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Potential of trace elements as supplements for the metabolic control of Type 2 Diabetes Mellitus: A systematic review

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ABSTRACT

The objective of this review was to understand the role of trace elements in the form of supplements in metabolic control of Type 2 Diabetes Mellitus (T2DM). A systematic research was performed following PRISMA recommendations. Although 3236 studies were identified, only 18 studies composed of nine animal studies and nine clinical studies were included in this review. The included trace elements were Chromium (Cr), Selenium (Se), Zinc (Zn) and Vanadium (V). The time, dose and type of supplement varied among the studies. Se, Cr, Zn and V improved glycemic profile and antioxidant status while Se, Cr and Zn affected lipid profile. Se and Zn supplementation improved endothelial function. Also, Se modified inflammatory profile. In general, cautious supplementation of trace elements promotes the metabolic control of T2DM.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic disease with multiple and systemic etiology. It is considered the eighth largest cause of death in the world and a public health problem. The progression of T2DM is associated with other chronic non-communicable diseases, such as cardiovascular diseases (CVD) and cancer (International Diabetes Federation. (2017) (2017), 2017; Brasileira, 2013; World Health Organization. (2016) (2016), 2016).

One of the strategies to control glycemia and complications of diabetes is eating a balanced diet based on functional foods such as vegetables, fruits, cereals, seeds and nuts, rich in bioactive compounds, dietary fiber, vitamins and minerals (Fasano et al., 2014; García-Vicente et al., 2007; Gite, Yadav, Nilegaonkar, & Agte, 2017). Among the minerals, trace elements are known to potentialize insulin action and glycemic control, processes directly involved in the treatment of T2DM (Siddiqui, Bawazeer, & Joy, 2014).

Given that changes in the status of trace elements and metabolic changes can aggravate the progression of diabetes, dietary supplementation of trace elements may be an alternative method to treat T2DM (Badran, Morsya, Solimanb, & Elnimr, 2016; Fasano et al., 2014; Friederich, Hansell, & Palm, 2009). Despite evidence on the beneficial effects of trace elements on T2DM, the mechanisms involved as well as adequate levels of supplementation, are still unclear. Understanding the role of trace elements in T2DM and the establishment of adequate levels of supplementation are important steps towards the treatment of the disease with trace elements. Thus, the aim of this review was to understand the role of trace element supplements in the metabolic control of T2DM.

2. Material and methods

A systematic search was carried out in the Lilacs, Medline/Pubmed, Scopus and Science Direct databases. The search considered original articles on the role of trace elements in T2DM published in the last 10 years. This restriction allowed the inclusion of recent studies on the relationship between trace elements and T2DM. It is important to emphasize that only original *in vivo* articles were included in this review. The search terms used were: “trace elements”, “trace minerals” and “oligo-elements” combined with diabetes, dyslipidemia, “insulin resistance” and hyperglycemia. To select the studies, titles and abstracts were read first, followed by complete articles. The studies were considered eligible based on the following aspects: original articles, observational, clinical or animal studies; articles that evaluated trace elements (chromium, copper, iodine, iron, manganese, molybdenum, selenium, zinc, fluorine, boron, nickel, silicon or vanadium) and their

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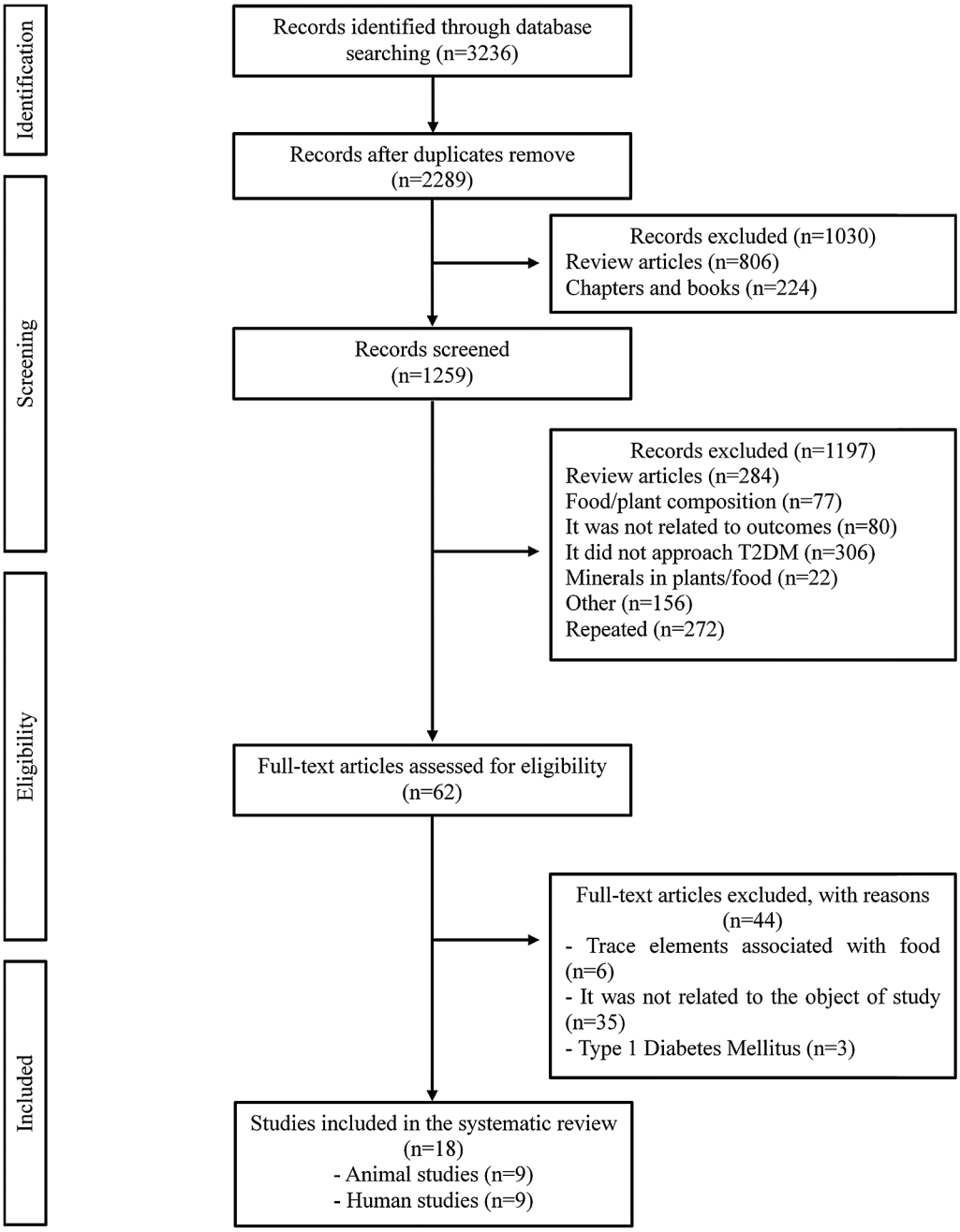

Fig. 1. Flowchart of the search and selection process for articles included in the systematic review, according to PRISMA recommendation.

possible effects on T2DM. The exclusion criteria were: review articles, book chapters, dissertations, theses, analysis of mineral composition in plants and foods, studies that assessed macro elements such as calcium, phosphorus, magnesium, sodium, potassium, chlorine and sulphur, dietary trace elements, studies that presented no relation between trace elements and T2DM, and *in vitro* studies (Fig. 1). At every selection stage, each article was read by two researchers, following the recommendations of the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) document, ensuring that the review protocol and the inclusion and exclusion criteria were followed.

3. Results and discussion

3.1. Study selection and characteristics

Initially, 3236 studies were identified and after reading the titles and abstracts, 62 titles were considered relevant for full reading. After the complete review, 18 studies fulfilled all the inclusion criteria and were included in this review (Fig. 1). The trace elements found in the review were chromium (Cr), selenium (Se), vanadium (V) and zinc (Zn). They were administered individually and the doses varied among the studies. Regarding the studies, nine were animal studies (Table 1) and nine were conducted in humans (Table 2). Among the human studies, seven were randomized clinical trials and two were observational studies. The nine animal studies used rat models of a single-dose streptozotocin (STZ) induced T2DM. The dose was applied by intraperitoneal injection and typical values ranged from 45 mg/Kg (Dhanya, Swathy, & Indira, 2014), 50 mg/Kg (Aydemir-Koksoy & Turan, 2008; Sundaram, Singhal, & Sandhir, 2012, 2013; Sundaram, Aggarwal, & Sandhir, 2013; Xu, Yuan, Zou, & Zang, 2009) to 65 mg/Kg (Karatug, Kaptan, Bolkent, Mutlu, & Yanardag, 2013; Kurt et al., 2011; Ozsoy, Can, Mutlu, Akev, & Yanardag, 2012).

Table 1
Characteristics of the animal studies.

Author/year	Animals	Trace elements studied	T2DM induction	Duration	Intervention*	Observed effects on T2DM
Sundaram, Aggarwal, et al., 2013	24 Wistar male rats 160–180 g	Chromium picolinate	Single intraperitoneal dose of STZ (50 mg/kg body weight)	4 weeks	– Control: citrate buffer – Control + CrPic: 1 mg CrPic/kg of body weight – T2DM: isotonic saline solution – T2DM + CrPic: 1 mg CrPic/kg body weight. – Standard diet and water *ad libitum*	↓ Glycemia ↓ ALT and AST ↑ GSH, GR, SOD and CAT ↑ Alpha-tocopherol and ascorbic acid↓ Lipid peroxidation
Sundaram, Singhal, et al., 2013	24 Wistar male rats 160–180 g	Chromium picolinate	Single intraperitoneal dose of STZ (50 mg/kg body weight)	4 weeks	– Control: citrate buffer – Control + CrPic: 1 mg CrPic/kg of body weight) – T2DM: isotonic saline solution – T2DM + CrPic: 1 mg CrPic/kg body weight. – Standard diet and water *ad libitum*	↓ Total lipidis, TG and TC:HDL-c ↑ HDL-c:LDL-c ↓ TC, LDL-c and VLDL-c ↑ G6PDH activity
Sundaram et al., 2012	24 Wistar male rats 160–180 g	Chromium picolinate	Single intraperitoneal dose of STZ (50 mg/kg body weight)	4 weeks	– Control: citrate buffer – Control + CrPic: 1 mg CrPic/kg of body weight – T2DM: isotonic saline solution – T2DM + CrPic: 1 mg CrPic/kg body weight. – Standard diet and water *ad libitum*	↑ GK activity, PFK and PK, hepatic glycogen ↓ G-6-Phase and PEPCK ↓ Glycemia ↑ Glucose uptake
Dhanya et al., 2014	24 Sprague dawley albino male rats 245–250 g	Sodium selenate	Single intraperitoneal dose of STZ (45 mg/kg body weight)	4 weeks	– Control – Control + Se: 1 μg sodium selenate/kg weigh – T2DM – T2DM + Se: 1 μg of sodium selenate/kg of body weight. – Water and commercial diet *ad libitum*	↑ SOD, CAT, GPx in heart ↓ MDA, HP and CD ↓ Glycemia and HbA1c ↓ 5-LOX, COX-2, NF-κB expression ↓ CRP ↑ Na^+/K^+ATPase and Ca^{2+}/ATPase
Xu et al., 2009	35 Sprague dawley male rats 180–220 g	Sodium selenite	Single intraperitoneal dose of STZ (50 mg/kg body weight)	4 weeks	– Control – T2DM – T2DM + In: 1U/kg body weight/day – T2DM + Se: 180 μg/kg body weight/day – T2DM + In + Se: 1U/kg body weight/day of In and 180 μg/kg body weight/day of Se – Standard diet and water *ad libitum*	↓ Glycemia and HbA1c in T2DM + In + Se ↑ GLUT4 in the cardiac muscle in T2DM + In + Se ↓ GLUT4 on the cardiac muscle cell membrane in T2DM + Se
Aydemir-Koksoy & Turan, 2008	18 Wistar male rats 200–250 g	Sodium selenate	Single intraperitoneal dose of STZ (50 mg/kg body weight)	4 weeks	– Control – T2DM: saline solution – T2DM + Se: 15 μmol/kg body weight/day – Standard diet and water *ad libitum*	↓ Cav1 expression in the aorta inhibited MAPK42/44 phosphorylation in the aorta ↑ Na^+/K^+ATPase activity of the aorta ↓ MMP-2 activity
Karatug et al., 2013 Ozsoy et al., 2012	26 Swiss female mice 150–200 g 26 Swiss albino female mice 150–200 g	Zinc sulfate Zinc sulfate	Single intraperitoneal dose of STZ (65 mg/kg body weight) Single intraperitoneal dose of STZ (65 mg/kg body weight)	8 weeks 8 weeks	– Control – Control + ZnS: 100 mg/kg body weight/day – T2DM – T2DM + ZnS: 100 mg/kg body weight/day – Standard diet and water *ad libitum* – Control – Control + ZnS: 100 mg/kg body weight/day – T2DM – T2DM + ZnS: 100 mg/kg body weight/day – Standard diet and water *ad libitum*	↓ Glycemia ↓ Urea, creatinine ↓ Lipid peroxidation ↓ Non-enzymatic glycosylation ↑ GSH ↓ CAT, GPx and GST ↓ MPO and CA
Kurt et al., 2011	36 Swiss albino male mice	Vanadyl sulfate	Single intraperitoneal dose of STZ (65 mg/kg body weight)	8 weeks	– Control – Control + V: 100 mg/kg body weight – T2DM – T2DM + V: 100 mg/kg body weight – Standard diet and water *ad libitum*	↓ Glycemia ↓ SOD, CAT, GR, GPx, GST

* All treatment of the animal studies was administered by gavage. ↑: increase ↓: decrease; ALT: alanine aminotransferase; AST: aspartate transaminase; CA: carbonic anhydrase; Ca^{2+} ATPase: calcium pump; CAT: Catalase; Cav1: caveolin-1; CD: conjugated dienes; COX-2:cyclooxygenase-2,CRP: C-reactive protein; CrPic: chromium picolinate;; G6PDH: glucose-6-Phosphatase Dehydrogenase; G-6-Phase: glucose-6-Phosphatase; GK: glycoquinase; GLUT4: glucose transporter type 4; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: glutathione; GST: glutathione-S-transferase; HbA1c: glycated hemoglobin; HDL-c: high Density lipoprotein; In: insulin; HP: Hydroperoxides; LDL-c: low density lipoprotein; 5- LOX: 5-lipoxygenase; MDA: malondialdehyde; MAPK 42/44: mitogen-activated protein-kinase 42/44; MMP-2, metalloproteinase-2; MPO: myeloperoxidase; PEPCK: phosphoenolpyruvate carboxykinase; PFK: phosphofructokinase; PK: pyruvate kinase; Se: selenium; SOD: superoxide dismutase; STZ: streptozotocin; T2DM: type 2 diabetes mellitus; TC: total cholesterol; TG: triglyceride; V: vanadium; VLDL-c: very low density lipoprotein; ZnS: zinc sulfate.

STZ can induce both Type 1 Diabetes Mellitus (T1DM) and T2DM depending on the dose. A single low dose has been reported to induce T2DM while a single high dose induced T1DM. In addition, a high fat diet (HFD) combined with STZ induces T2DM in animal (Skovsø, 2014). The development of T1DM and T2DM culminates in β cell failure. It is speculated that 60–80% of the β cell mass is lost in early T1DM and approximately 54% is lost in late T2DM (after 15 years of diagnosis), indicating that early T1DM and advanced stage T2DM present similar β cell mass. Thus, treatment with STZ induces T2DM very quickly as opposed to natural occurring T2DM. The doses used in the included studies ranged from 45 to 65 mg/kg STZ, which can be considered sufficient for the rapid induction of T2DM characterized by a more advanced pathophysiology (Mazo, Sidorova, Zorin, & Kochetkova, 2016; Skovsø, 2014). All the animal studies did not confirm STZ induced T2DM through homeostasis model assessment-insulin resistance (HOMA-IR).

3.2. Chromium

3.2.1. Animal studies

In three studies, Wistar male rats received 1 mg/kg of chromium picolinate (CrPic) for four weeks (Table 1). The three studies observed an improvement in carbohydrate metabolism, which was confirmed by an increase in hepatic glucose uptake, hepatic glycogen uptake and glycolytic enzymes, in addition to a reduction of glycemia and glyconeogenic enzymes in the liver. (Sundaram, Singhal, & Sandhir, 2012) (Table 1). Plasma lipid profile also improved, with a decrease in total lipids, triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL-c) and TC:HDL-c ratio, and an increase in HDL-c:LDL-c ratio (Sundaram, Singhal, et al., 2013) (Table 1). The animals showed improved antioxidant defense system with increased glutathione (GSH), glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT), alpha-tocopherol and ascorbic acid and reduced lipid peroxidation. Also, there was a decrease in hepatic enzymes, such as aspartate transaminase (AST) and alanine aminotransferase (ALT) (Sundaram, Aggarwal, et al., 2013) (Table 1).

Cr is an essential element for optimal insulin activity, which may act in the maintenance of normoglycemia (Anderson, 1998). CrPic is a complex of chromium and picolinic acid. Previous studies show that it has anti-diabetic and anti-obesity activity (Doddigarla, Ahmad, & Parwez, 2016; Mackowiak et al., 2010). CrPic showed to be efficient in increasing insulin receptor substrate 1 (IRS-1) in the liver, as well as peroxisome proliferator-activated receptor gamma (PPAR-γ) in the adipose tissue (Sahin et al., 2013). These genes are involved in obesity and T2DM, thus are important biomarkers of insulin resistance as well as inflammation (Saad et al., 1992). IRS-1 has a central role in insulin signal transduction pathway and links the insulin receptor to its final biological actions via a series of intermediate effectors (Cheatham & Kahn, 1995). An *in vitro* study conducted with insulin-resistant 3 T3-L1 adipocytes showed that CrPic improves glucose metabolism, increasing the capture and translocation of glucose transporter type 4 (GLUT4) to the plasmatic membrane through the activation of the P38 mitogen-activated protein kinase pathway (Wang & Yao, 2009). PPAR-γ participates in insulin and glucose metabolism, improving insulin sensibility in T2DM, which reduces hyperglycemia (Derosa & Maffioli, 2012).

Previous studies showed that CrPic is capable of increasing adenosine monophosphate activity (AMP) – activated protein kinase (AMPK) (Hoffman et al., 2014). AMPK acts as an energy regulator, which benefits carbohydrate metabolism (Ruderman, Saha, & Kraegen, 2013). In the studies of the review, AMPK improved lipid profile. Phosphorylated and activated AMPK may phosphorylate and deactivate acetyl-CoA carboxylase (ACC), which catalyzes the conversion of acetyl-CoA to malonyl-CoA. The latter is a potent inhibitor of carnitine palmitoyl transferase (CPT-1) (Abu-Elheiga et al., 2000; Mcgarry & Foster, 1980). Once ACC is deactivated, there is an increase in CPT-1, an enzyme that transports long chain fatty acids in the mitochondria, essential for the β-oxidation of fatty acids, which then reduces lipogenic enzymes. This pathway suppresses lipogenesis and oxidative activities and increases glycolytic and lipolytic enzymes (Ruderman et al., 2013; Saha & Ruderman, 2003). Moreover, chromium may promote the biosynthesis of apolipoprotein and HDL-c in the liver, which can lead to an improved lipid profile (Mooradian, Haas, & Wong, 2004). Corroborating with the literature, a study carried out with IR male Wistar rats reported improved lipid profile through the increase of serum HDL-c (Doddigarla et al., 2016).

Hepatic enzymes, AST and ALT, are important markers of liver injury, and their increase is expected in T2DM due to hepatocellular damage caused by alterations in lipid metabolism (Liu, Que, Xu, & Peng, 2014). Cr participates in glycemic and lipid metabolism by improving insulin action, thus improving the concentrations of these enzymes (Yeghiazaryan, Schild, & Golubnitschaja, 2012). To corroborate with the findings of this review, a study in the literature found that the supplementation of CrPic in rats with type 2 diabetes induced by HFD and STZ was effective in improving hepatic injury with reduction in AST and ALT enzymes (Sahin et al., 2013). In another study with rats, a decrease of these enzymes was found which suggests that CrPic prevents hepatic lesions even in animal model of alloxan-induced T1DM (Weijiang et al., 2013).

The mechanism behind insulin resistance (IR) in T2DM also hinders the uptake of glucose. It also activates 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, and decreases oxidation of TG in the extra-hepatic tissue. This results in hyperglycemia and dyslipidemia (Sahin et al., 2013), which increase reactive oxygen species (ROS) during the oxidation of glucose in the mitochondria (Jana, Chintamaneni, Krishnamurthy, Wadhwani, & Mohankumar, 2018). Previous studies suggest that Cr enhances total antioxidant capacity (Shinde, Sharma, Xu, Dhalla, & Goyal, 2004), preventing T2DM complications (Anderson et al., 2001; Anderson, 1998). However, the mechanisms involved are still unclear (Panchal, Wanyonyi, & Brown, 2017). Organic Cr such as CrPic is absorbed better than inorganic Cr, a condition which favors redox interactions with the former (Lewicki et al., 2014). This can explain the observed advantageous outcomes of CrPic supplementation.

Therefore, we hypothesized that the main role of CrPic is the activation of IRS-1, PPAR-γ and AMPK, which improves glycemia and insulin transduction signal in the target tissue and consequently regulating glucose metabolism. This key mechanism may improve lipid profile by reducing lipid peroxidation, and increasing the levels of alpha-tocopherol, ascorbic acid, SOD, CAT, GSH and GR. Thus, Cr may restore the antioxidant system and improve hepatic function. In addition, the effects of CrPic supplementation in low doses (1 mg CrPic/Kg of body weight) observed in three studies included in this review indicate that it may improve glucose homeostasis. More studies are necessary to verify the action of Cr in different animal models of T2DM submitted to CrPic supplementation, in order to find an optimal dose for T2DM control, which is safe, and does not present a risk of toxicity.

3.2.2. Human studies

We identified five studies that analyzed Cr in T2DM individuals, of which one is an observational study (Table 2). The studies used Cr supplements in the form of chromium nicotinate (Guimarães, Carvalho, & Silva, 2013, 2016; Paiva et al., 2015) or CrPic (Cefalu et al., 2010). In the observational study, Ahmed and Helal (2012) found an inverse correlation between low Cr concentration and increased biochemical parameters, such as glycated hemoglobin (HbA1c), TC, TG and LDL-c (Table 2). Previous studies showed that the absorption and excretion of Cr in T2DM individuals are higher than individuals without diabetes (Hamad, Krishan, Quasem, & Mazahreh, 2009), since inflammation in T2DM individuals causes excess iron (Vela et al., 2017), which competes with Cr for transferrin, an iron-binding plasma glycoprotein also responsible for the cellular transport of Cr (Da Silva & Cozzolino, 2007).

Supplementation of Cr in humans was evaluated using clinical, randomized and controlled studies with placebo (Table 2). The studies

Table 2
Characteristics of the human studies.

Author/year	Type of study	Study population	Trace element/ formulations used	Duration	Intervention	Observed effects on T2DM
Guimarães et al., 2016	Clinical, randomized	n = 42 M/W Age: 30–60 y T2DM	Chromium nicotinate	12 weeks	– NC0: placebo (cellulose and Mg stearate) – NC50: 50 μg chromium nicotinate – NC200: 200 μg chromium nicotinate – Maintained lifestyle	↓ HOMA-β in NC50 ↓ Body weight in NC50
Paiva et al., 2015	Clinical, randomized	n = 71 M/W Age: 30–70 y T2DM	Chromium picolinate	16 weeks	– T2DM: placebo (90 mg lactose, 23,5mg microcrystalline cellulose, 1,2mg aerosil and 0,5 mg stearate) – T2DM + CrPic: 600 μg CrPic capsule (2 × daily 300 μg)	↓ Fasting blood glucose ↓ Postprandial glucose ↓ HbA1c ↑ Serum Cr
Guimarães et al., 2013	Clinical, randomized	n = 42 M/W Age: 30–60 y T2DM	Chromium nicotinate	12 weeks	– NC0: placebo (cellulose and Mg stearate) – NC200: 200 μg chromium nicotinate – NC50: 50 μg chromium nicotinate. – Maintained lifestyle	↓ HOMA-β in NC50 ↓ TG in NC50 and NC200 ↓ TC in NC50
Ahmed & Helal, 2012	Clinical, transverse, observational	n = 30 M/W T2DM Median age: 58 y n = 20 M/W healthy Median age: 58y	Chromium	–	–	Correlation: T2DM ↓ Cr ↑ TC, TG, LDL-c, HbA1c
Cefalu et al., 2010	Clinical, double-blind, randomized, placebo, controlled	n = 137 M/W Age: 30–70 y BMI: 25 to 40 Fasting blood glucose: 125 mg/dL T2DM	Chromium picolinate	24 weeks	– T2DM control: placebo 1000 μg calcium diphosphate (500 μg 2x day) – T2DM + CrPic: 1000 μg CrPic (500 μg 2x daily). – All were instructed to consume a weight maintenance diet	↓ Glycemia, HbA1c and AUC glucose in T2DM + CrPic respondent at the end compared with pre-intervention and placebo and T2DM + CrPic nonresponsive ↑ Glycemia and HbA1c in T2DM + CrPic respondent compared to nonresponsive and placebo in pre-intervention
Othman et al., 2016	Observational, control case	n = 82 M/W newly diagnosed T2DM n = 82 M/W healthy Age: 35–55 y	Serum Selenium	–	–	↑ BMI, visceral fat, WC, ↑ Blood pressure, ↑ HbA1c ↑ Oxidative stress Correlation: ↑ Se – ↑ DNA damage markers
Faghihi et al., 2014	Clinical, randomized	n = 60 M/W Age:18–70 y T2DM	Sodium selenate	12 weeks	– T2DM (placebo) – T2DM + Se: sodium selenite (200 μg/day). – Maintained diet and PA	↑ Glycemia and HbA1c ↑ HDL-c ↑ Plasma Se
Seet et al., 2011	Clinical randomized	n = 40 M Age: ≥21 y T2DM	Zinc gluconate	12 weeks	– T2DM control: placebo (99% microcrystalline cellulose + 1% stearate Mg) – T2DM + ZnG: capsule 200 mg zinc gluconate (2 × 100 mg day)	↑ Serum Zn ↓ Serum Cu
Afkhami et al., 2008	Clinical, randomized, controlled	n = 40 M/W Median age: 52 y T2DM	Zinc sulfate	6 weeks	– T2DM: control – T2DM + Zn: zinc sulfate 660 mg (3x/ 220 mg day). – Maintained diet and PA	↓ TG, TC, LDL-c ↓ SBP ↓ HbA1c

↑: increase; ↓: decrease; AUC: area under the curve; BMI: body mass index; Cr: chromium; CrPic: chromium picolinate; Cu: copper; DNA: deoxyribonucleic acid; HbA1c: glycated hemoglobin; HDL-c: high density lipoprotein; HOMA-β: homeostasis model assessment-pancreatic β cell function; IS: insulin sensitivity; LDL-c: low density lipoprotein; M: men; Mg: magnesium; n: sample number; NC: chromium nicotinate; PA: physical activity; SBP: systolic blood pressure; Se: selenium; T2DM: type 2 diabetes mellitus; TC: total cholesterol; TG: triglyceride; W: woman; WC: waist circumference; y: years; Zn: zinc; ZnG: zinc gluconate.

observed improved glycemic profile, reduced fasting glucose, postprandial glucose, and Hb1Ac (Cefalu et al., 2010; Paiva et al., 2015), improved homeostasis in model assessment-pancreatic β cell function (HOMA-β) (Guimarães et al., 2013, 2016), decreased area under the curve (AUC) (Cefalu et al., 2010) and body weight (Guimarães, Carvalho, & Silva, 2016) (Table 2). The improved lipid profile was observed along with a reduction of TG and TC (Guimarães, Carvalho, & Silva, 2013) (Table 2).

These results agree with the literature, indicating that Cr is strongly related to improved insulin sensibility because it increases the number of insulin receptors, which favors insulin binding and sensibility (Sahin et al., 2013). Dyslipidemia, a common condition in diabetes, increases the risk of CVD by two to four times (Sociedade Brasileira de Cardiologia, 2013, 2014). Similar to animal studies, Cr improved glucose metabolism and lipid profile in humans (Sundaram et al., 2012; Sundaram, Singhal, et al., 2013; Sundaram, Aggarwal, et al., 2013). In this review, Cefalu et al. (2010) did not observe a decrease in body weight and change in body fat distribution after 1000 μg/day supplementation of CrPic for 24 weeks, however Guimarães et al., 2016 observed a decrease in body weight with supplementation of 50 μg/day of chromium nicotinate for 12 weeks. This discrepancy may be due to the use of different compounds, doses and experimental designs. Despite the beneficial effects of Cr supplementation on T2DM, evidence in humans is still divergent, especially due to study heterogeneity (Costello, Dwyer, & Bailey, 2016). Thus, more studies that analyze Cr as regards its bioavailability, safe dose and supplementation time for the control of T2DM are needed.

3.3. Selenium

3.3.1. Animal studies

We identified three studies that analyzed the action of Se in diabetic animals (Table 1). Dhanya et al. (2014) supplemented male Sprague Dawley rats with 1 μg/Kg sodium selenite equivalent to 0.45 μg of Se during four weeks and observed a decrease of oxidative stress through the enhancement of SOD, CAT, glutathione peroxidase (GPx) lipid peroxidation in the form of malondialdehyde (MDA), and decrease in hydroperoxides and conjugated dienes. In addition, an improvement of inflammation was observed with a decrease in 5-lipoxygenase (5-LOX), cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF-κB) expression and C-reactive protein (CRP), as well as an improved glycemic profile with consequent decrease in glycemia and HbA1c. Xu et al. (2009) carried out an experiment with male Sprague Dawley rats treated with 180 μg/Kg sodium selenite combined with 1 U/Kg insulin and observed a decrease in glycemia and HbA1c and an increase of GLUT4 in the cardiac membrane. However, Aydemir-Koksoy and Turan (2008), supplemented male Wistar rats with sodium selenite, 15 μmol/kg, for four weeks and observed a decrease in caveolin-1 (Cav1) expression, Na +/K+ ATPase, metalloproteinase-2 (MMP-2) activity, and aorta mitogen-activated protein-kinase 42/44 (MAPK42/44) phosphorylation inhibition (Table 1).

The glycemic profile observed by Xu et al. (2009) may be explained by the synergistic association between Se and insulin. Considering GLUT4 as insulin-dependent, it can be hypothesized that Se can improve the effect of insulin in the rats by increasing GLUT4 translocation, enhancing glucose uptake and glycemic control (Fig. 2). Moreover, Se participates in glucose metabolism through redox-active selenoproteins. Cellular redox potential regulates insulin secretion and signaling which may influence insulin-dependent metabolic pathways (Steinbrenner, 2013).

Se exhibits antioxidant activity and serves as a cofactor of GPx, which decomposes both peroxide lipids and inorganic compounds (Balaban, Nazıroğlu, Demirci, & Övey, 2017; Demirci, Nazıroğlu, Övey, & Balaban, 2017; Kahya, Nazıroğlu, & Övey, 2017). The function of Se is evident in selenoproteins, which are Se-dependent proteins responsible for peroxide removal, reduction of oxidized proteins and/or lipids and regulation of redox signaling (Cominetti, Bortoli, Abdalla, & Cozzolino, 2011). This fact may explain the improved antioxidant status and lipid profile with Se supplementation.

Se reduces lipopolysaccharides (LPS), which inhibit AMPK and decreases tumor necrosis factor, resulting in a reduction of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), leukocyte adhesion molecule-1 (E-selectin) and COX-2. (Vunta et al., 2008). Se regulates GPx enzyme in low concentrations of ROS (Kretz-Remy & Arrigo, 2001), by inhibiting the phosphorylation of the kappa B inhibitor (IκB-α) and consequently the NF-κB translocation, reducing inflammatory cytokines. Another mechanism is that Se can affect adhesion of monocytes to endothelial cells through L-selectin modulation, which facilitates the migration of neutrophils in response to inflammation (Wang, Fuster, Sriramarao, & Esko, 2005).

MMP-2 activity is activated by ROS (Okamoto et al., 2001). It can be suggested that Se, a cofactor of GPx enzyme, decreases the concentrations of ROS, and consequently diminishes MMP-2 activation. Moreover, Cav1 expression inhibits nitric oxide, important for the relaxation of the vascular smooth muscle walls (Trane et al., 2014). In the literature, the effect of Se on MAPK42/44 activation has been evaluated in few studies, however the findings were conflicting (Kim, Johnson, Shin, Sharma, & Sharma, 2004; Sarker et al., 2003). In T2DM, there was a decrease in the activity and expression of Na+/K + ATPase (Iannello, Milazzo, & Belfiore, 2007). Its regulation involves protein kinase A (PKA), protein kinase C (PKC) and tyrosine kinases. Se decreases PKA and PKC phosphorylation (Gopalakrishna & Jaken, 2000), restoring Na +/K + ATPase function (Aydemir-Koksoy & Turan, 2008).

3.3.2. Human studies

Two studies addressed Se supplementation in humans, one being an observational study (Othman et al., 2016) and the other a clinical trial (Faghihi et al., 2014) (Table 2). In the observational study, Othman et al. (2016) analyzed 82 T2DM subjects and 82 healthy subjects and reported higher body mass index (BMI), visceral fat, waist circumference (WC), blood pressure, HbA1c, and oxidative stress in T2DM subjects compared with healthy subjects. They also reported a positive correlation between plasmatic Se and DNA damage marker in subjects with T2DM (Table 2). Se may have acted as a damage inhibitor and DNA repair promoter, offering protection against oxidative stress and considered an indicator of metabolic response (Battin, Perron, & Brumaghim, 2006; Fischer, Mihelc, Pollok, & Smith, 2007; Seo, Sweeney, & Smith, 2002).

Faghihi et al. (2014) supplemented 200 μg/day sodium selenate in men and women with T2DM for 12 weeks and found an increase in fasting blood glucose, Hb1Ac, HDL-c and plasma Se levels (Table 2). The increase in plasma Se may have been responsible for the adverse effects on glucose homeostasis, since there was a reduction in glycemia in the placebo group. A possible mechanism is that Se increases selenoproteins, which increases ROS production in the mitochondria culminating in the disruption of insulin signaling (Wang et al., 2014). Further studies on the antioxidant mechanisms of Se are necessary since it can either generate ROS or act as an antioxidant depending on dose. Furthermore, studies that evaluate the effect of Se on glucose homeostasis are also necessary, since an excess supplementation of Se in patients with T2DM may induce hepatic IR.

3.4. Zinc

3.4.1. Animal studies

Two studies analyzed the supplementation of zinc sulfate in Swiss female mice with 100 mg/Kg of body weight (Karatug et al., 2013; Ozsoy et al., 2012) (Table 1). The authors observed a decrease in glycemia, lipid peroxidation, non-enzymatic glycosylation, urea and creatinine (Karatug et al., 2013) and an improvement in antioxidant status evidenced through the reduction of GSH (Karatug et al., 2013; Ozsoy et al., 2012), CAT, GPx, myeloperoxidase (MPO) and carbonic

anhydrase (CA) (Ozsoy et al., 2012) (Table 1).

Zn acts as a structural and functional compound of metalloenzymes and metalloproteins. It participates in various reactions as regards cellular metabolism, immune function, antioxidant defense, and growth and development. The antioxidant properties of Zn are explained through the regulation of metallothionein synthesis in the structure of SOD and the protection of sulfhydric groups present in membrane proteins. Zn promotes the inhibition of ROS production by antagonizing pro-oxidant metals, such as iron and copper (Marreiro et al., 2017). It also activates GSH, GPx and CAT, which are able to neutralize ROS, decreasing oxidative damage (Marreiro et al., 2017). In the study of Ozsoy et al. (2012), an increase in these enzymes were found in the diabetic individuals, however with Zn supplementation, a decrease of these enzymes was observed, indicating a reduction in oxidative stress. CA may be involved in oxidative stress, and may contribute to increased lipid peroxidation and T2DM complications such as nephropathy, with CA found in kidney mitochondria (Sarkar, Kar, Mondal, Chakraborty, & Kar, 2010). Zn showed itself to be efficient in reducing lipid peroxidation, observed by a reduction in CA and MPO.

Hyperglycemia changes oxidative state by increasing ROS production, which may increase non-enzymatic glycosylation (Zheng, Ma, Wu, & Lu, 2012). In addition, Zn has the capacity to reduce non-enzymatic glycosylation in kidneys of animals with T2DM (Karatug et al., 2013). This is probably related to its insulinomimetic effect, which improves glucose homeostasis and IR, and consequently antioxidant status, reducing oxidative stress in T2DM animals (Kloubert & Rink, 2015). T2DM increases urea and creatinine markers, which may cause renal damage. However, Zn was efficient in reducing these markers, improving renal function (Karatug et al., 2013).

3.4.2. Human studies

Two clinical randomized studies assessed Zn supplementation in patients with T2DM. Seet et al. (2011) used 200 mg/day of zinc gluconate supplement for 12 weeks and noticed an increase and decrease in serum Zn and Cu, respectively (Table 2). In the study of Afkhami, Seid, and Forough (2008), 660 mg/day of zinc sulfate supplement was used by 40 patients during six weeks. A decrease of TG, TC, LDL-c and systolic blood pressure after six weeks was reported as well as a decrease of HbA1c after 12 weeks (Table 2), showing the long term effect of Zn supplementation.

A 660 mg/day of Zn sulfate supplement (Afkhami et al., 2008) corresponds to 150 mg of elemental Zn (Ativus Farmacêutica LTDA, n.d.) which exceeds UL. It was found that two of the 40 participants reported mild abdominal pain; nevertheless, they were able to complete the study. Similarly, Seet et al., 2011 conducted the experiment with 200 mg of Zn gluconate, corresponding to 240 mg of elemental Zn. Fifteen of the 40 participants in the study reported mild symptoms of gastrointestinal intolerance in the first days of the intervention but all participants completed the study. The authors justified the supplement dosage and the chosen intervention period based on the safety profile reported in previous studies. Regarding current knowledge on Zn supplementation, there are no specific Zn intake recommendations for patients with T2DM. Therefore, researchers should use Dietary Reference Intakes as the basis for the general population (Institute of Medicine, 2011). Although the bioavailability of Zn is affected by a lot of physiological and dietary factors, its UL is established. Thus, the elevated doses used in both studies are not justified (Della Lucia et al., 2014; World Health Organization. (1996) (1996), 1996).

T2DM individuals should take Zn supplements only in the case of zinc deficiency. Zn deficiency is considered an aggravating factor for hypertension. The capacity of SOD antioxidant enzyme to catalyze superoxide ($O2-$) is dependent on zinc and copper cofactors. When there is a decrease in Zn concentrations, there is excess $O2-$ formation which reduces SOD activity. These excess $O2-$ reacts with nitric oxide to form peroxynitrite, which mitigates nitric oxide concentrations (Carpenter, Lam, Toney, Weintraub, & Qin, 2013). Therefore, the reduction of this mineral may affect blood pressure by reducing Cu/Zn-SOD enzyme activity.

Zn has structural, catalytic, regulatory and immunological functions, and interferes in macronutrient metabolism (Institute of Medicine, 2011). Regarding glycemic metabolism, Zn participates in the synthesis, storage, crystallization and secretion of insulin (Capdor, Foster, Petocz, & Samman, 2013; Maruthur, Fu Mao, Kao, & Shuldiner, 2016; Shan et al., 2014). This mineral is found in the pancreatic β-cells responsible for insulin receptor phosphorylation and regulation of tyrosine phosphatase signaling (Shan et al., 2014). Moreover, Zn enhances the binding of insulin to its receptors, by increasing glucose transporter translocation to the plasma membrane, a process which improves glycemic profile, stimulates lipogenesis, and consequently improves lipid profile (Chausmer, 1998; Maret, 2005; Praveeena, Pasula, & Sameera, 2013).

3.5. Vanadium

3.5.1. Animal study

Only one animal study was found. The study was conducted with Swiss male mice, which received a supplementation of 100 mg/Kg of vanadium sulfate (Kurt et al., 2011) (Table 1). The authors observed improved glycemic profile and antioxidant status, with reduced glycemia and antioxidant enzymes like SOD, CAT, GR, GPx and glutathione-S-transferase (GST) (Kurt et al., 2011) (Table 1).

Studies in the literature showed that V and its compounds are potent for glycemic control, being capable of reducing hyperglycemia and hyperinsulinemia, and producing insulin-mimetic effects. Furthermore, it improves glucose homeostasis in animals (Meyerovitch, Rothenberg, Shechter, Bonner-Weir, & Kahn, 1991; Ramanadham, Cros, Mongold, Serrano, & McNeill, 1990). Insulin sensitivity may be modulated by phosphotyrosine phosphatase inhibition (PTP), through the stimulation of tyrosine quinase receptors (RTK) (García-Vicente et al., 2007; Thompson, 1999). However, studies suggest that V stimulates glycose absorption regardless of any change in RTK activity (García-Vicente et al., 2007). In diabetic rats, the decrease of glycemia may be due to increased GLUT4 translocation to the skeletal muscle membrane caused by V (Mohammad, Sharma, & McNeill, 2002) coupled with muscular glycogen synthesis activation and stimulation of protein phosphatase-1 activity by insulin (Semiz, Orvig, & McNeill, 2002).

In T2DM, the increase in free radicals leads to lipid peroxidation, oxidative stress and cellular integrity harm. Oxidative stress increases antioxidant defense, which may increase the expression of these enzymes. V can be considered antioxidant or pro-oxidant, depending on its dosage and can accelerate the oxidative deterioration of biomolecules (Wronska-Nofer, Wisniewska-Knypl, Dziubaltowska, & Wysznska, 1999). Thus, the reduction of these antioxidant enzymes may be a feedback mechanism to maintain homeostasis of the antioxidant system.

Although the current review does not contain studies with V supplementation in humans, it is important to relate its effects in humans. A systematic review of individuals with T2DM showed a clinical efficacy of vanadyl sulphate oral supplementation for glycemic control. However, the quality of the evidence was low due to the study design (Smith, Pickering, & Lewith, 2008).

V supplementation recommended for diabetic patients is approximately 60 mg/day (Bhuiyan et al., 2007; Ivancsits, Pilger, Diem, Schaffer, & Rudiger, 2002). Its toxicity inhibits cellular respiratory processes, compromising oxidative metabolism and antioxidant enzymes (Boulassel, Sadeg, Roussel, Perrin, & Belhadj-Tahar, 2011; Domingo, 2002; Gruzewska, Pawelczyk, & Bielarczyk, 2014). Thus, V supplementation should be analyzed carefully because high doses may result in adverse effects and metabolic alterations (O'Connell, 2001; Yeh, Eisenberg, Kaptchuk, & Phillips, 2003). Also, more human studies focused on V supplementation are necessary.

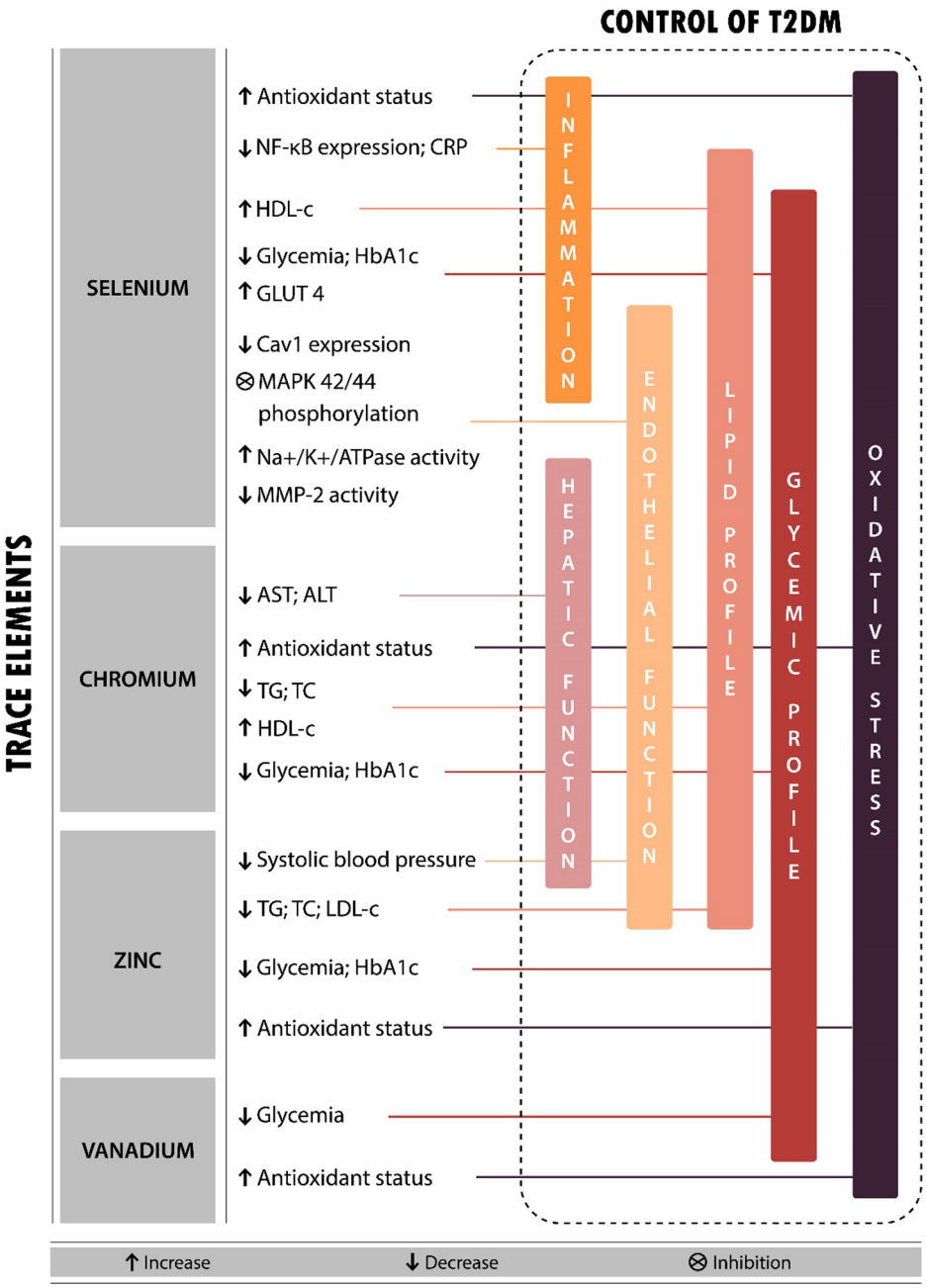

Fig. 2. The main effects of trace elements in control of T2DM were proposed based on the results of animal and human studies. This control is due to the effect of these trace elements on glycemic and lipid profile, antioxidant status and inflammation, which favor the improvement of oxidative stress and lipid peroxidation, and reduction of inflammatory processes. Therefore, the control of these biomarkers improves the regulation of hepatic and endothelial functions in T2DM individuals. ALT: alanine aminotransferase; AST: aspartate transaminase; Cav1: Caveolin; CRP: C-reactive protein; GLUT4: glucose transporter type 4; HbA1c: glycated hemoglobin; HDL-c: high density lipoprotein; LDL-c: low density lipoprotein; MAPK 42/44: mitogen-activated protein kinase 42/44; MMP-2, metalloproteinase-2; NF-κB: nuclear factor kappa B; T2DM: type 2 diabetes mellitus; TC: total cholesterol; TG: triglyceride.

3.6. Ranking of effectiveness of the trace elements

The effects of trace element supplementation on T2DM were evaluated based on number of articles (both animal and human studies). An improvement in the metabolic control of T2DM due to trace elements was observed. Therefore, effectiveness of these elements in the control of T2DM was ranged, being Se the most effective, followed by Cr, Zn and V. The most studied trace element was Cr, appearing in eight studies. Despite this, no information about the effect of Cr on inflammatory and endothelial parameters was reported. On the other hand, five studies showed that Se has an effect on inflammatory and endothelial parameters. Zn improved lipid and glycemic parameters, antioxidant status and endothelial function. V appeared in only one animal study and was effective in improving glycemic profile and antioxidant status.

3.7. Main strengths and weaknesses

Although the systematic search included all trace elements, only results for Cr, Se, Zn and V were found. Based on animal studies, the mechanisms and pathways of the trace elements in relation to T2DM were elaborated. Furthermore, the trace elements were ranked according to effectiveness in the metabolic control of diabetes. A limitation of the study lies in the non-assessment of IR in animal tests where diabetes was induced by STZ and HOMA-IR. As previously mentioned, STZ induces the rapid death of pancreatic beta cells, which is different from the processes observed in humans with T2DM. Despite this, some animal studies used STZ at low dosage combined with a HFD or high carbohydrate diet (HCD) to induce T2DM. Moreover, the designs of the animal and human studies were very heterogeneous, making it difficult to reach a plausible conclusion on the recommended dosage for the control of T2DM. Studies with animals presented insufficient information about experimental and statistical methods, related to

randomization, research blindness and study design. Thus, we suggest that future studies on T2DM be carried out in different animal models following the ARRIVE guidelines, which can improve research quality and avoid possible bias. This can permit the extrapolation of future data to humans. At the same time, we suggest more clinical trials to verify the mechanisms of trace elements as well as their optimal dosage.

4. Conclusion

The supplementation of trace elements improves glycemic and lipid profile, antioxidant status, endothelial function and inflammation. Within the scope of this review, Se was the most effective trace element for the metabolic control of T2DM, followed by Cr, Zn and V. However, trace element supplements should be taken under professional guidance and following established recommendations since high doses of some trace elements can be toxic. Accordingly, more animals and human studies are needed to elucidate the metabolic pathways of trace elements in the control of T2DM as well as establish an effective and safe dose according to intervention time and element.

Ethics statements

The authors state that the study is based on a systematic research on literature data. Therefore, there was no experiment with humans or animals.

Conflict of interest

The authors declare that there is no conflict of interest.

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