Boron – A potential goiterogen?

Elizaveta V. Popova a,b, Alexey A. Tinkov a,c,d,⇑, Olga P. Ajsuvakova e, Margarita G. Skalnaya d, Anatoly V. Skalny c,d,f

a Orenburg State Medical University, Orenburg, Russia
b St Joseph University in Tanzania, St Joseph College of Health Sciences, Dar es salaam, Tanzania
c Yaroslavl State University, Yaroslavl, Russia
d RUDN University, Moscow, Russia
e Orenburg State Pedagogical University, Orenburg, Russia
f Orenburg State University, Orenburg, Russia

Introduction

The iodine deficiency disorders (IDD) include a variety of disturbances such as decreased fertility [1], increased perinatal and infant mortality, impaired physical and intellectual development, mental retardation, cretinism, hypothyroidism, and endemic goiter (EG). The occurrence of the latter is determined by interplay between genetic and environmental factors. The major environmental factor is iodine status that is required for normal thyroid hormone synthesis. However, other factors like intake of micronutrients and goiterogens also have a significant impact. Essential and toxic trace elements both play a significant role in thyroid physiology. We hypothesize that in terms of overexposure boron may serve as a potential goiterogen. In particular, it is proposed that boron overload may impair thyroid physiology ultimately leading to goiter formation. Certain studies provide evidential support of the hypothesis. In particular, it has been demonstrated that serum and urinary B levels are characterized by a negative association with thyroid hormone levels in exposed subjects. Single indications on the potential efficiency of B in hypothyroidism also exist. Moreover, the levels of B were found to be interrelated with thyroid volume in children environmentally exposed to boron. Experimental studies also demonstrated a significant impact of boron on thyroid structure and hormone levels. Finally, the high rate of B accumulation in thyroid may also indicate that thyroid is the target for B activity. Chemical properties of iodine and boron also provide a background for certain competition. However, it is questionable whether these interactions may occur in the biological systems. Further clinical and experimental studies are required to support the hypothesis of the involvement of boron overexposure in goiter formation. If such association will be confirmed and the potential mechanisms elucidated, it will help to regulate the incidence of hypothyroidism and goiter in endemic regions with high boron levels in soil and water.

The main clinical sign of IDD in affected population is EG [8], by palpation defined “when each of the lateral lobes of the thyroid gland (TG) is larger than the terminal phalanges of the thumb of the person examined” [23]. In comparison to boys, girls have a higher risk of EG among schoolchildren [24]. EG is an adaptive disease [25], which develops when the full amount of iodine necessary for metabolism in TG is insufficient [26]. Adaptive process is triggered and in turn is controlled by augmented stimulation of thyroid-stimulating hormone (TSH) [27]. If iodine intakes is decreased, TSH secretion is increased respectively [2] and stimulates transcription of the sodium/iodine symporter (NIS) gene [28,29]. Increased clearance of iodide into TG subsequently results to a progressive reduction of renal iodide excretion [2]. TSH stimulates all steps of thyroid hormones (TH) biosynthesis and secretion [27]. When a number of daily iodine intake stays above a
threshold level (near 50 μg/d) [2], absolute uptake of iodine by the TG remains adequate and the content of iodine in the TG stays within normal limits in spite of a decreased inorganic iodine circulating in plasma [2]. Hence, adequate secretion of TH may still be achieved despite to low or even very low iodine intake [30]. In chronic ID, the iodine content of the TG might fall below threshold limit. Thereby, despite to augmented clearance of iodine by the TG, absolute uptake is fallen. It leads to EG development [2].

In spite to the first comprehensive review of the EG worldwide was presented in 1960 [8] the problem of IDD still represent a major public health problem [24,31,32]. Ongoing almost 30% of the world population being exposed to the consequences of nutritional iodine deficiency [32,44], that is 29.8% of school-age children (246 million) are estimated to have insufficient iodine intake [33].

Commonly, the occurrence of EG is determined by interplay between genetic and environmental factors. The major environmental factor is iodine status, but other factors, such as Vitamin A deficiency [34], decreased or increased supplementation of some trace elements can also cause to goiter development [35]. Moreover, some nutrients containing in food and drinking water can affect to iodine and thyroid hormones metabolism. Such nutrients are called as goitrogens [36]. For example, the anions perchlorate, thiocyanate (SCN), and nitrate are competitive inhibitors of the NIS [15,16,37–39]. SCN also causes the formation of insoluble iodinated Tg in thyroid [40], increases iodine efflux [41], inhibits TPO activity [42,43] and competes with iodide in the incorporation into Tg [44]. Moreover, thyroid glands can concentrate other ions, including astatide, bromide, chloride, pertechnetate, rhenate and but not fluoride [45,46].

Trace elements in thyroid disorders

In particular, it has been demonstrated that patients with thyroid pathology (thyroid cancer, nodular goiter, and Graves’ disease) are characterized by significantly higher whole blood Cu and Zn levels, whereas Se concentration was decreased in comparison to the control group. The content of Cu, Zn, and Se in thyroid tissue also varied significantly between the groups [47]. At the same time, later studies failed to detect any significant difference in plasma Se, Zn, and Fe levels in patients with multinodular goiter and controls, whereas plasma Cu and Mn were increased in goiterous patients. Moreover, plasma Cu concentration was significantly associated with free T3/T4 ratio [48]. In turn, serum Zn levels were also associated with thyroid volume and TSH concentration in nodular goiter patients [49]. Population studies have also confirmed the association between serum Se, Cu, and Zn levels with thyroid hormones [50]. The disturbances of trace element status in thyroid diseases are also aggravated with advanced age [51]. Experimental studies demonstrated that both hypothyroidism [52] and hyperthyroidism [53] affect trace element status of the organism.

It is also notable that goiter is associated with altered thyroid trace element content. In particular, it has been revealed that thyroid Cu, Mn, Fe, and Zn levels in patients with nodular goiter was significantly lower as compared to the controls [54]. Iodine content in nodular goiter tissues was also found to be lower than that in the healthy tissue [55]. These findings demonstrate that certain trace elements like Zn, Se, and Fe play a significant role in thyroid physiology their deficiency may alter thyroid functions and significantly reduce the efficiency of iodine supplementation [56].

Briefly, selenium plays a crucial role in thyroid physiology through its role in selenoproteins and especially selenocysteine-containing iodothyronine deiodinases [57]. Antioxidant Se-proteins are also known to be required for normal thyroid function [58]. Copper is involved in regulation of TPO expression and proliferation of thyroid follicular cells through modulation of redox environment [59]. In turn, serum copper was considered as thyroid hormone resistance marker [60]. Certain studies have also demonstrated that iron status is associated with TPO activity [61].

At the same time, not only essential trace elements interfere with thyroid function. In particular, exposure to arsenic [62], cadmium [63] was shown to result in impaired thyroid function. It has been demonstrated that adolescents with non-toxic diffuse goiter are characterized by significantly higher whole blood lead and cadmium levels [64]. Finally, habituation in specific geochemical provinces with high exposure of potentially essential trace elements like strontium and chromium also increases the risk of thyroid disorders [65].

Therefore, both essential and toxic trace elements play a significant role in regulation of thyroid functioning and trace element imbalance due to dietary restriction or environmental exposure may result in various pathologies including goiter.

Boron and human health

Boron is known to be essential for vascular plants due to its structural role in the cell wall [66]. At the same time, the role of boron in human health and its nutritional relevance are still questionable [67]. However, it has been revealed that B may be beneficial. In particular, boron-containing compounds are currently investigated as potential drugs [68]. In particular, certain B-containing compounds were considered as anti-inflammatory [69,70], anti-cancer [71], antiprotozoal [72] and antibacterial agents [73], as well as pharmacophores [74]. Such properties are related to biological effects of boron. In particular, boron was shown to regulate inflammatory response [75,76] through various mechanisms including down-regulation of NF-kB [77]. Other mechanisms mediating beneficial effects of boron may involve modulation of enzymes [78] including those regulating availability of S-adenosylmethionine and diadenosine phosphates [79], and interference with essential micronutrients including calcium, magnesium, and vitamin D [78]. It is also notable that boron compounds may counteract heavy metal (Cd, Hg, Bi, Pb) toxicity through their antioxidant effects [80]. However, the intimate biochemical mechanisms of the biological action of boron in the human organism are still unclear [81]. Experimental and clinical studies have demonstrated that boron may be beneficial for various tissues and organs including bones, brain, endocrine system [82], including steroid hormone [78] and leptin production [83]. At the same time, despite the earlier supposition of the positive effect of B on thyroid gland [67], it does not play a significant role in the maintenance of thyroid physiology in a healthy state according to EFSA’s Scientific Panel [84].

Hypothesis

We hypothesize that in terms of overexposure boron may serve as a potential goitrogen. In particular, it is proposed that boron overload may impair thyroid physiology ultimately leading to goiter formation.

Evidential support of the hypothesis

Boron status and thyroid function

In the middle of the XX century it was proposed that boron may be included into the list of compounds resulting in thyroid pathology [85]. However, no serious experimental or clinical support was provided at the moment. Interesting data on the interference between boron and thyroid function were obtained by Nielsen and Penland [86]. In particular, they have demonstrated that B supplementation significantly increased urinary and serum B