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Role of selenium in type 2 diabetes, insulin resistance and insulin secretion

Casanova P *et al* Selenium and type 2 diabetes

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Abstract

Selenium is a trace mineral essential for life that acts physiologically through selenoproteins. Among other actions, the antioxidant endogenous selenoprotein glutathione peroxidase and the Se transporter in blood, selenoprotein P, seem to play an important role in diabetes mellitus type 2 and insulin resistance by weakening the insulin signaling cascade through different mechanisms. Recent findings also suggest that selenoproteins also affect insulin biosynthesis and insulin secretion. This review discusses the role of selenium in type 2 diabetes and the complex interplay between selenoproteins and insulin pathways.

Key Words: Selenium; Diabetes; Insulin resistance; Metabolism; Antioxidants

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Core Tip: In this review we explore the evidence for a role of selenium in insulin resistance and β-cell secretory function. The response to selenium intake has a U-shaped dose-dependent effect so that when it is above the recommended dose, it causes hyperglycemia and hyperinsulinemia which alters not only oxidative stress but also the insulin signaling cascade and lipid and glucose metabolism. Recent findings also suggest that selenoproteins also affect insulin biosynthesis and insulin secretion. Current evidence suggests that the ingestion of selenium supplements should be taken

with caution considering the basal levels of selenium in the daily food intake to avoid the development of type 2 diabetes mellitus.

INTRODUCTION

Global increase in obesity, ageing population, sedentary lifestyles, physical inactivity, alcohol consumption, smoking and high fat and sugar diets intake has contributed to an unprecedented increase in the incidence of type 2 diabetes mellitus (T2DM), quadrupling between 1980 and 2004. In 2015, a total of 415 million people were estimated to have diabetes, more than 90% of whom were T2DM, making it the sixth leading cause of disability in the world[1].

This is the reason why T2DM is the most rapidly growing global health emergencies since the incidence has already achieved 9.3% in 2019 among adults aged 20 to 79 years[2] and, although advancing age is a risk factor, the increase in childhood obesity resulted in an alarming increase in T2DM in children and adolescents too[3].

T2DM is characterized by insulin action deficiency caused by pancreatic β-cell dysfunction and a consequent insulin resistance in target organs. The main organs involved in the development of T2DM are the pancreas, liver, muscle, brain, kidneys, adipose tissue and small intestine[1]. The state of chronic hyperglycemia and impaired carbohydrate, lipid and protein metabolism give rise to complications such as cardiovascular diseases, nephropathies or diabetic neuropathies[3]. Consequently, this situation leads to a 15% increased risk of mortality from any other disease, being twice as high in young patients[1].

Many studies have shown that it is not only lifestyle that causes T2DM, but it also results from an interaction between genetic factors, lifestyle, gut metagenome and different types of vitamins that have a potential role in controlling T2DM and insulin sensitivity[3].

Insulin resistance and β-cell dysfunction

Under normal conditions, insulin binds to insulin receptor (IR) and promotes lipids and glucose uptake into adipose tissue. Any failure in this signaling cascade leads to an increase in circulating glucose (hyperglycemia) and lipids (hyperlipidemia), a phenomenon observed in T2DM[4,5].

Prospective studies in subjects with a high risk for T2DM or newly diagnosed have shown that in contrast to insulin resistance that remains relatively stable over time, β-cell functionality has a rapid and steady decline[6]. Indeed, another study performed in the Tanzanian adult population demonstrated that β-cell dysfunction is of greater contribution in T2DM compared to insulin resistance contribution[7].

Regarding insulin resistance, it refers to a failure or impairment in the transduction of the insulin-mediated signaling cascade in certain tissues, especially in muscle, adipose tissue and liver. This leads to an elevated circulating glucose level which together with elevated hepatic glucose output results in very high plasma glucose levels. These glucose levels require a high demand for insulin production and secretion by the β-cells. When insulin resistance is prolonged over time, the β-cells are submitted to high glucose and lipid exposure that results in β-cell dysfunction and death[4,5].

On the other hand, β-cell organ dysfunction (BCOD) can develop before it can be clearly appreciated and it is related to a reversible loss of β-cell functionality and β-cell content that only becomes irreversible when there is a large loss of cell mass due to β-cell apoptosis. If this loss of β-cell mass persists and the damage is significant enough, it results in β-cell organ failure (BCOF). Thus, it highlights the need for an earlier preventive approach so that early pharmacological and dietary treatment can rescue the reduced and reversible BCOD associated with T2DM[8].

Animal and human studies have demonstrated that the progressive failure of β-cell insulin-secreting function is not only due to apoptosis and loss of cell mass, but also to the phenomena of cellular dedifferentiation and conversion to other endocrine cells. Many studies have stablished that β-cell become dedifferentiated in response to hyperglycemia, reverting to a progenitor-like state and, then, β-cell conversion to

glucagon producing "α-like" cells takes places. This transdifferentiation process could explain the typical glucagon overproduction and hyperglucagonemia in T2DM[6,9,10].

Glucolipotoxicity is another added risk factor studied in rodent models because of excessive and chronic exposure to fatty acids, lipid storage and synthesis. This increase directly impairs glucose-stimulated insulin secretion resulting in β-cell stress and dysfunction[9,11].

Regarding other risk factors as micronutrients, particularly selenium (Se) is a trace element that interferes with cellular antioxidant capacity through enzymes such as glutathione peroxidase (GPx) and it has been linked on several occasions to T2DM. However, there are many controversial studies on the beneficial or detrimental effects of Se on the risk of developing type II diabetes. This review discusses the role of Se in type 2 diabetes and the complex interplay between selenoproteins and insulin pathways reflecting the need for new knowledge and better mechanistic understanding.

THE CONTROVERSIAL ROLE OF SELENIUM IN T2DM

Selenium: An essential trace element

Se is a trace element that represents an essential micronutrient for humans, plants and microorganisms and it is involved in a wide variety of physiological processes. Adequate levels of Se bioavailability in the organism are crucial for different aspects of human biology including the endocrine system, muscle function or the cardiovascular system[12].

In nature, inorganic Se is found in four different oxidation states: Selenate, selenite, elemental Se and selenide (in decreasing order of redox state). Biological systems are able to convert this inorganic Se into more bioavailable organic forms such as the two Se-containing amino acids, selenocysteine and selenomethionine, which will become part of proteins, the so-called selenoproteins[13].

Selenoproteins comprise a total of 25 proteins in the human proteome with different functions including, among others, protection against oxidative stress, Se storage and

transport or redox signaling. Their crucial role in oxidative stress system is due to their ability to neutralize reactive oxygen and nitrogen species[14].

These selenoproteins can be differentiated by having enzymatic activity as the GPx family, or by the absence of such activity as the selenoprotein K family[12].

Worldwide variation in selenium intake

In contrast to other micronutrients, selenium intake varies widely worldwide from deficiency to toxic concentrations leading to nail loss, hair loss, poor dental health or even nervous system or skin disorders. Regarding adequate Se concentrations, the recommended Se intake is around 55 µg/d and it can be found in foods such as grains, meat, seafood, vegetables, nuts or dairy products[12].

Selenium intake from food depends not only on the selenium content of the soil but also on factors which determine the availability of selenium in food. In general, intakes are higher in countries such as Venezuela, Canada, United States and Japan. In Europe, on the other hand, intakes are lower and in countries such as New Zealand, Finland or Denmark they are especially low[15].

Dietary supplements containing selenium are very common, especially in countries such as the United States where 50% of the population takes daily supplements. This extra intake of selenium added to the daily food intake makes the average selenium intake vary from 40 µg/d in Europe to 93 µg/d (in women) and 134 µg/d (in men) in the United States[15].

Thus, below and above the recommended intake range, Se can have detrimental effects. A Se deficiency has been shown to be involved in the appearance of different pathologies such as Kaschin-Beck disease or Keshan disease. In the same way, a high and chronic exposure to Se can cause selenosis with severe manifestations in the organism[12,13].

Studies on Se supplementation effect

Many studies have demonstrated the beneficial effect of Se in different pathologies such as cancer, the immune system or, among others, hyperlipidemia.

Se supplementation in patients with Hashimoto's thyroiditis has been associated with a decrease in thyroid autoantibodies and thyroid stimulating hormone levels due to its antioxidant capacity and overregulation of regulatory T cells[16]. Similarly, in patients with autoimmune thyroiditis, after three months of Se supplementation, the levels of antithyroid peroxidase antibody decreased, revealing beneficial effects of the antioxidant capacity of Se[17].

In a study on leukocyte DNA integrity, they found that it was enhanced by Se supplementation depending on the interaction with dietary micronutrients. Particularly, Se supplementation was found to be beneficial when there were low folate and high methionine intake levels through increased homeostatic apoptosis[18].

On the other hand, in a study with septic patients it was seen that Se administration was beneficial in those patients with bronchopneumonia where there is greater oxidative stress in the lung parenchyma and the action of antioxidant molecules helps to improve. This is not the case in patients with persistent renal failure since continuous renal replacement therapy does not ensure GPx synthesis[19]. However, a separate study with septic patients shows that although it may seem logical to administer antioxidant elements because of the high oxidative stress and low Se levels in these patients, Se does not increase the release of cytokines or the activation of innate immune cells, suggesting a neutral effect of Se on the immune system[20].

The beneficial effect of Se on cancer is a controversial topic too. Many reviews have gathered a large amount of information and clinical trials to analyze and conclude that Se has no effect in preventing cancer overall, neither the type of cancer with the most consistent association with antecedent Se exposure, prostate cancer, nor in patients with low Se levels[21]. In addition, it has been shown that Se at the recommended daily intake concentrations is protective against cancer, so supplementing Se to people with Se deficiency improves prevention due to elimination of such deficiency, not as a result of elevated Se levels. In fact, raising Se levels above the recommended dose does not

improve cancer prevention and is not recommended since it favors the appearance of other diseases such as T2DM[22]. However, a recent study supports the use of different Se species as co-adjuvant agents in cancer treatment due to their lower toxicity, higher selectivity and efficacy in inducing cell apoptosis[23].

In a cross-selectional study regarding the relationship between Se and hypertension in the Chinese population, a higher incidence of hypertension was found in the group with higher serum Se concentration, especially in women, as well as a higher amount of blood lipids[14]. On the other hand, a 20-year cohort study also in Chinese population, Se intake was inversely associated with the risk of hypertension in participants from the northern region and positively associated in participants from the southern region suggesting a protective factor for blood pressure in low-Se regions[24].

Regarding the relationship between plasma lipids and Se is also a controversial question. In a randomized trial with participants over 60 years, they found that Se supplementation decreased total and non-high density lipoprotein (non-HDL) cholesterol in their sample of relatively low Se status[25]. Similarly, a decrease in total cholesterol and an increase in HDL were found in relation with increasing Se in elderly Chinese population with low dietary Se intake[26]. However, in a cross-selectional study in a Spanish population, Se was positively associated with total and low-density lipoprotein cholesterol[27]. In addition, in a study with hyperlipidemic patients, Se was found to be in higher levels than in healthy volunteers[28]. Finally, in a cross-selectional study they found that Se decreased lipid dysregulation caused by elevated toenail levels of mercury confirming the beneficial effects of Se against the harmful effects of mercury[29].

There are also studies on the effect of Se in the improvement of critically ill patients such as patients with cardiac surgery, major trauma or subarachnoid hemorrhage. It has been seen that the administration of Se-containing antioxidant supplements corrects the initial alterations and restores antioxidant defenses such as GPx activity but fails to achieve a significant improvement in organ dysfunction[30]. In a small observational study in patients who have undergone cardiopulmonary resuscitation, they observed

an improvement in neurological outcome and survival rate with early Se treatment[31]. In terms of neurotoxicity, in a population-based study from four different geographic areas, high Se levels were associated with a greater probability of having depressive symptoms[32].

With regard to metabolic diseases, in a study of 7.5 years of follow-up they concluded that there is no benefit or adverse effect of multiple antioxidant supplementation on the incidence of metabolic syndrome[33]. Finally, non-linear associations have been found between serum Se and the prevalence of non-alcoholic fatty liver disease, only positive associations were found above serum Se level > 130 µg/L[34].

As explained above and shown in Table 1, Se supplementation is a controversial subject given the large number of factors (age, region, diet, genetic factors, and diseases, *etc.*) that influence in Se beneficial or adverse effect.

Evidence showing higher levels of Se in T2DM

Among all the beneficial and harmful properties of Se, the association between high Se levels and the risk of developing type II diabetes is relatively recent. By analyzing non-experimental studies based on dietary and blood Se concentrations, they determined a non-linear dose-response association with T2DM risk, existing a dramatically increase from 80 µg of daily Se intake and above[35]. Another non-linear dose-response meta-analysis suggests that this positive association also occurs at low Se concentrations[36]. In fact, dose response to Se has been found to be U-shaped, damage occuring both below and above the recommended concentration. In the case of increased risk of T2DM, an excess of Se promotes hyperinsulinaemia, hyperglycaemia and hyperlipidaemia[22,37]. Increased selenoprotein (SeP) levels have been found in T2DM patients and its expression is reduced by the characteristic inflammatory response of T2DM[38]. However, there are some studies where, conversely, negative associations have been found between Se dose and insulin resistance when Se intake is below 1.6 µg/kg/d[39].

It has also been suggested that the association between Se, obesity and T2DM may be due to abnormal metabolism in adipocytes by excessive release of fatty acids and/or hormones[40]. Moreover, a high Se intake (> 60 μg/d) in people without previous diabetes increases the risk of hospitalization for T2DM[41]. Similarly, the Hortega study found a positive association between plasma Se with prevalent and incident diabetes[42]. Nevertheless, in a cross-selectional study of the United States population, Se was found to be positively associated with diabetes but inversely associated with all-cause mortality[43].

Finally, in a randomized trial with T2DM patients, Se supplementation in those with deficient Se levels resulted in adverse effects on blood glucose homeostasis even when the Se concentration had reached the optimal level of antioxidant activity[44].

Regarding T2DM, the vast majority of epidemiological studies (Table 2) support the evidence of an increased risk of T2DM when Se concentrations are elevated above the recommended levels, which emphasizes the need for special caution when supplementing with Se to obtain other beneficial effects given the possibility of developing T2DM.

Clinical research on the relationship between selenium and treatment of diabetes

Despite the beneficial effect of many micronutrients on different diseases, including diabetes, there are many studies correlating the development of diabetes with selenium[45].

It has been observed that selenium supplementation is protective against different pathologies such as cancer or autoimmune thyroid disorders when there is a deficiency of this trace element. In contrast, selenium supplementation is not recommended when levels of this micronutrient are optimal because of its potential to promote the development of diabetes. Supplementation dose and duration should be carefully taken into account[22,46].

Human clinical trials have confirmed that selenium supplementation does not help in the prevention of type II diabetes, but that prolonged exposure to selenium

supplementation may increase the risk of this disease[47]. Indeed, selenium supplementation to treat micro-albuminuria in diabetic patients has been found to be ineffective[48].

Oxidative stress as potential mediator of Se in T2DM

Elevated plasma Se concentrations are associated with biomarkers of diabetes as Se antagonizes the effects of insulin *via* GPx1 and Selenoprotein P[40].

Due to the low activity of enzymes such as catalase, superoxide dismutase and GPx, β-cells are protected from oxidative stress by peroxiredoxins, thioredoxins and thioredoxins reductases. As the activity of GPx and thioredoxin reductases depends on the bioavailability of Se, a deficiency of this element leads to oxidative damage of β-cells and a reduction of insulin secretion. However, an excessive amount of Se also leads to a dysregulation of insulin secretion resulting in hyperinsulinaemia and a T2DM phenotype. In general, all these antioxidant enzymes, including selenoenzymes, play a role in cell differentiation and insulin secretion by interfering with critical redox signaling for these processes[49].

A supranutritional Se intake, leading to the aforementioned risk in T2DM, also results in endolethelial dysfunction *via* apoptosis mechanisms activated by endoplasmic reticulum (ER) stress and excess reactive oxygen species (ROS) production[50].

It is known that an increase in oxidative stress caused by hyperglycemia leads to an increase in the production of inflammatory cytokines such as IL-6 and tumour necrosis factor alpha and in turn to an increase in the production of free radicals, an increase in insulin resistance in the adipose tissue, liver and muscle, and a β-cell failure in the pancreas. Therefore, excessive Se levels promote this chain of events that leads to cellular damage and a direct relationship with insulin resistance[51,52].

Finally, they have shown that excessive Se exposure results in hepatic insulin resistance through the opposite regulation of ROS. Certain levels of ROS ("good ROS") generated at specific sites are essential for the signaling of different physiological processes such as the insulin signaling cascade. However, high levels of Se dysregulate

these "good ROS" signaling in response to insulin through the over-regulation of selenoproteins and this Se excess also increases the flux of fatty acids in the liver leading to increased production of "bad ROS" that impair insulin sensitivity[53] (Figure 1).

Relation between selenium and T2DM regarding the immune system and the inflammation process

Although there is much evidence from *in vitro* and animal studies on the role of selenium in the immune system, there are few studies that support it in humans. Selenium supplementation appears to have immunostimulant effects by promoting the proliferation of activated T cells, increasing the activity of natural killer cells and increasing cytotoxic lymphocyte-mediated tumor cytotoxicity[15].

Selenoproteins are essential for the function of activated T cells since they are particularly sensitive to oxidative stress and selenoproteins aid promoting the suppression of ROS production. Moreover, human studies have correlated selenium supplementation with lymphocyte proliferation preceded by increased expression of high-affinity interleukin-2 receptor[15].

Low-grade inflammation is involved in insulin resistance and increased selenoprotein P concentration has been positively correlated with high-sensitivity C-reactive protein, a biomarker of inflammation, in patients with prediabetes and diabetes[54].

In addition, the relation of selenium with T2DM *via* the inflammatory pathway has been described through SELENOS, a transmembrane protein located in the membrane of the ER and the plasma membrane. Its increase has been related, among other things, to a decrease in glucose uptake and glycogen biosynthesis as well as to an increase in circulating cytokines[55].

SELENIUM AND INSULIN RESISTANCE

Se and its relation with insulin signaling pathway

The pancreas is essential for the control of metabolism and energy consumption. It is composed of the exocrine pancreas and the endocrine pancreas which are

morphologically and functionally different. The exocrine pancreas comprises ductal cells and acinar cells which are responsible for the production and release of digestive enzymes into the small intestine for the digestion of fats, carbohydrates and proteins for absorption. The endocrine pancreas is represented by the islets of Langerhans containing five different hormone-secreting cell types: Insulin (β-cells), glucagon (α-cells), soma-tostatin (δ-cells), pancreatic polypeptide (PP cells), and ghrelin (ε-cells). Among these, insulin and glucagon are secreted directly into the blood to control glucose levels. In contrast to diseases such as pancreatic cancer or pancreatitis which are related to the exocrine pancreas, diabetes is related to the endocrine islets[56].

Existing data on β-cells show that not all of them behave in unison, but rather exhibit considerable heterogeneity including differential vascular supply, local environment changes, neural innervation or pancreatic exocrine alterations[8].

Binding of insulin to its receptor initiates an intracellular insulin signaling cascade with a large number of molecules. Among them, the insulin receptor substrate (IRS)-2, the protein tyrosine phosphatase (PTP)-1B and the protein kinase B (serine/threonine kinase Akt), the forkhead box class (Fox) O1a transcription factor and its coactivator per-oxisomal proliferator-activated receptor gamma coactivator (PGC)-1α are of key importance. Dysregulation in the expression, localization or activity of any of these proteins results in insulin resistance. Indeed, elements such as Se can act as insulin-mimetic by activating Akt and other kinases of this signaling cascade[57].

Besides, it is also said that Se acts as an insulin-mimic since at high concentrations it enhances glucose uptake in adipocytes by promoting the translocation of glucose transporters to the plasma membrane and activating serine/threonine kinases. Numerous animal studies have shown that high Se intake induces hyperinsulinemia, hyperglycemia, insulin resistance, glucose intolerance and altered lipid metabolism[58].

Se influence on glucose and lipid metabolism

Altered expression of key factors and enzymes of glycolysis, gluconeogenesis and lipogenesis is implicated in the pro-diabetic effect of high Se intake. It has been shown that an over intake of Se increases gene expression of forkhead box O1 and PGC-1α and reduces gene expression of glycolytic enzyme pyruvate kinase in muscle tissue essential in glucose metabolism. Likewise, adipose tissue is involved in lipid metabolism by increasing, among others, the expression of sterol regulatory element-binding transcription factor 1 and lipoprotein lipase[58] (Figure 1).

Moreover, in a study on the effect of Se supplementation on fatty acid metabolism in mice, they found that an excess of Se increases the expression of genes of glucose transport and increases the β-oxidation of fatty acids associated to the accumulation of acylcarnitines and other lipid metabolites and in turn to the decrease of bile acids metabolites. Thus, it suggests that an excess of Se alters the β-oxidation of fatty acids and creates an imbalance in acetyl-CoA-dependent metabolism[59].

On the other hand, another study in pigs also confirmed this association of Se with lipid metabolism through the activation of AMPK and different selenoproteins depending on the tissue. In the case of liver tissue, lipid accumulation caused by high Se intake has been associated with a stimulation of lipogenesis and gluconeogenesis, as well as with the suppression of lipolysis, with GPx3 playing an important role. Whereas, in muscle tissue, it is SelP that contributes to the development of insulin resistance and hyperinsulinemia[60].

SELENIUM, BETA-CELLS AND INSULIN SECRETION

Effect of oxidative stress in β-cells

Compared to liver, β-cells are particularly sensitive to oxidative stress given their high production of ROS and their low antioxidant capacity since they have 1% catalase, 2% GPx1 and 29% SOD1 activities[58]. A normal production of ROS derived from glucose metabolism, especially H_2O_2, are important for signaling. The binding of insulin to its receptor on the plasma membrane causes a transient release of ROS which serve as

second messengers promoting the phosphorylation of downstream molecules in the insulin signaling cascade[57].

However, just as elevated concentrations of glucose and cytokines mostly trigger β-cell apoptosis, overproduction of ROS leads to impaired insulin synthesis by affecting β-cell key regulators such as pancreatic duodenal homebox transcription factor 1 (PDX1) or mitochondrial uncoupling protein 2 (UCP2). Moreover, an overproduction of ROS has a damaging effect by activating a variety of serine/threonine kinases that in turn phosphorylate a large number of targets such as insulin receptor (IR) and IRS proteins. Consequently, increased serine phosphorylation of IRS-1 decreases the insulin-stimulated threonine phosphorylation of IRS-1 Leading to an insulin resistance response and the subsequent development of T2DM[58].

β-cell failure caused by inflammation, hyperglycemia or hyperlipidemia characteristic of diabetes is mainly explained by three phenomena: ER stress, mitochondrial dysfunction and oxidative stress, existing a link between them. Regarding the first one, the increased demand for insulin production and secretion under diabetic conditions saturates the ER folding capacity and, thus, the amount of misfolded proinsulin increases. In response, β-cells activate two unfolded protein response (UPR) mechanisms: adaptive UPR and apoptotic UPR. These response mechanisms fail when ER stress occurs due to a prolonged glucotoxicity and lipotoxicity. Concerning mitochondrial dysfunction, glucose stimulated insulin secretion (GSIS) is reduced in diabetic conditions which results in the reduction of ATP/ADP ratio and decreasing, consequently, the mitochondrial membrane potential and the expression of genes related to energy metabolism.

Finally, in β-cells, ROS and the antioxidant defense system [such as catalase (CAT) or GPx] play a crucial role in insulin secretion. However, under chronic pathological conditions, the accumulation of ROS causes both oxidative stress and reduction in CAT and GPx1 expression leading to a high susceptibility of β-cells to ROS damage[4,11,61].

Moreover, under normal conditions, high oxidative phosphorylation rate occurring in pancreatic islets relies on the availability of a constant oxygen supply. Nevertheless,

high glucose exposure not only increases ROS but also hypoxia, thereby activating mechanisms of apoptosis and necrosis[11].

Potential role of Se-dependent antioxidants in beta-cell function and insulin secretion

High Se intake increases the production of ROS involved in the molecular mechanisms for the insulin-like effects of Se consequently initiating different signaling cascades of programmed cell death, pro-inflammatory signaling and other adaptive system responses[62]. Particularly, elevated H_2O_2 attenuates oxidative inhibition of protein tyrosine phospatases as PTP1b or PTEN, suppressing insulin-stimulated IR/IRS/PI3-K/Akt signaling and stimulating the lipogenic pathway, aggravating insulin resistance[58] (Figure 1).

In relation to the influence of selenoproteins, an overexpression of GPx1 alters intracellular ROS, enhances β-cells mass and subsequent redox regulation of key events in insulin synthesis, secretion and function resulting in dysregulation of lipid and glucose metabolism mentioned above[58]. Overly diminishing intracellular ROS by overexpression of GPx1 desensitizes insulin signaling together with chronic hyperinsulinemia resulting from dysregulation of β-cells mass, insulin synthesis and secretion, this desensitization leads to insulin resistance[63] (Figure 1).

Specifically, overproduction of GPx1 over-regulates PDX1 mRNA and protein levels and decreases its degradation. Elevated PDX1 functionality in islets results in hypertrophy of β-cells and increased pancreatic and plasma insulin concentrations. On the other hand, overproduction of GPx1 down-regulates UCP2 protein and elevates mitochondrial membrane potential contributing to an accelerated increase in GSIS and hyperinsulinemia[58].

While Se supplementation is not associated with a risk of T2DM in individuals with low concentrations or in individuals maintaining the recommended nutritional dose, excessive long-term Se exposure has been shown to increase the risk of T2DM due to excessive GPx1 activity[64] and a consequent impairment of insulin sensitivity[57] (Figure 1).

Regarding SelP, specifically SelP1 represents the most important selenoprotein for systemic Se homeostasis as it is involved in Se transport and supply[65]. Positive associations have been found between SelP levels and fasting plasma glucose, hemoglobin A1c and insulin resistance. The metabolic actions of SelP are due to the inactivation of adenosine monophosphate-activated protein kinase severely affecting insulin sensitivity. The metabolic effect is similar to that produced by GPx overexpression, but without affecting insulin synthesis and secretion[58].

CONCLUSION

T2DM incidence and global burden

Global increase in obesity, ageing population, sedentary lifestyles, physical inactivity, alcohol consumption, smoking and high fat and sugar diets intake has contributed to an unprecedented increase in the incidence of type 2 diabetes mellitus (T2DM), quadrupling between 1980 and 2004. In 2015, a total of 415 million people were estimated to have diabetes, more than 90% of whom were T2DM, making it the sixth leading cause of disability in the world[1].

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Insulin resistance and β-cell dysfunction

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Regarding insulin resistance, it refers to a failure or impairment in the transduction of the insulin-mediated signalling cascade in certain tissues, especially in muscle, adipose tissue and liver. This leads to an elevated circulating glucose level which together with elevated hepatic glucose output results in very high plasma glucose levels. These glucose levels require a high demand for insulin production and secretion by the β-cells. When insulin resistance is prolonged over time, the β-cells are submitted to high glucose and lipid exposure that results in β-cell dysfunction and death[4] (Petersen & Shulman, 2018).

On the other hand, BCOD can develop before it can be clearly appreciated and it is related to a reversible loss of β-cell functionality and β-cell content that only becomes irreversible when there is a large loss of cell mass due to β-cell apoptosis. If this loss of β-cell mass persists and the damage is significant enough, it results in BCOF. Thus, it highlights the need for an earlier preventive approach so that early pharmacological

and dietary treatment can rescue the reduced and reversible BCOD associated with T2DM (Charles & Leslie, 2021).

Animal and human studies have demonstrated that the progressive failure of β-cell insulin-secreting function is not only due to apoptosis and loss of cell mass, but also to the phenomena of cellular dedifferentiation and conversion to other endocrine cells. Many studies have stablished that β-cell become dedifferentiated in response to hyperglycemia, reverting to a progenitor-like state and, then, β-cell conversion to glucagon producing "α-like" cells takes places. This transdifferentiation process could explain the typical glucagon overproduction and hyperglucagonemia in T2DM[6] (White, Shaw, & Taylor, 2016) (Brereton, Rohm, & Ashcroft, 2016).

Glucolipotoxicity is another added risk factor studied in rodent models because of excessive and chronic exposure to fatty acids, lipid storage and synthesis. This increase directly impairs glucose-stimulated insulin secretion resulting in β-cell stress and dysfunction (White, Shaw, & Taylor, 2016) (Gerber & Rutter, 2017).

Regarding other risk factors as micronutrients, particularly selenium (Se) is a trace element that interferes with cellular antioxidant capacity through enzymes such as GpX and it has been linked on several occasions to T2DM. However, there are many controversial studies on the beneficial or detrimental effects of Se on the risk of developing type II diabetes. This review discusses the role of Se in type 2 diabetes and the complex interplay between selenoproteins and insulin pathways reflecting the need for new knowledge and better mechanistic understanding.

Figure 1 Role of selenium as a risk factor in the chain of events that triggers the development of type 2 diabetes mellitus. Se: selenium; ER: Endoplasmic reticulum; GPx: Glutathione peroxidase; ROS: Reactive oxygen species.

Table 1 Summary of a wide variety of studies suggesting a beneficial or detrimental role of selenium in different diseases and physiological processes

Ref.	Type of study	Number of participants	Effects on Se intake
Hu *et al*[16], 2021	Longitudinal study (6 mo)	90 with HT; 36 healthy subjects	Reductions in thyroid autoantibodies and thyroid stimulating hormone levels in HT patients
(Karimi & Omrani, 2018)	Longitudinal study (3 mo)	102 with AIT	Decrease on antithyroid peroxidase antibody levels
(Karunasinghe, Zhu, & Ferguson, 2016)	Longitudinal study (6 mo)	572 men	Improved leukocyte DNA integrity through increased homeostatic apoptosis when folate intake levels are low and methionine intake levels are high
(Kočan *et al*, 2014)	Longitudinal study (6 d)	65 septic patients	Improvement of patients with acute lung injury and elevated oxidative stress
(Guo *et al*, 2019)	Longitudinal study (21 d)	76 severe septic patients	Neutral effect
(Vinceti *et al*, 2018)	Review	-	Se has no effect in preventing cancer overall, neither in patients with low Se levels
(Rocourt & Cheng, 2013)	Review	-	Supplementing Se to people with Se deficiency improves cancer prevention due to elimination of such

			deficiency
(Radomska, Czarnomysy, Radomski, & Bielawski, 2021)	Review	-	Se species as co-adjuvant agents in cancer treatment due to their lower toxicity, higher selectivity and efficacy in inducing cell apoptosis
(Wu *et al*, 2018)	Cross-selectional study	8011 participants	Higher incidence of hypertension in the group with higher serum Se concentration
(Xie *et al*, 2021)	Longitudinal study (20 yr)	10025 participants	Protective factor for blood pressure in low-Se regions
(Rayman, Stranges, Griffin, Pastor-Barriuso, & Guallar, 2011)	Longitudinal study (6 mo)	501 people aged 60 yr to 74 yr	Se supplementation decreased total and non-HDL cholesterol
(Chen *et al*, 2014)	Longitudinal study (7 yr)	2000 aged 65 and older	Decrease in total cholesterol and an increase in HDL in relation with increasing Se
(González-Estecha *et al*, 2017)	Cross-selectional study	372 participants	Positive association of Se with total and LDL cholesterol
(Fülöp, Seres, Jenei, Juhász, & Paragh, 2013)	Study population	81 hyperlipidemic patients 43 healthy volunteers	Higher Se levels in hyperlipidemic patients
(Park & Seo,	Cross-	501 participants	Decrease on lipid

2017)	selectional study		dysregulation caused by elevated toenail levels of mercury
(Berger *et al*, 2008)	Longitudinal study (5 d)	2000 cardiac surgery or major trauma or subarachnoid hemorrhage patients	Correction of initial alterations and restore of antioxidant defenses
(Fink & Busch, 2018)	Longitudinal study (24 h)	28 resuscitated patients	Improvement in neurological outcome and survival rate with early Se treatment in patients after cardiopulmonary resuscitation
(Colangelo *et al*, 2014)	Study population	5115 participants	High Se levels were associated with a greater probability of having depressive symptoms
(Czernichow *et al*, 2009)	Longitudinal study (7.5 yr)	5220 participants	No benefit or adverse effect of multiple antioxidant supplementation on the incidence of metabolic syndrom
(Wang, Seo, & Park, 2021)	Cross-selectional study	3827 participants	Only positive associations were found above serum Se level > 130 µg/L with NAFLD

Se: selenium; HT: Hashimoto's thyroiditis; AIT: Autoimmune thyroiditis; HDL: High density lipoprotein; LDL: Low-density lipoprotein; NAFLD: Non-alcoholic fatty liver disease.

Table 2 Summary of evidence showing primarily an association between elevated Se levels and increased risk of type 2 diabetes mellitus

Ref.	Type of study	Number of participants	Evidence for T2DM risk
(Vinceti, Filippini, Wise, & Rothman, 2021)	Dose-response meta-analysis	-	Non-linear dose-response association. Dramatically increase from 80 µg of daily Se intake and above
(Wang, Yang, Wei, Lei, & Zeng, 2015)	Dose-response meta-analysis	-	Non-linear dose-response association with T2DM at low and high Se concentrations
(Duntas & Benvenga, 2014) (Rocourt & Cheng, 2013)	Reviews	-	U-shaped risk response. An excess of Se promotes hyperinsulinaemia, hyperglycaemia and hyperlipidaemia
(Rayman & Stranges, 2013)	Review	-	Increased selenoprotein (SeP) levels in T2DM patients are reduced by the characteristic inflammatory response of T2DM
(Wang *et al*, 2017)	Cross-selectional	2420 participants	Negative associations have been found

	study		between Se dose and insulin resistance
(Wongdokmai *et al*, 2021)	Cross-selectional study	655 men	Abnormal metabolism in adipocytes by excessive release of fatty acids and/or hormones
(Vinceti *et al*, 2021)	Prospective study	24325 participants	High Se intake increases the risk of hospitalization for T2DM
(Galan-Chilet *et al*, 2017)	Cross-selectional study	1452 participants	Positive association between plasma Se with prevalent and incident diabetes
(Hoque & Shi, 2022)	Cross-selectional study	18932 participants	Positively associated with diabetes but inversely associated with all-cause mortality
(Faghihi *et al*, 2014)	3 mo	60 T2DM patients	Se supplementation in T2DM patients with deficient Se levels resulted in adverse effects on blood glucose homeostasis

T2DM: Type 2 diabetes mellitus; Se: selenium.

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