2 Peer-review report

Reviewer #1: *This manuscript reviewed the the role of selenium in type 2 diabetes and the complex interplay between selenoproteins and insulin pathways. The conclusion is a U-shaped dose-dependent effect between selenium exposure and type 2 diabetes, and selenium supplements should be taken with caution. 1. Manuscript should be further focused on the selenium, selenoproteins, and type 2 diabetes, insulin resistance and β-cell secretory function, especially the evidences of selenium exposure and type 2 diabetes by different designs, overall selenium exposure in the world. 2. 1.1 and 1.2 could be presented briefly.*

Reviewer #2: *This manuscript reviewed the relationship between selenium and The relationship among the diabetes, islets β cell function and insulin resistance，the advices were as follows: 1.Insulin resistance and β Cell function is closely related to inflammation and immunity, and selenium is closely related to the immune system, so the authors should review the literature and comment in this regard 2.Clinical research on the relationship between selenium and treatment of diabetes should be included*

ANSWER TO REVIEWERS

Sections 1.1 and 1.2 have been shortened

It has been added a new section called "2.2 Worldwide variation in selenium intake" with final paragraphs of 2.1 section and new information:

2.2. Worldwide variation in selenium intake

In contrast to other micronutrients, selenium intake varies widely worldwide from deficiency to toxic concentrations leading to nail loss, hair loss, poor dental health or even nervous system or skin disorders. Regarding adequate Se concentrations, the recommended Se intake is around 55 ug/day and it can be found in foods such as grains, meat, seafood, vegetables, nuts or dairy products (Avery & Hoffmann, 2018).

Selenium intake from food depends not only on the selenium content of the soil but also on factors which determine the availability of selenium in food. In general, intakes are higher in countries such as Venezuela, Canada, USA and Japan. In Europe, on the other hand, intakes are lower and in countries such as New Zealand, Finland or Denmark they are especially low (Rayman, 2012).

Dietary supplements containing selenium are very common, especially in countries such as the United States where 50% of the population takes daily supplements. This extra intake of selenium added to the daily food intake makes the average selenium intake vary from 40 ug/day in Europe to 93 ug/day (in women) and 134 ug/day (in men) in the United States (Rayman, 2012).

Thus, below and above the recommended intake range, Se can have detrimental effects. A Se deficiency has been shown to be involved in the appearance of different pathologies such as

Kaschin-Beck disease or Keshan disease. In the same way, a high and chronic exposure to Se can cause selenosis with severe manifestations in the organism (Avery & Hoffmann, 2018) (Mangiapane, Pessione, & Pessione, 2014).

It has been added a new section called "2.5. Clinical research on the relationship between selenium and treatment of diabetes":

2.5. Clinical research on the relationship between selenium and treatment of diabetes

Despite the beneficial effect of many micronutrients on different diseases, including diabetes, there are many studies correlating the development of diabetes with selenium (Sanmartin, Plano, Font, & Palop, 2011).

It has been observed that selenium supplementation is protective against different pathologies such as cancer or autoimmune thyroid disorders when there is a deficiency of this trace element. In contrast, selenium supplementation is not recommended when levels of this micronutrient are optimal because of its potential to promote the development of diabetes. Supplementation dose and duration should be carefully taken into account (Rocourt & Cheng, 2013) (Drutel, Archambeaud, & Caron, 2013).

Human clinical trials have confirmed that selenium supplementation does not help in the prevention of type II diabetes, but that prolonged exposure to selenium supplementation may increase the risk of this disease (Stranges et al., 2007). Indeed, selenium supplementation to treat micro-albuminuria in diabetic patients has been found to be ineffective (Ghadiri-Anari, Jam-Ashkezari, Fallah-Tafti, Rahmanian, & Namiranian, 2021).

It has been added a new section called "2.7. Relation between selenium and T2DM regarding the immune system and the inflammation process":

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

Although there is much evidence from *in vitro* and animal studies on the role of selenium in the immune system, there are few studies that support it in humans. Selenium supplementation appears to have immunostimulant effects by promoting the proliferation of activated T cells, increasing the activity of natural killer cells and increasing cytotoxic lymphocyte-mediated tumor cytotoxicity (Rayman, 2012).

Selenoproteins are essential for the function of activated T cells since they are particularly sensitive to oxidative stress and selenoproteins aid promoting the suppression of ROS production. Moreover, human studies have correlated selenium supplementation with lymphocyte proliferation preceded by increased expression of high-affinity interleukin-2 receptor. (Rayman, 2012).

Low-grade inflammation is involved in insulin resistance and increased selenoprotein P concentration has been positively correlated with high-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation, in patients with prediabetes and diabetes (Yang et al., 2011).

In addition, the relation of selenium with T2DM via the inflammatory pathway has been described through SELENOS, a transmembrane protein located in the membrane of the endoplasmic reticulum and the plasma membrane. Its increase has been related, among other things, to a decrease in glucose uptake and glycogen biosynthesis as well as to an increase in circulating cytokines (Michalke, 2022).

It has been added new references:

Drutel, A., Archambeaud, F., & Caron, P. (2013). Selenium and the thyroid gland: More good news for clinicians. *Clinical Endocrinology (Oxford), 78*(2), 155-164. doi:10.1111/cen.12066

Ghadiri-Anari, A., Jam-Ashkezari, S., Fallah-Tafti, B., Rahmanian, M., & Namiranian, N. (2021). The effect of selenium on micro-albuminuria in diabetic patients: A randomized clinical trial. *Iranian Journal of Diabetes and Obesity, 12*(4) doi:10.18502/ijdo.v12i4.5177

Michalke, B. (2022). Review about powerful combinations of advanced and hyphenated sample introduction techniques with inductively coupled plasma-mass spectrometry (ICP-MS) for elucidating trace element species in pathologic conditions on a molecular level. *International Journal of Molecular Sciences, 23*(11), 6109. doi:10.3390/ijms23116109

Rayman, M. P. (2012). Selenium and human health. *The lancet*. doi:10.1016/S0140-6736(11)61452-9

Sanmartin, C., Plano, D., Font, M., & Palop, J. A. (2011). Selenium and clinical trials: New therapeutic evidence for multiple diseases. *Current Medicinal Chemistry, 18*(30), 4635-4650. doi:10.2174/092986711797379249

Stranges, S., Marshall, J. R., Navas-Acien, A., Guallar, E., Natarajan, R., Donahue, R. P., et al. (2007). Effects of long-term selenium supplementation on the incidence of type 2 diabetes A : A randomized trial. *Annals of Internal Medicine, 147*(4), 217-223. doi:10.7326/0003-4819-147-4-200708210-00175

Yang, S. J., Hwang, S. Y., Choi, H. Y., Yoo, H. J., Seo, J. A., Kim, S. G., et al. (2011). Serum selenoprotein P levels in patients with type 2 diabetes and prediabetes: Implications for insulin resistance, inflammation, and atherosclerosis. *The Journal of Clinical Endocrinology and Metabolism, 96*(8), E1325-E1329. doi:10.1210/jc.2011-0620