Free Radical Research, November 2009; 43(11): 1029–1059

informa
healthcare

REVIEW ARTICLE

Selenium and diabetes: an enigma?

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(Received 28 April 2009; revised 15 July 2009)

Abstract
In recent years diabetes has become one of the most common metabolic diseases in developed countries and it is closely related to supernutrition and obesity. Since untreated diabetes produces oxidative stress responsible for secondary complications of the disease, antioxidant supplements were considered as being favourable for the therapy of diabetes. However, the situation has changed recently, since large cross-sectional and interventional trials revealed a positive correlation between a high Se status and diabetes incidence in humans. Thus, currently available data on the role of Se in diabetes are inconsistent and an enigma appears to exist for the relation between selenium and diabetes. This review summarizes selected human and animal studies, pointing to beneficial and critical virtues of Se in diabetes. Moreover, the review discusses possible underlying mechanisms how Se may influence diabetes in both directions. From the current literature, the following information can be extracted: (1) In populations with a high Se status, with the single exception of pregnant women, Se supplements cannot be recommended for the prevention of diabetes; (2) Anti-diabetic effects of Se seem to be restricted to high and nearly toxic doses which cannot be used in humans; and (3) Future investigations should consider the stage of the disease.

Keywords: *Selenium, insulin resistance, diabetes, molecular mechanisms*

Introduction, definitions and epidemiology of diabetes

In recent years diabetes has become one of the most common and expensive metabolic disorders worldwide, particularly in the developed countries. By definition diabetes is generally a dysfunction of glucose metabolism resulting in hyperglycaemia. Beside glucose metabolism a number of other basic metabolic pathways such as fatty acid metabolism and amino acid metabolism deteriorate in diabetes. In developed countries super nutrition and inactivity are two important environmental factors for the accelerated development of obesity, insulin resistance and diabetes. Depending on the cause of the disease, four general forms of diabetes are distinguished: Type I diabetes (syn: juvenile diabetes, autoimmune diabetes), Type II diabetes (syn: adult type diabetes), gestational diabetes and further specific forms of diabetes based on genetic defects of pancreatic transcription factors [1]. In the developed countries type II diabetes is, however, the most prevalent form of the disease. In pregnancy, gestational diabetes is the most common metabolic dysfunction and it occurs in 1–5% of all pregnancies [2]. According to the data of the National Diabetes Statistics (2007), 5–10% of women with gestational diabetes develop type II diabetes immediately after pregnancy. Furthermore, women with gestational diabetes have a 40–60% total risk of developing diabetes within the next 5–10 years after pregnancy [3].

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ISSN 1071-5762 print/ISSN 1029-2470 online
DOI: 10.1080/10715760903196925

Despite incomplete information with regard to epidemiological facts about diabetes in European countries, a meta-analysis of data from European diabetes studies revealed a permanent and distinct increase in diabetes prevalence. These data also include the prevalence of the pre-diabetic states impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Thus, for instance, ~8.2% of Germans suffer from diabetes [4]. However, in addition it is assumed that a large number of unreported cases exist. In Germany the estimated annual increase in diabetes prevalence is ~5% [5]. Moreover the data of the German Health Survey 1997/1998 suggest a distinct correlation between the occurrence of diabetes and social class. In this context it could be analysed that 5.6% of persons from the lower class, 3.5% of the middle class and 2.5% of the upper class have type II diabetes [4]. In other countries, like the USA, more extensive data with regard to the prevalence of diabetes are available. In 2007, ~19.3% of the American adults, aged ≥20 years, displayed impaired fasting glucose (IFG), whereas ~7.8% of Americans suffer from manifest diabetes. The prevalence of diabetes in the USA depends on race and ethnic differences. For instance, ethnic minorities such as non-Hispanic Blacks, American Indians, Inuits and Hispanics tend to develop diabetes earlier in life than non-Hispanic Whites [3].

In addition the number of children and young adolescents with type II diabetes is increasing worldwide, in particular in North America, Asia and Europe. This rise was preceded by a massive increase in the number of overweight or obese children and young adolescents [6]. The global increase in obesity is closely linked to the development of diseases of the metabolic syndrome complex [7], which again includes a cluster of disorders such as insulin resistance, hyperlipidemia and hypertension. Persons with metabolic syndrome have a 5-fold increased risk of developing manifest type II diabetes and a 2-fold increased risk for cardiovascular diseases [8]. Ischaemic heart disease, other cardiovascular complications, strokes and peripheral arterial occlusion rank among macroangiopathic secondary diabetes complications, whereas nephropathies and terminal renal insufficiency are the consequence of microangiopathy [4,9]. In this context it is generally accepted that oxidative stress plays an important role both in the generation and progress of insulin resistance and diabetes and in the development of secondary diabetic complications. For this reason in recent years a large number of trials have been carried out focusing on the preventive and healing role of antioxidants, including selenium (Se), in diabetes and in secondary diabetic complications.

Modelling the ambivalent role of selenium in the therapy or in the generation and progress of diabetes

In recent years Se has been the subject of a controversial and partially somewhat emotional discussion with regard to a beneficial or even critical role of the trace element in diabetes. This review discusses the ambivalent role of Se in conjunction with the role of oxidative stress in the generation and progress of diabetes.

The following main chapter of this review gives an introduction on Se metabolism and deals with both sides of the 'moon', discussing contradictory results of studies regarding the influence of Se on diabetes. Moreover, some possible hypotheses as to how Se may influence diabetes either way are given.

Selenium, a trace element with a narrow therapeutic range

Similar to its controversial role in diabetes, Se has had a chequered history since its discovery by the Swedish chemist Jöns Jacob Berzelius in 1817. Se poisoning of various intensity, commonly referred to as alkali disease or blind stagger, has been found for centuries to be endemic in areas with Se-rich soil and Se accumulating plants. The consequences of chronic Se intoxication for humans were also noticed in seleniferous geographic areas long before Se was recognized as the causative agent. A change in attitude to Se in life sciences and its establishment as an essential trace element occurred in the 1950s and 1960s of the last century, when a number of animal diseases could be attributed to nutritional Se deficiency. [10]. Liver necrosis in rats and pigs [11,12], nutritional muscular dystrophy (NMD) in ruminants [13] and poultry [10] and mulberry heart disease in pigs [12] are such typical degenerative disorders of various organs associated with nutritional Se deficiency. In humans a dilatative cardiomyopathy referred to as Keshan disease occurring particularly in some areas of China is based on Se deficiency in combination with a coxsackie B4 virus infection [14]. The fact that Se was recognized as an integral part of the antioxidant enzyme glutathione peroxidase 1 [15] in the early 1970s provided a plausible explanation for the beneficial effects of Se in preventing the deficiency symptoms mentioned. To date four further selenocysteine containing glutathione peroxidases have been discovered (gastrointestinal glutathione peroxidase = GPx2, plasma glutathione peroxidase = GPx3, phospholipid-hydroperoxide glutathione peroxidase = GPx4 and olfactory glutathione peroxidase = GPx6). Except for the tetrameric GPx1, which is highly expressed in nearly all tissues, the other members of the GPx family have specific characteristics (e.g. GPx4 is a monomeric enzyme mainly associated with cellular membranes and GPx3 is a glycosylated enzyme synthesized in the kidney and released into plasma). They are expressed

to a different extent in various tissues. A wide spectrum of peroxides, including hydrogen peroxide (H_2O_2), lipid hydroperoxides (LOOH) and other organic peroxides (ROOH) is reduced by GPxs to water or water and the corresponding alcohol in a reaction depending on reduced glutathione (GSH) [16]. Further progress in Se research was made by the identification of three monodeiodinases (MDIs) [17], of three thioredoxin reductases (TrxRs) [18], of selenorotein P (SePP) [19] and of selenophosphate synthetase (SPS) [20] as selenocysteine containing functional Se proteins.

These enzymes are of outstanding physiological relevance since they have important functions in the fine tuning of thyroid hormone metabolism, in DNA synthesis, in the inter-organ distribution of Se in the body and in the cotranslational mechanism of selenoprotein synthesis. Thus, to date a total number of 26 functional selenoproteins have been identified in humans [21]. In order to obtain an almost saturated expression and activity of all functional selenoproteins, the recommended uptake currently is 30–70 μg/day for humans [22,23] and 0.15–0.30 mg/kg dietary dry matter for animals [24–26]. The critical intake level in order to prevent deficiency symptoms is ~10 μg/day in humans and 0.05 mg/kg dietary dry matter for animals. The highest tolerable level for Se intake is estimated to be 400 μg/day for humans and 2 mg/kg dietary dry matter for animals [27,28]. The LD_{50} for various Se compounds ranges from 2.0 to ~5.0 mg/kg body weight [29]. The range between essentiality of Se and chronic toxicity reflected by massive prooxidant effects of Se is, however, very narrow. Antioxidant properties of Se are mainly mediated by the activity of the different GPxs. Amongst GPxs a hierarchy exists with regard to their response to a lack of dietary Se supply. Under conditions of dietary Se deficiency GPx1 and GPx3 for instance are downregulated more rapidly and severely compared to GPx2 and GPx4, indicating a higher rank of both the latter mentioned peroxidases [30–36]. An eminent function of GPx4 in male fertility [37] and in antiproliferative effects in tumour cells [38], as well as the inhibition of migration and invasion of cancer cells by GPx2 [38] provide other plausible explanations for their high conservation during dietary Se deficiency. Accordingly, the expression and activity of other functional selenoproteins with outstanding physiological functions, such as MDIs and TrxRs, are also conserved for a longer time during Se deficiency [30].

In human food and animal feed Se is present in two major forms. Foodstuffs and feed-derived from animal sources mainly contain Se in the form of selenocysteine from functional selenoproteins, while Se from plant-derived foodstuffs and feed is present predominantly as selenomethionine. In mineral and trace element supplements Se is frequently added in the form of the inorganic salts, sodium selenite (Se oxidation state +IV) and sodium selenate (Se oxidation state +VI) [10]. As mentioned above, all functional selenoproteins contain Se in the form of the 21st proteinogen amino acid selenocysteine (Sec) which is encoded by the unusual UGA triplet formerly know as stop code. During the synthesis of functional selenoproteins, UGA is decoded as Sec, which in turn is cotranslationally synthesized from a specific transfer RNA which is first loaded with serine [tRNA Ser (Sec)] and phosphorylated selenide (Se oxidation state −II) [21].

Due to individual mechanisms of absorption and of intermediary metabolism of the food-derived Se, the generation of hydrogen selenide undergoes different reactions (Figure 1) [39]. For their absorption in the upper small intestine the amino acid derivatives selenomethionine and selenocysteine use the same carriers as their sulphur analogues methionine and cysteine [40]. Selenate is absorbed unmodified from the small intestine, using either the same sodium-dependent cotransport system as sulphate or a hydroxyl ion exchanger [41]. In contrast the thiol reactive selenite is absorbed either by passive diffusion or after the reaction with cysteine containing peptides and proteins to selenodiglutathione, selenotrisulphides and selenopersulphides in the lumen of the small intestine. Another portion of selenite is entirely reduced by glutathione to selenide (Se oxidation state −II) which again can be readily absorbed. The fraction of selenite which has been taken up into the enterocytes by passive diffusion reacts intracellularly with cysteine containing compounds to form selenodiglutathione, selenotrisulphides and selenopersulphides [42,43]. Following absorption into the enterocytes, the different intermediate Se compounds are released into the blood. The reaction products of selenite are mainly transported in an albumin associated form [44], whereas selenate and the Se amino acids reach peripheral tissues unmodified [45,46]. As a consequence of the above mentioned differences in selenite and selenate absorption, major differences may also exist in their further reduction to H_2Se. Thus, in peripheral organs the absorption products from dietary selenite (e.g. selenodiglutathione: oxidation state 0) need far fewer reduction steps catalysed by glutathione reductase or thioredoxin reductase than selenate (oxidation state +VI). Moreover, in the first glutathione-dependent reduction step of selenate in the peripheral organs, the thiol-reactive selenious oxidation state +IV can be generated. Selenomethionine is transsulphurated to Sec and subsequently, as Sec per se, cleaved via the activity of selenocysteine-β-lyase to H_2Se and alanine. Selenomethionine is the only Se compound which can be incorporated unspecifically into other proteins instead of its sulphur analogue methionine. Excess Se in the organism is removed in the form of the di- and trimethylated Se compounds dimethylselenide and trimethyl selenonium. After the first methylation step from hydrogen

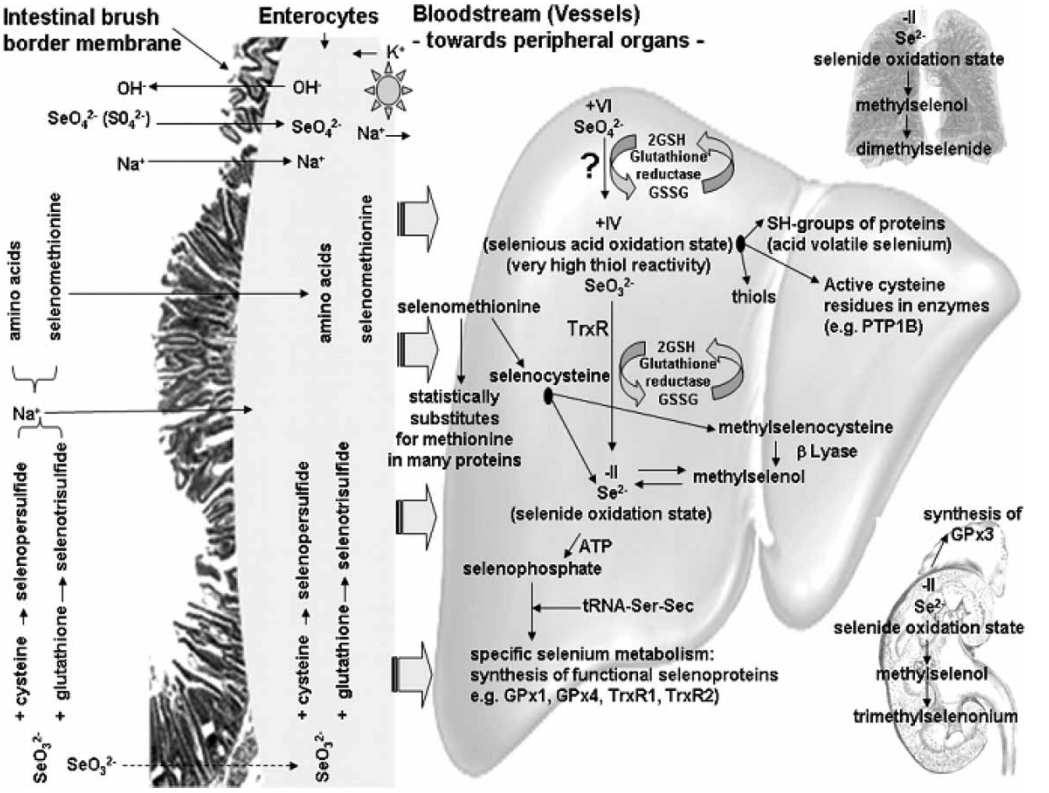

Figure 1. Current view of mammalian Se metabolism.

selenide to methylselenol, a spontaneous oxidation to methylselenenic acid can take place. Methylselenol can also be liberated from selenomethionine by methionine-γ-lyase. Both methylselenol and methylselenenic acid possess a high reactivity towards thiols [46–48]. In the presence of oxygen, high concentrations of hydrogenselenide, which again may be derived from the reduction of the inorganic Se compounds selenite and selenate, can produce elementary Se and superoxide radicals [48]. In conclusion, current knowledge of Se metabolism and functional selenoproteins suggests that Se exerts its physiological functions via the activity of functional selenoproteins only within a very narrow range of supplementation. Long-term Se intake beyond the recommendations carries the risk of serious pro-oxidative damage to various organs due to the loss of GPx activity. A permanently high Se intake above the recommendations may lead to the production of rather chemical effects of Se due to the generation of the thiol-reactive selenocompounds methylselenide and methylselenol and to increased oxidative stress via the generation of superoxide radicals. Thus, if assertions are made about the therapeutic or about a rather critical influence of Se on diabetes the question arises: Is the particular influence investigated based on effects of Se as part of selenoproteins or on chemical reactions of the trace element? In Figure 1 the current view of mammalian Se metabolism is presented [39].

Glucose metabolism and oxidative stress: a complicated relationship presumably deteriorating during the development of insulin resistance and diabetes

Se is commonly considered as part of the antioxidant system since it participates in peroxide detoxification via glutathione peroxidases, mainly GPx1. However, as mentioned above this antioxidant effect only takes place within a very small therapeutic range. Therefore, the following paragraphs give insight into the role of oxidative stress in the normal physiology of glucose metabolism and into events triggered during the generation of insulin resistance and diabetes which may deteriorate in this system.

Pancreatic insulin secretion and oxidative stress. In healthy humans glucose metabolism sensitively responds to changes in blood glucose concentration. If blood glucose concentration increases, glucose is rapidly taken up into pancreatic β-cells via the insulin-independent glucose transporters GLUT 1 and 2 and enters the glycolytic pathway after phosphorylation to glucose-6-phosphate by a specific pancreatic glucokinase with a high Km for glucose. Both the efficient uptake and phosphorylation of glucose enables the β-cells to increase glucose metabolism in relation to extracellular glucose, underlying the dependence of the β-cell insulin secretory response to blood glucose concentrations in the physiological range [49]. The increased glycolytic flux in

β-cells stimulates a steep increase in the production of reducing equivalents, leading to increased ATP production in mitochondria and an increase in the ATP:ADP ratio in the cytoplasm. A decreased free ADP concentration, rather than an increase in ATP, serves as the primary signal for a glucose-induced block of ATP sensitive K^+ channels, decreasing the hyperpolarizing outward K^+ flux. The inward cation current results in depolarization of the plasma membrane, influx of extracellular Ca^{2+}, a sharp increase in intracellular Ca^{2+} and activation of protein motors and kinases, which then mediate exocytosis of insulin. In β-cells, in contrast to most other mammalian cell types, increased glucose concentration stimulates a steeply increased glycolytic flux followed by a high increase in the production of reducing equivalents that *per se* can cause an enhanced production of reactive oxygen species (ROS) [50–52]. Accordingly, it could be demonstrated that an increase in glucose concentration from 2 mmol/L to 10 mmol/L in the media of cultured β-cells from lean Zucker control rats increased superoxide radical production ($O_2^{-\bullet}$) 2-fold [53]. Addition of glucose to these cells decreased free ADP concentration in β-cells distinctly. This decrease in free ADP may again be a further direct cause for an over-production of ROS. This hypothesis has been recently confirmed for β-cells in which ADP addition to the media inhibited ROS generation [54].

Other mechanisms of glucose toxicity for the β-cell include alternative pathways for glucose utilization, like glycerinaldehyde autoxidation to methylglyoxal, glycation of proteins, enediol and α-ketoaldehyde formation, dihydroxyacetone and diacylglycerol formation with subsequent protein kinase C activation and an increase in glucosamine-, hexosamine- and sorbitol metabolism. All these pathways contribute to additional ROS production and may therefore damage β-cells [55]. A rise in intracellular Ca^{2+} due to an increased Ca^{2+} influx through voltage-gated Ca^{2+} channels is an integral part in the mechanism of glucose-dependent insulin release. However, a further increase in intracellular Ca^{2+} due to chronically high glucose levels causes mitochondrial generation of ROS leading to apoptosis [56]. Another interesting mechanism which may contribute to ROS production in pancreatic β-cells concerns insulin production *per se*. There is evidence that disulphide bond formation during peptide and protein synthesis can significantly contribute to ROS production. Due to the localization of this particular ROS source in the endoplasmic reticulum (ER), specialized secretory cells, such as the β-cell, may be especially affected by this stress response [57]. Finally, glucolipotoxicity contributing to the damage of β-cells should be mentioned. This mechanism may be of particular relevance when an impaired glucose metabolism is accompanied by obesity.

A number of studies have shown that fatty acids can induce β-cell death by apoptosis in the presence of high glucose [58–63]. *In vitro*, saturated fatty acids induce β-cell apoptosis, whereas unsaturated fatty acids are usually protective [58–60]. This difference in the proapoptotic effects of fatty acids can be explained by the greater ability of unsaturated fatty acids to form intracellular triglycerides [64,65]. The expression level of stearoyl coenzyme A desaturase seems to modulate the resistance of β-cells to the proapoptotic effect of palmitate, indicating that the capability of a cell to desaturate fatty acids protects from glucolipotoxicity [66]. Thus, several mechanisms have been proposed mediating fatty acid-induced apoptosis in β-cells, including ceramide formation, altered lipid partitioning and the generation of oxidative stress [59,61,63,64,67–72]. Further, free fatty acids and cytokines (TNFα, IL-1), which are frequently present when diabetes is accompanied by obesity, have been demonstrated to trigger β-cell death by different mechanisms in INS 1 cells. Whereas cytokines activated the nuclear factor κB pathway (NFκB) and the expression of its target genes like inducible nitric oxide synthase (iNOS) and monocyte chemoattractant protein-1, free fatty acids increased ER stress via the unfolded protein response (UPR) machinery [72]. Both pathways showed no interferences. More recently it could be demonstrated that saturated fatty acids (palmitate) again possess a particular role in the promotion of ER stress, whereas unsaturated fatty acids (oleate) are less reactive [73]. Markers of ER stress could also be found as being increased in islets from db/db mice and pancreatic sections of type 2 diabetic patients [74]. Despite a generally high exposition of β-cells to oxidative stress, these cells hold relatively low expression levels of enzymes detoxifying free radicals and their secondary products (H_2O_2, lipid peroxides), such as superoxide dismutase, glutathione peroxidase and catalase [75–77]. However, in this context the influence of the mentioned antioxidant enzymes in protecting pancreatic β-cells against oxidative stress-induced apoptosis and on the preservation of insulin production remains to date unclear and needs intensive investigation in the future. This issue is addressed in Figure 2. The differentiated regulation of the two transcription factors Pancreatic and duodenal homeobox 1 (PDX1) and of Forkhead box O1 (FOXO1) by oxidative stress [78–80], as well as various antioxidants and antioxidant enzymes [81,82], seems to play a crucial role with regard to the above-mentioned pathways. The transcription factor PDX1 is a master regulator of pancreatic β-cell differentiation, maturation and of insulin production. To achieve these functions the nuclear localization of PDX1 is essential [78,80]. Oxidative stress causes nuclear translocation of FOXO1, another transcription factor, and leads to a differentiated response. On the one hand antioxidant

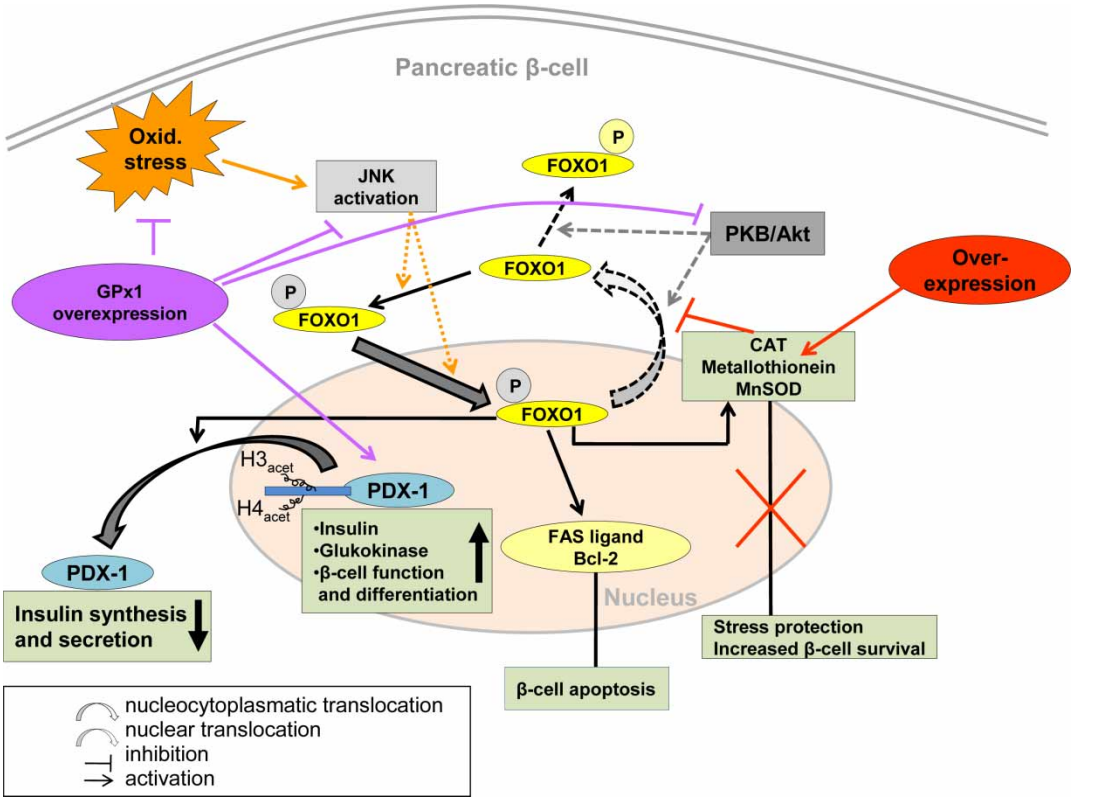

Figure 2. Regulation of the transcription factors PDX1 and FOXO in pancreatic β-cells. AKT = protein kinase B, Bcl-2 = B-cell lymphoma 2, CAT = catalase, FOXO1 = forkhead box O1, GPx1 = glutathione peroxidase 1, JNK = c-Jun terminal kinase, MnSOD = manganese superoxide peroxidase, PDX-1 = pancreatic and duodenal homeobox 1.

enzymes such as mitochondrial manganese superoxide dismutase (MnSOD) and catalase (CAT) are up-regulated due to FOXO1 translocation, but on the other hand FOXO1 translocation increases the expression of a number of proapoptotic genes such as Fas ligand, Bcl-2 interacting mediator of cell death and TRAIL [79]. The alternative localization of FOXO1 in the nucleus or in the cytoplasma is the result of site-specific phosphorylation. Under normal physiological conditions with low oxidative stress FOXO1 is phosphorylated in response to growth factor- and insulin-signalling by Akt/PKB, leading to its nuclear exclusion. In contrast under conditions of oxidative stress, phosphorylation of FOXO1 by c-Jun terminal kinase (JNK) at other sites dominates and stimulates its translocation into the nucleus. Beside the above-mentioned induction of MnSOD, CAT and apoptosis the nuclear localization of FOXO1 effects the discharging of PDX1 from the nucleus, resulting in a reduced insulin production [78,80]. With regard to these very challenging pathways studies with β-cell lines and transgenic mice have investigated the role of various antioxidants or antioxidant enzymes on β-cell function. Contrary to the expected protection against early diabetes development, non-obese diabetic mice (NOD) over-expressing pancreatic catalase (CAT) or metallothionein were significantly more sensitive to diabetes development, as indicated by a loss of insulin production and a decrease in β-cell mass compared to the control mice. As the cause for this effect, the authors found a reduction of the above-mentioned protective Akt/PKB signalling pathway, resulting in an increase in intranuclear FOXO1 and a reduction of intranuclear PDX1 [81]. In complete contrast to these results for catalase over-expression, the pancreatic over-expression of GPx1, the second main enzyme in H_2O_2 removal, led to a 40% increased insulin synthesis and a nearly 2-fold higher β-cell mass in over-expressing mice compared to their wild type littermates. Despite an unclear response with regard to cellular signalling events (GPx1 over-expression reduced both Akt/PKB (protective) and JNK (proapoptotic) phosphorylation), the authors of this study found a hyperacetylation of histones H3 and H4 in the PDX1 promotor region as the cause for the increase in the PDX1 controlled processes [82]. In conclusion the results of this chapter indicate that β-cells have a uniquely high risk for oxidative damage and apoptosis and that this risk increases during the development of diabetes and in particular when diabetes is not treated adequately. The role of various antioxidants including Se on pancreatic health and therefore their pro- or anti-diabetic properties require further investigation.

Insulin resistance, manifest diabetes and oxidative stress. The insulin receptor is composed of two extracellular α sub-units and two transmembrane β sub-units linked to a heterotetramer by disulphide bonds

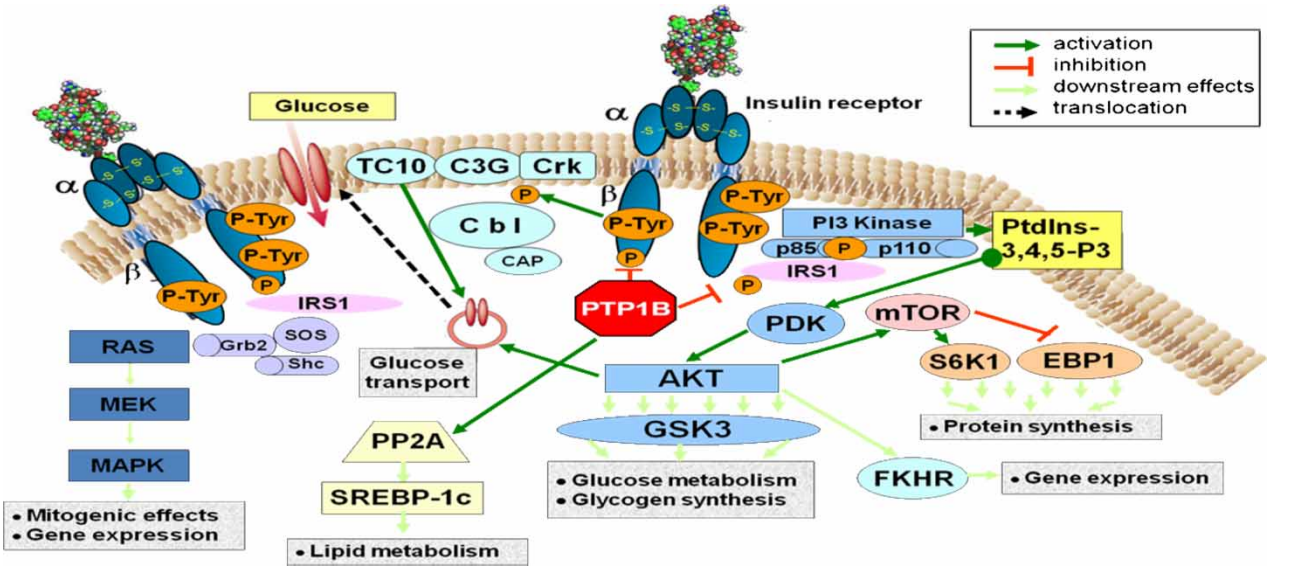

Figure 3. Major routes of the insulin signalling pathway. Possible alterations occurring due to diabetic oxidative stress are described in detail within text. AKT = protein kinase B, C3G = Crk-SH3-guanine-nucleotide-releasing-factor, CAP = c-Cbl-associated protein, Cbl = Casitas b-linage lymphoma, Crk = CT10 regulator of kinase, EBP1 = ErbB3-binding protein 1, FKHR = Forkhead box O1, Grb2 = growth factor receptor-bound protein 2, GSK 3 = glycogen synthase kinase, IRS1 = insulin receptor substrate 1, MAPK = mitogen-activated protein kinase, MEK = mitogen activated ERK activating kinase, mTOR = mammalian target of rapamycin, PDK = phosphoinositol-dependent kinase, PI3K = phosphatidylinositol 3-Kinase, PP2A = protein phosphatase 2A, Ptdlns-3,4,5-P3 = phosphatidylinositol-3,4,5-trisphosphate, PTP1B = protein tyrosine phosphatase 1B, RAS = proto-onkogene rat sarcoma, S6K1 = ribosomal S6 kinase 1, Shc = Src-homolgy/collagen, Sos = son-of sevenless, SREBP-1c = sterol regulatory element binding protein 1c, TC10 = a Rho family member GTPase.

(Figure 3). Binding of insulin to the α sub-unit induces a conformational change resulting in the autophosphorylation of a number of tyrosine residues in the β sub-unit [83]. Receptor activation leads to the phosphorylation of key tyrosine residues of IRS proteins, some of which are recognized by the Src homology 2 (SH2) domain of the p85 regulatory sub-unit of PI3-kinase (a lipid kinase). The catalytic sub-unit of PI3-kinase, p110, then phosphorylates phosphatidylinositol-4,5-bisphosphate (PtdIns-4,5-P_2) to phosphatidylinositol-3,4,5-trisphosphate (Ptd-3,4,5-P_3). A key downstream effector of Ptd-3,4,5-P_3 is AKT, which is recruited to the plasma membrane where it becomes phosphorylated by the phosphoinositide-dependent protein kinase-1 (PDK1). Thus activated, AKT moves back to the cytoplasm where it phosphorylates and thereby inactivates glycogen synthase kinase 3 (GSK3). Phosphorylation of glycogen synthase by GSK3 inhibits glycogen synthesis. The inactivation of GSK3 by AKT promotes glucose storage in the form of glycogen. In addition to promoting glucose storage, insulin inhibits the production and release of glucose through the liver by blocking gluconeogenesis and glycogenolysis [84]. Insulin directly controls the activities of a set of metabolic enzymes by phosphorylation and dephosphorylation events and also regulates the expression of genes encoding hepatic enzymes involved in gluconeogenesis. Recent results suggest that forkhead transcription factors, which are excluded from the nucleus following phosphorylation by AKT, play a role in hepatic enzyme regulation by insulin [85,86].

A key action of insulin is to stimulate glucose uptake into cells by inducing translocation of the glucose transporter, GLUT4, from intracellular vesicles to the plasma membrane. PI3 kinase and AKT are known to play a role in GLUT4 translocation [87]. In addition, a PI3 kinase-independent pathway provides a second clue for GLUT4 recruitment to the plasma membrane [84]. In this pathway, insulin receptor activation leads to the phosphorylation of Casitas b-lineage lymphoma (Cbl), which is associated with c-Cbl-associated protein (CAP). Following phosphorylation, the Cbl-CAP complex translocates to lipid rafts in the plasma membrane. Cbl then interacts with the adaptor protein Crk, which is constitutively associated with the Rho-family guanine nucleotide exchange factor, C3G. C3G, in turn, activates members of the GTP-binding protein family, TC10, which promote GLUT4 translocation to the plasma membrane through the activation of as yet unknown adaptor molecules. AKT also activates the mammalian target of rapamycin (mTOR), which promotes protein synthesis through p70 ribosomal S6 kinase (p70S6k) and inhibition of EBP1 [88].

Insulin also promotes the uptake of fatty acids and the synthesis of lipids, but inhibits lipolysis. Lipid synthesis requires an increase in the transcription factor sterol regulatory element-binding protein SREBP-1c [89]. However, the pathways leading to changes in SREBP expression are not yet fully understood. Interestingly, a high activity of the

insulin signal antagonizing protein tyrosine phosphatase 1B (PTP1B) also has a lipogenic effect and induces SREBP-1c expression. Other signal transduction proteins interact with IRS, including GRB2, an adaptor protein that contains SH3 domains and which associates with the guanine nucleotide exchange factor son-of sevenless (sos) and elicits activation of the MAPK cascade leading to mitogenic responses [90]. Also SHC is a substrate of the insulin receptor. Upon phosphorylation SHC associates with GRB2 and can thereby activate the MAPK pathway independently of IRS.

Formation of insulin resistance. Since a number of publications suggest that increased oxidative stress may promote insulin resistance and diabetes on the one hand and that oxidative stress is one consequence of untreated diabetes on the other hand, mechanisms producing increased oxidative stress are discussed in the following section.

In this context it should be noted that even in the healthy organism controlled oxidative stress secures an optimum action of insulin in insulin-sensitive tissues. In fact, binding of insulin to its receptor leads to the generation of H_2O_2, which contributes to the inhibition of PTP1B by thiol modification [91]. PTP1B is involved in the termination of insulin signalling by dephosphorylation of the insulin receptor β sub-unit and of IRS1. Likewise it could be demonstrated in 3T3L1 adipocytes that a short-term exposure to an increased glucose concentration (25 mmol/L vs 5 mmol/L) increased the insulin sensitivity of these cells by the additional generation of H_2O_2, which again inhibited PTP1B and thus increased insulin signalling and glucose metabolism [91,92]. However, the long-term exposition of cells or an organism to high glucose concentrations can be assumed as promoting oxidative stress and insulin resistance.

In most cases of established type II diabetes a combination of reduced β-cell function and peripheral insulin resistance (IR) is present. IR is defined as an attenuated effect of insulin in insulin-sensitive target tissues, mainly muscle, fat and liver. In adipose tissue, IR is manifested by impaired glucose-uptake and utilization, but also by impaired suppression of lipolysis through hormone-sensitive lipase (HSL), leading to a higher release of free fatty acids into plasma. Liver insulin resistance may predominantly contribute to a further increase in blood glucose concentration via an insufficient repression of gluconeogenesis.

The first step in the generation of insulin resistance consists in an overload of cells with glucose leading to an increase in the electron donors NADH and $FADH_2$ and an accelerated electron flux through the mitochondrial inner membrane. This excess generates a higher proton threshold gradient across the mitochondrial membrane, partially inhibiting electron transfer from coenzyme Q (CoQ) to complex III. Electrons transferred to CoQ are instead released within the mitochondria and generate superoxide radicals ($O_2^{-\bullet}$) in the presence of molecular oxygen [93].

Further steps in hyperglycaemia-induced insulin resistance include the $O_2^{-\bullet}$ induced inhibition of glucose-6-phosphate-dehydrogenase, the key enzyme of the pentose phosphate pathway. NADPH, produced by the glucose-6-phosphate-dehydrogenase reaction, is the cell's principal reducing equivalent for the glutathione peroxidase-glutathione-reductase system [94]. Thus, an absence of this particular system may be a further contributor to oxidative stress in insulin resistance. As a reaction to respond to increased oxidative stress, mitochondria associated kinases are activated or phosphatases inhibited. One of these stress-sensitive kinases is protein kinase D (PKD). Once activated PKD stimulates the activation of nuclear genes encoding protective and antioxidant proteins. Another target of PKD is c-Jun N terminal kinase (JNK) [95]. JNK, synonymously known as stress-activated protein kinase, reduces glucose metabolism and induces insulin resistance by the serine phosphorylation of the insulin receptor β sub-unit, of the insulin receptor substrates and of AKT [96]. Serine instead of tyrosine phosphorylation of key molecules of the insulin signalling pathway is accepted as one main mechanism in building up insulin resistance. As likewise reported for pancreatic β-cells, the activation of JNK in insulin-sensitive tissues promotes nuclear translocation of the transcription factor FOXO to the nucleus, which again activates the transcription of the antioxidant enzymes manganese superoxide dismutase (MnSOD) and catalase (CAT) [97–99].

At this point it should be stated that insulin resistance may represent one important mechanism to protect insulin-sensitive tissues against exorbitant oxidative stress.

Insulin resistance and the importance of visceral fat and obesity. Increased levels of free fatty acids either derived from plasma or released from intracellular triglyceride stores are discussed as a further factor stimulating serine phosphorylation of critical proteins in the insulin signalling pathway via the activation of some isoforms of protein kinase c (PKC) and of JNK [100–102].

Obesity, frequently coexistant in type II diabetic humans and animals, may particularly promote the development of insulin resistance and diabetes, since adipose tissue is an important production site of a number of adipokines such as leptin, adiponectin, interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF α). Via various mechanisms these adipokines can contribute to the manifestation of insulin

resistance [103–108]. After binding of leptin to its hypothalamic receptor, α-melanocyte stimulating hormone (α-MSH) becomes activated and neuropeptide Y (NPY) signalling inhibited. The net effect is a suppression of food intake and an increase in energy expenditure. By these effects leptin helps to maintain whole body energy homeostasis, to prevent fat deposition in non-adipose tissues and to preserve insulin sensitivity. Normally leptin production mainly depends on the size of subcutaneous adipose tissue. In obesity, fat is predominantly stored in the abdomen. Abdominal adipose tissue produces less leptin compared to subcutaneous adipose tissue. One hypothesis with regard to a loss of control of energy homeostasis, of body fat stores and of insulin sensitivity suggests that a relative leptin deficit causes these effects [103]. Another hypothesis suggests that leptin directly increases insulin resistance via an increased serine phosphorylation of IRS1 [104].

Insulin resistance and inflammatory stress. The proinflammatory cytokine IL-6 could be shown to increase insulin resistance in muscle and liver by affecting insulin phosphorylation signalling at different sites. Thus, in skeletal muscle, IL-6 reduces insulin signalling by increasing IRS1 serine phosphorylation and activating PTP1B [105]. In liver the inactivation of STAT 3-signalling by serine phosphorylation seems to mediate the IL-6 generated insulin resistance [106]. As mentioned above, TNFα seems to reduce insulin sensitivity by an increase in IRS1 serine phosphorylation [107]. Moreover, TNFα reduces the expression of adiponectin, which is important for the preservation of insulin sensitivity [108].

The increased formation of advanced glycation end products (AGES) resulting from permanently high blood glucose levels are discussed to further contribute to an augmentation of insulin resistance. In skeletal muscle the activation of protein kinase C alpha (PKC alpha) by AGES seems to play a key role in the decrease of IRS1 tyrosine phosphorylation. A more detailed mechanism has not yet been investigated [109].

In contrast to type II diabetes (with or without obesity) different mechanisms seem to be involved in the generation of insulin resistance in gestational diabetes. Human placental lactogen (hPL) increases up to 30-fold throughout pregnancy and induces insulin release from the pancreas in pregnancy. Studies not involving pregnancy indicate that hPL can cause peripheral insulin resistance, although the results have been variable [110–112]. Another hormone recently implicated in the insulin resistance during pregnancy is human placental growth hormone (hPGH), which differs from pituitary growth hormone by 13 amino acids. hPGH increases 6–8-fold during gestation and replaces the normal pituitary growth hormone in the maternal circulation by week 20 of gestation [113]. Similarly to the well-documented effects of excess pituitary growth hormone on insulin sensitivity, overexpression of hPGH in transgenic mice to levels comparable with the third trimester of pregnancy causes severe peripheral insulin resistance [114]. Surprisingly, little work has been undertaken to identify the molecular mechanisms of insulin resistance in skeletal muscle in response to elevated hPL or hPGH. Recent evidence has shown that an important effect of hPGH is to specifically increase the expression of the p85 sub-unit PI3K in skeletal muscle. Studies in pregnant and non-pregnant humans [115,116] indicate that an increase in the p85 sub-unit of PI3K acts as a dominant-negative competitor in forming a PI3K heterodimer with the p110 sub-unit, thereby inhibiting PI3K activity and preventing downstream insulin signalling [117]. When obesity is present as an additional risk factor in pregnancy the increased secretion of adipokines from adipose tissue can cause the above-mentioned interferences with insulin signalling [103–108].

Survey of human and animal studies suggesting beneficial effects of Se in diabetes

The results of selected studies investigating beneficial effects of Se on diabetes in humans and animals are shown in Tables I and II [118–133]. With regard to human trials it is conspicuous that only very few studies report a genuine anti-diabetic effect of Se. Moreover, in humans hardly any placebo controlled intervention trial with an acceptable number of participants report on the beneficial effects of Se supplementation on diabetes. Furthermore, due to the substantial variation of experimental settings in the single trials (e.g. the Se concentration applied, health status of the participants) a valid comparison of data is not possible. Thus, for instance two single Se intervention trials which could be extracted from the literature recruited completely different subjects with regard to the state of diabetes (patients affected with a long-term diabetic late syndrome vs well controlled diabetic patients with a HbA1c value < 7 g/dL) [119,120]. In addition, in both studies the participants received different Se amounts during the 3 month intervention period. While in the first study 100 μg of Se per day was used, a dose comparable to that used in studies regarding cancer prevention, in the latter trial the recommended upper safe level for Se supplementation (400 μg/day) was exceeded by more than 2-fold during intervention [119,120]. However, in both studies beneficial effects of Se supplementation were reported with regard to a reduction of thiobarbituric acid reactive substances in the plasma. In the first trial, moreover, a reduction of renal albuminuria was found. In the latter trial it was reported that Se reduced diabetes associated inflammatory disorders (microangiopathy and

Table I. Human studies suggesting beneficial effects of Se on diabetes or other factors of the metabolic syndrome.

Type of diabetes, study design, human population considered	Selenium status by means of plasma Se (μg/L)	Results and conclusion	Reference
Type II diabetes, two groups: diabetic group with a disease duration ≤2 years (GP1), $n=20$; diabetic group with a disease duration between 4–6 years (GP2), $n=20$, healthy control (CG), $n=20$	GP1: 132±63.2, GP2: 38.7±22.9, CG: 141±20.5	Corresponding to the significantly lowered plasma Se concentration in group GP2 compared to GP1 and CG the activities of erythrocyte GPx1 and of plasma GPx3 were also significantly reduced in this group. Erythrocyte GPx1 (U/g Hb): GP1: 57.0±4.31, GP2: 24.0±8.94, CG: 67.6±4.29; GPx3 (U/L): GP1: 6.16±1.56, GP2: 2.67±0.47, CG: 8.72±0.31. It was concluded that untreated diabetes increases the generation of free radicals and lipid peroxidation and lowers antioxidant status.	[118]
Type II diabetes, three groups: well controlled diabetic group with a HbA1c <7 g/dL and Se intervention (DS), $n=21$; well controlled diabetic group receiving a placebo (DP), $n=27$, healthy control (H), $n=10$. Se status in the diabetic groups DS and DP was determined before and after the intervention with Se [960 μg/day from Granions de Selenium (selenite)] or placebo for 3 months and compared with untreated healthy subjects (H)	Before intervention: DS, 82.1±15.0; DP, 83.0±12.6; after intervention: DS, 100.3±14.2; DP, 76.6±13.4; Reference group H without intervention: 86.1±14.2	Although Se intervention in group DS significantly elevated plasma Se concentration compared with group DP, erythrocyte GPx1 activity in group DS increased only slightly to 44.8±8.7 U/g Hb compared to a value of 41.4±9.8 U/g Hb in group DP. Despite similar plasma Se levels in group H compared to the level in the diabetic groups DS and DP before intervention, erythrocyte GPx1 activity was the highest (47.4±9.8 U/g Hb) in this group. Independent of Se intervention the plasma TBA-RS values were ~ 15-times higher in groups DS and DP compared to group H. Se intervention in group DS reduced NF-kappa-B activity to the level in group H. Se supplementation for diabetics is recommended in order to reduce the risk of secondary diabetes complications (microangiopathy, nephropathy) which involve inflammatory reactions.	[119]
Type II diabetes, all participants had a diabetic late syndrome: $n=80$ were divided into four groups: untreated control (UC), $n=20$; α lipoic acid intervention (AI), $n=20$; vitamin E intervention group (EI), $n=20$; Se intervention with 100 μg Se as selenite (SI). All supplements were applied for 3 months	—	In comparison with group UC all treatment groups (AI, EI, SI) showed significantly diminished serum concentrations of thiobarbituric acid reactive substances and of urinary albumin excretion rates. It was concluded that oxidative stress plays a promoting role in developing of long-term diabetic late complications and that a therapy with adjuvant antioxidants may lead to a regression of diabetic late complications.	[120]
Gestational diabetes, one group: 22 healthy pregnant women were subjected to oral glucose tolerance tests (OGTT) at weeks 12 and 34 of pregnancy	Week 12: 126±15, week 34: 111±12	Plasma Se significantly decreased in the course of pregnancy. Fasting plasma glucose was not influenced by the changed Se status, whereas the 120 min blood glucose value during OGTT was significantly inversely related to plasma Se (week 12: 94.9±21.9 mg/dL, week 34: 125±28 mg/dL).	[121]
Gestational diabetes, three groups: healthy non-pregnant women (NW), $n=90$; normal pregnant women (NPW), $n=136$; women with gestational diabetes (GDM), $n=98$	NW: 108.0±17.0, NPW: 74.1±16.7, GDM: 63.5±12.0	NW had a significantly higher plasma Se concentration compared to NPW and GDM. Plasma Se decreased with the progress of pregnancy. Plasma Se values tended to be lower in GDM than in NPW. It was concluded that Se supplementation in pregnancy and in particular in women with gestational diabetes may be beneficial.	[122]

Table I (*Continued*)

Type of diabetes, study design, human population considered	Selenium status by means of plasma Se (μg/L)	Results and conclusion	Reference
Gestational diabetes; three groups: healthy pregnant women (HP), $n = 101$; pregnant women with impaired glucose tolerance (PI), $n = 49$; pregnant women with gestational diabetes (PD), $n = 30$. All recruited women were subjected to an oral glucose tolerance test between weeks 24 and 28 of gestation and allocated to the respective groups according to the result of the test	HP: 50.7 ± 9.8, PI: 39.9 ± 5.6, PD: 34.7 ± 8.7	HP had a significantly higher plasma Se concentration compared to PI and PD. Se supplementation during pregnancy is recommended.	[123]

nephropathy) based on the reduction of NFκB activity. Another trial investigating the connection between Se and type II diabetes resulted in a significant decrease of plasma Se concentration in patients with untreated diabetes over a period of 4–6 years. The authors conclude that increased oxidative stress during untreated diabetes leads to an exhaustion of antioxidative systems in the organism. Similarly large variations as reported for type II diabetes also exist for studies investigating the link between Se status and gestational diabetes. Although in the studies selected it was consistently reported that Se status decreases with progressing pregnancy and that gestational diabetes or impaired glucose tolerance are associated with a particularly low Se status, the large discrepancies in plasma Se concentration between the studies raise the question if a low Se status is one actual cause for gestational diabetes [121–123]. In this context, Se supplementation during pregnancy should be considered against the background of an obviously high Se transfer to the offspring rather than against the background of an increased risk of gestational diabetes.

In contrast to the few human studies investigating a protective role of Se supplementation in diabetes, a number of animal trials have been carried out on this topic. However, one important difference between the human trials and the animal trials is that most of the animal studies were carried out with rodents in which type I diabetes was induced with streptozotocin or alloxan [124–130,132]. Only a few studies exist on the treatment of type II diabetes with Se [39,133]. Another important aspect of the animal trials is that much higher doses of Se were applied to the animals. Thus, when the human study with a Se intervention of 960 μg per day [119] is compared to rat and dbdb mouse trials with the lowest Se dose used amongst the rodent studies (900 μg/kg body per day) [127,128,130,131,133], the dose per kilogram body weight administered to the rodents is $\sim$75-fold higher. Another important issue in the context of the antidiabetic effects of Se is that orally or intraperitoneally applied selenate (Se oxidation state +VI) is much more effective in correcting diabetic metabolic dysfunction (e.g. lowering blood glucose concentration, normalization of lipid metabolism) [124,125,133] compared to selenite (Se oxidation state +IV) or selenomethionine [126–131]. For selenite treatment of diabetic animals, more general benefits for various cellular processes which deteriorate in diabetes were found, e.g. the reduction of lipid peroxidation, the maintenance of osteoblast activity and protection from ER stress [126–128,131].

The following section discusses anti-diabetic mechanisms of high supranutritive Se doses and analyses differences in the effectiveness of different Se compounds in diabetes treatment.

Table II. Animal studies suggesting beneficial effects of Se on diabetes or other factors of the metabolic syndrome.

Experimental model (animals used)	Se compound used and applied concentration; experiment duration	Results	Reference
Rats with streptozotocin induced type I diabetes; four groups ($n=5$): control, diabetics insulin treated, diabetics selenate treated, diabetics vanadate treated.	Sodium selenate,15.0 μmol/kg body weight per day (=2.9 mg/kg body weight per day) was applied by intraperitoneal injection for 3 weeks.	Selenate treatment effected a strong reduction of plasma glucose close to the level reached in control rats (9.5 mmol/L) and increased glucose-6-phosphate-dehydrogenase and fatty acid synthase expression and activity to values measured in the control group.	[124]
Rats with streptozotocin induced type I diabetes; four groups ($n=8$): control, control selenate treated, diabetics untreated, diabetics selenate treated.	Sodium selenate, 13.0–23.8 μmol/kg body weight per day (=2.5–4.5 mg/kg body weight per day) was applied by intraperitoneal injection for 8 weeks.	Selenate strongly reduced plasma glucose, plasma triglycerides and cholesterol and achieved improvement of left atrial filling pressure.	[125]
Mice with alloxan-induced type I diabetes; five groups ($n=8$): control, control selenite treated; diabetics untreated, diabetics selenite treated, diabetics insulin treated.	Sodium selenite, 21.0 μmol/kg body weight per day (=4.0 mg/kg body weight per day) was applied orally for 4 weeks.	Selenite treatment doubled the Se concentration in plasma and liver to 150 and 300 μg/kg and affected a slight increase in erythrocyte GPx1 activity. Moreover liver TBA-RS were reduced by selenite compared to untreated diabetics. However, selenite application did not reduce blood glucose in diabetic mice. Six mice of the selenite treated controls died during the experiment and all selenite treated mice (diabetics and control) became blind.	[126]
Rats with streptozotocin induced type I diabetes; four groups ($n=6$): control, control selenite treated, diabetics untreated, diabetics selenite treated.	Sodium selenite, 5.0 μmol/kg body weight per day (=0.90 mg/kg body weight per day) was applied by intraperitoneal injection for 5 weeks.	Compared to untreated diabetics, selenite application slightly but significantly reduced blood glucose concentration. Selenite rescued the number of active osteoblasts which had been reduced by diabetes. As the result of saving osteoblast activity the injection of selenite increased the number of newly formed trabeculae.	[127]
Rats with streptozotocin induced type I diabetes; four groups ($n=7$–16): control, control selenite treated, diabetics untreated, diabetics selenite treated.	Sodium selenite, 5.0 μmol/kg body weight per day (0.90 mg/kg body weight per day) was applied by intraperitoneal injection for 5 weeks.	Selenite reduced diabetes-induced weight loss and lowered the activities of glutathione-S-transferases, glucose-6-phosphate-dehydrogenase and 6-phosphogluconate-dehydrogenase in the heart close to the level in controls and selenite treated controls. Blood glucose concentration was reduced slightly but significantly in selenite treated diabetic rats (460 ± 19.0 mg/dL) vs 407 ± 18.1 in untreated diabetics. Intriguingly in healthy rats blood glucose significantly increased due to selenite treatment (127 ± 4.21 vs 109 ± 3.14 mg/dL).	[128]
Hamsters with streptozotocin induced type I diabetes; five groups ($n=9$); Control chow, HFD low Se+low GSH, HFD low Se+high GSH, HFD high Se+low GSH, HFD high Se+high GSH.	High fat diet (HFD) containing Se from selenium yeast (72 μmol Se/kg diet =5.75 mg Se/kg diet) either alone or in combination with high glutathione (40 mg/kg diet); 3 month feeding trial; According to an uptake of $\sim$ 2.0 mmol/kg body weight.	High Se either alone or in combination with high GSH significantly reduced plasma triglycerides (23.5 mg/dL, 26.2 mg/dL) and glucose (200 mg/dL, 236 mg/dL) compared to companions on low Se diets with low or high GSH (triglycerides: 63.1 mg/dL, 100 mg/dL; glucose: 263 mg/dL, 244 mg/dL).	[129]
Rats with streptozotocin-induced type I diabetes; four groups ($n=8$): control, diabetic control, diabetics selenate treated, diabetics selenomethionine treated.	Sodium selenate, 4.8 μmol/kg body weight per day (= 0.91 mg/kg body weight per day) and selenomethionine 5.0 μmol/kg body weight per day (= 0.99 mg/kg body weight per day) was applied by tube feeding for 12 weeks.	Neither selenate nor selenomethionine treatment reduced blood glucose concentration significantly compared to the diabetic control group. Only selenomethionine lowered blood glucose in tendency. Selenomethione elevated plasma Se concentration more significantly than selenate, whereas erythrocyte GPx1 activity was influenced on the contrary by both Se compounds.	[130]

Table II (*Continued*)

Experimental model (animals used)	Se compound used and applied concentration; experiment duration	Results	Reference
NOD mice from which ~ 30% naturally develop type I diabetes; four groups ($n=4$): non-diabetic control, non-diabetic control selenite treated, diabetics untreated, diabetics selenite treated.	Sodium selenite, 5.0 μmol/kg body weight per day (= 0.90 mg/kg body weight per day) was applied by intraperitoneal injection for 3 weeks.	In non-diabetic mice selenite treatment showed no influence on body weight, plasma glucose and plasma insulin levels. Selenite-treated diabetic mice had a higher body weight compared to their untreated littermates. Selenite treatment of diabetic mice reduced plasma cholesterol and triglyceride levels as well as the activity of AP, ALT and AST. Selenite treatment of diabetics altered protein expression and phosphorylation status of IRE1, a protein related to endoplasmatic reticulum stress and of iEF2, an important factor in the initiation of eukaryotic protein translation.	[131]
Rats with streptozotocin induced type I diabetes; four groups ($n=6$): control, control selenate treated, diabetics untreated, diabetics selenate treated.	Sodium selenate, 15.0 μmol/kg body weight per day (= 2.9 mg/kg body weight per day) was applied by tube feeding for 4 weeks.	Selenate treatment reduced diabetes-induced proliferation signalling by reducing the phosphorylation of the 42 kDa MAPK sub-unit and increased the activity of Na+/K+ ATPase. Moreover, selenate lowered the expression of caveolin, an eNOS inhibitor.	[132]
Db/db mice suffering from obesity, insulin resistance and type II diabetes as a consequence of the defective leptin receptor; three groups ($n=7$): Se deficient, selenite treated, selenate treated.	Sodium selenite and sodium selenate, 5.0–11.5 μmol/kg body weight per day (=up to 2.10 and 2.28 mg/kg body weight per day) were applied by tube feeding for 8 weeks.	Only selenate application preserved insulin sensitivity at the initial level and strongly reduced the activity and expression of gluconeogenic marker enzymes. The reduction of liver PTP1B activity by selenate treatment to 50% compared with Se deficient and selenite treated mice provides a plausible explanation for the altered insulin sensitivity. *In vitro* tests showed that anti-diabetic effects of Se only evolve from high oral selenate doses.	[39]
Db/db mice suffering from obesity, insulin resistance and type II diabetes as a consequence of the defective leptin receptor; three groups ($n=7$): Se deficient, selenite treated, selenate treated.	Sodium selenite and sodium selenate, 5.0 μmol/kg body weight per day (=0.90 and 0.98 mg/kg body weight per day) were applied by tube feeding for 10 weeks.	Selenate but not selenite treatment ameliorated insulin sensitivity. The insulin sensitivity of selenate treated mice could be preserved at the initial level, whereas the insulin sensitivity in Se deficient and selenite treated mice worsened to a similar extent until the end of the study. Corresponding to these results the activity of the glycolytic marker enzymes, hexokinase, phosphofructokinase and pyruvate kinase in the liver increased due to selenate treatment, whereas the activity of the gluconeogenic marker enzymes glucose-6-phosphatase, fructose-1,6-bisphosphatase and pyruvate carboxylase decreased.	[133]

Hypotheses on anti-diabetic mechanisms of selenium

Insulin-like effects of selenium. The anti-diabetic features of Se in humans and animals as shown above strongly suggest that genuine effects of Se on glucose metabolism or on other insulin-controlled metabolic pathways such as lipid metabolism can only be achieved with very high and nearly toxic Se concentrations. In this section possible molecular mechanisms for insulin-like effects of Se will be elaborated. The first observations on the insulin-like effects of Se were made in rat adipocytes. The incubation of these cells with selenate (Se oxidation state + VI) in concentrations ranging from 100 μmol/L to 1 mmol/L resulted in a stimulation of glucose transport in a concentration-dependent manner. The 100 μmmol/L concentration thereby was equipotent to 1 nmol/L insulin. In contrast, treatment of cells with equal concentrations of selenite (Se oxidation state + IV) was less effective. In this experiment the stimulation of glucose transport into adipocytes could be attributed to an augmentation of the phosphorylation of the insulin receptor β sub-unit (95 kDa) and of other endogenous proteins with molecular weights of 60 and 170 kDa. The 170 kDa band presumably corresponded to IRS1. In addition, the phosphorylation of ribosomal S6 kinase was significantly increased by selenate treatment.

The next topic examined in this fundamental study on insulin-like effects of Se was to test if the increased phosphorylation of the insulin receptor β sub-unit is the result of the activation of receptor tyrosine kinase activity rather than of the inhibition of insulin signal antagonizing protein tyrosine phosphatases. However, when both hypotheses were checked in cell free systems, selenate neither stimulated tyrosine kinase activity nor inhibited protein tyrosine phosphatase activity. An explanation for this lies in the nature of Se metabolism and will be discussed in detail later in this section [134]. Further studies with NIH3T3 fibroblasts and in primary rat adipocytes confirmed both the concentration range and the increased phosphorylation of the insulin receptor β sub-unit as well as other downstream signalling proteins due to selenate treatment [135–137].

As likewise suggested by the data of the above-mentioned cell culture studies also in type I and type II diabetic animals (Table II) [39,124,125,133] the strongest anti-diabetic effects of Se appear to be exerted by the application of high oral or interperitoneal doses of selenate. Thus, a potent reduction of blood glucose concentration in type I diabetic rats was obtained with the application of selenate concentrations > 13 μmol/kg body weight [125,126]. Also in insulin-resistant type II diabetic dbdb mice, lower oral selenate doses (5 μmol/kg body weight) have beneficial effects on insulin sensitivity and on the regulation of some glycolytic and gluconeogenic enzymes [133]. A significant reduction of blood glucose concentration could, however, not be achieved until selenate doses of 11.5 μmol/kg body weight were used [39]. In accordance with the results of the above-mentioned experiment with adipocytes, the effect of selenite treatment seems to be much less pronounced also in diabetic animals. In both studies with type II diabetic dbdb mice and a study with type I diabetic mice, high selenite doses of 11.5 and 21 μmol/kg body weight, respectively, remained without influence on insulin sensitivity and blood glucose concentration [39,126,133]. The authors of the latter study achieved a beneficial influence of selenite treatment on the reduction of TBA-RS. However in this particular study all selenite treated mice became blind [126]. Similarly the results of further studies with type I diabetic animals show that selenite in contrast to selenate fails to reduce blood glucose concentration potently [127,128,131].

Modelling anti-diabetic effects of selenium compounds. Only few studies exist with regard to the anti-diabetic effects of selenomethionine. In one experiment selenomethionine application (5 μmol/kg body weight) to type I diabetic rats lowered blood glucose concentration only slightly [130]. In the same experiment, 4.8 μmol selenate/kg body weight had no lowering effect on blood glucose, which is in accordance with the data from an experiment with dbdb mice [39]. In another trial with type I diabetic hamsters fed ~2 μmol Se in form of Se yeast in combination with high dietary GSH led to a small but significant decrease in blood glucose concentration compared to a group with low dietary Se and GSH concentrations [129]. The results of the studies with cell cultures and with model animals, however, uniquely demonstrate that only very high Se concentrations which cannot be applied to humans exert some genuine anti-diabetic effects. Amongst the different Se compounds, selenate is most effective in reducing blood glucose concentration and in changing other metabolic pathways impaired in diabetes. The anti-diabetic effects of selenite and selenomethionine seem to be less distinct. However, currently the availability of data for selenomethionine is limited compared to data for selenate and selenite. The variation in effectiveness of high doses of selenite, selenate and selenomethionine in the treatment of diabetes is, in our opinion, the consequence of fundamental differences in the absorption and the intermediary metabolism of the different Se compounds. Among Se compounds, selenate may exert the strongest insulin-like features due to its unmodified uptake through the small intestine into the organism [41]. During its reduction in peripheral organs the following reactions resulting in an inhibition of the insulin signal antagonizing PTP1B are feasible (Figure 4A).

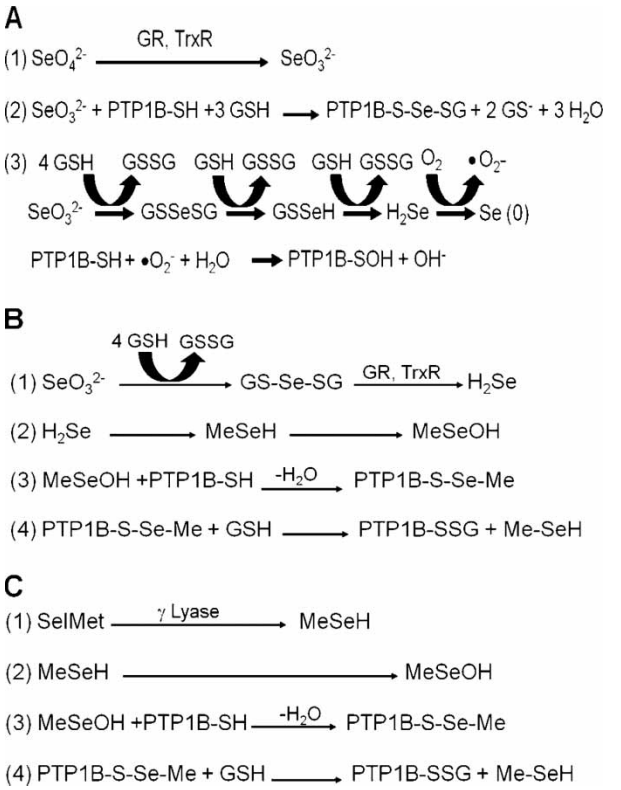

Figure 4. Reactions by which high supranutritional doses of selenate, selenite and selenomethionine may exert anti-diabetic effects. SeO_4^{2-} = selenate, SeO_3^{2-} = selenite, SelMet = selenomethionine, GSH = reduced glutathione, GSSG = oxidazed glutathione (glutathione disulphide), GSSeSG = selenodiglutathione, H_2Se = hydrogen selenide, MeSeH = methylselenol, MeSeOH = methylselenenic acid, GR = glutathione reductase, TrxR = thioredoxin reductase, $\bullet O_2^-$ = superoxide anion radical, PTP1B-SH = active form of PTP1B with reduced Cys215 residue, PTP1B-S-Se-SG = trisulphide intermediate of PTP1B, PTP1B-SOH = sulphenic acid intermediate of PTP1B, PTP1B-SSG = glutathionylated PTP1B.

Selenate. In the first reaction step the unreactive selenate (oxidation state + VI) is reduced in a GR- or TrxR-dependent reaction to the highly thiol reactive selenite (oxidation state + IV). In the further course, selenite can react with protein thiol groups (e.g. the catalytic active cysteine 215 of PTP1B) to a selenotrisulfide intermediate (PTP1B-S-Se-SG), which can be assumed as being catalytically inactive. Excess selenite reacts with GSH to hydrogen selenide. In the further course of the reaction in the presence of oxygen, superoxide anion radicals ($O_2^{-\bullet}$) and elemental Se are formed. The superoxide radical again can attack the active site cysteine 215 of PTP1B and oxidize it to the catalytically inactive sulfenic acid derivative (R-Se-OH) [138,139] (Figure 4A).

The increased phosphorylation of the insulin receptor β sub-unit and of other downstream proteins of the insulin signalling pathway by selenate treatment therefore seems to be based on the inhibition of protein tyrosine phosphatases rather than on kinase activation. These hypotheses about the strong insulin-like effects of selenate are also consolidated by the results of the adipocyte study in which selenate in a cell free system did not inhibit protein tyrosine phosphatase activity, since selenate *per se* is unreactive towards protein thiols [39,140]. In accordance with these hypotheses a dbdb mouse study also did not show any inhibition of PTPs by selenate, but a very powerful PTP inhibition by selenite as measured in an *in vitro* protein tyrosine phosphatase inhibition assay. Thus, with regard to the inhibition of PTPs both the *in vivo* selenate application and selenate treatment of living cells match the *in vitro* effects of thiol reactive selenite [39,140].

Selenite and selenomethionine. The much weaker insulin-mimicking and anti-diabetic effects of selenite and selenomethionine may be explained by their particular metabolism. Compared to selenate, selenite already reacts during its absorptions with thiol compounds, such as GSH, to form selenodiglutathione (GSSeSG) or proteins forming selenotrisulphides (RSSeSR). Thus, selenite-derived Se metabolites delivered to tissues are GSSeSG, RSSeSR or hydrogen selenide (H_2Se). A hypothetical pathway by which orally-administered selenite can at least influence the activity of PTP1B involves the formation of methylselenenic acid (MeSeOH) from methylselenol (MeSeH), which can be produced by the methylation of hydrogen selenide (H_2Se), obtained from the complete reduction of selenite [47,48]. Methylselenenic (MeSeOH) acid may modify the active site cysteine from PTP1B and redound to inactive glutathionylated PTP1B by the release of methylselenol (MeSeH) in the presence of glutathione [141] (Figure 4B). A similar modification of PTP1B can be assumed to occur with selenomethionine, since methylselenol can be released from selenomethionine by methionine-γ-lyase and oxidized to MeSeOH [47,48,141] (Figure 4C).

In conclusion the most effective anti-diabetic properties of selenate may derive from a PTP1B inhibition due to intermediary selenite- and superoxide generation from high selenate doses. The hypothetical inhibition of PTP1B by methylselenol derived from oral selenite and selenomethionine seems to be less effective. Further studies using Se species analysis and proteomic techniques are desirable to investigate the detailed chemical and biochemical mechanisms of how Se compounds can inhibit enzymes with catalytically active cysteine-SH residues as well as interactions of Se metabolites with sulphur containing cellular proteins. However, it should again be considered that insulin-mimicking and anti-diabetic effects of Se can only be obtained with toxicological doses of Se which cannot be given to humans.

Table III. Human studies suggesting rather critical effects of Se on diabetes or other factors of the metabolic syndrome.

Study design, human population considered	Selenium status by means of plasma Se (μg/L)	Results and conclusion	Reference
Type I diabetes, two groups: diabetics ($n=27$, 16 girls, 11 boys, aged 5–18), non-diabetic control ($n=13$, aged 5–18).	Diabetics: 74.0 ± 8.0, non-diabetic control: 65.0 ± 8.0	Diabetics had significantly higher plasma Se values. Age and sex of the children within one group had no influence on the altered Se status. It was concluded that plasma Se increases due to higher oxidative stress in diabetes.	[141]
Type I diabetes, four groups: Hungarian children with type I diabetes (HD), $n=40$; Healthy Hungarian children (HH), $n=38$; German children with type I diabetes (GD), $n=18$; Healthy German children (HG), $n=16$. Blood was withdrawn in the fasting state and Se status as well as parameters of lipid metabolism were determined.	Whole blood Se: HD, ~102; HH, ~88; GD, 139; HG, ~110. Plasma Se: HD, ~79; HH, ~63; GD, ~95; HG, ~75	Se concentration in whole blood and in plasma was significantly lower both in HD and HH compared with the respective German groups (GD and HG). In both populations Se values in whole blood and in plasma of diabetics (HD, GD) were significantly higher than in healthy controls (HH, HG). The Se values in whole blood and plasma corresponded to GPx3 activity. A highly positive correlation existed between Se status and plasma triglyceride concentration (e.g. HD: 0.62 ± 0.23 mmol/L, HH: 0.39 ± 0.11 mmol/L).	[142]
Type I diabetes, two groups: diabetic children (DC), $n=237$, healthy control (HC), consisting of 107 siblings of DCs and 107 other healthy children. The influence of a nationwide agricultural Se fertilization programme on the Se status of the participants was tested.	Initial Se status: DC: ~78, HC: ~65. Se status after 6 years of agricultural Se fertilization: DC: ~107, HC: ~105	Se fertilization abolished differences in Se status between diabetics and non-diabetics. Thus Se status cannot considered as a diabetes marker.	[143]
Fasting plasma glucose (SU.VI.MAX), placebo-controlled, double-blind intervention trial originally designed to examine the preventive effect of antioxidants on the reduction of cardiovascular diseases and cancer; two groups: intervention group ($n=1613$) receiving a combined supplementation of 120 mg vitamin C, 30 mg vitamin E, 6 mg β carotene, 100 μg Se from Se enriched yeast and 20 mg zinc/day for up to 7.5 years; placebo group receiving none of the supplements.	Baseline in all groups: 88.3 ± 15.6	The results do not provide information on the plasma concentration of the supplemented nutrients after 7.5 years. Multiple regression analysis showed a highly significant correlation between fasting blood glucose and plasma Se, whereas negative correlations were analysed for β-carotene and vitamin C. A general supplementation with antioxidants including Se is not recommended since even adverse effects on cancer and metabolic disease cannot be excluded.	[144]
Type II diabetes (NHANES III), cross-sectional study including 8876 adult participants ≥20 years with conventional nutrition. Blood samples for glucose determination were withdrawn after 8 h of fasting. Prevalent diabetes was defined as a fasting plasma glucose ≥ 126 mg/dL, the self-report of a physician diabetes diagnosis or current use of insulin or oral hypoglycaemic medication.	Quintile 1: <111.6; Quintile 5: ≥137.6	Plasma Se status positively correlated with diabetes prevalence. Diabetes prevalence in quintile 5 was 1.60-fold higher compared to quintile 1. An additional Se supplementation was not recommended.	[145]
Metabolic syndrome (hyperlipidemia) [NHANES III], cross-sectional study including 5452 adult participants ≥20 years with conventional nutrition. Blood samples for the determination of lipid parameters were withdrawn after 9 h of fasting.	Quintile 1: <113.7; Quintile 5: ≥134.7	In quintile 5 all measured serum lipid parameters were significantly higher compared to quintile 1: Total cholesterol: 208.8 mg/dL vs192.6, LDL cholesterol: 131.1 mg/dL vs 120.1, HDL cholesterol: 52.1 mg/dL vs 49.1, apoB: 106.2 mg/dL vs 99.8, apoA-1: 147.8 mg/dL vs 140.0. An additional Se supplementation was not recommended.	[146]

Table III (*Continued*)

Study design, human population considered	Selenium status by means of plasma Se (μg/L)	Results and conclusion	Reference
Type II diabetes (NPC), placebo controlled intervention trial to examine the protective effect of Se against non-melanoma skin cancer, two groups: intervention group ($n=600$) receiving 200 μg Se from Se yeast/day for 7.7 years; placebo group ($n=602$) receiving no Se supplement. At baseline none of the selected participants had a history of diabetes.	Placebo group at baseline and at the end of intervention ≤ 120; in the Se supplemented group at baseline 114 and ≥ 120 ($\sim$ 140–150) at the end of the intervention	In the selected participants at the 7.7 year follow-up a total number of 97 cases of type II diabetes were diagnosed from which 39 developed in the placebo group and 58 in the Se supplemented group. These data suggest a 1.5-fold higher incidence of diabetes by the use of Se supplements in the examined period of time. The calculated hazard ratio of 2.5 for Se supplements was even higher. An additional Se supplementation in populations with an already high Se status is not recommended.	[147]
Type II diabetes (SELECT), randomized placebo controlled intervention study, originally carried out to examine the effects of Se and vitamin E (VE) on the prevention of prostate cancer, four groups: Se intervention group ($n=8752$) receiving 200 μg Se from selenomethionine/day for up to 7.3 years; VE intervention group receiving 400 mg α-tocopheryl acetate/day ($n=8737$); Se and VE intervention group receiving both supplements ($n=8703$); placebo group receiving no supplements ($n=8696$).		In October 2008 the SELECT study was discontinued since both supplements showed no beneficial effect for the prevention of prostate cancer. VE even tended to increase the incidence of prostate cancer. With regard to diabetes incidence a slight but not significant increase ($p=0.16$) could be diagnosed in the Se group. For VE supplementation and combined Se and VE supplementation a very small increase and decrease for diabetes incidence were observed.	[148]
Type II diabetes, three groups: non-diabetic control (NC), $n=50$; diabetics (DM), $n=50$, diabetics with diabetic foot (DF), $n=50$.	Not determined	Erythrocyte GPx1 values and 8-OH-dG values were $\sim$1.3- and 1.5-fold higher in the DM and DF group compared to the NC group. It was concluded that increased GPx1 activities result from a higher need to protect against diabetes-induced lipid peroxidation.	[149]
Type II diabetes (metabolic syndrome), cross-sectional study including 398 adult participants from the Lebanon: 159 men, 285 women. 0.6% of the men were underweight, 45.3% overweight and 28.3% obese. 3.4% of the women were underweight, 29.4% overweight and 25.2% obese. Blood samples were collected and analysed for selenium-, copper- and zinc-status and for markers of metabolic syndrome.	Mean blood glucose concentration was 97.5 ± 22.6 in men and 90.0 ± 22.1 in women	Mean plasma Se concentration was 151 ± 25.7 in men and 135 ± 24.4 in women. Plasma Se concentration correlated positively and significantly with the following markers of metabolic syndrome: waist circumference, plasma total cholesterol, plasma triglycerides, plasma glucose, systolic and diastolic blood pressure.	[150]
Type II diabetes, two groups: healthy control group (ND), $n=50$; type II diabetics (D), $n=53$. The status of seven trace elements including Se; none of the participants used mineral supplements.	Plasma Se: ND, 86.3 ± 24.4; D, 91.0 ± 22.9. Whole blood Se: ND, 83.9 ± 23.6; D, 91.5 ± 22.2	Both the Se concentration in plasma and in whole blood tended to be higher in diabetics compared to the healthy control.	[151]
Gestational diabetes, three groups: non-pregnant healthy controls (HC), $n=24$; healthy pregnants (HP), $n=20$; women with gestational diabetes (GD), $n=17$.	HC: 77.4 ± 14.82, HP: 40.5 ± 8.03, GD: 51.7 ± 11.62	High-sensitive-C-reactive protein (hsCRP) was $\sim$ 6-fold higher in HP and GD compared to HC.	
		Fasting glucose, the 120 min blood glucose value after a glucose challenge, total plasma cholesterol and plasma triglycerides were highest in the GD group. HsCRP concentration correlated positively and significantly with the height of the metabolic parameters investigated. Plasma Se tended to correlate positively with the metabolic parameters when groups HP and GD were compared.	[152]

Table III (*Continued*)

Study design, human population considered	Selenium status by means of plasma Se (μg/L)	Results and conclusion	Reference
Gestational diabetes, one group ($n = 408$) of women screened at the beginning and in the 3rd trimester of pregnancy for erythrocyte GPx1 activity and metabolic parameters of glucose metabolism and insulin resistance.		Erythrocyte GPx1 activity significantly increased in the course of pregnancy. The height of erythrocyte GPx1 activity was positively and significantly correlated with fasting blood glucose, plasma insulin, plasma insulin C-peptide and with the HOMA insulin resistance index.	[153]
Gestational diabetes; two groups: pregnant obese women without gestational diabetes (C), $n = 11$; pregnant obese women with gestational diabetes (GD), $n = 10$; Blood samples were withdrawn after spontaneous delivery or caesarean section.	C: 85.3 ±4.4, GD: 88.3 ±5.2	Plasma Se concentration was elevated in tendency in the group GD compared to group C and corresponded to an increased GPx1 activity (C: 8115 ± 1707 U/L, GD 10711 ± 3015 U/L).	[154]

Survey of human and animal studies suggesting a rather critical role of Se in diabetes

The results of selected studies suggesting rather critical effects of Se on diabetes in humans and animals are shown in Tables III and IV [140,142–157]. Intriguingly the number of studies reporting on rather adverse effects of a high Se status or of a permanent Se supplementation on diabetes and/or metabolic syndrome is distinctly higher than the number of studies indicating positive effects. The existing studies include results for type I diabetes, for type II diabetes and metabolic syndrome, as well as for gestational diabetes. However, the previously mentioned studies reporting on positive effects of Se on diabetes as well as the large number of studies showing a critical influence are often flawed in their experimental setup. Thus, all trials examining the connection between Se and type I diabetes merely examine the relation of plasma (serum) Se concentration and blood glucose control [140,142,143]. For type I diabetes, however, no intervention trials exist investigating the influence of Se on the disease. Only one study reports that type I diabetic children had higher plasma Se concentrations compared to healthy controls. After a 'semi-intervention' by the uptake of Se fertilized grain for 6 years, differences in Se status between the groups have disappeared [140]. The data of trials investigating the influence of Se on the prevalence or development (incidence) of type II diabetes are more relevant. In particular over the last 3 years a number of studies, which included large populations, have reported on a negative influence of Se supplementation and a high Se status on blood glucose regulation. In addition, these studies used Se intervention [144,147,148]. For example, in the study 'Supplementation en Vitamines et Mineraux Antioxydants' (SU.VI.MAX.) an intervention with combined vitamin C, vitamin E, β carotene and 100 μg Se was carried out [144]. In the 'Nutritional Prevention of Cancer Trial' (NPC) and in the 'Selenium and Vitamin E Cancer Prevention Trial' (SELECT), Se supplementation was 200 μg/day [147,148]. In this context it should be mentioned that the SELECT trial was abandoned early, in autumn 2008, since no effects of vitamin E and Se could be noted with regard to cancer prevention and Se supplementation was analysed as a factor slightly increasing diabetes risk [148]. Another study, including a large population, which investigated a positive correlation between a high Se status and diabetes prevalence and increased serum lipids, respectively, is the NHANES III trial. In contrast to the above-mentioned studies the NHANES III trial is not an intervention trial, but is based on conventional nutrition [145,146]. Besides the NPC trial a number of other non-intervention trials exist reporting on a positive correlation between a high Se status and

Table IV. Animal studies suggesting rather critical effects of Se on diabetes or other factors of the metabolic syndrome.

Experimental model (animals used)	Se compound used and applied concentration; experiment duration	Results	Reference
Wild type black 6 mice (WT, $n=40$) and black 6 mice with GPx1 over-expression (OE, $n=40$) were fed a commercial diet for 24 weeks and then subjected to different tests for insulin resistance and diabetes. Moreover body fat concentration was analysed.	The diet contained adequate sodium selenite (0.4 mg/kg diet) for optimum selenoprotein synthesis	In the OE mice GPx1 activity in the liver and in skeletal muscle was 0.5- and 3.0-fold higher compared to WT mice. The OE mice were 37% heavier (37 vs 27 g) and had 20% more body fat (37% vs 17%) than the WT mice. Plasma insulin and plasma glucose concentration were 3.2-fold and 27% higher in OE mice than in their WT littermates. Established insulin resistance in OE mice could be detected by a significantly reduced phosphorylation of the b sub-unit of the insulin receptor and of Akt after an insulin challenge test.	[155]
Healthy weaned albino rats ($n=49$) were divided into seven groups of seven. Se status, selenoenzymes, the regulation of the insulin antagonistic PTP1B and liver lipids were analysed after 8 weeks on the particular diets.	Group 0 Se received a Se deficient diet. The diets of the other six groups were supplemented with sodium selenite or sodium selenate at the recommended level (0.2 mg Se/kg) and at two supranutritional levels (1.0 and 2.0 mg Se/kg)	All Se supplemented rats had significantly higher body weights compared to 0 Se rats. Liver and plasma Se concentration gradually increased by raising the dietary Se concentration. Liver GPx1 activity in 0Se rats was decreased to $\sim$ 1% of that in Se supplemented rats. The saturation of GPx1 activity and mRNA levels was already obtained with 0.2 mg Se/kg diet. Liver triglyceride concentration was the lowest in 0 Se rats and increased with increasing dietary Se concentration. The insulin antagonistic PTP1B had the lowest activity in group 0 Se and gradually increased by raising the dietary Se concentration. This result could be attributed to a higher inhibition of PTP1B in group 0Se by glutathionylation.	[156]
Healthy weaned albino rats ($n=30$) were divided into three groups of 10. Se status, selenoenzymes, the regulation of the insulin antagonistic and lipogenic PTP1B and liver lipids were analysed after 8 weeks on the particular diets.	Group NC (negative control) received a Se deficient diet. The diets of the other two groups (Se75 and Se150) were supplemented with sodium selenate at half the recommended dietary level (0.075 mg Se/kg) and at the recommended dietary amount (0.15 mg Se/kg)	Se supplemented rats had significantly higher body weights compared to 0 Se rats. Liver Se concentration gradually increased due to an increase in dietary Se concentration. Already at half the recommended dietary Se concentration a nearly saturated GPx1 activity and expression in the liver was measured. Due to a higher inhibition of the lipogenic PTP1B by glutathionylation in group 0 Se the enzyme activity was significantly lower than in the Se supplemented groups. Liver triglyceride concentration was the lowest in group NC (52.7 ± 14.1 μmol/g dry matter) and increased gradually by raising the dietary Se concentration (Se75: 111 ± 22.8, Se150: 127 ± 29.5). The increase in liver triglyceride concentration could be attributed to the increase in PTP1B activity and of its downstream target the lipogenic transcription factor SREBP-1c.	[157]

markers of diabetes and the metabolic syndrome [149–151]. The data with regard to a critical role of Se in gestational diabetes is somewhat ambiguous. According to studies reporting a protective role of Se in gestational diabetes, one study also finds a distinct depletion of plasma Se concentration during the course of pregnancy. However, in contrast to the first mentioned studies, in this particular study women with gestational diabetes had a higher Se status compared to healthy pregnant women [152]. In complete contrast, two other studies report an increase of erythrocyte GPx1 activity in the course of pregnancy and a higher plasma Se concentration combined with a higher erythrocyte GPx1 activity at the end of pregnancy [153,154].

Hypotheses on pro-diabetic mechanisms of selenium

In recent years, in particular for humans, critical effects of a high Se status on metabolic disorders have been reported. It is therefore of special interest how a long-term Se supplementation may accelerate the development of insulin resistance, diabetes or dyslipidemia. Although the data from the above-mentioned human studies describe a positive correlation between high serum Se concentrations or a high activity of GPx1 and diabetes or dyslipidemia they provide no plausible explanation for the underlying molecular mechanisms. Thus, the authors investigating the link between a high serum Se concentration and hyperlipidemia conclude: 'Experimental studies are needed to determine cause and effect relations and the potential mechanisms underlying these associations' [146]. Four recent animal studies have investigated potential pathways behind adverse effects of Se and selenoproteins on the development of obesity, insulin resistance and hyperlipidemia [82,155–157]. As discussed in detail above, a massive increase in β-cell mass and insulin production due to a high GPx1 activity may represent one essential mechanisms contributing to the early development of the above-mentioned diseases [82]. Whereas massive oxidative modification or thiol modification of PTP1B seems to provide a plausible explanation for insulin-like and anti-diabetic effects of very high Se doses, a changed physiological PTP1B regulation may underlie a further important mechanism of Se on the accelerated generation of obesity, insulin resistance and hyperlipidemia. In a mouse study the over-expression of GPx1, representing the most important antioxidative selenoprotein, had a number of metabolic consequences. GPx1 over-expressing mice became obese and had a significantly higher body fat content. Moreover GPx1 over-expressing mice developed severe insulin resistance. As proof for the increased insulin resistance in GPx1 over-expressing mice the authors found a decreased tyrosine phosphorylation of the insulin receptor β sub-unit and of AKT [155]. Presumably this effect on tyrosine phosphorylation is based on a reduced inhibition of PTP1B due to the augmented H_2O_2 rather than representing a direct influence on tyrosine phosphorylation [156,157]. An up-regulation of PTP1B expression together with an increase in intrinsic insulin resistance was also observed in mice over-expressing catalase [158]. In contrast, mice with a selenoprotein P knockout and consequential lack of peripheral GPx1 synthesis were emaciated [159].

According to these findings, studies with rats in which GPx1 activity was varied by a manipulation of dietary Se intake revealed that rats fed with lower dietary Se had a significantly lower body weight compared to companions with diets containing an adequate or a slightly supranutritive Se concentration. Moreover, Se-poor nutrition resulted in a significantly lower liver fat and triglyceride concentration. As the mechanism behind this lipid lowering effect, a significantly lowered activity of the insulin signal antagonizing and lipogenic PTP1B was found which was caused by an increased inhibition of the enzyme by glutathionylation due to a low liver GPx1 activity [156,157].

Apart from modulating the PTP1B activity by exogenously applied agents or by use of siRNA techniques [160–169], a number of recent investigations have focused on the physiological inhibition of PTP1B via oxidation of the active site cysteine residue, Cys125, by H_2O_2 and reactive oxygen species in the presence of glutathione. PTP1B activity can be partially recovered by dithiothreitol (DTT) which reduces the sulphenic acid intermediate (PTP1B-SOH) and glutathionylated enzyme (PTP1B-SSG). Two investigations using mass spectrometry further elucidated the stepwise oxidation of cysteine 215 in PTP1B by H_2O_2. The cysteine sulphenic acid can be oxidized further to irreversibly oxidized derivatives like cysteine sulphinic acid (PTP1B-SO_2H)[0] and cysteine sulphonic acid (PTP1B-SO_3H).

A possible way to prevent the formation of irreversibly oxidized derivatives is the cyclization to an internal sulphenyl amide with Ser-216 followed by the reaction with glutathione. This particular formation of a mixed disulphide between Cys-215 of PTP1B and GSH (or GSSG) is termed 'glutathionylation' [170–178] and is presumably catalysed by pi class glutathione-S-transferases [175,176].

The direct reaction of the reduced Cys 215-SH with high concentrations of GSSG (>25 mM) may also rebound to glutathionylated PTP1B [31]. This reaction however seems to be not of physiological relevance, since such high concentrations of GSSG cannot be reached *in vivo* [177].

Thus, permanent Se supplementation may increase the risk of obesity, insulin resistance, diabetes and hyperlipidemia by maintaining permanently high activities of glutathione peroxidases, in particular of GPx1, which may weaken the physiological inhibition

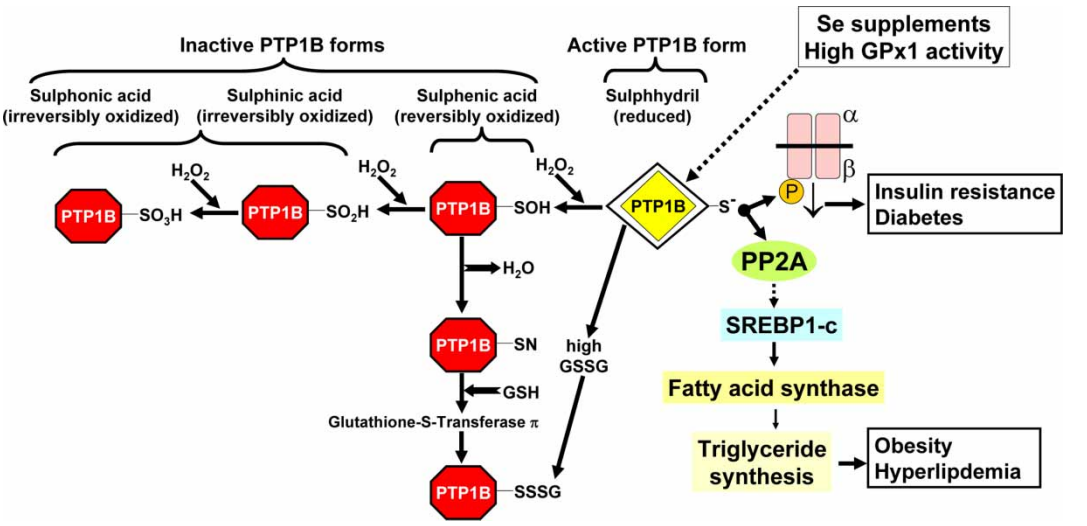

Figure 5. Current comprehension of the physiological regulation of PTP1B and metabolic consequences of a high PTP1B activity with regard to obesity, insulin resistance, diabetes and hyperlipidemia.

mechanism of PTP1B by removing H_2O_2 [155,157]. In addition to GPxs, which already reach plateau activity with the recommended dietary Se amounts, a slight supranutritive Se supplementation may contribute to a further deglutathionylation and therefore activation of PTP1B [156]. The underlying mechanisms with regard to this aspect, e.g. changes in thiols, thioredoxins or glutaredoxins, remain to be investigated.

Activated PTP1B (I) dephosphorylates the insulin receptor β sub-unit and IRS1 [178–180] and (II) stimulates the lipogenic pathway [181–184]. This on the one hand leads to a permanent inhibition of the insulin signal and to a permanent activation of the lipogenic pathway on the other hand. Therefore, the insulin secretion hypothesis (see Figure 2) [82] combined with the PTP1B activation hypothesis provides plausible explanations for the early development of insulin resistance and obesity due to permanent Se supplemention (Figure 5), as practised in the cancer prevention trials.

Conclusions from the current enigma of Se in diabetes and future perspectives

In conclusion, the relation between Se and diabetes currently seems to represent an enigma. However at the end of this review some critical questions regarding this nebulous relation should be put and some suggestions for future research should be given. Moreover a statement is given about how the permanent intake of Se supplements may exert opposite effects on diabetes and cancer and suggestions are made as to how these two health issues (risks) may be balanced.

The first question regarding the relation between Se and diabetes is:

Can a permanent Se deficiency contribute to a faster development of diabetes?

In our opinion: Yes

When Se is supplemented within the range of the current recommendations [22,23], it incontestably possesses positive effects, by protecting most tissues against oxidative stress via its function in the catalytically active centre of GPx1 and various other selenoproteins with a redox function. Since the pancreas holds only a relatively low expression level for glutathione peroxidases a continuous optimal Se supply within the recommendations is desirable and can contribute to the preservation of β-cell function [185]. A long-term Se-deficient diet can otherwise contribute to increased oxidative stress, the accelerated loss of pancreatic function and rebound to the development of insulin resistance and diabetes as discussed in detail above.

The second question regarding the relation of Se and diabetes is:

Can additional Se promote the development of obesity and the onset of type 2 diabetes with insulin resistance?

In our opinion: Yes

Very recent results from human epidemiological studies and from Se intervention trials, including large populations, increasingly suggest that a high Se status derived from conventional nutrition or from Se intervention increases the risk of developing type II diabetes and hyperlipidemia. The results of these trials are supported by studies with rodents using GPx1 over-expression or modulation of antioxidant selenoprotein activities by manipulation of dietary Se concentration. Both approaches suggest that an excess of antioxidant selenoproteins or a permanent slight surplus of Se may contribute to the development of obesity, insulin resistance, type II diabetes and

hyperlipidemia [144–151,155–157]. Two important molecular pathways underlying these undesirable effects of Se involve the tremendous increase in insulin production due to a high pancreatic GPx1 activity [82] and a high activity of the insulin antagonistic and lipogenic PTP1B [156,157] in peripheral tissues due to slightly supranutritive Se supplementation. The combination of both factors helps to explain plausibly the generation of the vicious cycle of peripheral insulin resistance and subsequently of diabesity and hyperlipidemia [82,156,157]. However, there remain a number of questions for future research to investigate the critical role of Se supplements with regard to the development of obesity, insulin resistance, diabetes and hyperlipidaemia. One approach in this direction may consist in the critical examination of the counter-regulation of antioxidant selenoproteins and phase II enzymes, e.g. several glutathione-S-transferases, heme oxygenases, some aldehyde reductases and epoxide hydrolases [186–191], for which a number of beneficial effects have again been reported with regard to diabetes prevention and therapy [192–198].

The third question regarding the relation between Se and diabetes which must be asked is:

Can additional Se help in reducing diabetic complications when the disease is already established?

In our opinion: No and yes

Only during untreated insulin resistance and inadequately adjusted diabetes does oxidative stress definitely increase and can cause fatal complications, such as terminal β-cell failure, micro- and macroangiopathies and nephropathies. However, from the literature currently available with regard to the relation between Se and diabetes it remains unclear if Se concentration in plasma and tissues as well as the activity of antioxidant selenoproteins drop or increase in manifest diabetes. Whereas some studies postulate a waste and therefore decrease of Se and antioxidant selenoproteins due to diabetic oxidative stress, other studies postulate exactly the opposite, namely that the higher need of antioxidants during diabetic oxidative stress effects an increase in plasma Se concentration and erythrocyte GPx1 activity. In addition to these inconsistent results in nearly all studies investigating the relation between Se and diabetes the state of the disease is not well defined. Thus an interesting aspect for future research would consist of the examination of Se fluxes and changes of tissue Se concentrations in the organism during different states of diabetes. One main pathway by which increased oxidative stress as well as adipokines may reduce insulin signalling is an increase in serine phosphorylation of critical proteins in the insulin signalling pathway. The influence of Se supplements with regard to a stimulation or reduction of serine phosphorylation thus would be another interesting topic for future investigations. According to present knowledge additional Se supplementation in diabetes may only be helpful during episodes of poorly controlled glucose metabolism and therefore increased oxidative stress, as reported in detail above. However, in our opinion, an increase in dietary Se supplementation in patients suffering from diabetes should always be considered carefully and the following points should be checked:

- Is the supplementation of cofactors of other antioxidant enzymes, e.g. superoxide dismutases (copper, zinc, manganese) and catalase (iron) [199–202] and of precursors for glutathione synthesis (naturally: sulphur containing amino acids; medicinal supplement: acetyl cysteine) [203,204] sufficient?
- When Se supplementation as determined by serum (plasma) Se concentration is within a normal physiological range (50–120 ng/mL) [28], a further supplementation with Se should not be recommended since it will not rebound to an increased biosynthesis of antioxidant selenoproteins. This aspect could be demonstrated for different human populations [205,206]. Moreover, it is fairly evident from recent literature that besides Se other dietary factors such as soy isoflavones like genistein [207–210] or isothiocyanates from cruciferous plants (mustard, cauliflower, radish, horseradish) [211–213] may have a protective function against diabetes and other dysfunctions associated with the metabolic syndrom. One mechanism by which these substances evolve anti-diabetic features is based on the powerful activation of phase II enzymes via the liberation of the transcription factors nrf-1 and nrf-2 and their subsequent interaction with the antioxidant response element of these enzymes [214–217]. In this context it should be noted again that a counter-regulation mechanism exists for antioxidant selenoenzymes and phase II enzymes [186–191]. To complicate matters, GPx2 and TrxR1 however are both target genes for Nrf2.

The fourth question regarding the relation between Se and diabetes which should be addressed is:

Is there an exception for Se supplementation in gestational diabetes?

In our opinion: Yes and no

The majority of studies investigating the relation of Se status and gestational diabetes show impressively that plasma Se concentration in healthy women also generally strongly decreases as pregnancy advances. A high Se transfer to the foetus may be responsible for this fact and was shown in mice and pigs [159,218]. Thus, the above addressed question should rather read: 'Is an additional Se supplementa-

tion in pregnancy advisable?' In our opinion this question can be clearly answered with 'yes', provided that Se status by means of plasma Se concentration drops below the physiologically recommended range of 50–120 μg/L [28].

How can Se exert opposite effects on cancer on the one hand and the development of insulin resistance, diabesity and hyperlipidemia on the other and how can this serious antagonism be balanced?

Long-term Se supplemention in the prevention of cancer has been tested in a number of larger and smaller intervention trials. However, the results of these studies are not consistent and not all cancers are positively influenced by Se supplementation. In the NPC trial [147,219] a 25% reduction of total cancers could be achieved by Se supplementation with 200 μg Se for 7.7 years. This reduction was based in particular on lower incidence rates for prostate cancer and colon cancer, whereas the incidence of non-melanoma skin cancer and squamous cell cancers increased. The SELECT study [148] which originally planned to investigate the preventive effect of Se and vitamin E supplementation on prostate cancer incidence was early abandoned in autumn 2008 after 7 years (scheduled duration: 12 years) because Se supplementation alone and in combination with vitamin E even tended to increase prostate cancer incidence by 4 and 5%, respectively. With regard to the positive effects of Se supplementation on prostate- and colon cancer a number of different and promising approaches concerning the underlying molecular mechanisms have been made. Thus, one study investigates the fact that Se (methylseleninic acid) reduces the phosphorylation of Akt/PKB at threonine 308 and serine 473 in cultured cancer cells and by these mechanisms reduces cell proliferation and differentiation [220]. According to Figure 2, dealing with pancreatic health full Akt/PKB phosphorylation is a differentiation signal in many tissues. A high Akt/PKB phosphorylation is further an indicator for insulin sensitivity, since it ultimately mediates the metabolic effects of insulin. In this context it is remarkable that in the study with GPx1 over-expressing mice, a reduced phosphorylation of Akt/PKB at exactly the threonine 308 residue and at the serine 473 residue indicated the insulin resistance of the animals [155]. Thus, at this point it must be stated that potentially the same signalling pathways contributing to a reduced proliferation and differentiation of cancer cells by Se may mediate the pro-diabetic and pro-adipogen effects of the trace element. Another investigation into the anti-carcinogenic properties in prostate cancer cells suggests that Se treatment influences the epigenetic mechanism via the reduction of DNA methylation and the increase of DNA- and histone acetylation in the promoter region of genes critical to the inhibition of tumour growth and metastasis [221]. Whereas methylation is a silencing signal for gene transcription, acetylation generally increases gene expression. In this context a similar observation could be made in the mouse trial in which pancreatic GPx1 over-expression strongly increased DNA- and histone acetylation in the PDX1 promotor region leading to a massive increase in β-cell mass and insulin production [82]. As described above for phosphorylation and signalling processes the influence of Se on DNA methylation and acetylation also impressively shows that one and the same mechanism may provide protection against cancer and increase the risk of early diabetes development. Recent results suggest that the coincidence of polymorphisms in the selenoprotein P gene and in the MnSOD gene may increase the risk of prostate cancer [222]. A reduced delivery of Se to the prostate gland leading to the subsequent reduced synthesis of antioxidant selenoproteins combined with a reduced detoxification of initially produced superoxide radicals is thought to raise the prostate cancer risk via increased oxidative stress. An influence of seleonprotein P polymorphisms was also described with regard to the protection of humans against colon cancer [223]. Generally two isoforms of seleoprotein P exist (a 50 kDa isoform and a 60 kDa isoform). Depending on the genotype and on specific polymorphisms, either the 50 kDa or the 60 kDa form dominates. The 60 kDa form seems to be more effective in supplying peripheral tissues sufficiently with Se and therefore providing the basis for the synthesis of antioxidant selenoproteins and cancer protection. In this context the observation that in case of the existence of polymorphisms forwarding the synthesis of the 50 kDa selenoprotein P isoform, Se supplementation of these patients leads to a strong increase in the favourable 60 kDa form. This opens perspectives to advise individuals with those polymorphisms to intermittently take Se supplements. That the gastrointestinal glutathione peroxidase GPx2 may play a key role in the prevention of colon cancer could be demonstrated by the ability of GPx2 to dampen the expression of cyclooxygenase 2 and microsomal prostaglandin E2 synthase-1 and therefore to reduce inflammation driven initiation of carcinogenesis by prostaglandin E2 [224]. Finally it should be mentioned that accompanying Se supplementation seems to be useful during radiotherapy of cancers, since Se increases the radiosensitivity of tumours cells [225,226]. As described in this section in certain respects permanent supranutritional Se supplementation seems therefore to influence protection from cancer and diabetes development exactly contrariwise. As stated below in our concluding remarks with regard to diabetes, the currently available data do not uniquely support the necessity of permanent supranutritive Se supply for cancer prophylaxis. This recommendation is supported by the

fact that Se seems to have a certain protective effect against prostate cancer and colon cancer whereas it may increase the risk of skin cancers and squamous cell cancers [219]. In the future, modern molecular biological methods (e.g. for the detection of polymorhisms such as in selenoprotein P) may represent a helpful tool to give well-directed advice to patients to take intermittently Se supplements. A very simple approach for the prevention of colon cancer could be the encapsulation of Se into hemicellulose or other fibres which are not digestible in the small intestine. This would represent a simple tool to obtain a high local Se concentration where it is desired and to avoid it where it is not needed.

Concluding remarks

In conclusion we are of the opinion that Se supplementation above the officially recommended amounts (up to 70 μg/day, depending on age and physiological status) [2,3] is not indicated for the prevention of insulin resistance and diabetes, since the currently recommended amounts are adequate for optimum activities of functional selenoproteins. On the contrary the permanent intake of Se supplements may even accelerate the development of obesity, insulin resistance and diabetes. Genuine anti-diabetic effects of Se can only be obtained with nearly toxic doses and are out of the question for humans.

Acknowledgements

Thanks are addressed to our Diploma students Claudia Lennicke and Christina Duerbaum for their help with the preparation of the manuscript within their internship in the 'Preventive Nutrition Group' at the Institute of Agricultural and Nutritional Sciences, Martin Luther University Halle Wittenberg.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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This paper was first published online on iFirst on 7 September 2009.

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