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Epidemiological trends of iodine-related thyroid disorders: an example from Slovenia

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The epidemiology of thyroid disorders is significantly associated with iodine supply. In 1999, Slovenia increased iodine content in kitchen salt from 10 mg to 25 mg of potassium iodide per kg of salt. According to the WHO criteria, Slovenia shifted from a mildly iodine-deficient country to a country with adequate iodine intake. Ten years after the increase in iodine intake, the incidence of diffuse goitre and thyroid autonomy decreased. Now patients with diffuse goitre and thyroid autonomy reach older age than the patients before the increase in iodine intake. In addition, patients with thyroid autonomy are less frequently hyperthyroid than ten years ago and iodine-induced hyperthyroidism is less severe. The incidence of highly malignant thyroid carcinoma has also dropped. However, the incidence of Hashimoto's thyroiditis increased, most probably in genetically predisposed individuals. Over the last ten years, many animal and *in vitro* studies evaluated the effects of endocrine disrupting chemicals (EDC) on various aspects of the thyroid function. They mostly studied the effects of polychlorinated biphenyls (PCBs) and dioxins, brominated flame retardants, phthalates, bisphenol A, perfluorinated chemicals, and perchlorate. However, human studies on the effects of EDCs on the thyroid function are very scarce, especially the long-term ones. What they do suggest is that PCBs and dioxins interfere with the transport of thyroid hormones and adversely affect the thyroid function. Many authors agree that iodine deficiency predisposes the thyroid gland to harmful effects of EDCs. Therefore the effects of EDCs in iodine-deficient areas could be more severe than in areas with adequate iodine intake.

KEY WORDS: *diffuse goitre; dioxins; endocrine disrupting chemicals; Hashimoto's thyroiditis; iodine supply; iodine-induced hyperthyroidism; polychlorinated biphenyls; thyroid autonomy*

Beside diabetes, the most frequent disorders of endocrine glands are those affecting the thyroid gland. Genetic factors largely contribute to the occurrence of various thyroid diseases such as Graves' disease, Hashimoto's thyroiditis, or goitre (1). However, their prevalence is also strongly associated with iodine supply in the environment (2), as the thyroid gland requires adequate amounts of iodine to function properly (3). Of all endocrine glands, the thyroid exhibits a unique connection with the environment. It is sensitive to iodine intake and the influence of endocrine disrupting chemicals (EDC) (4). The aim of this article is to review the effects of environmental factors on the thyroid function and size with the focus on iodine intake and EDCs.

Iodine and thyroid hormones

Ingested iodine is absorbed as I^- in the stomach and upper small intestine. Adult body contains around 15 to 20 mg of iodine, of which 70 to 80 % is in the thyroid gland (5, 6). Iodine concentration within thyroid cells is 20 to 40 times higher than in the blood. The ability of thyroid cells to accumulate iodine against the concentration gradient is enabled by the transport protein called sodium (Na^+)-iodide (I^-) symporter (NIS). NIS combines the transport of Na^+ along the concentration gradient with the transport of I^- against the concentration gradient using the energy from adenosine triphosphate (ATP) obtained from the activity of Na^+-potassium (K^+)-ATPase (7). With the help of thyroid peroxidise (TPO), I^- is first oxidised, then integrated into glycoprotein thyroglobulin (Tg) as monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are finally coupled into thyroxine (T_4) or triiodothyronine (T_3) (8). The accumulation of I^- and the synthesis of thyroid hormones is regulated by the thyroid-stimulating hormone (TSH, aka thyrotropin), secreted from the pituitary gland (9), as well as by iodine itself (10).

The thyroid gland produces all T_4 and only 20 % of T_3. The remaining T_3 originates from the conversion of weakly active T_4 into very active T_3 by enzymes deiodinases, which are present in several tissues (11). To a high degree T_4 and T_3 bind to transport proteins in serum. Less than 1 % of T_4 and T_3 circulate as free thyroxine (fT_4) and free triiodothyronine (fT_3) (12). However, only free thyroid hormones are active and are transported to different cells,

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where they bind to nuclear, plasma membrane, cytoplasm, and mitochondrial receptors and perform their genomic and non-genomic actions (13, 14). Thyroid hormones regulate metabolism and are especially important for the development of human brain during foetal life and early childhood (15). In areas with severe iodine deficiency, lack of iodine during pregnancy may cause iodine-deficiency disorders in offspring (16).

Iodine supply

In most developed countries the main source of iodine is iodised kitchen salt, since iodine content in soil, and, consequently, in ground water, vegetables, and meat is too low to meet daily needs. The World Health Organization (WHO) recommends iodisation of kitchen salt with 20 to 40 mg of potassium iodide per kg of salt (3). Daily intake of iodine for adults should reach 150 μg. For pregnant and lactating women, a higher daily intake of around 250 μg is recommended. In pregnancy, more thyroid hormones are produced because of increased levels of transport proteins (17). Additionally, iodine is partly transported to the foetus via placenta. During lactation, adequate iodine intake is especially important since a breastfed child depends only on iodine from mother's milk.

As iodine intake cannot be measured directly, and iodine is largely secreted in urine, its urinary concentration makes a good estimate of the intake. According to the WHO criteria, urinary iodine concentration (UIC) between 50 and 99 μg L^{-1} suggests mild iodine deficiency, 20 to 49 μg L^{-1} moderate deficiency, and below 20 μg L^{-1} severe deficiency (3). A great portion of the world's population still lives in areas where iodine supply is deficient. Even in Europe, countries without stable and mandatory iodisation of kitchen salt can have areas of mild or moderate iodine deficiency.

Iodine and thyroid disorders

Optimal iodine intake lies within a relatively narrow range between 150 and 250 μg a day (3). Too low an intake may lead to iodine deficiency disorders and enlarged thyroid gland, known as goitre. Intake which is too high leads to autoimmune thyroid disorders and hypothyroidism. In addition, any change in iodine supply is associated with a change in the epidemiology of thyroid disorders. One such epidemiological change occurred with the increase in iodine supply in Slovenia in 1999.

From 1953 to 1999, kitchen salt in Slovenia had been iodised with 10 mg of potassium iodide per kg. In 1991 to 1994, we measured UIC in a population of 1740 schoolchildren to be 82.9 μg g^{-1} of creatinine (18, 19), which suggested a mild iodine deficiency. The average volume of their thyroid gland, measured by ultrasound, was 7.2 mL.

In the early 1999, kitchen salt iodisation increased to 25 mg (range: 20 to 30 mg) of potassium iodide per kg of salt. Measurements since 1999 show a daily intake of 9.4 g of kitchen salt in girls and 11.5 g in boys (20) and 9.9 g in women and 13.0 g in men (21). As soon as 2003, UIC in schoolchildren increased to 148 μg L^{-1}, which suggests adequate iodine intake (19). In pregnant women, it was also high enough - 170.5 μg g^{-1} of creatinine in the third trimester, and 144 μg g^{-1} of creatinine after childbirth (22). The volume of the thyroid gland in schoolchildren decreased to 5.8 mL (19).

From 1999 to 2009, the incidence of diffuse goitre dropped over 80 % (19). In 2009, patients with newly diagnosed diffuse goitre were significantly older than those diagnosed with the disease in 1999 (53 *vs*. 38 years, respectively). This clearly suggests that younger generations benefited from adequate iodine supply. After all, older patients had lived in iodine deficiency longer than the younger subjects.

Thyroid autonomy is caused by various mutations of TSH receptor and/or signalling proteins (23). Autonomous thyroid cells produce thyroid hormones irrespective of regulation by TSH. The incidence of thyroid autonomy has been reported to be higher in iodine-deficient than in iodine-sufficient areas (3). From 1999 to 2009, the incidence of thyroid autonomy in Slovenia decreased by 27 % (19). Furthermore, in 2009, patients with the newly diagnosed thyroid autonomy were older and less frequently hyperthyroid than patients in 1998. This again confirms the effects of iodine deficiency are time-dependent (24). Literature data regarding iodine supply and thyroid autonomy are scarce and inconclusive. Our data are in accordance with those from Switzerland (25, 26).

Excessive iodine intake is usually related to the antiarrhythmic drug amiodarone or iodinated contrast media in radiology. In predisposed individuals, such as patients with thyroid autonomy, iodine excess most frequently provokes hyperthyroidism. By contrast, in patients with Hashimoto's thyroiditis, iodine excess may induce hypothyroidism. Andersen et al. (27) reported that in areas with iodine deficiency iodine excess more often causes hyperthyroidism while in areas with adequate iodine intake it may cause hypothyroidism. Ten years after the increase in salt iodisation, our results show a higher incidence of iodine-induced hypothyroidism, a less severe iodine-induced hyperthyroidism, and a shorter duration of treatment of hyperthyroidism, which are all clinical improvements over the earlier period (28).

Literature data about iodine-induced thyroid disorders with respect to iodine supply are very scarce. In Slovenia, we have observed a lower incidence of the most malignant anaplastic thyroid carcinoma between 1998 and 2008 than between 1972 and 1998 (29). After the increase in iodine supply, patients with the newly diagnosed anaplastic thyroid carcinoma were older than before the increase. Again, it seems that younger generations have benefited from adequate iodine supply.

As for Hashimoto's thyroiditis, its incidence in Slovenia more than doubled after the increase in iodine supply (19). These findings confirm Iranian reports of up to four-fold

increase in the prevalence of thyroid autoantibodies after the improvement of iodine prophylaxis in iodine-deficient areas (30). Other authors reported the prevalence of thyroid autoantibodies of around 11 % in iodine deficiency (31), 18 % in iodine sufficiency (32), and around 25 % in excessive iodine intake (33, 34). Many tried to elucidate the influence of iodine supply on thyroid autoimmunity. Some suggest that higher intake of iodine may increase the iodination of thyroglobulin and the level of reactive oxygen species within thyroid cells, thus promoting immunogenicity (35, 36). Others believe that iodine may have a toxic effect on thyroid cells and stimulate the cells of the immune system (1, 37).

Whichever the reason, a change from mild iodine deficiency to iodine sufficiency is associated with many beneficial effects with regard to the incidence and severity of various thyroid disorders.

Endocrine disrupting chemicals

Endocrine disrupting chemicals most often affect the NIS, TPO, transport protein transthyretin, deiodinases, and thyroid hormone receptors (4, 38).

Polychlorinated biphenyls (PCBs) and dioxins are persistent environmental pollutants, which accumulate in the food chain and - due to lipophilic properties - in the human body, in spite of the ban from the 1970s. The chemical structure of PCBs and dioxins is similar to the chemical structure of thyroid hormones, as they all have two linked phenyl rings. PCBs displace T_4 from transport proteins (39), decrease the serum levels of thyroid hormones and, accordingly, increase the serum levels of TSH (40, 41). However, Goldey et al. (42) have also reported serum T_4 drop without an increase in TSH. Interestingly, hydroxylated PCBs were able to increase the activity of thyroid receptors in rats (43). *In vitro*, PCBs bind to transport proteins and inhibit the binding of T_3 to the receptor (44, 45). In humans, exposure to PCBs was associated with thyroid antibodies and hypothyroidism (1). All in all, it seems that PCBs and dioxins affect the thyroid function adversely.

Polybrominated diphenyl ethers (PBDEs) are used as flame retardants and also have chemical resemblance with the thyroid hormones with two halogenated phenyl rings (40). Since PBDEs are lipophilic, they accumulate in several human tissues (46). Human studies with PBDEs are very scarce. In animals, PBDEs decreased the levels of thyroid hormones (47), and affected binding proteins, thyroid hormone receptors, and hepatic clearance (48, 49).

Pesticides are still amply present in the environment. In animal studies, they adversely affected thyroid hormone levels (50). *In vitro*, phenol compounds inhibited TPO (51). Relevant human studies are not available.

In humans as well as in animals, perfluorooctanoate adversely affects fT_4 (52, 53). In the National Health and Nutrition Examination Survey carried out in the United States (54), individuals with high levels of perfluorooctanoic acid more frequently reported treated thyroid disease.

Human studies with phthalates are very scarce. In children, they negatively correlated with serum T_3 (55). A similar correlation was found between phthalates and fT_4 in men and pregnant women (56, 57).

In vitro, bisphenol A (BPA) binds to thyroid hormone receptors and therefore disrupts thyroid hormone activity (58). In rats, developmental exposure to BPA caused a condition similar to thyroid resistance syndrome, with increased serum levels of T_4 and normal or slightly increased levels of TSH, indicating that BPA could act as a specific antagonist of thyroid hormone receptor β, which is known to be impaired in the thyroid resistance syndrome (59, 60).

Perchlorate in drinking and irrigation waters and in food - a problem particularly familiar to the USA - reduces iodide uptake into the thyroid cells (38, 61). In the general population of women, urinary levels of perchlorate correlated with serum TSH levels (62). In women with urinary iodine below 100 $\mu g\ L^{-1}$ and in women who smoked this correlation was even stronger, since smokers have higher serum levels of thiocyanates than non-smokers, and thiocyanate reduces iodide uptake (63).

For many other EDCs human studies are not available. *In vitro* and animal studies indicate significant effects on the thyroid function, but solid data on humans are needed for a more objective view of EDCs. To summarise, potential EDCs are numerous, human studies with EDCs are scarce, exposure to EDCs is universal, and long-term effects are very difficult to study. Therefore, a long-term follow-up of larger groups of exposed individuals would bring valuable information about the effects of EDCs on the thyroid function.

CONCLUSION

Changes in iodine supply significantly reflect on the epidemiology of thyroid disorders in an area. Optimum iodine intake - which lies within a relatively narrow range - is the prerequisite for the normal growth and function of the thyroid gland. In contrast, iodine deficiency makes the thyroid gland more sensitive to various adverse effects, including the effects of EDCs. The Slovenian example confirms the importance of a sustained and mandatory iodination programme in abating thyroid disorders.

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Epidemiološki trendi bolezni ščitnice, ki so povezane z jodom: primer Slovenije

Epidemiologija bolezni ščitnice je pomembno povezana z jodno preskrbo. V Sloveniji smo leta 1999 zvečali vsebnost joda v kuhinjski soli z 10 mg na 25 mg kalijevega jodida na kg soli. Glede na kriterije SZO smo se iz države z blagim pomanjkanjem joda spremenili v državo z ustreznim vnosom joda. Ugotovili smo, da se je v desetih letih po zvečanju jodne preskrbe zmanjšala pojavnost difuzne golše in avtonomnega tkiva v ščitnici. Bolniki z difuzno golšo in avtonomnim tkivom so sedaj starejši kot pred zvečanjem jodne preskrbe. Poleg tega so bolniki z avtonomnim tkivom redkeje hipertirotični kot pred desetimi leti, hipertiroza, ki je posledica čezmernega vnosa joda, pa je manj izražena. Zmanjšala se je pojavnost najbolj maligne oblike ščitničnega karcinoma. Povečala se je pojavnost Hashimotovega tiroiditisa, verjetno pri genetsko predisponiranih posameznikih. V zadnjem desetletju so v številnih raziskavah na živalih in v raziskavah *in vitro* ugotavljali vpliv kemijskih povzročiteljev hormonskih motenj (KPHM) na različne vidike ščitnične funkcije. Najpogosteje testirani KPHM so bili poliklorirani bifenili (PCB) in dioksini, bromirani zaviralci gorenja, ftalati, bisfenol A, perfluorirane kemikalije in perklorat. Vendar pa so raziskave o učinkih KPHM na delovanje ščitnice pri ljudeh, zlasti dolgoročne raziskave, zelo redke. Zdi se, da zlasti PCB in dioksini vplivajo na transport ščitničnih hormonov in negativno učinkujejo na delovanje ščitnice. Številni avtorji menijo, da pomanjkanje joda poveča dovzetnost ščitnice za škodljive učinke KPHM. Torej bi lahko bili škodljivi učinki KPMH na področjih pomanjkanja joda resnejši kot na področjih zadostnega vnosa joda.

KLJUČNE BESEDE: *avtonomno tkivo ščitnice; difuzna golša; dioksini; Hashimotov tiroiditis; hipertiroza zaradi čezmernega vnosa joda; kemijski povzročitelji hormonskih motenj; poliklorirani bifenili; preskrba z jodom*