the expected rate

drawn from US life tables. An explanation for the beneficial effects of desiccated thyroid, not observed with T4 treatment, could include an independent effect of iodine or an effect of other iodinated thyroid hormones found in desiccated thyroid. However, in evaluating these results, it must also be considered that these were not randomized studies, and thus there were no comparative placebo controls.

Iodine, Selenium and Thyroid Function

Prospective epidemiological studies in humans as well as animal studies have shown that the development of numerous cardiovascular pathologies can be correlated with body selenium status [97]. Although best known for its role in various antioxidant enzymes such as the glutathione peroxidases, selenium plays many unique physiological roles as recently reviewed by Beckett and Arthur [98]. For example, selenium is incorporated into the thioredoxin reductases that are involved in regulating the cellular redox state, as well as, protecting against oxidative stress [99]. With respect to iodine, selenium is a component of the active site of the three enzymes that metabolize thyroid hormones, the iodothyronine deiodinases (D1, D2, and D3). D1 and D2 are involved in the activation of T3 from T4, whereas D3 as well as D1 can inactivate both T3 and T4 [100].

In studies of human tissues, it has been demonstrated that the thyroid contains more selenium per gram of tissue than any other organ [101], with the glutathione peroxidases and thioredoxin reductases predominating [102]. This underscores the critical role selenoenzymes play in this organ. In the thyroid, these enzymes are primarily involved in protecting thyrocytes from hydrogen peroxides and lipid hydroperoxides generated during thyroid hormone synthesis. Therefore, both iodine and selenium status may be important determinants in the development of thyroid autoimmunity. An increase in iodine intake under conditions of selenium deficiency may intensify the formation of hydrogen peroxides and lipid hydroperoxides [103,104] leading to an increased the risk of autoimmune thyroid disease [105,106]. In areas with mild selenium deficiency, selenium plasma levels have been shown to be lower in subjects with autoimmune thyroiditis [107,108] and Graves' disease [107] as compared to normal controls.

In support of these observations, several randomized double-blind studies have shown that selenium supplementation can reduce the titre of thyroid autoantibodies [106,109,110]. Gartner and Grasnier [106], who conducted a randomized study in 70 women with autoimmune thyroiditis, demonstrated that thyroperoxidase antibody (TPO-Ab) concentrations fell significantly in subjects on selenium for three months. In the 47 subjects crossed over for a further six months, TPO-Ab levels rose in subjects on placebo, yet declined further in those subjects on selenium [109]. Moreover, most subjects taking selenium also reported a subjective improvement of well-being

during periods of supplementation [109]. Similarly, in a six-month study by Duntas *et al.* [110] in 65 subjects with autoimmune thyroiditis, TPO-Ab levels declined by 56% in those receiving T4 and selenium *vs* 27% in those receiving T4 alone.

In a randomized, but unblinded study by Vrca *et al.* [111], 57 subjects with Graves' hyperthyroidism were treated with methimazole *vs* methimazole plus selenium and other antioxidants. Subjects in the latter group had a more rapid decline in serum free T4 and free T3 concentrations at 30 and 60 days, and more rapid increase in TSH activity at 60 days—demonstrating that those receiving selenium attained euthyroidism faster. Thus, the relative intake of both selenium and iodine may be an important factor with respect the etiology of autoimmune thyroid disease, and this may also have implications for the development cardiovascular disease.

A reduction in selenium intake and status has been noted in the United Kingdom and a number of other European countries over the last 20 to 25 years [112]. In many of these countries, daily intake is below recommended intake levels, which would lead to underexpression of glutathione peroxidase and other blood and tissue selenoproteins [98]. One exception to this trend has been Finland. Due to geological conditions, soil selenium concentrations are considered low in Finland compared with other countries [113]. As a result in 1978, high-selenium wheat was imported, and later in 1984, selenium was added to fertilizer for both grain and forage production [113]. Iodine intake has also increased significantly. Iodine is added to table salt, but prime sources are from dairy products and eggs, as iodine is now used in the dairy industry and added to animal salt [114]. In the past several decades, dramatic changes in health and life expectancy have occurred in Finland. For example, cardiovascular disease mortality has declined by over 50%, while the average life expectancy has increased by about five years [115]. Whether the increased iodine and selenium intake (both now considered the highest in Europe [113,116]) played any role one can only speculate. In Japan, the intake of iodine [117,118] and selenium [119,120] is also higher than most western nations due to a diet rich in seafood, a key source of both elements [120–122]. However, cross-national studies have demonstrated that salt intake in Japan is also markedly higher than western nations and that stroke mortality is also high [120]. Despite the high sodium intake, rates of coronary heart disease are lower in the Japanese [120], while overall life expectancy is higher [2]. Although there are many other dietary differences between Japan and the west, elucidating the synergistic role iodine and selenium play in cardiovascular health in countries such as Japan and Finland could provide novel insights into the etiology of this disease.

Mechanisms

Iodinated contrast media are commonly used agents for radiographic imaging. A notable side effect of all types of clinically employed iodinated contrast media is vasorelaxation

[123,124]. The vasodilatation is associated with a decrease in peripheral resistance, increased blood flow and decreased arterial blood pressure [124]. It has been suggested that these effects may involve modulating the release of endogenous vasoactive mediators such as prostacyclin, nitric oxide, endothelin, adenosine, histamine, serotonin, bradykinin, atrial natriuretic peptide, antidiuretic hormone and/or through direct effects on vascular smooth muscle cells [123]. Moreover, these effects also depend to varying degrees on their chemical structures (ionic or nonionic), and on the osmolality, viscosity, buffer and stabilizer composition of the preparations [123]. Whether iodine alone has some of the vasoactive properties of these contrast media is unknown.

Another effect of iodine may relate to its place within the Hofmeister series of anions (*i.e.* sulfate, citrate, tartrate, acetate, chloride, bromide, iodide, and thiocyanate). Hofmeister [125] demonstrated that the former compounds were effective precipitators of proteins in solution, whereas the latter compounds inhibited protein aggregation. Within this series, iodine is only superseded by thiocyanate in its ability to denature, depolymerize and solubilize proteins [126,127]. This latter attribute may enable iodine to reduce blood viscosity as has been noted for thiocyanate [128].

Finally, accumulating evidence has revealed that iodine has a number of natural physiological roles independent of its role in thyroid hormones; these include various anti-microbial, anti-inflammatory and anti-proliferative activities [129–134]. Such activities may also be important for overall cardiovascular health [69].

As to desiccated thyroid, one explanation for the benefits achieved in euthyroid subjects could be that some of the subjects may have had subclinical hypothyroidism, although such subjects would be expected to represent only a minority of arteriosclerotic or hypertensive patients. Alternatively, some effects may arise from the iodine, or from other iodinated components, within the desiccated thyroid. As mentioned previously, animal studies have demonstrated that T4 administration in hypothyroid or iodine-deficient animals does not ensure euthyroidism in all tissues [67,68]. Therefore, prolonged administration of desiccated thyroid may induce cardiovascular effects not evident with T4.

Future Directions

In the US, mortality from coronary heart disease and stroke has declined over the past several decades, despite the increasing prevalence of obesity and an apparent decline in iodine intake. The introduction of improved primary and secondary prevention and treatment measures have been implicated for most of the declines in cardiovascular disease [135]. These changes have encompassed a broad range of interventions such as: smoking cessation, improved diabetes management, treatment of hyperlipidemia and hypertension, thrombolytic therapies, and coronary angioplasty [136]. However, these improvements have also led to a growing sector of the population with

chronic heart failure. Although sodium restriction may improve immediate physiological variables such as blood pressure, the adverse effects of concomitantly reduced iodine intake (in regions where salt is iodized) over the long term are unknown.

Natural physiological roles for iodine, independent of its role in thyroid hormones, exist but have not been investigated as they relate to disease [129–134]. It would be intriguing to determine whether these various anti-inflammatory, anti-proliferative and anti-microbial properties of iodine could play a role in the prevention of cardiovascular disease. Cardiovascular diseases remain leading causes of morbidity and mortality in the developed, and increasingly, the developing world. Prospective studies are needed to resolve what role iodine, as well as selenium status plays in the etiology of cardiovascular diseases.

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