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Selenium and iodine in diabetes mellitus with a focus on the interplay and speciation of the elements

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ABSTRACT

Diabetes mellitus is a chronic metabolic disease caused by insulin deficiency (type I) or dysfunction (type II). Diabetes is a threatening public health concern. It is considered as one of the priority non-communicable diseases, due to its high and increasing incidence, the associated healthcare costs, and threatening medical complications. Two trace elements selenium (Se) and iodine (I) were intensively discussed in the context of diabetic pathology and, possibly, etiology. It seems there is a multilayer involvement of these essential nutrients in glucose tolerance, energy metabolism, insulin signaling and resistance, which are mainly related to the antioxidant selenoenzymes and the thyroid hormones. Other factors might be related to (auto)immunity, protection against endoplasmic reticulum stress, and leptin signaling. The aim of the current review is to evaluate the current understanding of the role of selenium and iodine in diabetes with a focus on the biochemical interplay between the elements, their possible role as biomarkers, and their chemical speciation. Possible impacts from novel analytical techniques related to trace element speciation and isotopic analysis are outlined.

1. Introduction

Diabetes mellitus is a chronic metabolic disease caused by insulin deficiency (type I) or dysfunction (type II). Diabetes is a threatening public health concern and is named as one of the four priority non-communicable diseases [1]. Type I diabetes (T1DM) is characterized by autoimmune-mediated selective destruction of insulin-producing β-cells in the pancreatic islets [2,3]. Type II diabetes (T2DM) is a heterogeneous group of metabolic insulin resistance syndromes [4]. Overweight and obese patients often tend to T2DM [5]. Obesity promotes inflammation and systemic insulin resistance, thus affecting in the β-cells of the pancreatic islets [6]. The World Health Organization reported the age-standardized global prevalence of diabetes in the adult population to have nearly doubled between 1980 and 2014, rising from 4.7% to 8.5%, which is a disturbing trend [7]. Additionally, the epidemiologic prognosis for T2DM is threatening, corresponding to an increase of about 54% worldwide between 2010 and 2030 [8]. According to the triage theory, the misbalance of essential nutrients, vitamins, and minerals, are causing insidious events, which in the long term lead to elevated risks for age-related metabolic diseases, including diabetes mellitus [9]. The role of trace elements selenium (Se) and iodine (I) in relation to diabetic etiology and pathogenesis has already been discussed rather intensively.

Selenium is involved in the biosynthesis of essential selenoproteins, contributing to antioxidant protection and redox-regulation [10], whereas iodine is utilized as iodide by the body to produce thyroid hormones. Thyroid hormones regulate energy metabolism, affecting the insulin pathways both directly and intermediately. The metabolisms of these two trace elements seem to be closely connected [11]. Selenoproteins are necessary for normal thyroid function and also seem to be involved in the redox pathways related to insulin signaling. The iodine-containing thyroid prohormone thyroxine (T_4) and active thyroid

Abbreviations: AD, Alzheimer's disease; DIO, deiodinase; DIO2, deiodinase type II; ER, endoplasmic reticulum; ESI, electrospray ionization; GPX, glutathione peroxidase; GPX1, glutathione peroxidase type I; GPX3, glutathione peroxidase type III; GPX4, glutathione peroxidase type IV; HPLC, high-performance liquid chromatography; ICP, inductively coupled plasma; I, iodine; LC, liquid chromatography; MC, multi-collector; MS, mass spectrometry; ROS, reactive oxygen species; Se, selenium; SEC, size exclusion chromatography; SELENOM, selenoprotein M; SELENOP (Selenop to denote the corresponding gene for rodents), selenoprotein P; SELENOS, selenoprotein S; T1DM, type I diabetes mellitus; T_2, diiodothyronine; T2DM, type II diabetes mellitus; T_3, triiodothyronine; T_4, thyroxine; TXNRD, thioredoxin reductase; TSH, thyroid-stimulating hormone

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hormone triiodothyronine (T_3) regulate energy metabolism, including glucose catabolism, *via* the thyroid hormone receptor.

Although iodine intake and status are not directly related to thyroid hormones levels [12], both severe iodine deficiency, as well as severe iodine excess may lead to hypothyroidism. Glucose intolerance is developed in case of both hypothyroidism and thyrotoxicosis [13,14] and, *vice versa*, both type I and type II diabetes might bring about an elevated risk of thyroid disease [15,16].

Epidemiologic and clinical intervention studies on selenium supplementation provided quite controversial results [17] concerning diabetes risk, with some studies showing beneficial outcomes and some reporting elevated risks [18]. For recent reviews, mainly focusing on epidemiological and intervention studies, the reader is referred to, *e.g.*, refs. [18–21]. The current review is aiming to survey the possible role of two trace elements, selenium and iodine, in the pathology of diabetes with the focus on the element interplay, the chemical speciation of the elements and biomarkers. The biochemical pathways of selenoproteins and thyroid hormones in diabetic pathology are discussed in brief in the first part of the paper to illustrate the role of the essential elements selenium and iodine. For more details in this context, the reader is referred to refs. [11,22–24]. In-depth epidemiological analysis on diabetes incidence, clinical trials involving trace elements and observational studies are also outside the scope of the review; for more information the reader is referred to specialized reviews [17–20,25–27].

2. Selenium and diabetes mellitus

Biological functions of selenium are mainly attributed to the highly specific selenoproteins [28], containing the 21st proteinogenic amino acid selenocysteine (Sec) [29,30], a Se-analog of the sulfur-containing amino acid cysteine. The production of glutathione peroxidases (GPX) and other selenoproteins increases with increasing selenium intake until the dose-response relationship reaches a plateau; for GPX, the plateau values are reached at plasma Se levels of *ca.* 70–90 μg/L [31]. There is still debate concerning optimal selenium intake, providing the most beneficial health outcomes with minimized side effects [32–35]. For more details, please consult the studies focusing on epidemiology and clinical trials.

2.1. Short overview on some epidemiologic studies on Se action in DM

The initial *in vivo* studies in animals during the 1990s and early 2000s demonstrated that selenium (as inorganic species) showed an antidiabetic and insulin-mimetic action [23]. However, the doses employed, 0.9–4.5 mg/kg body weight [23,36–38], are toxic to humans [39], putting doubts on the insulin-mimetic action of selenium found.

On the contrary, up to now, human-based studies on selenium in diabetes mainly indicated a pro-diabetic effect of selenium. For instance, a Nutritional Prevention of Cancer (NPC) trial [40] showed that selenium supplementation for 4.5 years caused a significant higher risk of T2DM. The follow-up underlined this finding with *ca.* 3-fold more cases/1000 and a 1.55 (95 CI) hazard rate. The T2DM risk even reached a hazard rate of 2.50 in individuals with plasma selenium > 113 μg/L. The SELECT trial (Selenium and Vitamin E Cancer Prevention Trial), aiming at evaluating prostate cancer prevention, showed a statistically insignificant increase of T2DM risk [41]. Importantly, the study population of the SELECT had optimal/super-optimal nutritional Se-intake already before supplementation. [42–44]. So the pro-diabetic side effect reported in a follow-up to the SELECT trial may be attributed to an over-nutritional intake.

Pro-diabetic action was further reported in a recent case-control study from Northern Taiwan, (847 adults age ≥40 years) [45] and another cross-sectional study on Asians (5423 subjects, age ≥40) by Wei et al. Those authors demonstrated significant positive correlation between dietary selenium intake and the prevalence of diabetes [46]. For more details on human-based studies concerning selenium intake and relevant randomized controlled trials, the reader is referred to the focused reviews and meta-analyses [18,20,47]

2.2. Studies on molecular mechanisms of Se-action

Further studies on selenium in diabetology can be categorized based on whether they are focusing on oxidative stress, insulin signaling or resistance, and influence on carbohydrate and fatty acid metabolism [48].

2.2.1. Selenium, selenoproteins and oxidative stress in diabetes mellitus

T2DM is associated with increased oxidative stress [49,50]. Thus, the antioxidant properties of selenoproteins led to the hypothesis that selenium has a protective effect against T2DM, ameliorating potential cell damage in the pancreas and normalizing insulin production and release [18]. The original protective theory arose from the fact that, generally, the β-cells of the pancreas islets have limited antioxidant capacities due to the low intrinsic expression of antioxidant enzymes [51]. Among selenoproteins, these are GPX type I (GPX1), other isoforms of GPX (predominantly, GPX type IV GPX4 [11,52,53]), and, possibly, selenoprotein S (SELENOS), which was shown to be glucose-regulated [54] and thus, implicated in diabetes [55,56]. The antioxidant SELENOS [57] seems to be involved in ER stress response, acute phase response, and inflammation [58–60]; it also serves as a receptor for the acute phase protein serum amyloid A [61]. Insulin treatment induced a significant upregulation of SELENOS in the adipocytes of T2DM patients, but not in matched controls [62] and there seems to also be no increased risk of T1DM with SELENOS single nucleotide polymorphism [63].

Other selenoproteins may also contribute to the pancreatic protection; for instance, selenoprotein T, was found to be involved in the proper insulin release in cultured murine β-cells [64] and seems to be important for proper metabolic regulation [65,66]. Regulation of the cellular redox balance is crucial for pancreatic insulin secretion since β-cells are likely damaged by reactive oxygen species (ROS) [22]. Contrary however, excessive H_2O_2 depletion interfered with insulin signaling (see below).

2.2.2. Selenium and selenoproteins in insulin signaling and resistance

The effect of selenium and selenoproteins on carbohydrate metabolism and insulin signaling is undoubtedly complicated and requires further study [67]. Some model studies have shown that selenium may positively contribute to insulin signaling *via* normalizing K^+/Na^+ ATPase activity [68], decreasing the expression of pro-inflammatory cytokines (interleukin-1β, tumor necrosis factor-α, and interferon-γ), and influencing the intracellular calcium and zinc homeostasis [69].

Binding of insulin to its receptor at the plasma membrane of adipocytes initiates the insulin-signaling cascade (see also Section 4), which is accompanied by a burst of hydrogen peroxide that acts as a second messenger [70,71]. That is why the high antioxidant activity of selenoproteins like cytosolic selenoprotein GPX1 may interfere with insulin signaling by scavenging messenger hydrogen peroxide molecules [23,72]. Excessive antioxidant protection, as was demonstrated by McClung et al. [48], may suppress insulin-signaling cascades, inducing excessive scavenging of redox-active messengers by upregulating the H_2O_2-reducing selenoenzymes [48,67].

Consequently, selenoproteins received special attention in diabetology. Selenoprotein P (SELENOP for humans or Selenop when the corresponding gene in rodents is referred to [28]), a circulating protein with Se-transport function [73–76] and antioxidant activity, was reported to be implicated in insulin resistance [77,78]. Significantly increased SELENOP levels correlated with glucose tolerance status in individuals with normal glucose tolerance and pre-diabetes and T2DM patients [79,80]. Serial analysis of gene expression and DNA chip methods found higher hepatic SELENOP mRNA levels in diabetic

patients ($n = 5$) than in oncological patients ($n = 5$) [77]. SELENOP expression in the pancreas [22], was shown to be affected by glucose and insulin [22,77]. Aside from the antioxidant action, SELENOP is mainly considered as a potential effector of insulin signaling since it is negatively correlated with circulating adiponectin, a strong independent predictor of T2DM [81]. However, human-based studies on SELENOP were recently criticized for reporting non-physiologically high levels of the protein [82], probably due to flaws of the analytical methodology used [80], which puts the findings into question and recommends further studies and validation of analytical techniques (see also Section 5). In line with that, the plasma proteome of T2DM patients (compared to healthy individuals with normal blood glucose levels) showed an elevated level for over 60 proteins, including SELENOP [83]. Thus, consequence or causation are hardly distinguished, as, in general, a considerable amount of the upregulated proteins are insulin resistance-associated hepatokines [84].

2.2.3. Influence of selenium on carbohydrate and fatty acid metabolism

Selenium may contribute to the metabolism of fatty acids and carbohydrates. Zhao et al. observed alteration of lipid and protein metabolism in growing pigs, fed with a high-selenium diet [85]. The authors found increased triglycerides, non-esterified fatty acids, and total cholesterol in liver and/or adipose tissue. [85]. There were other indications that excess selenium intake may affect fatty acid metabolism [86]. Selenium-supplemented mice (as 20 μmol/L sodium selenate in drinking water, 16 weeks) exhibited alteration in energy and fatty acid metabolism in the liver with an increase of body weight [87]. Two major gene-metabolite clusters were affected: (*i*) gene transcripts and metabolites related to the bidirectional glucose transporter 2 (Glut2) and (*ii*) these related to the carnitine-palmitoyl transferase 2 (Cpt2) and acetyl-CoA acyltransferase (Acaa1). Several fatty acid metabolism related compounds were enriched but no changes in enzyme activities of selenoenzymes were established [87].

To conclude, human-based studies on selenium and diabetes are not fully conclusive yet; at the same time, selenoproteins of other than GPX and iodothyronine deiodinase (DIO) families and SELENOP were unfortunately nearly not studied with respect to their probable role in endocrine regulation. So the hypotheses on their role in diabetic pathology are more or less speculative at this point. We consider that deeper insight into not yet explored selenoproteins may shed further light on the role of Se in different aspects of human health and disease (see also Section 5). Additionally, an attempt to implement the transcriptome–metabolome-wide association approach (as in studies by Hu et al. [87], see above) to evaluate the potential metabolome and transcriptome shifts in selenium-supplemented humans (*e.g.,* in participants in one of the ongoing clinical trials on selenium) would benefit further research on selenium in diabetology.

3. Iodine and diabetes mellitus

The iodine-containing thyroid hormones triiodothyronine (T_3, metabolically active hormone) and thyroxine (T_4, prohormone) are responsible for the regulation of numerous biochemical processes in the body, which are essential for normal development, metabolism, and neural activity [88]. Although the thyroid is highly adaptive to the actual iodine intake, the production of thyroid hormones chemically relies on the body's iodine supply and its potential to convert other iodine species into iodide. Iodine deficiency, especially in pregnant women, still remains a common global problem [24,89–91]. Thyroid hormones are involved, first of all, in growth and development and regulation of the basal body metabolism. They have a potent metabolic effect and their role in the metabolism of carbohydrates and fats may affect systemic insulin sensitivity and glucose tolerance [14,92]. In particular, the genetic expression of insulin-sensitive glucose transporters GLUT4 is upregulated by T_3 [13,93].

Diabetes is often associated with thyroid diseases [15,94], especially autoimmune thyroiditis [95]. Screening for hypothyroidism is suggested for subjects with T1DM [15]. For T1DM, the ongoing autoimmune process towards islet cells can also cause alterations in the thyroid gland; for instance, increased volume (11.2 ± 2.9 *vs.* 9.6 ± 2.9 cm^3, $p = 0.0001$, 9.5 ± 2.3 *vs.* 7.7 ± 2.0 cm^3, $p = 0.002$, in males and females, respectively) of the thyroid was reported in T1DM patients when compared to the controls with similar anthropometry [96]. On the other hand, T1DM patients tend towards an increased fat-free body mass [97], thus potentially having a larger size of the thyroid. In this respect, the connection with iodine uptake probably requires more research in clinical studies.

The association between thyroid function and diabetes mellitus was primarily studied for T1DM, especially when concerning the development of thyroid diseases in diabetic patients [15,95,96,98]. Importantly, it should be mentioned that iodine deficiency may stimulate pathologic processes in the thyroid *via* insulin-like growth factor-1 (IGF-1), promoting autocrine growth of the thyrocytes *ex vivo* [99]. Furthermore, it has also been shown that for IGF1-receptor knockout mice (TIGF1RKO), the development of goiter under the exposure to such goitrogens as methimazole or sodium perchlorate was completely abrogated [100]. This demonstrates the importance of IGF-1 for the regulation of thyroid growth. Interestingly, in the recent proteomic study of Li et al., major antigenic epitopes, promoting co-occurrence of autoimmune thyroiditis and T1DM, were identified in a transgenic mice model [101]. This might indicate the interrelation between autoimmune events in autoimmune thyroiditis and islet-specific T-cell response in T1DM. Notably, the data should be considered with care, since the transgenic model used may be not adequate for drawing conclusions concerning humans.

In studies on the relationship between diabetes and thyroid disorders, urinary iodine excretion levels were typically monitored (see also Section 5) to evaluate the iodine status [15,94–96]. Also, the thyroid hormones free T_4, total T_4, free T_3, total T_3, as well as the thyroid-stimulating hormone (TSH) were determined in some studies, mainly by a chemiluminometric method [15,95]. Völzke et al. reported elevated urinary iodine concentrations as well as higher urinary iodine/creatinine and thiocyanate/creatinine ratios in adult T1DM patients compared to the reference population. According to Okten et al., there was no significant difference in the prevalence of thyroid dysfunction between diabetics and controls. Still, the authors reported a significant difference in thyroid hormone levels (T_3, T_4, and free T_3).

Some associations were reported between diabetes and non-autoimmune thyroid disorder. Rednina et al. reported an increased risk of multinodular non-toxic goiter in patients with metabolic syndrome (a cohort of 1422 Caucasian patients), when adjusted for age, sex, body mass index, and lifestyle factors [102]. Additionally, there was evidence for a higher thyroid cancer risk in T2DM patients and individuals with metabolic syndrome and insulin resistance [103]. Hyperinsulinemia and hyperglycemia may increase thyroid nodules vascularization, promoting angiogenesis, especially in the larger nodules [104]. In the recent study of Buscemi et al., the association between obesity, diabetes and thyroid nodules was also confirmed in an Italian cohort (455 males, 746 females; age 18–90); in this case, obesity was found to positively correlate with the increased size of the nodules [105].

Higher incidence of common thyroid disorders, such as autoimmune thyroiditis, goiter, and thyroid cancer, was reported for diabetic patients. *Vice versa*, the thyroid disorders seem to be deleterious for carbohydrate metabolism. For instance, Dimitriadis et al. [16] have shown insulin resistance in muscle and adipose tissue of hyperthyroid female patients (12 hyperthyroid and 10 euthyroid subjects). Notably, the authors pointed to the absence of impaired lipolysis in their cohort [16].

For T2DM, the interconnection with thyroid diseases seems less transparent and would appear to be sex-, ethnic origin-, and probably, also age-dependent [106]. There was a hypothesis that for obese and

diabetic patients, there may be a decreased expression of sodium/iodide symporters on the apical side of the enterocytes [103,107]. This may promote iodine deficiency, due to the effect of pro-inflammatory cytokines (tumor necrosis factor-α, tumor growth factor-α, tumor growth factor-β, interleukin-8, fibroblast growth factor-2, and VEGF-α) [103,107]. Notably, to the best of our knowledge, there were no clinical or even solid experimental data supporting this notion. Finally, when considering severe untreated diabetes cases, it should be kept in mind that altered thyroid status, *e.g.*, increased excretion of iodine and elevated degradation of thyroid hormones, may not represent the real relation to diabetes *per se*. Such observations may be attributed to the non-thyroidal illness syndrome [108,109], a condition characterized by reduced T_3 and T_4 levels under increased reverse-T_3 and normal or slightly decreased TSH as an adaptation to excessive catabolism under severe illness [108]. Finally, the emerging research direction in the field of the interplay between iodine/thyroid and diabetes can be related to the role of thyroid hormones in the gestational development of the pancreas [110], which was recently reported. Harris et al. demonstrated that hypothyroidism in sheep fetus led to an increased pancreatic β-cell mass and proliferation, and was associated with increased circulating concentrations of insulin [111]. The authors suggested that thyroid hormones, insulin, and leptin affect the developing pancreatic β-cells *in utero* with possible consequences for the pancreatic function in later life. This definitely requires further study [112].

4. Integrated role of iodine and selenium

The thyroid gland utilizes selenoproteins rather intensively and ranks high in selenoprotein expression hierarchy [113]. Similar to β-cells of the pancreas, thyrocytes are prone to oxidative damage, due to the high production of H_2O_2 [114], required for the synthesis of thyroid hormones (Fig. 1). Selenoproteins are known to be expressed in the thyroid at high quantities [115]. Two families of selenoproteins have been implicated in the thyroid axis: the DIOs and GPXs [113]. Lower Se status was reported for the autoimmune thyroid diseases, Hashimoto's and Graves' diseases [116].

Selenium-dependent DIOs regulate intracellular thyroid hormone levels independent of systemic levels [14]. For many tissues, the intrinsic level of active thyroid hormones is mainly dependent on the activity of the DIOs (the rate of the conversion of T_4 to T_3 and the deactivating rate of T_3 to diiodothyronine, T_2), rather than on circulating T_3 [120]. The T_4-activating selenoprotein enzyme DIO type II (DIO2) seems to be associated with T2DM risk [9]. There is epidemiological evidence for the relation of gene polymorphism in DIO2 with glycemic control and insulin resistance in T2DM patients [121]. This enzyme was shown to be of primary importance in the regulation of the local, tissue-specific intracellular concentration of T_3 in the brain, pituitary, and brown adipose tissue [122]. Thus, modulation of the activity of the DIOs may be a possible therapeutic target for insulin resistance and diabetes. Interestingly, Castillo et al. reported that, although hypothyroidism is intuitively associated with obesity, the obese phenotype in DIO2-knockout mice, kept on a high-fat diet, forms only under an increased housing temperature of 30 °C [123].

Importantly, both normal insulin signal transduction [71] and T_3/T_4 biosynthesis require hydrogen peroxide [124,125]. However, extracellular H_2O_2 is toxic to β-cells. So, redox signaling may be another common point between iodine and selenium in glucose metabolism. Epidemiological studies show that autoimmune thyroid disease is much more common in children with T1DM [126]. However, this correlation may also be attributed to general immunity malfunction in both stances. Seroconversion to autoimmune thyroiditis occurs later than that for T1DM, suggesting different environmental triggers [126]. The

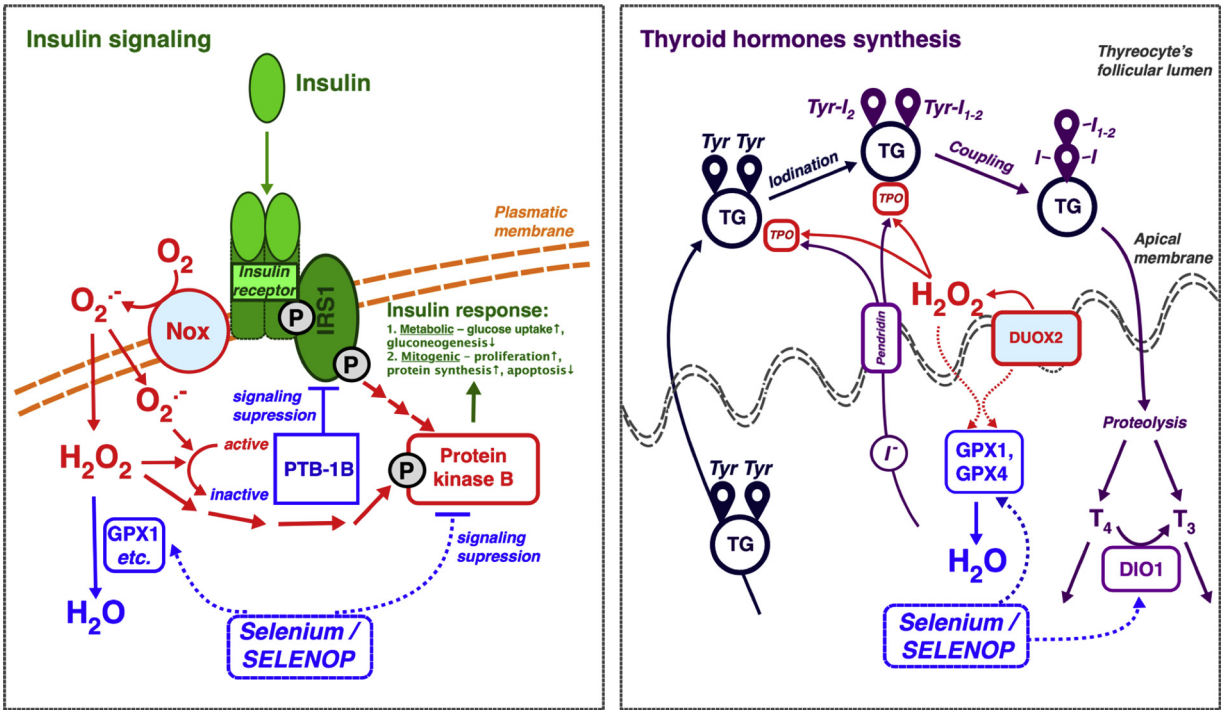

Fig. 1. The role of hydrogen peroxide (H_2O_2) in insulin signaling and thyroid hormones synthesis and the interplay with selenium and selenoproteins. Summarized from several sources [43,117–119]. Solid arrows – signaling and metabolite flows; dashed blue arrows – selenium interaction with these flows; dashed red arrows refer to non-desired reactive oxygen species (ROS) formation; simplified pathways are denoted with several sequential arrows. Abbreviation: DIO1 – deiodinase type I; DUOX2 – ROS-generating NADPH-dependent dual oxidase type II; IRS1 – insulin receptor substrate-1; GPX1 – glutathione peroxide type I; GPX4 – glutathione peroxide type IV; Nox – ROS-generating NADPH oxidase of NOX family; P – phosphorylated groups on the proteins; PTB-1B – protein tyrosine phosphatase-1B; SELENOP – selenoprotein P; T_3 – triiodothyronine; T_4 – thyroxine; TG – thyroglobulin; TPO – thyroid peroxidase; Tyr – tyrosine residue at TG. To see this illustration in color and for the interpretation of the reference to color in the figure legend, the reader is referred to the web version of this article (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

whole genome linkage analysis in human T-cells showed several genes to be related to both T1DM and autoimmune thyroiditis risks, including HLA class II genes, CTLA-4, PTPN22, and FOXP3, which seem to promote the development of the autoimmune polyglandular syndrome type 3 (autoimmune thyroiditis associated with other autoimmune diseases, excluding Addison's disease) [127].

To the best of the authors' knowledge, there are no reports on diabetes (especially T2DM) incidence in the populations with endemic and myxedematous cretinism [128], the stances related to the extreme iodine deficiency at fetal and postnatal development phases, accompanied with a low intake of other nutrients, including selenium [11,115]. Kashin-Beck disease, a chronic osteoarthropathy, is another endemic disorder related to the simultaneous effect of iodine and selenium [129]. It is an example of a devastating effect of impaired antioxidant defense, immunity and thyroid signaling, related to simultaneous iodine and selenium deficiency [130]. Another important issue is a possible interplay [131–133] between gestational diabetes [134] and "hypothyroxiemia" [91] in pregnant women, which also should be addressed more closely in future studies. Since gestational diabetes is outside the scope of the current review, the reader is referred to more specialized publications, *e.g.*, ref. [133,135–138].

The exact biochemical mechanisms underpinning mutual effects of the trace elements selenium and iodine still remain to be elucidated. The information available in the literature so far is summarized in Fig. 2. The intuitive vision on the effect of selenium on the insulin production and thyroid axis is related to the action of the antioxidant selenoproteins (*i.e.* GPX1, GPX3, SELENOP, SELENOS, and probably other) in both systems and the essential role of selenoproteins DIO1-3 in T_4/T_3 signaling. The possibility that selenium and selenoproteins affect glucose metabolism through influencing the expression of DIOs and affecting the activation and deactivation of thyroid hormones seems rather intriguing. Another important point of interplay may be related to leptin signaling having an effect on feeding behavior and general energy metabolism [139]. The involvement in the appetite regulation seems to be quite obvious for iodine and thyroid hormones [140,141], but it seems to be the case for selenium as well. The mechanisms are associated with both DIO enzymes and are directly related to T_4/T_3 conversion, and leptin signaling [19,142]. Selenoprotein M (SELENOM), an ER-associated selenoprotein, seems to be involved in the leptin pathway [19], since the deletion of SELENOM causes obesity in mice [143], possibly through increased ER-stress and leptin resistance [142]. However, the knockout model may not at all reflect the actual physiological situation, so this information should be considered with caution and further studies are required to confirm or reject the hypothesis on the interplay between SELENOM and leptin pathway.

5. Chemical speciation of the elements and biomarkers of selenium and iodine status in diabetes research

Recent advancements in the field of analytical chemistry opened new possibilities for studying trace element metabolism and their role in human health and disease [144,145]. Investigation of the chemical species of selenium and iodine relevant to diabetes mellitus is required, which may decrease the degree of controversy in some cases, *e.g.*, related, to the protective and diabetogenic effects reported. An issue to be stressed is related to trace element status biomarkers and the control for their metabolization (*i.e.* the conversion of the elemental species with the formation of biochemically active molecules like selenoproteins or other active metabolites) during model studies. Adequate and strict control of the baseline level together with follow-up monitoring of trace element status of the population in the intervention studies is sometimes a prerogative of the wider trials with considerable resources

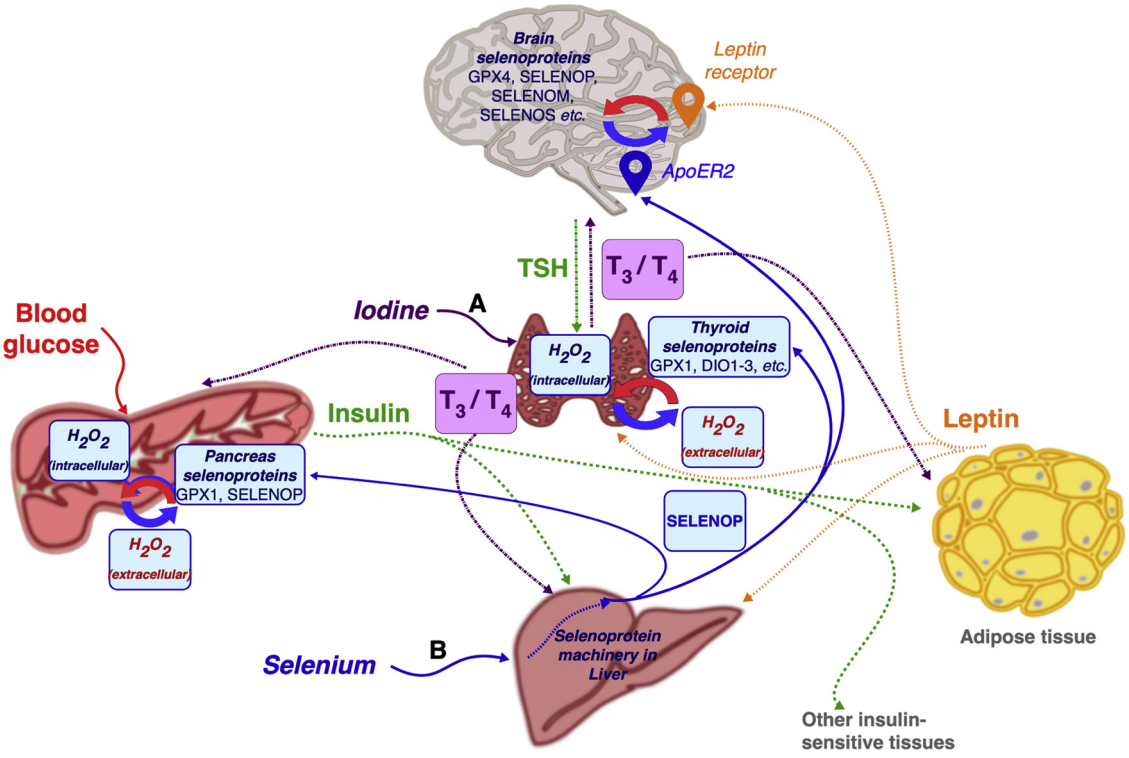

Fig. 2. Putative scheme of an integrative influence of selenium and iodine on insulin signaling. Solid lines – trace element flows corresponding to their biochemical conversion into metabolites, including selenoproteins for selenium and thyroid hormones for iodine; dashed lines – hormone (endocrine) flows; bar-dotted lines – thyroid hormone flow; reciprocal arrows – a mutual interplay of several factors. A – iodine uptake to produce thyroid hormones; B – selenium uptake to produce selenoproteins, first of all, secreted SELENOP. Abbreviations: ApoER2 – apolipoprotein E receptor type II (also known as lipoprotein receptor-related protein 8, LRP8); DIO1-4 – deiodinases type I-III; GPX1 – glutathione peroxidase type I; GPX4 – glutathione peroxidase type IV; H_2O_2 – hydrogen peroxide; SELENOM – selenoprotein M; SELENOP – selenoprotein P; SELENOS – selenoprotein S; T_3 – triiodothyronine; T_4 – thyroxine; TSH – thyroid-stimulating hormone. To see this illustration in color, the reader is referred to the web-version of this article.

available. Smaller studies sometimes have to rely on preliminary data in this respect. Additionally, not always the most adequate status/exposure biomarkers are accessible, for instance, in short-term studies, the use of nail or hair Se is sometimes reported. In model research, the assessment of element metabolization (change of speciation after introduction into the biological system) and/or activation of certain relevant systems (*i.e.* expressions of selenoproteins in the case of selenium and thyroid hormone sensitive proteins for iodine) is not always reported. Instead, only the "desired effect", such as an increased or decreased glucose uptake in the case of diabetes is considered. However, if proper involvement of the element into the biochemical processes is not attested, the observation may produce false causation, related, for instance, to the effects of general toxicity or other confounders. This hinders data interpretation and often makes inter-study comparisons hardly possible. Additionally, for model experiments in the T2DM domain, it is not always clear which sub-type of the syndrome the data should be attributed to, so the translation to humans may be of limited relevance.

Another limitation of the studies can be of methodical nature: cross-sectional and case-control studies may come to biased conclusions compared to longitudinal, follow-up studies, as has been shown recently for the total selenium level and even for the Se-speciation in cerebrospinal fluid samples from patients with Alzheimer's disease (AD) *vs.* mild cognitive impairement patients [146,147]. In this comparative study, the selenium status in the central nervous system and the AD risk in the participants with established AD and controls with mild cognitive impairment were evaluated. It was found that a case-control approach showed an inverse association between overall selenium exposure and the disease, even when exposure assessment was limited to inorganic Se, while the risk positively correlated with some Se species, most of which were selenoproteins. These results were markedly different and even opposite to those generated by a longitudinal study carried out in a fraction of the same study population (42 months follow-up, 21 of 56 mild cognitive impairment patients developed AD). There, a positive correlation between baseline levels of inorganic hexavalent Se and subsequent dementia occurrence was established, while no relation was found for the other Se species [146]. This biasing effect was supposed to affect cross-sectional studies on total selenium, as well as Se-speciation in general. This also can be the case for other acute and chronic diseases [148,149], which may alter trace element intake and metabolism as a consequence of disease progression, and therefore induce a reverse causation bias.

Though Se-speciation analysis would be invaluable for diabetes research, some problems still exist. There are several biomarkers for selenium status available, such as: blood serum or plasma total Se concentration, hair or nail Se concentration (most suited for the retrospective evaluation) and concentration/activity of certain selenoproteins, first of all, plasma GPX3 and SELENOP [32,150,151]. Mainly in the model studies, the activity of the red blood cell GPX1 is also used sometimes. It should be noted though that the most frequently used biomarkers of Se status (*i.e.* plasma/serum or nail Se) are sometimes criticized for not reflecting the activity of the selenoprotein machinery of the body and Se speciation in general [152]. According to Combs, selenoproteins from all major groups, *i.e.* GPXs, TXNRDs, DIOs or SELENOP, can in principle be used as biomarkers of the "Se function" [32]. The interest in SELENOP as a Se biomarker seems to increase over time [32,151]. Since for SELENOP determination in biological fluids, modern metallomics and ELISA protocols were recently designed, it is considered here in more detail. The methods for SELENOP quantification include immunochemistry-based approaches [80,153–155] and mass spectrometry methods [149,156,157]. Importantly, recently, the quality of some commercial kits for SELENOP determination was criticized for the lack of reliability, so the users should be aware of possible shortcomings of the methodology applied [80]. Noteworthy, Deitrich et al. proposed a species-specific isotope dilution high-performance liquid chromatography (HPLC) - inductively coupled plasma-mass spectrometry (ICP-MS) method [157], which is fully SI-traceable (SI; System International d'Unites), which can be a valuable validation tool for the ELISA methods used in clinical and model research. Notably, the HPLC-ICP-MS technique was shown to be capable of determining the concentration of other circulating selenoproteins, such as GPX3 and TXNRD type I [148,156], which thus also can be considered as potential biomarkers [32]. The use of concentration rather than enzymatic activity could be beneficial since activity assays are often prone to interferences and sample handling bias. Finally, some researchers criticize the general approach of considering the maximal activity/concentration of SELENOP or GPX3 [32] as unquestionable optimum [158], applicable in all health conditions and for all populations [75,152].

Se-speciation work related to native human samples often suffers from the low concentration of Se species. This is a challenge even for ICP-MS based hyphenated systems. This also precludes Se speciation studies with electrospray ionization-mass spectrometry (ESI-MS(/MS)) systems. The latter could provide clear identification of relevant Se-compounds for which no standards are available for comparison in liquid chromatography-(LC)-ICP-MS approaches. LC-ICP-MS monitoring with missing matching standards leaves those compounds as not identified "unknowns". Here, more joint research initiatives from molecular biologists and analytical chemists could underpin and set forward new relevant insights into Se-metabolism in diabetes.

A comparative literature screening for iodine speciation has been published several years ago by Moreda et al. [159] and this review paper still reflects the current situation. A considerable fraction of these papers investigates iodide *vs.* iodate in water samples, some research groups also addressed partly unidentified I-containing molecules in seaweed. However, only very few papers report iodine speciation analysis of human samples covering I-species from human metabolism. An application of size exclusion chromatography (SEC)-ICP-MS to assess iodine-binding biomolecules was described by Makarov & Szpunar [160] and targeted iodine bound to serum proteins which were separated from one another in a Progel TSK under isocratic elution. Three iodine-organic-ligand fractions were monitored, but not identified. This is due to the limited separation power of SEC. An orthogonal – two-dimensional speciation approach would have been necessary to obtain more specific information on the identity of the species, but was not performed in this work. Takatera & Watanabe [161] developed a two-stage method based on reversed phase chromatography-ICP-MS for iodine speciation, covering relevant small iodine species (iodide, iodothyrosines, and iodothyronines) in the first step and thyroid hormones (T_3, reversed-T_3, and T_4) in the second stage, both runs lasting *ca.* 20 min each. Michalke et al. first improved this approach by optimizing chromatographic gradient elution and temperature settings, permitting successful separation within a single run of 25 min, and subsequently applied this method to the serum of thyroid disease patients and healthy controls [162]. Also, the feasibility of capillary electrophoresis hyphenated to ICP-MS has been demonstrated by Michalke & Schramel for iodine speciation [163]. Aside from other applications, the paper reports the separation of iodide, iodate, T_4, and T_3 in human serum and urine. This shows that methods for iodine and selenium speciation in the human body fluids are available.

Similar to selenium, the biomarkers for iodine status were also under intensive study. The most widely accepted ones are: urinary iodine concentration/urinary iodine excretion (for children, adolescent and low-to-moderate iodine intake populations), thyroglobulin level (except for pregnant or lactating women), serum T_4 (except for pregnant or lactating women), and serum TSH (for pregnant and lactating women) [25,164–166]; for the meta-analysis the reader is referred to see Ristic-Medic et al. [167]. Notably, T_3 is not considered as a relevant biomarker. The breast milk iodine concentration is also actively studied as a possible iodine status and intake biomarker in lactating women or infants, respectively [168]. Under adequate iodine status, elevated fractional secretion of iodine into breast milk, when compared to the

urinary excretion, was observed in healthy lactating women. However, in chronically iodine-deficient mothers, the urinary excretion showed the presence of renal losses of iodine. That may be related to the increased cardiac output during pregnancy causing increased iodine excretion *via* the kidneys. So, there is probably competition for the circulating iodine between the maternal thyroid and mammary glands, which may compromise the euthyroid status of chronically iodine-deficient lactating women [168]. Thus, in lactating women, breast milk can be considered as a more relevant iodine status biomarker compared to urinary excretion [168]. Importantly, the most widely used iodine biomarker, urinary iodine excretion, which is effective for characterizing populations [167,169], is sometimes criticized as an individual marker of the iodine status, providing limited precision [165] and short-term information on the recent iodine intake only [166]. In turn, the functional biomarkers T_4 and TSH are quite variable within a population, due to the high inter-individual variability of the thyroid to adapt to the iodine intake [169]. Speciation studies might assist biomarker research for iodine, since speciation techniques are capable of providing a wider range of information, for instance, to simultaneously assess the concentrations of inorganic iodine (iodide and iodate), thyroid hormones (T_4 and T_3), and their metabolites [170] (reverse-T_3, 3,3′-diiodothyronine, 3′,5′-diiodothyronine, thyronamines, such as 3-iodothyronamine *etc.*) in an accurate and traceable manner, improving the reliability of the data. The effectivity of such an approach should still be further evaluated in clinical research.

Concerning iodine speciation, it should also be noted that certain minor metabolites occurring upon synthesis and degradation of thyroid hormones and other iododerivatives, such as iodothyramines and iodolactones, received only scarce attention, possibly due to their presence in biological systems in very low quantities. For instance, 3-iodothyronamine, a possible product of T_3 and T_4 degradation may contribute to lipid catabolism, inducing anti-insulin response [171]. Galli et al. quantified 3-iodothyronamine together with total T_3 and total T_4 in human serum using HPLC-tandem MS [172]. The limit of detection of 3-iodothyronamine was *ca.* 35 fmol/mL; the authors reported a slightly increased level of 3-iodothyronamine in T2DM patients [172]. Other potentially iodine-containing metabolites that can be relevant to endocrinological regulation are iodinated derivatives of fatty acids (arachidonic acid, first of all). These compounds may form as byproducts of iodine organification, during the synthesis of thyroid hormones [173]. For instance, 6-iodo-8, 11, 14-eicosatrienoic-5-lactone was shown to inhibit the thyroid cell growth *in vitro* [174]. The effect was dose-dependent and exceeded that of potassium iodide 50-fold (the so-called, Wolff-Chaikoff effect, the transient reduction of thyroid hormone production under high iodine loads [12]). Unlike potassium iodide, iodolactone maintained its effect under simultaneous incubation of isolated porcine thyroid follicles with the epidermal growth factor (EGF) and in the presence of thyroid peroxidase inhibitors [174]. Finally, cAMP formation was found not to be affected by iodolactone [174]. Importantly, iodinated lipids were also observed in the human thyroid. Dugrillon et al. demonstrated the *in vivo* formation of 5-hydroxy-6-iodo-8, 11, 14-eicosatrienoic δ-lactone in the thyroid of a Graves' disease patient, treated with high doses of iodide [175]. Thus, it seems that iodinated lipids and iodolactones may be involved in the Wolff-Chaikoff effect. Finally, iodine metabolites such as molecular iodine (I_2) and iodolactones may have potent antiproliferative or cytotoxic activity [176,177], which also makes them relevant in speciation studies. Iodine-containing metabolites may contribute to the development of tissues, expressing sodium/iodide symporters, such as oral and stomach mucosa and salivary glands [173,178]; however, this aspect is beyond the scope of the current review.

Another possible future direction for research concerning the role of trace elements in diabetes pathology on the edge of medicine, biology, biochemistry, and analytical chemistry may focus on natural isotope ratio variation caused by isotope fractionation. High-precision isotopic analysis using multi-collector ICP-MS (MC-ICP-MS) is an emerging approach to obtain additional information on biochemical processes involving trace elements. A number of metabolic pathways are accompanied by isotope fractionation. For the lighter of any two isotopes, physicochemical processes proceed slightly faster (kinetic mass-dependent fractionation), while in chemical reactions, the heavier of any two isotopes has a slight preference for the strongest, hardest bonds (thermodynamic mass-dependent fractionation) [179]. MC-ICP-MS offers the precision required to reveal such isotope fractionation [180]. High-precision isotopic analysis is therefore currently explored as means of diagnosis of diseases that can otherwise only be established at a later stage and/or *via* more invasive techniques, or for obtaining a more profound insight into biochemical processes involving the element of interest [144,181]. So far, the isotopic analysis of calcium has, *e.g.*, proven useful for signaling bone loss in osteoporosis and multiple myeloma [182,183], that of copper in the context of liver disease [184] and cancer [185], and that of iron as a robust marker for establishing an individual's iron status, also in cases in which the currently used markers are no longer reliable [186,187]. Very recently, the serum Mg isotopic composition was demonstrated to be systematically lighter in a T1D patient cohort than in an age- and sex-matched reference population [188]. *Via* animal experiments, not only body fluids, but also tissues can be analyzed for the isotopic composition of the mineral element of interest, while genetically identical individuals can be addressed, which can contribute to a further insight into the factors governing the differences in isotopic composition observed [189]. Selected features, such as the isotope fractionation accompanying intestinal uptake of iron [190], or the effect of oxidative stress on the isotope fractionation accompanying transfer of copper between hepatoblastoma cells and the culture medium [191] or different copper isotopic signature in differentiated and non-differentiated neuroblastoma cells [192], were studied *in vitro* using cell lines. Additionally, *in vivo* models using genetically modified organisms are currently exploited to provide an enhanced insight [193–195].

Also for Se, high-precision isotopic analysis could provide additional and potentially useful information, helping to unravel its role in specific processes, including diabetes mellitus and other metabolic disorders. However, accurate and sufficiently precise isotopic analysis of Se with MC-ICP-MS is seriously hampered by spectral interferences. For most Se isotopes, the mass resolution required to free the analyte's signal from spectral overlap is beyond the capabilities of present-day MC-ICP-MS instrumentation [196,197]. Recently, an MC-ICP-MS instrument equipped with a collision/reaction cell has been introduced onto the market [198], potentially offering a solution relying on chemical resolution (*i.e.* relying on selective chemical reactions between either the interfering or the analyte ions and the gas molecules, thus creating interference-free measurement conditions) [197,199]. In any case, to the best of the authors' knowledge, no such efforts have been done yet. For iodine, on the other hand, such an approach is void as this element has only one naturally occurring stable isotope. Dold et al. [168], however, applied isotope dilution for iodine quantification with MC-ICP-MS using long-lived ^{129}I as a spike and tellurium as an internal standard relied on for mass bias correction [179,200]. This approach enabled very precise, accurate, and traceable iodine quantification in breast milk. The matrix of the milk is very challenging for the conventional photometric-based assays, such as Sandell-Kolthoff method [167,201], routinely used for the urinary iodine excretion assessments. Importantly, the method was implemented in a wide cohort (n = 866) of lactating mothers, so its applicability was properly demonstrated.

It should be stressed that problems are not necessarily connected with the analytical methods *per se*, but are a consequence of a non-optimal experimental design. For human studies, strict inclusion criteria should be followed, which is not always the case especially for small, "chemical analysis-oriented" studies. Currently, published data concerning the role of selenium or iodine species in diabetes are really scarce, especially for iodine. The iodine speciation studies focus primarily on environmental and nutritional contexts [44,202–205], rather

than on human health. Right now, studies on human samples are mainly related to method development [162,206,207]. Finally, in future studies, special attention, related to chemical speciation in diabetology and human health in general, should be focused on trace element interplay in the context of transition metal redox balance shift [145,208–211] and ferroptosis [30,60,212]. From the point of view of the authors of the current review, future speciation studies related to biochemical activity of essential trace elements such as selenium and iodine should focus more on potential minor metabolites, such as minor selenoproteins, minor selenometabolites (*e.g.,* selenosugars, exotic selenoamino acids like selenohomosysteine [213,214] or even not yet identified Se-compounds) and "side-products" of thyroid hormones production, *e.g.*, iodolactones and iodinated lipids. Certainly, the quantification of such compounds is much more challenging than focusing on that of "traditional" species, such as inorganic ions (selenite, selenate, iodide, and iodate) or widely acknowledged status and/or function biomarkers (SELENOP, GPX3, T_4 *etc*.). Although minor iodine- and selenium-containing metabolites are considered as potentially relevant in metabolic and endocrine disorders, the studies on their biological activity are scarce. Often, a qualitative approach is used in such research, which may put the findings into question. Reliable determination of minor selenoproteins, which mostly have intracellular localization, and minor selenium and iodine metabolites, both present in extremely low concentration and often highly redox-sensitive, will require considerable efforts into designing novel sample preparation protocols, including isolation and pre-concentration, and potentially advancement in the analytical techniques to provide even lower limits of detection. Additionally, integrated studies on selenium and iodine speciation with a focus on proteomic and metabolomic profiles could provide new insight into the role of these elements in diabetes. The authors recommend common research initiatives from molecular biologists and analytical chemists, which will provide new relevant insights into Se-metabolism in diabetes.

6. Conclusion

Although both iodine and selenium were addressed in a number of epidemiological and model studies concerning diabetes, the exact chemical form of the elements – elemental speciation – was to a certain extent disregarded and needs to be investigated further. Moreover, the biochemical pathways of selenium and iodine species in diabetes mellitus pathology (both type I and II) require further study employing adequate *in vitro* and animal models. The focus on speciation is especially relevant for selenium, whereas for iodine the most important issue, concerning deficiency and supplementation, is related to adequate study groups, dosages, and terms of trace element intake, due to the paramount importance of sufficient iodine supply during gestation and the first year of life [91]. Notably, for selenium, studying the possible isotope fractionation accompanying metabolic processes under different health stances, including diabetes and other metabolic disorders, seems to be an attractive approach that potentially can supply additional information. The knowledge on the interplay of selenium and iodine in diabetic pathology is nowadays mainly limited to the role of selenoproteins in insulin signaling and thyroid hormones metabolism. However, there are other possible factors, such as the role of thyroid hormones in the *in utero* development of the pancreas or putative involvement of selenoproteins in leptin signaling, which require further study. Upcoming human-based studies should be justified based on "predecessor" model research to ensure optimal speciation and dosage of the elements and adequate population inclusion criteria. This should be especially strictly followed for randomized controlled trials.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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