Chromium supplementation and type 2 diabetes mellitus: An extensive systematic review

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Abstract

Diabetes is a global public health concern with increasing prevalence worldwide. Chromium (Cr), a trace element found in soil, water, and food, has been proposed to have a possible positive effect in glucose metabolism and diabetes mellitus prevention. However, the relationship between trivalent chromium (Cr (III)) exposure, mainly through the consumption of diet supplements, and type 2 diabetes mellitus (T2DM) remains controversial. An extensive systematic review of the current literature on randomized controlled studies (RCTs) was conducted, using the databases, PubMed, Scopus, ScienceDirect, and Cochrane, with specific keywords and inclusion as well as exclusion criteria. After close screening of the research studies retrieved from the mentioned websites was conducted, the most related studies were included in the final systematic review. The studies were evaluated for the degree og relevance, quality, and risk bias, using appropriate quality assessment tools. Several of the included RCT studies reported possible benefits of Cr (III) supplementation, mainly in the form of chromium picolinate (CrPic), chromium yeast (CY), chromium chloride ($CrCl_3$), and chromium nicotinate (CrN). The dosage of chromium was between 50 and 1000 μg/day and it was consumed from 2 to 6 months. Glycemic control markers, including FPG, insulin, HbA1C, and HOMA-IR levels, significantly decrease following chromium supplementation, mainly in studies with a longer intervention period. Supplementing with chromium (Cr) indicated that could significantly improve lipid profile by raising high-density lipoprotein (HDL) and lowering triglyceride (TG) and total cholesterol (TC) while having little effect on low-density lipoprotein (LDL). However, most research findings include significant limitations, such as inconsistent dosage and type of chromium, formulation of supplements, and study duration. Further well-designed and high-quality research is needed to fully understand the role of chromium dietary supplementation and the potential risks related to its mechanisms of action, type, and dose, in the prevention and treatment of type 2 diabetes mellitus (T2DM).

1. Introduction

Diabetes mellitus is characterized as a chronic metabolic disorder with significantly elevated blood glucose levels (HBG) (Yeghiazaryan, et al., 2012). Globally, diabetes mellitus is a major public health issue due to its high prevalence, morbidity, and mortality (Chen et al., 2012; Cho et al., 2018). According to the International Diabetes Federation (IDF), the global prevalence among adults between the ages of 20-79 was 10.5% in 2021 and is expected to double to 46% by 2045. Patients suffering from diabetes mellitus, are at greater risk for stroke, kidney failure, heart attack, lower limb amputation, and blindness (Deshpande et al., 2008). However, there are millions of people worldwide with diabetes, with half of them unaware of its impact on the body, treatment options, or even that they have the condition.

The etiology of the chronic condition is multifactorial wit genetic and environmental factors being the main source. Environmental contributors include contributors such as exposure to air pollutants and heavy metals leading to the development and progression of the condition. In addition, dietary factors, such as the daily intake of dietary supplements of various minerals, contribute significantly to the pathogenesis of diabetes mellitus. Type 2 diabetes mellitus (T2DM) has been proposed to be treated mainly using drug therapies, combined with the administration of appropriate nutritional supplements and daily lifestyle modification. Many diabetes patients focus on the intake of herbal products and food supplements, such as chromium (Cr), vitamin D, magnesium, n-3 polyunsaturated fatty acids (PUFAs) and zinc. Dietary supplements are in high demand due to their lower purchase price, easy access to stores and simple administration. However, the effectiveness of the treatment and prevention of diabetic patients remains a controversial issue (Koh-Banerjee et al., 2004).

In recent years, more and more diabetic patients choose chromium-rich diet or the intake of dietary supplements containing Cr to supplement their existing drug therapy. Cr-containing compounds are abundant in the environment (Flachuk, 1998). In nature, Cr can be found in two main forms, with the one being trivalent chromium (Cr (III)) in the form of Cr oxides and hydroxides and the other being hexavalent chromium (Cr (VI)) in the form of chromate salts. According to the oxidation state of Cr, there are beneficial and harmful effects on human health (Georgaki et al., 2023). Although hexavalent chromium is characterized as strongly carcinogenic (Mishra et al., 2016) and mutagenic (Costa et al., 1997) trivalent chromium is an essential trace element for the human body (Stern, 2010) with an important role mainly in glucose metabolism and in the prevention of diabetes (Georgaki et al., 2023). Drinking water is one of the main ways in which humans are exposed to Cr(VI) and is responsible for significant damage to vital organs, while Cr (III) is mainly found in food and dietary supplements.

It is important to mention that Cr (III) is one of the fifteen essential trace elements, for the proper functioning of the metabolism for both lipids and carbohydrates (Vincent, 2000). Foods characterized as rich in trivalent chromium include egg yolks, almonds, whole grains, broccoli, beer, and wine (Anderson et al., 1992; Campbell, 2001; Wang & Cefalu, 2010). There are several forms of Cr supplementation accessible, such as trivalent chromium chloride ($CrCl_3$), which is widely present in common foods like broccoli, green beans, and whole grains (Dubey et al., 2010). Another synthetic substance called trivalent chromium picolinate (CrPic) is an additional variant (Yin and Phung, 2015). Currently, there is limited data available regarding the degree of absorption and the dosage level needed required. According to national health agencies, the recommended daily dosage of chromium supplements for both genders is between 25 and 35 mg (Rabinovitz et al., 2004).

Previous studies have reported beneficial effects of the chemical, which is involved in insulin activation and glucose metabolism by lowering blood sugar, while its deficiency has been associated with impaired glucose tolerance, insulin resistance, and a lipid profile that confirms the two others (Anderson, 1998; Wang & Cefalu, 2010; Derakhshanian et al., 2017). A case-control study investigated the relationship between Cr metabolism, diabetes mellitus, and cardiovascular risk, concluding that Cr levels correlate with insulin and C-reactive protein (CRP), suggesting an important role in their secretion. Furthermore, higher Cr levels are associated with lower blood pressure (LBP) and improved lipid profile (LP) (Yin & Phung, 2015), thereby reducing cardiovascular risk (Ngala et al., 2018). Contrasting results were found in a literature review, with a limited effect of Cr supplementation on improving glycemic control (HbA1c) and fasting plasma glucose (FPG) and improving type 2 diabetes (T2DM). Only five of twenty RCTs on chromium supplementation in T2DM patients showed an FPG of less than 7 .2 mmol/dL, while five of the fourteen trials found a drop in HbA1c greater than 0.5% (Costello et al., 2016).

Results from therapeutic trials using Cr (III) supplementation have been inconclusive. The large quantitative difference among the results is due to lack of standard protocol when it comes to the implementation of the experiments. The difference of duration and randomized as well as non-randomized designs

play a crucial role when it comes to the examination of a research papers and built-up of an experimental study. Thus, data out of the ideal intervals must be excluded for more accurate results (Landman et al., 2014).

In the present investigation, an extensive systematic review of the recent scientific literature, randomized controlled trials (RCTs) with treatment intervention, was performed to evaluate the effectiveness of chromium in the prevention, management, and treatment of type 2 diabetes mellitus. Synthesis of existing research on the potential beneficial health effects, focusing on type 2 diabetes mellitus of dietary chromium supplementation provides important insights into the effects on glucose metabolism and insulin resistance, reducing complications of the condition.

2. Methods

2.1. Search Strategy and Selection of Randomized controlled trials (RCTs)

The current study was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standard (Moher et al., 2009). The databases PubMed, Scopus, ScienceDirect and Cochrane were used to conduct a thorough search of the scientific literature through January 15, 2024. Searches were made using subject heading (MeSHs), abstracts, related keywords, specified language and type of study.

Databases were systematically searched from January 1, 2000, to January 2024, using the following search keywords: chromium, Cr (III), CrPic, $CrCl_3$, trivalent chromium, chromium picolinate, chromium chloride, chromium supplementation, diabetes, diabetic, diabetes mellitus, type 2 diabetes mellitus, insulin resistance, T2DM, insulin, glucose, glucose tolerance. Two authors (M.-N.G and S.T.) conducted the research simultaneously and in duplicate. Any differences in this regard were resolved via discussion with the third researcher (S.K.).

2.2. Eligibility Criteria (Inclusion and Exclusion)

Two investigators chose appropriate articles by examining titles, abstracts, and the full text of the publications. The research question was defined as the relationship between type 2 diabetes mellitus and consumption of chromium, particularly through dietary supplementation. All available full text human RCTs with treatment intervention, in English language, that stated the effect of chromium supplementation on type 2 diabetes mellitus, were evaluated.

Concisely, inclusion criteria were as follows: Original research studies investigating (1) the relationship between chromium supplementation and type 2 diabetes mellitus on humans, (2) the impact of chromium supplementation on glycemic control indicators, including insulin, hemoglobin A1C (HbA1C), fasting plasma glucose (FPG), and the homeostatic model assessment for insulin resistance (HOMA-IR) in people diagnosed with type 2 diabetes mellitus, and (3) studies that used human samples, and (4) studies that were published in English between January 1, 2000, and January 15, 2024.

Exclusion criteria were outlined as follows: (1) Studies without any comparing control group, (2) Non-randomized controlled trial with treatment intervention, animal studies, in vitro studies, review articles, meta-analyses, cross-sectional studies, cohort studies, case-control studies, and observational studies, (3) RCTs with treatment duration less than 2 weeks, (4) Studies not investigating the link between type 2 diabetes mellitus and chromium or investigating the correlation with other micronutrients, and not alone and (5) Studies which focus on related metabolic disorders and on women with other related disorders like polycystic ovary syndrome, (6), Studies published in languages other than English.

The chosen trials were greater sample size to prevent duplication. Conflicts about the study selection procedure were resolved through in-person conversations.

2.3. Data Extraction and Analysis

Two reviewers independently screened the titles and abstracts of the studies identified by the search strategy. Full texts of eligible studies were retrieved and assessed for eligibility. Data were extracted using pre-designed abstraction form, from the eligible studies, including first author with publication year, study design, location – study's country, type of patient, length of trial, total sample size, population characteristics, type, and dose of treatment of chromium.

2.4. Quality assessment of Randomized controlled trials (RCT)

The quality of the studies was assessed using the Cochrane Risk of Bias tool for Randomized controlled trials (RCT) (Higgins et al., 2011). The results quality assessment tool provides a framework for examining the risk of bias in the findings of any type of randomized trial. The assessment is divided into a series of six different domains, through which bias can be introduced into a test. Two researchers (M.-N.G. and S.T.) assessed the quality of the eligible studies using the tools of the Cochrane Collaboration, in the following six domains: 1) Create a random sequence-Randomization. 2) Deception of allocation. 3) Participant and personnel blinding. 4) A blind evaluation of the result. 5) Incomplete results & biased reporting, 6) Further biased sources (Higgins et al., 2011). There were three categories assigned to each domain: low, unclear, and high risk of bias (Higgins et al., 2011).

3. Results

3.1. Flowchart and studies selection

From a total of 1.129 publications that were obtained by the combined searches on databases Pubmed, Scopus, ScienceDirect, Cochrane, and other additional sources like Google Scholar and Academic databases, 346 were removed because they were duplicates publications and 783 were evaluated by title and whole abstract. After reading title and abstracts, 731 were excluded because they were unrelated to the topics- they were not randomized clinical studies, but they were observational studies, epidemiological studies, animal studies, review studies, previous systematics reviews and metanalysis. Other studies evaluated patients without type 2 diabetes mellitus but related diseases or they evaluated other substances on food or other dietary supplementation without

chromium. When full-text version of remaining 52 articles were read, 37 studies did not fulfill the inclusion criteria. Finally, 15 RCTs were included in the systematic review (Fig1., Table 1-2), and they were evaluated (Table 3) with Cochrane assessment tool of quality.

3.2. Main characteristics of selected studies

The included RCT studies which were published between 2002-2023, included a total of 1.223 participants and were conducted in 11 different countries. The studies provided evidence for a potential link between chromium (picolinate, chloride, yeast, nicotinate) exposure through dietary supplementation and affection of type 2 diabetes mellitus (Table 1). Previous several studies had identified significant associations between chromium supplementation and inadequate glucose regulation or insulin resistance, indicating that chromium supplementation may benefit glucose metabolism in type 2 diabetes.

The design of the included trials was either a double-blind randomized placebo-controlled study, or single-blind randomized placebo-controlled study, and a parallel or crossover study. The mean age of the participants ranged from 30 to 70 years. All studies were done on both genders except for two trials that did not report the distinction of the genders of participants. Participants in all studies were patients with type 2 diabetes mellitus. In each study there were specific criteria for the patient-participants in the research. Most studies excluded diabetic patients with preexisting chronic conditions or a family history of cardiovascular disease, a history of liver or kidney disease, sickle cell anemia, or metabolic disorders, including uncontrolled hypertension, hypothyroidism, or hyperthyroidism. Patients also with a gastrointestinal disorder, peptic ulcer, severe constipation, or diarrhea requiring long-term medication, lactose intolerance, pregnant and lactating women, patients who have recently undergone surgery or had an acute infection, renal dysfunction with serum creatinine 1.5 mg /dl or greater, increased liver enzymes aspartate aminotransferase and aminotransferase (AST) (ALT) more than 2.5 times. People who used drugs or consumed alcohol daily were also excluded from the studies (Table 2).

3.3. Assessment of studies methodological quality

Eleven researches indicated an unclear possibility of bias, whereas four studies revealed a random assignment of participants. Five trials with allocation concealment were reported, and the remaining trials had an unclear risk of bias. Bias in participants, individuals, and evaluation of outcomes blinding was minor throughout the most of trials. Based on incomplete outcome data and selective reporting, six studies reported a low probability of bias. For further biased sources, ten studies indicated a low risk of bias (Table 3). Overall, based on Cochrane tool scores, 7 studies were classified as good-quality (score > 3), 6 studies were fair-quality (score = 3), and 2 study were weak-quality (score < 2). More details of the risk of bias assessment are described in Table 2 and illustrated in Fig2..

Table 1. Main characteristics of studies selected.

Author/Publication	Study's Country	Study Design	Type of patient	Total Sample size	Male/Female (Sex)	M. Age (yo)	Duration of trial (months)	Intervention		
								Experimental Group	Dose of Chromium	Control Group
Ghosh et al., 2002	India	DBRP-CCS	T2DM	100	50M:50F	53-63	3	CrPic	400 µg	placebo
Vrtovec et al., 2005	Slovenia	DBRP-CCS	T2DM	60	NR	NR	3	CrPic	1000 µg	placebo
Racek et al., 2006	Denmark	RP-CPS	T2DM	36	9M:27F	60-70	4	CY	400 µg	placebo
Kleefstra et al., 2006	Netherlands	DBRP-CS	T2DM	46	19M:27F	60-62	6	CrPic	500 µg & 1000 µg	placebo
Lai, 2008	Taiwan	RP-CPS	T2DM	20	9M:11F	50-53	5	CY	1000 µg	placebo
Sharma et al., 2011	India	RP-CPS	T2DM	40	NR	35-67	3	CY	378 µg	placebo
Chen et al, 2013	Taiwan	DBRP-CS	T2DM	66	43M:23F	30–75	4	$CrCl_3$	200 lg/tablet	placebo
Rocha et al., 2014	Brazil	CRCT	T2DM	17	2M:15F	59	3	CrPic	100 µg BID	placebo
Paiva et al., 2015	Brazil	SBRP-CS	T2DM	71	25M:46F	30-70	4	CrPic	600 µg/day	placebo
Guimaraes et al., 2016	Brazil	DBRP-CS	T2DM	56	12M:30F	30-60	3	CrN	50 µg & 200 µg	placebo
Karim et al., 2018	Pakistan	DBRP-CS	T2DM	400	200M:200F	30-60	6	CrPic	200 µg/day	sitagliptin
Derosa et al., 2019	Italy	DBRP-CS	T2DM	164	38M:43F	62-63	6	CrPic	1/day	placebo
Imanparas et al.. 2020	Iran	RP-CS	T2DM	46	23M:23F	35-70	4	CrPic	500 µg	placebo
Talab et al., 2020	Iran	DBRP-CS	T2DM	41	7M:34F	50-51	2	CrPic	400 µg	placebo
Alkhalidi , 2023	Iraq	SBRP-CS	T2DM	60	28M:32F	40-60	3	CrPic	200 µg	placebo

Abbreviations: DBRP-CCS: Double-blind randomized placebo-controlled crossover study; RP-CS: Randomized placebo-controlled study; RP-CPS: Randomized p controlled study; CRCT: Crossover randomised controlled trial; DBRP-CS: Double-blind randomized placebo-controlled study; SBRP-CS: Single-blind randomize controlled study; T2DM: Type 2 diabetes mellitus; M: Male; F: Female; yo: years old; CP: Chromium picolinate; EG: Experimental group; CG: Control group; FPG plasma glucose; HbA1c: hemoglobin A1c; BMI: Body Mass Index; CHD: Coronary heart disease; BID: twice daily; NR: No Reply or Response; CrPic: Chromium p Chromium chloride; CrN: Chromium nicotinate; CY: Chromium yeast

Table 2. Eligibility criteria of selected studies

Author	Eligibility Criteria
Ghosh et al., 2002	Patients with diet alone for T2DM or diet and oral hypoglycaemic agents with reasonably stable (not optimum in all cases) glycemic control.
Vrtovec et al., 2005	No patients were using medications that could affect glucose homeostasis or QTc interval duration (thiazides, corticosteroids, phenothiazines, estrogens, sympathomimetics, type I and type II antiarrhythmic agents).
Racek et al., 2006	Patients with clinically diagnosed type 2 diabetes mellitus.
Kleefstra et al., 2006	1. A1C: 8%, daily use of insulin 50 units. 2. Creatinine: 150 mol/l for men and 120 mol/l for women. 3. Creatinine clearance: 50 ml/min. 4. Alanine aminotransferase: 90 units/l.
Lai, 2008	1. Patients who had been diagnosed with diabetes at least 5 years previously (fasting glucose >8.5 mmol/L and HbA1c >8.5%). 2. No trace element and vitamin supplementation in the preceding 3 months, and ongoing gastric or diuretic treatment.
Sharma et al., 2011	New-onset patients with type 2 diabetes.
Chen et al, 2013	1. FPG: 140 - 250 mg/dl & HbA1c: 7.5–12 % & BMI: 20 - 35 kg/m2. 2. No patients who received an insulin injection in the last three months. 3. No patients with other diseases.
Rocha et al., 2014	1. No patients who received an insulin therapy. 2. No patients with schemic heart disease.
Paiva et al., 2015	1. HbA1c ≥7% 2. 2. No patients who characterized with poorly controlled diabetes. 3. No patients with use of chromium supplements within the 4 months prior to the study.
Guimaraes et al., 2016	1. BMI: > 25 Kg/m2 & increased waist circumference (men ≥ 102 cm and women ≥ 88 cm). 2. No patients with insulin therapy & with chronic complications of diabetes.
Karim et al., 2018	1. HbAlc >8% & Hb >12-14. 2. No patients with kidney disease. 3. Last 2 months, the patient did not take vitamins or minerals.
Derosa et al., 2019	1. Patients needed to take different anti-diabetic treatments at a stable dose form at least 3 months. 2. HbA1c >6.5%, & BMI ≥25 and <30 Kg/m2. 3. No previous ketoacidosis or unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy.
Imanparas et al.. 2020	1. BMI <35 kg/m2. 2. Patients not to change their diabetes drugs or diet.
Talab et al., 2020	1. No patients with background of thyroid, liver, and any chronic diseases or under medical therapy for hyperlipidemia. 2. No consumption of any other supplements (antioxidants, minerals or vitamins, omega 3, and carnitine) or herbal medicines.
Alkhalidi , 2023	Uncontrolled type two diabetes mellitus.

Abbreviations: T2DM: Type 2 diabetes mellitus; FPG: Fasting plasma glucose; HbA1c: hemoglobin A1c; BMI: Body Mass Index; CHD: Coronary heart disease; BID: twice daily; NR: No Reply or response

Table 3. Reporting the quality/risk of bias with Cochrane quality assessment tool (Higgins et al., 2011).

Author	Publication Year	Random sequence generation	Allocation concealment	Participant & personnel blinding	Outcome assesment blinding	Incomplete outcome data & biased reporting	Further biased sources	Total score
Ghosh et al.	2002	+	+	-	+	-	+	4
Vrtovec et al.	2005	+	?	+	+	?	?	3
Racek et al.	2006	-	?	-	?	-	+	1
Kleefstra et al.	2006	+	?	+	+	?	+	4
Lai	2008	-	?	-	+	?	-	1
Sharma et al.	2011	-	-	-	+	+	+	3
Chen et al	2013	+	?	+	+	+	+	5
Rocha et al.	2014	+	?	?	+	+	?	3
Paiva et al.	2015	+	+	+	+	+	?	5
Guimaraes et al.	2016	+	+	+	-	+	+	5
Karim et al.	2018	+	+	+	+	-	-	4
Derosa et al.	2019	+	?	+	+	+	+	5
Imanparas et al.	2020	?	+	?	+	?	+	3
Talab et al.	2020	+	?	-	+	-	+	3
Alkhalidi	2023	+	?	-	+	?	+	3

Low risk of bias (+); High risk of bias (-); Unclear risk of bias (?)

3.4.Trivalent chromium and its types

Chromium is an essential nutrient, with a particularly significant function in carbohydrate and lipid metabolism (Abdollahi et al., 2013). The problem with chromium is that it has a generally low bioavailability, causing the question of which form of supplemental chromium has the best bioavailability essential. In the systematic review, in terms of supplement type, 10 studies chromium picolinate, 3 studies chromium yeast, 1 study chromium chloride, and 1 study chromium nicotinate. The dosage of chromium was between 50 and 1000 µg/day and it was consumed from 2 to 6 months.

Trivalent chromium is available on the market as a dietary supplement in various forms, with chromium picolinate, chromium chloride, and chromium yeast being the dominant forms. Chromium chloride is the naturally occurring trivalent variety of chromium found in common food sources such as whole grains, broccoli, mushrooms, and green beans. Cr picolinate, a trivalent variety of chromium, is the synthetic salt form of Cr chloride. Chromium yeast is a nutritional supplement that is used in the food industry to fortify diets with trivalent chromium. To increase the nutritional content of processed goods like bread, cereals, and pasta, chromium yeast is commonly added. Furthermore, it has the potential to decrease the sugar and fat content of some foods, which will enhance their nutritional value.

These forms of chromium are provided either as stand-alone supplements or in combination products with other minerals or vitamins, such as nicotinic chromium. Chromium nicotinate is a chromium complex combining chromium, and niacin - a B vitamin (B3). Previous studies support the effectiveness of nicotinic chromium in regulating glycemic control in type 2 diabetes, balancing blood sugar levels, reducing relative weight, and lowering cholesterol levels.

3.5. Relationship between chromium and type 2 diabetes mellitus

The results highlight the potential role of trivalent chromium as an adjunctive pharmaceutical supplement in the management of T2DM, emphasizing the importance of nutritional interventions for the greater well-being of diabetic patients. Several studies investigated the impact of trivalent chromium supplementation, as chromium picolinate, on glycemic control (GC), on insulin sensitivity (ISF), on insulin resistance (HOMA-IR), on glycated hemoglobin levels (HbA1c), fasting blood sugar (FBS or fasting plasma glucose-FPG)), on postprandial glucose (PPG), on waist circumference (WC), on electrocardiographic interval (QTc) and on related parameters in patients with type 2 diabetes mellitus (T2DM). The potential positive effect of chromium chloride, chromium nicotine and chromium yeast has been investigated to a lesser extent. These types of trivalent chromium, emphasize on reduced insulin sensitivity (SI), on β-cell function, on low-grade inflammatory state, on insulin sensitivity (ISF), on markers of oxidative stress (glutathione peroxidase, reduced glutathione) and on other related parameters in patients with type 2 diabetes mellitus (T2DM).

Ghosh et al. (2002) found that by administering chromium picolinate (200 µg BID), there was significantly increased serum chromium levels, improving glycemic control (GC) and insulin sensitivity (ISF) in T2DM patients. In contrast, other parameters such as cardiovascular potential and lipid profile changes had no significant change. Kleefstra et al., 2006 evaluated the effect of chromium picolinate treatment on glycemic control (GC) in an obese Western population of insulin-dependent patients with poorly controlled type 2 diabetes. Daily administration of chromium picolinate resulted in its change. Other parameters such as lipid profile, BMI, blood pressure and insulin requirements had no significant differences.

In another RCT study with 600 diabetic patients, the combination of low-dose niacin and chromium picolinate with sitagliptin proved highly effective in their fasting blood sugar values (FBS), as well as in glycated hemoglobin levels (HbA1c), positioning it as a viable therapeutic option for diabetes management (Karim et. al, 2008). A similar study, (Rocha et al., 2014) investigated the effect of twice-daily chromium picolinate supplementation (100 µg) in T2DM patients. Although, there was no significant changes in anthropometric measures, there was a significant reduction in HbA1c, indicating improved glycemic control.

Another study (Paiva et al., 2015) highlighted chromium picolinate's role as an adjunctive therapy for glycemic control (GC) in patients with uncontrolled T2DM, showing reductions in fasting and postprandial glucose concentrations and greater reductions in glycated hemoglobin (HbA1c). However, lipid profile changes were not significant, except for a decrease in serum ferritin. Only one study investigated the effect of chromium picolinate supplementation on the duration of the electrocardiographic interval (QTc) in patients with type 2 diabetes (Vrtovec et al. 2015). They observed a significant reduction in QTc duration after three months with chromium picolinate administration, particularly in patients with higher BMI, suggesting potential benefits in obese patients with significant insulin resistance (HOMA-IR). Derosa et al. (2019) evaluated a dietary combination of polyphenolic extracts and chromium picolinate as an additional supplement to the existing antidiabetic treatment in T2DM patients. The group consuming the supplement showed significant reductions in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial glucose (PPG) and waist circumference (WC) compared to baseline and placebo. The combination's inhibitory effects on enzyme activities contributed to glucose reduction, highlighting its effectiveness as an adjunct to antidiabetic therapy. Polyunsaturated fatty acids (PUFAs) and chromium in the nutrient mixture further improved glycometabolic parameters.

Talab et al. (2020) reported modest beneficial effects of chromium picolinate on insulin resistance (HOMA-IR) and lipid profile in T2DM patients. Specifically, no significant changes were observed in body weight, body mass index and fasting blood glucose (FBG), but significant differences in total cholesterol, low-density lipoprotein cholesterol and on insulin resistance (HOMA-IR). Imanparast et al. (2020) conducted a randomized trial with vitamin D3 and chromium picolinate supplementation, showing a synergistic effect in controlling insulin and insulin resistance (HOMA-IR), with a decrease in tumor necrosis factor-α (TNF-α). In a similar study by Alkhalidi (2023), chromium supplementation significantly reduced glycated hemoglobin levels (HbA1c) and approached normal fasting blood sugar levels (FBS) in T2DM patients. Serum cholesterol decreased, and high-density lipoprotein (HDL) increased, aligning with previous studies emphasizing chromium's positive effects on blood sugar and lipid levels, indicative of its role in insulin sensitivity and glucose regulation. Chen et al., 2014, investigated the effects of chromium chloride on insulin sensitivity (SI), β-cell function, and inflammatory markers in type 2 diabetes mellitus. Chromium chloride supplementation significantly improved insulin sensitivity (SI), while an increased static insulin response index (US) and a decrease in interleukin-6 (IL-6) were observed. However, no significant correlation was observed between changes in IL-6 and SI or Us. Consequently, there was a significant improvement in the second phase of insulin and IL-6 response, with positive implications for the management of type 2 diabetes mellitus. Other study focused

on nicotinic chromium supplementation at two doses of 50 µg and 200 µg in T2DM patients. The patients who receiving nicotinic chromium 50 µg had a moderate to significant reduction in body weight, without significant changes in body composition or insulin sensitivity (ISF) (Guimaraes et al., 2016).

The study by Racek et al., 2006 evaluated the effect of chromium-enriched yeast on blood glucose, insulin variables, blood lipids, and markers of oxidative stress in people with type 2 diabetes mellitus. The study showed a significant increase in serum chromium levels and a reduction in fasting serum glucose. Oxidative stress markers (glutathione peroxidase, reduced glutathione) remained stable, and glycated hemoglobin levels (HbA1c) tended to increase in the placebo group. HbA1c and fructosamine were essentially unchanged in the the patients who consumed chromium yeast. In contrast, HbA1c tended to increase on placebo. Serum chromium levels were significantly increased in both patients and controls, possibly influenced by dietary variations. Serum chromium measurements reflected good compliance and absorption in the patients who consumed chromium yeast. Lai (2008) explored yeast chromium supplementation independently and in combination with vitamins C and E in patients with type 2 diabetes mellitus, with glycosylated hemoglobin (HbA1c) >8.5%. The findings indicated significant reductions in thiobarbituric acid active substances (TBARS) and improvements in fasting glucose (FPG), HbA1c, and insulin resistance (ISF). This suggests the efficacy of chromium supplementation, alone or combined with vitamins C and E, in minimizing oxidative stress and improving glucose metabolism in T2DM. In a similar study, patients newly diagnosed as type 2 diabetics showed a significant reduction in fasting blood glucose levels, improved glycemic control with reduced HbA1C values, and positive changes in lipid variables. In addition, total cholesterol, triglyceride, and LDL levels were significantly reduced. This suggests a positive effect of yeast chromium supplementation on glycemic control and lipid variables in patients with newly diagnosed type 2 diabetes (Sharma et al., 2011).

4. Discussion

Chromodulin, a low-molecular-weight oligopeptide, can bind chromium ions and mediate their intracellular actions. The oligopeptide's chromium content affects whether insulin is required for this stimulation, which occurs when it binds with the insulin receptor's b subunit and triggers the insulin receptor tyrosine kinase activity. Four equal chromic ion concentrations stimulate the chromodulin oligopeptide to its highest concentration (Hua et al., 2012). Effector molecules that are located downstream of the insulin receptor are impacted by chromium, which enhances insulin signal transduction. Furthermore, in conditions of insulin resistance, chromium has been shown to enhance the translocation of glucose transporter protein 4, which promotes glucose transport across the cell membrane (Wang 2006; Anderson 1998).

In the current extensive study between 2000 to 2024, we observed that patients with type 2 diabetes had a significant reduction in FPG and insulin levels, as well as HbA1C and HOMA-IR levels, after a 2-to-6-month intervention with chromium trivalent supplementation at dosages of 50 to 1000 µg/day. However, our systematic review included only 15 RCTs of which the study duration of seven of them was less than 4 weeks. Therefore, the intervention time may not be counterproductive for the hyperglycemia and hyperinsulinemia indices.

In similar studies, it has been shown that chromium can enhance insulin sensitivity, with beneficial effects on glycemic control indicators on HbA1C and FPG levels, in diabetic patients (Parsaeyan & Khosravi, 2012; Bahijiri 2000). These studies indicated that chromium increases the transport of glucose and amino acids by engaging intracellular signaling pathways that include the translocation of the glucose transporter (GLUT4). Furthermore, chromium affects the metabolism of cholesterol and decreases the liver enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase (Lewicki 2014; Vincent 2019). Other systematic reviews indicated that chromium supplementation improved glycemic control in diabetes patients (Balk et al., 2007; Suksomboon et al., 2014). However, there are earlier studies, of a clinical nature, which do not report significant changes in blood glucose variables (Hunt et al., 1985; Abraham, 1992; Dinarto et al., 1998).

It is noteworthy that some of the included trials in this study combined vitamin E, vitamin C, and vitamin D administration with chromium subtypes. Research findings indicate that there is an inverse correlation between serum concentrations or dietary consumption of vitamin A, vitamin E, vitamin C, 25-hydroxyvitamin D, and some chemicals, and type 2 diabetes. (Ekmekcioglu et al., 2017; Villegas et al., 2009). Increased insulin-mediated glucose absorption or its impact on beta cell function could be responsible for the inverse relationship between this food consumption and type 2 diabetes (Ekmekcioglu et al., 2017).

It's uncertain whether chromium supplementation affects lipid profile. One study found that using chromium as a supplement considerably improved the lipid profile by lowering TG and TC while increasing HDL but had no effect on LDL. Moreover, our findings demonstrated that only patients with an HDL level below 50 mg/dl would benefit from the increase in HDL produced with chromium supplementation. This study contrasts with a cross-sectional study that found a negative connection between serum chromium and lipid profile (TG, TC, and LDL) in 214 patients with type 2 diabetes (Wolide et al., 2017). The reduction of oxidative stress seems to indicate the beneficial outcome of chromium treatment. Prior research examined the effects of chromium on the regulation of metabolic variables. The results indicated that chromium had protective effects against oxidative stress in individuals with a recognized pathogenic status (Marmett, 2016).

The systematic review was performed in four major online databases, Pubmed, Scopus, ScienceDirect, and Cochrane, as well as secondary platforms to include “gray literature”. Although this study is retrospective in a systematic way based on PRISMA guidelines (, and the evaluation of the quality of the included studies is optional, the evaluation of the quality of the articles was carried out, with a specific evaluation tool, a fact that is one of the strong points of the study. It is important to consider the limitations of the systematic review. Although data extraction was performed for each Cr subtype (picolinate, chloride, yeast nicotinate, dinicocysteine) assessed in each study, a meta-analysis of the data could not be performed as publication bias was either not detected or not possible due to small numbers of studies. Therefore, although publication bias could not be statistically assessed, it is important to mention that there are main variables for conducting the overall result, such as age, sex, dose frequency, patient-participant inclusion criteria, study design, and duration, which can lead to erroneous conclusion or high heterogeneity among results.

The included studies were conducted from 2002 to 2024. The way patients are treated with the administration of pharmaceuticals and par pharmaceuticals is changing as new classes of pharmaceuticals are added. Most of the studies reviewed differed in the dose, type, and duration of chromium administration

(100–1000μg). Conclusions may vary depending on the dose, type, and duration of Cr supplementation. Furthermore, there is a different target population, with different inclusion and exclusion criteria. Although patients with pre-existing secondary diseases were removed, the patient population studied sometimes had controlled type 2 diabetes before the start of the study and sometimes uncontrolled type 2 diabetes, adding error to the overall result. In addition, the studies included patients of different ethnic origins, attributing error in terms of diet, lifestyle, adequate education, and knowledge of alternative ways of treating the disease, as well as the possibility of providing pharmaceutical and para-pharmaceutical products according to their area of residence. The standard of care for patients with type 2 diabetes mellitus changes over time (2000-2024).

5. Conclusion

Based on current research, dietary supplements containing chromium may lead to potential benefits in the management of type 2 diabetes mellitus. Glycemic control markers, including FPG, insulin, HbA1C, and HOMA-IR levels, significantly decrease following chromium supplementation, mainly in studies with a longer intervention period. Supplementing with chromium indicated that could significantly improve lipid profile by raising HDL and lowering TG and TC while having little effect on LDL. However, most of studies results are inconsistent in several ways, including supplement composition and dosage, duration of treatment, and the included participants receiving the intervention. Although chromium, from various subtypes of trivalent chromium, is characterized as one of the nutrients with levels up to 1000 mg/day beneficial to human health (Heimbach & Anderson, 2005), the consequences of its administration to patients with type 2 diabetes mellitus have not yet received much research attention. It is important to carry out additional randomized clinical studies, of long-term duration and with more statistical power, to fully understand the contribution of chromium, also to record adverse effects, such as constipation, skin changes, flatulence, and anorexia (Costello et al., 2016). Therefore, it is recommended that healthcare professionals advise diabetic patients to take their diabetes medication in conjunction with the necessary changes in diet and physical activity.

Declarations

6. Author contributions

Conceptualization, M.-N.G.; methodology, M.-N.G.; validation, M.-N.G., and S.T.; formal analysis, M.-N.G., S.T., and S.K.; investigation, M.-N.G. and S.T.; data curation, M.-N.G., A.K., and S.T.; writing—original draft preparation, M.-N.G. and N.K.; writing—review and editing, M.-N.G., N.K., T.P., and S.K..; visualization, M.-N.G.; supervision, M.-N.G., N.K., T.P., and S.K.; project administration, M.-N.G., A.K., and S.T. All authors have read and agreed to the published version of the manuscript.

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References

1. Yeghiazaryan K, Schild HH, Golubnitschaja O. Chromium-picolinate therapy in diabetes care: individual outcomes require new guidelines and navigation by predictive diagnostics. Infect Disord Drug Targets. 2012;12(5):332–9.
2. Chen, L., Magliano, D. J., & Zimmet, P. Z. (2012). The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews endocrinology, 8(4), 228-236.
3. Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. I. D. F. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes research and clinical practice, 138, 271-281.
4. Deshpande, A. D., Harris-Hayes, M., & Schootman, M. (2008). Epidemiology of diabetes and diabetes-related complications. Physical therapy, 88(11), 1254-1264.
5. Koh-Banerjee, P., Wang, Y., Hu, F. B., Spiegelman, D., Willett, W. C., & Rimm, E. B. (2004). Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. American journal of epidemiology, 159(12), 1150-1159.
6. M. Flachuk, Disturbances in trace elements: Harrison's Principles of Internal Medicine, 14th ed., McGraw Hill, NY, 1998, pp. 490–491.
7. Georgaki, M. N., Charalambous, M., Kazakis, N., Talias, M. A., Georgakis, C., Papamitsou, T., & Mytiglaki, C. (2023). Chromium in water and carcinogenic human health risk. Environments, 10(2), 33.
8. Vincent JB. Elucidating a biological role for chromium at a molecular level. Acc Chem Res, 2000;33:503–510.
9. Anderson, R. A. (1998). Chromium, glucose intolerance and diabetes. Journal of the American College of Nutrition, 17(6), 548-555.
10. Campbell JD: Lifestyle, minerals, and health. Med Hypotheses 2001;57:521–531.
11. Wang, Z. Q., & Cefalu, W. T. (2010). Current concepts about chromium supplementation in type 2 diabetes and insulin resistance. Current diabetes reports, 10, 145-151.
12. Dubey P, Thakur V, Chattopadhyay M. Role of Minerals and Trace Elements in Diabetes and Insulin Resistance. Nutrients. 2020 Jun 23;12(6):1864. doi: 10.3390/nu12061864.
13. Yin RV, Phung OJ. Effect of chromium supplementation on glycated hemoglobin and fasting plasma glucose in patients with diabetes mellitus. Nutr J. 2015 Feb 13;14:14. doi: 10.1186/1475-2891-14-14
14. Rabinovitz H, Friedensohn A, Leibovitz A, Gabay G, Rocas C, Habot B. Effect of chromium supplementation on blood glucose and lipid levels in type 2 diabetes mellitus elderly patients. Int J Vitam Nutr Res. 2004;74(3):178–82.

15. Derakhshanian H, Javanbakht MH, Zarei M, Djalali E, Djalali M. Vitamin D increases IGF-I and insulin levels in experimental diabetic rats. Growth Horm IGF Res. 2017 Oct;36:57-59. doi: 10.1016/j.ghir.2017.09.002
16. Ngala, R. A., Awe, M. A., & Nsiah, P. (2018). The effects of plasma chromium on lipid profile, glucose metabolism and cardiovascular risk in type 2 diabetes mellitus. A case-control study. PloS one, 13(7), e0197977.
17. Costello, R. B., Dwyer, J. T., & Bailey, R. L. (2016). Chromium supplements for glycemic control in type 2 diabetes: limited evidence of effectiveness. Nutrition reviews, 74(7), 455-468.
18. Landman GW, Bilo HJ, Houweling ST, Kleefstra N. Chromium does not belong in the diabetes treatment arsenal: Current evidence and future perspectives. World J Diabetes. 2014 Apr 15;5(2):160-4. doi: 10.4239/wjd.v5.i2.160.
19. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group*. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine, 151(4), 264-269.
20. Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savović, J., F Schulz, K., Weeks., L., and Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj, 343.
21. Kleefstra, N., Houweling, S. T., Jansman, F. G., Groenier, K. H., Gans, R. O., Meyboom-de Jong, B., ... & Bilo, H. J. (2006). Chromium treatment has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. Diabetes care, 29(3), 521-525.
22. Vrtovec, M., Vrtovec, B., Briski, A., Kocijancic, A., Anderson, R. A., & Radovancevic, B. (2005). Chromium supplementation shortens QTc interval duration in patients with type 2 diabetes mellitus. American heart journal, 149(4), 632-636.
23. Ghosh, B. Bhattacharya, B. Mukherjee, B. Manna, M. Sinha, J. Chowdhury, et al., Role of chromium supplementation in Indians with type 2 diabetes mellitus, The Journal of nutritional biochemistry. 13 (11) (2002) 690–697.
24. Racek, J., Trefil, L., Rajdl, D., Mudrova, V., Hunter, D., & Senft, V. (2006). Influence of chromium-enriched yeast on blood glucose and insulin variables, blood lipids, and markers of oxidative stress in subjects with type 2 diabetes mellitus. Biological trace element research, 109, 215-230.
25. Sharma, S., Agrawal, R. P., Choudhary, M., Jain, S., Goyal, S., & Agarwal, V. (2011). Beneficial effect of chromium supplementation on glucose, HbA1C and lipid variables in individuals with newly onset type-2 diabetes. Journal of Trace Elements in Medicine and Biology, 25(3), 149-153.
26. Lai, M. H. (2008). Antioxidant effects and insulin resistance improvement of chromium combined with vitamin C and E supplementation for type 2 diabetes mellitus. Journal of clinical biochemistry and nutrition, 43(3), 191-198.
27. Chen, Y. L., Lin, J. D., Hsia, T. L., Mao, F. C., Hsu, C. H., & Pei, D. (2014). The effect of chromium on inflammatory markers, 1st and 2nd phase insulin secretion in type 2 diabetes. European journal of nutrition, 53, 127-133.
28. Rocha, N. R., Carrara, M. A., Stefanello, T., Teixeira, C. J., Pozzi, A. C. O., & Batista, M. R. (2014). Effects of chromium picolinate supplementation in type 2 diabetic patients. Acta Scientiarum. Health Sciences, 36(2), 161-164.
29. Paiva, A. N., de Lima, J. G., de Medeiros, A. C., Figueiredo, H. A., de Andrade, R. L., Ururahy, M. A., ... & Almeida, M. D. G. (2015). Beneficial effects of oral chromium picolinate supplementation on glycemic control in patients with type 2 diabetes: a randomized clinical study. Journal of Trace Elements in Medicine and Biology, 32, 66-72.
30. Karim, F., Najam, K., Sharif, A., Shakir, L., Ajmal, S., Anwar, A., ... & Zaidi, A. A. (2018). The therapeutic effectiveness of sitagliptin with niacin and chromium picolinate on glycosylated hemoglobin in type 2 diabetes mellitus patients. Biomedical Research and Therapy, 5(8), 2610-2619.
31. Alkhalidi, F. (2023). A comparative study to assess the use of chromium in type 2 diabetes mellitus. Journal of Medicine and Life, 16(8), 1178.
32. Derosa, G., Pascuzzo, M. D., D'Angelo, A., & Maffioli, P. (2019). Ascophyllum nodosum, Fucus vesiculosus and chromium picolinate nutraceutical composition can help to treat type 2 diabetic patients. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 1861-1865.
33. Imanparast, F., Javaheri, J., Kamankesh, F., Rafiei, F., Salehi, A., Mollaaliakbari, Z., ... & Abbasi, E. (2020). The effects of chromium and vitamin D3 co-supplementation on insulin resistance and tumor necrosis factor-alpha in type 2 diabetes: a randomized placebo-controlled trial. Applied Physiology, Nutrition, and Metabolism, 45(5), 471-477.
34. Talab, A. T., Abdollahzad, H., Nachvak, S. M., Pasdar, Y., Eghtesadi, S., Izadi, A., ... & Moradi, S. (2020). Effects of chromium picolinate supplementation on cardiometabolic biomarkers in patients with type 2 diabetes mellitus: A randomized clinical trial. Clinical nutrition research, 9(2), 97.
35. Guimaraes, M. M., Carvalho, A. C. M. S., & Silva, M. S. (2016). Effect of chromium supplementation on the glucose homeostasis and anthropometry of type 2 diabetic patients: Double blind, randomized clinical trial: Chromium, glucose homeostasis and anthropometry. Journal of Trace Elements in Medicine and Biology, 36, 65-72.
36. Abdollahi, A. Farshchi, S. Nikfar, M. Seyedifar, Effect of chromium on glucose
37. and lipid profiles in patients with type 2 diabetes; a meta-analysis review of randomized
38. trials, Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 16 (1) (2013) 99–114.
39. Hua Y, Clark S, Ren J, Sreejayan N. Molecular mechanisms of chromium in alleviating insulin resistance. J. Nutr. Biochem. 2012;23(4):313e9.
40. Wang ZQ, Zhang XH, Russell JC, Hulver M, Cefalu WT. Chromium picolinate enhances skeletal muscle cellular insulin signaling in vivo in obese, insulinresistant JCR: LA-cp rats. J Nutr 2006;136(2):415e20.
41. Parsaeyan, H. Mozaffari–Khosravi, Effect of Chromium Supplementation on Blood Glucose, Hemoglobin A1c, Lipid Profile and Lipid Peroxidation in Type 2 Diabetic Patients, IJDO. 4 (4) (2012) 178–184.
42. M. Bahijiri, S.A. Mira, A.M. Mufti, M.A. Ajabnoor, The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes, Saudi medical journal. 21 (9) (2000) 831–837.

43. B. Vincent, Effects of chromium supplementation on body composition, human and animal health, and insulin and glucose metabolism, Current Opinion in Clinical Nutrition & Metabolic Care. 22 (6) (2019) 483–489.
44. Lewicki, R. Zdanowski, M. Krzyzowska, A. Lewicka, B. Debski, M. Niemcewicz, et al., The role of Chromium III in the organism and its possible use in diabetes and obesity treatment, Annals of agricultural and environmental medicine : AAEM. 21 (2) (2014) 331–335.
45. Suksomboon, N. Poolsup, A. Yuwanakorn, Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes, Journal of clinical pharmacy and therapeutics 39 (3) (2014) 292–306.
46. M. Balk, A. Tatsioni, A.H. Lichtenstein, J. Lau, A.G. Pittas, Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials, Diabetes care. 30 (8) (2007) 2154–2163
47. E. Hunt, K.G.D. Allen, B.A. Smith, Effect of chromium supplementation on hair chromium concentration and diabetic status, Nutrition Research. 5 (2) (1985) 131–140.
48. S. Abraham, B.A. Brooks, U. Eylath, The effects of chromium supplementation on serum glucose and lipids in patients with and without non-insulin-dependent diabetes, Metabolism: clinical and experimental. 41 (7) (1992) 768–771.
49. Dinarto, A. Suyardi, S. Waspadji, Effect of chromium supplementation on chromium status, insulin and glucose level in Non-insulin Dependent Diabetes Mellitus (NIDDM) subjects, Medical Journal of Indonesia. 7 (1) (1998) 33–37.
50. Villegas, Y.-T. Gao, Q. Dai, G. Yang, H. Cai, H. Li, et al., Dietary calcium and magnesium intakes and the risk of type 2 diabetes: the Shanghai Women's Health Study, The American journal of clinical nutrition 89 (4) (2009) 1059–1067.
51. Ekmekcioglu, D. Haluza, M. Kundi, 25-Hydroxyvitamin D status and risk for colorectal cancer and type 2 diabetes mellitus: a systematic review and meta-analysis of epidemiological studies, International journal of environmental research and public health 14 (2) (2017) 127.
52. D. Wolide, B. Zawdie, T. Alemayehu, S.J.B.E.D. Tadesse, Association of trace metal elements with lipid profiles in type 2 diabetes mellitus patients: a cross sectional study, BMC Endocr. Disord. 17 (1) (2017) 64.
53. Marmett, R. Barcos Nunes, Effects of chromium picolinate supplementation on control of metabolic variables: a systematic review, J. Food Nutr. Res. 4 (2016) 633–639.
54. Heimbach, J. T., & Anderson, R. A. (2005). Chromium: recent studies regarding nutritional roles and safety. Nutrition Today, 40(4), 189-195.
55. Stern, A. H. (2010). A quantitative assessment of the carcinogenicity of hexavalent chromium by the oral route and its relevance to human exposure. Environmental Research, 110(8), 798-807.
56. Mishra, S., & Bharagava, R. N. (2016). Toxic and genotoxic effects of hexavalent chromium in environment and its bioremediation strategies. Journal of Environmental Science and Health, Part C, 34(1), 1-32.
57. Costa, M., Zhitkovich, A., Harris, M., Paustenbach, D., & Gargas, M. (1997). DNA-protein cross-links produced by various chemicals in cultured human lymphoma cells. Journal of toxicology and environmental health, 50(5), 433-449.

Figures

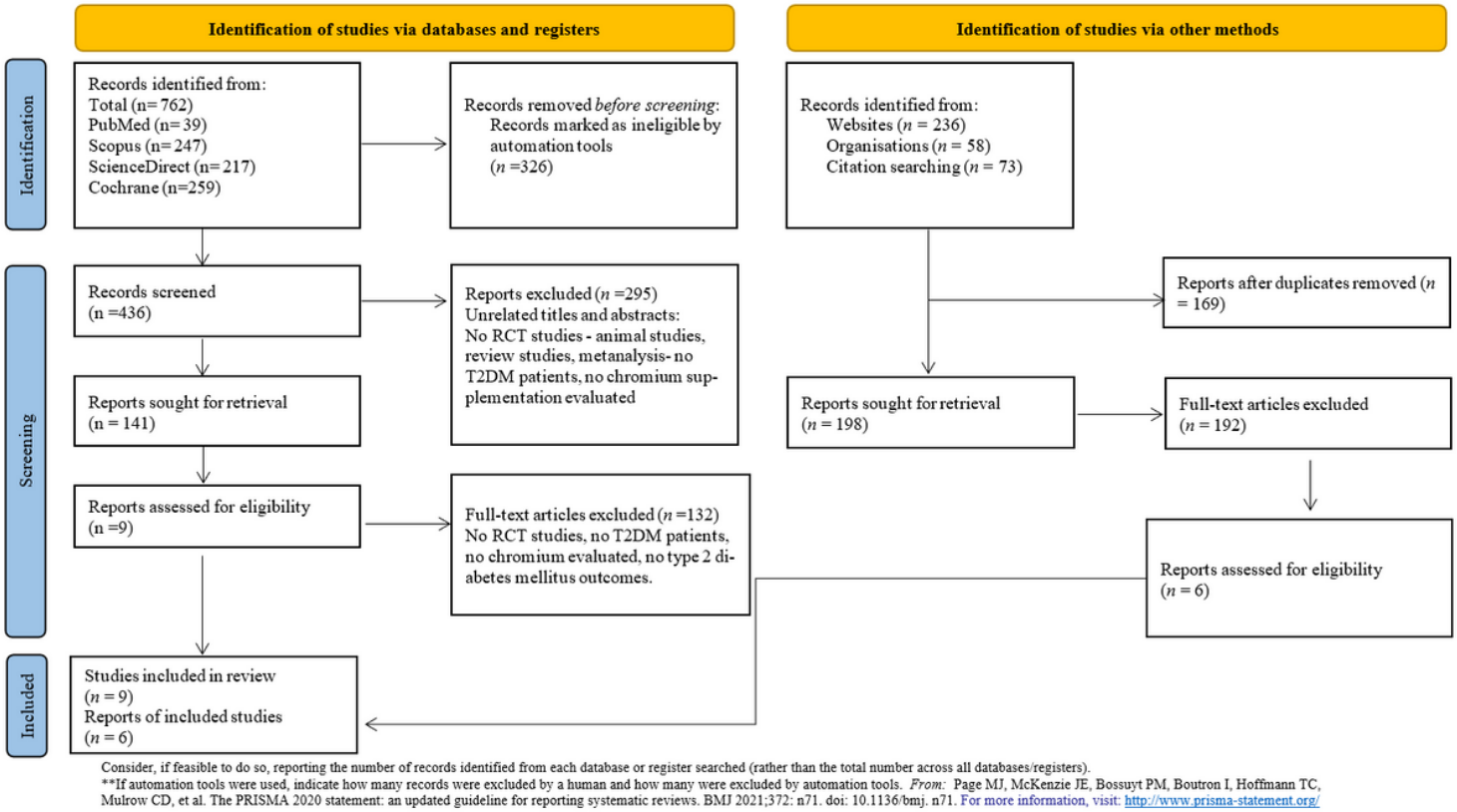

Figure 1

Flowchart of study selection for inclusion RCTs in the systematic review. (Moher et al., 2009).

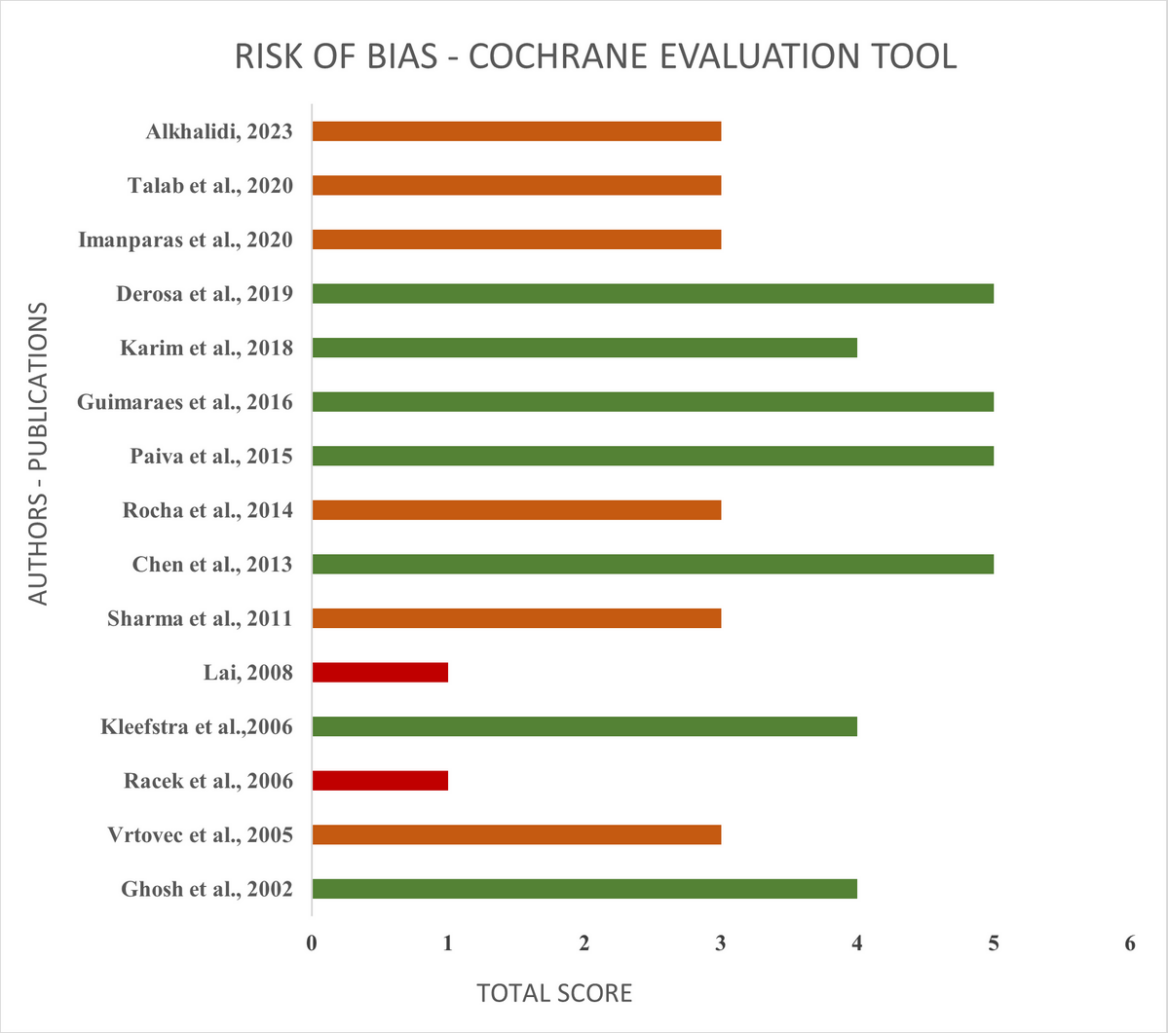

Figure 2

Risk of bias- Cochrane evaluation tool

Supplementary Files

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