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Selenium and type 2 diabetes mellitus: A double-edged sword

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ABSTRACT

Selenium (Se) is a pivotal micronutrient crucial for human health, particularly in type 2 diabetes mellitus (T2DM). This review explores the impact of Se on T2DM, considering its delicate balance between deficiency and excess. It has antioxidant properties, but its relationship with T2DM follows a U-shaped curve. Se mimics insulin, guarding beta cells, but clinical studies discourage supplementation due to T2DM risk. Elevated Se disrupts glucose and lipid metabolism, causing hyperinsulinemia, hyperglycemia, and hyperlipidemia. This connection warrants further investigation in nutritional science to manage Se intake carefully and promote overall well-being while reducing diabetes risk.

KEYWORDS

Selenium; Type 2 diabetes mellitus; Antioxidant; Micronutrient

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Introduction

Selenium (Se) stands as a critical micronutrient, intricately entwined with human health. It is estimated that the human body typically harbors 3–20 mg of Se, underscoring its essentiality in our diet [1,2]. At the molecular level, Se is indispensable for the synthesis of selenocysteine, a unique and vital amino acid, which serves as the 21st member in the amino acid family. Selenocysteine plays a central role in the constitution of various selenoproteins, encompassing significant players such as thioredoxin reductase, dioiodinases, and selenoprotein P, along with the Se-dependent glutathione peroxidases, including GPX1, GPX2, GPX3, and GPX4. These selenoproteins, working in concert with Se-dependent glutathione peroxidases, form a robust line of defense against the menacing reactive oxygen and nitrogen species. Their collective mission is to thwart the risk of insulin resistance and β-cell dysfunction, two pivotal factors in the onset of type 2 diabetes mellitus (T2DM) (Figure 1) [3,4].

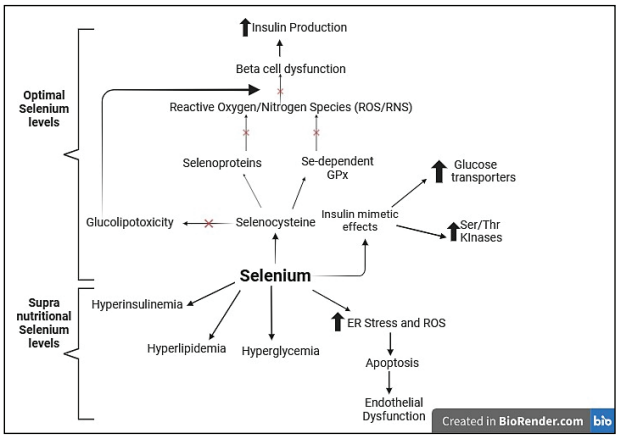

Figure 1. Effects of varying selenium levels on different metabolic pathways related to T2DM.

Se, endowed with substantial antioxidant properties, emerges as a promising candidate for mitigating the risk of T2DM. However, the interplay between Se and T2DM is a complex one, characterized by a U-shaped curve. This curve implies that both Se deficiency and excess can exert detrimental effects on T2DM risk and overall health. The world of Se and T2DM research is replete with controversies and contradictions, necessitating a deeper exploration [5].

Se showcases an intriguing ability to mimic the actions of insulin by activating serine/threonine kinases and facilitating the translocation of glucose transporters to the plasma membrane [6]. This capability holds significant promise for T2DM prevention and management. Moreover, Se's antioxidant prowess may act as a shield for beta cells, which are often exposed to chronic, elevated levels of fatty acids—a phenomenon known as glucolipotoxicity. This protection, offered by serotonin-dependent antioxidants like GPx1, sustains beta cell function, promoting insulin synthesis and secretion [7].

The saga of Se and T2DM continues with numerous twists and turns. While findings from the Hunan province study suggested a positive correlation between dietary Se intake and diabetes prevalence, the tale is far from linear. Clinical investigations in humans have not uniformly supported Se supplementation as a means of preventing T2DM. Paradoxically, sustained Se supplementation may elevate the risk of contracting this very illness. Alarming evidence has even surfaced, indicating that high Se intake, surpassing 60 µg/d, in diabetic patients may lead to higher hospitalization rates. The culprits behind these phenomena may include endoplasmic reticulum (ER) stress and the excessive generation of reactive oxygen species, both of which have been proposed as pathways by which supranutritional Se intake may precipitate endothelial dysfunction and T2DM [8].

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The intricate web of Se's effects extends to key elements and enzymes involved in glycolysis, gluconeogenesis, and lipogenesis. High Se consumption can perturb their expression, thereby affecting fatty acid metabolism. This disturbance leads to increased fatty acid oxidation and alterations in lipid metabolites. These consequences ultimately contribute to hyperinsulinemia, hyperglycemia, and hyperlipidemia, all of which are integral to the development of T2DM [5].

The labyrinthine relationship between Se and T2DM presents inconsistencies. For instance, Se was found to be positively correlated with diabetes in some studies, yet negatively associated with all-cause mortality in cross-sectional analyses of the U.S. population. This highlights the intricate and multifaceted interactions between Se and health outcomes. Further complexity emerges from a randomized experiment with T2DM patients, where Se supplementation showed adverse effects on blood glucose homeostasis, particularly in individuals with low Se levels. Surprisingly, these effects persisted even after Se concentrations reached the ideal antioxidant activity level [9]. The Se and Vitamin E Cancer Trial (SELECT) further muddles the waters, failing to establish a strong connection between supplemental Se and T2DM risk.

While the intricate relationship between Se and T2DM is well-documented, an in-depth analysis is essential. *In vivo* and *in vitro* studies can provide valuable insights into the mechanisms underlying these complex interactions. Case studies of individuals with varying Se levels and their T2DM outcomes would also shed light on this puzzling relationship [10]. For instance, an *in vivo* study examining the effects of Se supplementation on insulin sensitivity in a controlled group of individuals with Se deficiency could offer specific insights. Moreover, *in vitro* research exploring the impact of varying Se concentrations on beta-cell function and insulin synthesis would deepen our understanding [11].

Se antioxidant properties and its potential to enhance insulin sensitivity render it an intriguing micronutrient in the context of T2DM prevention. However, exercising caution is paramount when contemplating Se supplementation. The specter of excessive Se intake looms large, with the potential to inflict adverse effects on insulin sensitivity and β-cell function [12]. Striking the delicate balance in Se intake within recommended levels is the key to safeguarding overall health and minimizing the lurking perils associated with excessive Se intake [13]. Future research must delve deeper into the intricate mechanisms governing this relationship, refine dietary recommendations, and champion the cause of maintaining a balanced Se intake that simultaneously promotes health and well-being while mitigating diabetes risk [14]. Pursuing clarity in the complex interplay between Se and T2DM is a critical avenue for future investigation in nutritional science [15].

Gaps in Current Research

Despite the wealth of research on Se and its connection to T2DM, there is still a gap in our mechanistic understanding of how Se influences insulin sensitivity, beta-cell function, and the development of T2DM. A comprehensive exploration of the underlying molecular pathways and cellular interactions is needed to fill this gap. More research is needed to define specific dose-response relationships [16]. What is the optimal range of Se intake to maximize its benefits and minimize risks? Research should also explore individual variations in Se metabolism and how this impacts T2DM risk. Certain unanswered critical questions could be how Se compounds have varying effects on T2DM risk. Exploration of specific genetic markers or variations that make certain individuals more susceptible to the adverse effects of excessive Se intake in relation to T2DM. Can specific biomarkers or predictors be identified to determine which individuals are most likely to benefit from Se supplementation and which are at a higher risk of adverse effects? Impact of Se intake on the progression from prediabetes to T2DM. Addressing these gaps and unanswered questions through rigorous research will pave the way for a more comprehensive and nuanced understanding of the intricate relationship between Se and T2DM, enabling more targeted and effective prevention and management strategies.

Conclusions

Se role in T2DM is a complex one, marked by a U-shaped relationship where both deficiency and excess pose risks. While Se offers promise in enhancing insulin sensitivity and protecting beta cells, clinical research on supplementation does not uniformly support T2DM prevention. Excessive Se intake can lead to disruptions in glucose and lipid metabolism, contributing to T2DM development. The path forward calls for more comprehensive research, including mechanistic studies and exploration of Se compounds and interactions with other nutrients. As we seek answers, it is clear that maintaining the right balance in Se intake is essential, safeguarding overall health and minimizing risks. The intricate interplay between Se and T2DM remains a crucial avenue for future nutritional science research.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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