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Iodine deficiency, more than cretinism and goiter

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Summary Recent reports of the World Health Organization show iodine deficiency to be a worldwide occurring health problem. As iodine status is based on median urinary iodine excretion, even in countries regarded as iodine sufficient, a considerable part of the population may be iodine deficient. Iodine is a key element in the synthesis of thyroid hormones and as a consequence, severe iodine deficiency results in hypothyroidism, goiter, and cretinism with the well known biochemical alterations. However, it is also known that iodine deficiency may give rise to clinical symptoms of hypothyroidism without abnormality of thyroid hormone values.

This led us to the hypothesis that iodine deficiency may give rise to subtle impairment of thyroid function leading to clinical syndromes resembling hypothyroidism or diseases that have been associated with the occurrence of hypothyroidism. We describe several clinical conditions possibly linked to iodine deficiency, a connection that has not been made thus far. In this paper we will focus on the relationship between iodine deficiency and obesity, attention deficit hyperactivity disorder (ADHD), psychiatric disorders, fibromyalgia, and malignancies.

Introduction

After publication of recent WHO reports it has become clear that iodine deficiency, defined as urinary iodine excretion <100 μg/L, must be regarded as a worldwide occurring health problem [1,2]. Iodine deficiency is not only present in developing countries, but also widely spread in European countries and the USA. In above mentioned reports a sufficient median urinary iodine excretion rate excludes iodine deficiency, whereas, a sufficient median value may still implicate a considerable amount of people to be iodine deficient (Fig. 1) . Iodine was first described by Bernard Courtois (1777–1838), published upon by Gay-Lussac in 1814 and considered to play a key role in the prevention of goiter about one hundred years later [3]. In case of iodine deficiency the decreased production of the thyroid hormones thyroxin (T4) and triiodothyronine (T3) leads to increase of TSH levels, although TSH levels may stay within normal range. Under circumstances of sustained iodine deficiency, a shift in T3/T4 balance will occur in favor of T3. From the view of T3 being more potent and needing less iodine mol-

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Country	Survey data									Classification of iodine intake	Classification of iodine nutrition	Population affected	
	Date of survey	Level of survey	Population group and age (years)	Sample size	Median UI (μg/l)	Proportion of population with UI <100 μg/l (%)	95% CI of proportion of population with UI <100 μg/l	Notes	References			Children 6–12 yrs (000)[b]	General population (000)[b]
Netherlands	1995–1996	Local	SAC (6–18)	937	154	37.5	34.4–40.6	Thyromobile study. % <100 μg/l calculated from median.	(*103*)	Adequate	Optimal	523	6025
Norway	1999	Local	Adults (23–64)	63	117	39.7	27.6–51.8		(*143*)	Adequate	Optimal	169	1792
Ireland	1999	Local	Adults (22–61)	132	82	60.8	52.5–69.1	% <100 μg/l calculated from median.	(*130*)	Insufficient	Mild iodine deficiency	228	2378
France	1996	National	Adults (35–60)	12014	85	60.4	59.5–61.3	Medians from disaggregated data by sex pooled. % <100 μg/l calculated from median.	(*121*)	Insufficient	Mild iodine deficiency	3097	36149
Germany	1999	National	SAC (–6–12)	3065	148	27	25.4–28.6		(*122*)	Adequate	Optimal	1626	22 252
Greece	1996, 2001	Local	Adults (15–80), Adolescents (12–18)	1129	128.7	33.7	30.9–36.5	Median UI was calculated from % <100 μg/l for one survey. Medians from two local surveys pooled.	(*123,124*)	Adequate	Optimal	256	3697
Italy	1992–1994, 1993–1995, 1994P, 1997P, 1998P, 1999P	Regional, local	SAC (6–15)	11226	94	55.7	54.8–56.6	Medians from nine local and regional surveys pooled. % <100 μg/l calculated from median.	(*131–139*)	Insufficient	Mild iodine deficiency	2154	32018

Fig. 1 Classification of iodine status in several European countries by means of median urinary iodine excretion of the population investigated. Derived from Ref. [2].

ecules this seems an appropriate reaction for most tissues. Brain tissue, however, is only minimally able to take up T3. In the brain the selenium dependent type 2 iodothyronine deiodinase plays a crucial role in the conversion of T4 into T3. In case of selenium deficiency the iodothyronine deiodinase isoenzymes in the brain, endocrine and reproductive organs are spared for a relatively long time, resulting in no or only marginal effects of iodine deficiency [4]. In prolonged or severe iodine deficiency the effects will become more clear in disturbances of the biochemical parameters T3, T4 and TSH [5]. From this point of view it is obvious that the clinical effects of iodine deficiency can greatly vary, depending on the iodine—selenium balance in a tissue specific way. It should be noticed that other factors are known contributors to an optimal thyroid axis such as zinc, iron and retinoic acid [6].

Hypothesis

We postulate that iodine deficiency may not only give rise to hypothyroidism with the well known biochemical alterations and clinical manifestations such as goiter and cretinism, but to more subtle changes in thyroid hormone synthesis as well, thus leading to many other clinical conditions. Diseases that have been associated with the occurrence of hypothyroidism or the presence of symptoms of hypothyroidism may in fact be due to iodine deficiency. We describe several clinical conditions possibly linked to iodine deficiency, a connection that has thus far not been made. In this paper we will focus on the relationship between iodine deficiency and obesity, attention deficit hyperactivity disorder (ADHD), psychiatric disorders, fibromyalgia, and malignancies.

Support for the hypothesis

Many studies have been performed on the association between obesity and thyroid disease. Obesity has been associated with TSH increase within normal range and subsequent TSH mediated stimulation of leptin secretion by adipocytes [7,8]. As leptin is known to induce appetite, it is obvious that under circumstances of increased leptin secretion obesity may occur. Thus far, iodine deficiency has not been recognized as a cause of obesity. However, it can be hypothesized that the increased TSH levels found are due to iodine deficiency. It should be realized that leptin acts as a brain protective against iodine deficiency by up regulating type 2 iodothyronine deiodinase, leading to conversion of T4 into T3 [9].

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Recently, the association between iodine deficiency in pregnancy and ADHD of the child was shown [10]. Additionally, we know that ADHD can be influenced by food intake [11]. It can be assumed that in case of a mother having an iodine insufficient diet, the rest of the family will also have an insufficient iodine intake. Therefore it seems logical that iodine deficiency in the child itself is associated with the occurrence of ADHD.

A relationship between (subclinical) hypothyroidism and anxiety disorders, memory disturbances, neurotic and attention disorders has been described [12,13]. Several studies suggest brain hypothyroidism to be present under these conditions and from this point of view supplementation with T3 was performed, resulting in varying response rates. In the above mentioned disorders we also suppose brain hypothyroidism to be a crucial factor in the pathogenesis. We consider iodine deficiency and/or selenium deficiency to be underlying causes, eventually leading to low brain T3 levels.

Fibromyalgia is characterized by a complex of symptoms resembling hypothyroidism, whereas in blood tests hypothyroidism cannot be assessed. It is known that the more symptoms of hypothyroidism are present, the more likely the presence of this disorder becomes [14]. In fibromyalgia patients several symptoms are frequently present, however, without the marked TSH increase as seen in full blown hypothyroidism [15]. We hypothesize that the clinical diagnosis of hypothyroidism is correct, but is not recognized because of iodine deficiency as the crucial, but not investigated factor in pathogenesis.

Eventually, many studies have pointed out the relationship between cancer and thyroid disturbances. Apoptosis plays an important role in the pathogenesis of malignant diseases. Iodine and selenium have been described as two independent factors playing a crucial role in the prevention of breast and prostate cancer, respectively [16–18]. In 1996, Dai et al. described the existence of the natrium–iodine symporter (NIS), a receptor providing iodine uptake into the thyroid against a concentration gradient. Remarkably, this receptor is widely spread throughout the body [16,19]. Additionally, the receptor shows increased expression (mainly intracellular) in malignant cells of different origin [19]. These data suggest a role for iodine in the pathogenesis of cancer/apoptosis. It was recently shown that the iodine molecule itself induces apoptosis in human breast carcinoma cells involving a mitochondrial mediated pathway. In normal cells this effect could not be assessed [20]. In case of iodine deficiency these processes may be disturbed, leading to disturbed apoptosis and eventually to malignancies.

Testing the hypothesis

Evidence to prove the hypothesis stated above should be obtained by assessing iodine status in general population, but especially in subgroups affected by obesity, ADHD, anxiety disorders, fibromyalgia, and malignancies. The choice for a subgroup could be made on the basis of general importance for society and severity of problems. We suggest different supplementation strategies to be tested. In this respect, it is important to realize that the recommended daily allowance (RDA) for iodine has been assessed at 150 μg/day, a dosage based on the prevention of goiter. It should be considered, however, that the dosage necessary for optimal thyroid function might differ from a dosage only sufficient to prevent goiter. In line with these data not only patients with urinary iodine excretion <100 μg/L should be given supplementation. It might be useful to assess patient groups according to the level of urinary iodine excretion and investigate the effect of supplementation on clinical outcome.

Implications of the hypothesis

Given the known worldwide iodine deficiency and the crucial role of iodine in the synthesis of thyroid hormone, iodine may be the most important limiting step. However, we should realize that also Marine and Kimball in their supplementation studies reached a response percentage of only 60%, despite high iodine supplementation doses [3]. With the insights known today it seems of utmost importance to identify other co-factors as rate limiting. Hereby a crucial role for selenium seems most logical. Nowadays, prevention of goiter and cretinism still are the ultimate goals in iodine supplementation programs as existing in developing countries. From the data mentioned above it can be deduced that iodine deficiency may give rise to more subtle disturbances of thyroid hormone synthesis, leading however to clinical conditions that cause severe patient disability and huge health care costs.

References

[1] Bruno de Benoist, Maria Andersson, Ines Egli, Bahi Takkouche, Henrietta Allen. Iodine status worldwide: WHO global

database on iodine deficiency, Geneva: World Health Organization. Ref Type: Report; 2004.
[2] Maria Andersson, Bruno de Benoist, Ian Darnton-Hill, François Delange. Iodine deficiency in Europe: a continuing public health problem, Geneva: World Health Organization. Ref Type: Report; 2007.
[3] Marine D, Kimball OP. The prevention of simple goiter in man. A survey of the incidence and types of thyroid enlargements in the schoolgirls of Akron (Ohio), from the 5th to the 12th grades, inclusive — the plan of prevention proposed. 1917. J Lab Clin Med 1990;115:128—36.
[4] Kohrle J, Jakob F, Contempre B, Dumont JE. Selenium, the thyroid, and the endocrine system. Endocrinol Rev 2005;26:944—84.
[5] Obregon MJ, Escobar del RF, Morreale de EG. The effects of iodine deficiency on thyroid hormone deiodination. Thyroid 2005;15:917—29.
[6] Hess SY, Zimmermann MB. The effect of micronutrient deficiencies on iodine nutrition and thyroid metabolism. Int J Vitam Nutr Res 2004;74:103—15.
[7] Kok P, Roelfsema F, Frolich M, Meinders AE, Pijl H. Spontaneous diurnal thyrotropin secretion is enhanced in proportion to circulating leptin in obese premenopausal women. J Clin Endocrinol Metab 2005;90:6185—91.
[8] Menendez C, Baldelli R, Camina JP, et al. TSH stimulates leptin secretion by a direct effect on adipocytes. J Endocrinol 2003;176:7—12.
[9] Cettour-Rose P, Burger AG, Meier CA, Visser TJ, Rohner-Jeanrenaud F. Central stimulatory effect of leptin on T3 production is mediated by brown adipose tissue type II deiodinase. Am J Physiol Endocrinol Metab 2002;283:E980—7.
[10] Vermiglio F, Lo PV, Moleti M, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 2004;89:6054—60.
[11] Pelsser LM, Buitelaar JK. Favourable effect of a standard elimination diet on the behavior of young children with attention deficit hyperactivity disorder (ADHD): a pilot study. Ned Tijdschr Geneeskd 2002;146:2543—7.
[12] Tiwari BD, Godbole MM, Chattopadhyay N, Mandal A, Mithal A. Learning disabilities and poor motivation to achieve due to prolonged iodine deficiency. Am J Clin Nutr 1996;63:782—6.
[13] Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. J Clin Endocrinol Metab 2007;92:2545—51.
[14] Roberts CG, Ladenson PW. Hypothyroidism. Lancet 2004;363:793—803.
[15] Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006;367:346—55.
[16] Riesco-Eizaguirre G, Santisteban P. A perspective view of sodium iodide symporter research and its clinical implications. Eur J Endocrinol 2006;155:495—512.
[17] Hoption Cann SA, Qiu Z, van NC. A prospective study of iodine status, thyroid function, and prostate cancer risk: follow-up of the First National Health and Nutrition Examination Survey. Nutr Cancer 2007;58:28—34.
[18] Rayman MP. The importance of selenium to human health. Lancet 2000;356:233—41.
[19] Wapnir IL, van de RM, Nowels K, et al. Immunohistochemical profile of the sodium/iodide symporter in thyroid, breast, and other carcinomas using high density tissue microarrays and conventional sections. J Clin Endocrinol Metab 2003;88:1880—8.
[20] Shrivastava A, Tiwari M, Sinha RA, et al. Molecular iodine induces caspase-independent apoptosis in human breast carcinoma cells involving the mitochondria-mediated pathway. J Biol Chem 2006;281:19762—71.

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