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REVIEW ARTICLE

Chromium Supplementation; Negotiation with Diabetes Mellitus, Hyperlipidemia and Depression

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Abstract

Chromium (Cr) is an essential trace element which found naturally in a daily diet and available in the form of supplementary tablets to boost disorders like diabetes mellitus (DM) and functions like lipid metabolism and beneficial on depression too. Diabetes is one of the most prevalent endocrine diseases or in other words, the most severe metabolic syndrome (MS), which associated with high production of free-radicals which is out of bodies detoxifying machine capacity or high oxidative stress (HOS), vasculitis and elevated lipid profile. many research papers and clinical trials published about the significance of chromium on biological activities, pre and post clinical. For this review research articles, clinical trials, from 1st Jan'10 to 31st Dec'18 and refer literature for the biochemical, pharmacological and biological activity of Chromium. Primarily articles gathered from the above search engines. Then precisely according to our aim and goal and regarding designed objectives dismisses similar articles and finally came to 84 articles for the above said period. This review trying to cover the entire picture from what chromium is to the recent updates on their greater role in increasing insulin sensitivity of cells and enhancing lipid metabolism and even recent findings suggest its positive effects including prevention and ameliorating properties on depression. The biological activities, pharmacological features, clinical implications including efficacy and role of chromium compounds on the glycaemic index will be discussed. The outcome of this review is to bring the pros and cons of chromium supplementation along with is safety and toxicity concern beside molecular pathways, biochemistry and clinical trials, all in one comprehensive review.

Keywords Chromium · Cancer · Cardiovascular disease · Depression · Diabetes Mellitus · Hyperlipidaemia · Trace Elements

Introduction

Minerals are essential nutrients for the body and chromium is one of them. Cr with symbol "Cr" with a molecular weight of 51.9961 +/- 0.0006 u occupying allotted space number 24 in Mendeleev table [1]. Out of all forms of Cr compounds, trivalent Cr is the most stable form in a biological system and found in food, and hexavalent is a toxic agent and found in industrial pollution [2]. Cr can be found in air, water, and soil. You can inhale trace of Cr by breathing air [1]. Small amounts of trivalent Cr are needed for human health. Very less amount of Cr occurs naturally in a variety of foods (< 2 micrograms [mcg] per serving), such as fruits, vegetables, nuts, spices, and meats [2].

There are many Cr compounds in nature and synthesized in a laboratory that is biologically active. For example Trivalent Cr, notably Cr. Tri-picolinate and Cr. Nicotinate and histidine which shown effective signs in diabetic control by improving insulin sensitivity. The symptoms of Cr deficiency are the same as in metabolic syndrome, high TG, low HDL, hypertension and visceral obesity. The exceptional indicator of Cr deficiency is impaired glucose tolerance and there is numerous clinical trial which proven the beneficial effects of Cr on individuals with impaired glucose tolerance and T2DM. [3–5]. T2DM turns out to be a worldwide health issue, with the global cases of T2DM projected to be 350 million by the year 2030 [6, 7]. Diabetes is an independent risk factor for

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cardiovascular diseases [8, 9]. A major cause of the increased prevalence of T2DM is the growing epidemic of obesity [10, 11]. Chronic hyperalimentation such as high-fat diet, fried and junk food besides inactive and sedentary lifestyle along with lack of physical activity all together contributed to the increasing prevalence of diabetes [12]. T2DM is characterized by defects in pancreatic insulin secretion or action causing hyperglycaemia attributable to disturbances in carbohydrate, lipid metabolism [13]. First drug-based treatment for DM patients is anti-diabetic medications like Glibenclamide or Metformin if a change in lifestyle did not nail the set goals. Despite the advances in modern medicines, T2DM continues to be a public concern.

Methodology

Studies for current project based on published works in Medline/Pubmed, Scopus from 1st January 2010 to 31st December 2018 and also references from above papers also reviewed. The search narrowed in time for meant for latest and more updated papers. All clinical trials, research papers, *in vivo* which count eligible for current review considered. For this latest systematic review our search terms included, "chromium diabetes", "Chromium toxicity", "Chromium hyperlipidemia", "chromium depression", "Chromium cancer" found 852, 4512, 73, 171, 3636 papers respectively before applying time period. After applying our desired time period and discard unrelated papers, duplicate articles between Pubmed and scopus and also retract papers with indirect relation to our topics total numbers of article finalised for this review found to be 84 based on our set guidelines and aim for current work.

Chromium compounds

In 1929 Galser and team discovered that brewer's yeast had a potentiating effect on the hypoglycaemic action of insulin [14]. This observation was rediscovered by Schwartz and Mertz in 1957 who postulated that the occurrence is because of glucose tolerance factor' (GFT) and its association with Cr [15].

Chromium Chloride

Cr chloride found in common food such as broccoli, whole grain, green beans, and mushrooms. Cr chloride is occurring naturally in a variety of trivalent in edible forms. The result from the meta-analysis suggests that Cr chloride did not have a statistically significant effect on lowering Fasting Plasma Glucose (FPG) in patients with T2DM when compared to placebo [16].

Chromium Picolinate

Cr picolinate is a salt synthesizing from Cr chloride. Picolinate acid may help and increase the absorption of Cr. Base on the above analysis, Cr picolinate didn't show an improvement that is statistically significant for lowering glycated hemoglobin (HbA1c) or fasting Plasma glucose FPG [17].

Chromium yeast

The other form of Cr which is used as supplementary micronutrients is in the form of Cr yeast. Reports from these clinical trials show great significant improvement which is statistically notable in lowering HbA1c or fasting plasma glucose [18].

Trivalent Chromium (Brewer's yeast)

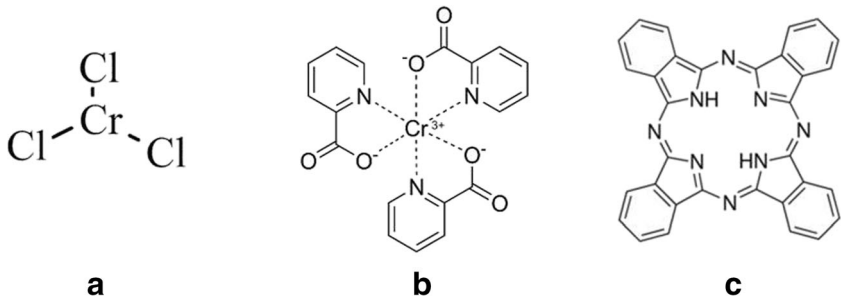
Trivalent Cr is believed to be a biologically active form of Cr and it was first discovered in Brewer's yeast. Brewer's yeast didn't show any remarkable changes in HbA1c but demonstrate a very great decrease in fasting plasma glucose in type 2 diabetes mellitus in comparison to placebo in the above clinical trial and analysis [19].

Chromium Phthalocyanine chloride

Cr. Phthalocyanine chloride shows totally different features in some in-situ and *in vivo* trials. The two important biological activities can be named as Anti-tumour activity and as a growth inhibitor in Bactria. Both of these two applications can be used in medical fields. In simple words Cr. Phthalocyanine chloride has anti-cancer and antimicrobial activity which is proven in clinical trials [20]. Further investigation required and suggested this new intriguing compound. Many *in vivo* and also clinical trials needed to elucidate its real capabilities toward a safe anti-microbial and anti-cancer agent (Fig. 1).

Mechanism

There are few mechanisms suggested for Cr activity towards the increase in insulin sensitivity: as FDA (Food and drug administration-USA) stated that in more than 20 years ago Cr is proven to increase numbers of insulin receptors and even increase their binding to the cells [21]. The fact is that Cr has a sublime role in normalizing insulin function regarding blood sugar, lipid and carbohydrate metabolism in many randomized clinical trials which prove that Cr deficiency can lead to T2DM [22].



a b c

Fig. 1 Structure A. Chromium chloride, structure B. chromium Picolinate, Structure C. phthalocyanine structure before joining of chromium to make chromium complex. After binding, chromium will stand at centre of the structure

Chromium and Insulin signaling (molecular pathways)

Chromium signaling cascade

despite the much-debated results in animal model and human clinical trials and in more controlled setting of *in vivo* studies on diabetes and insulin resistance, Cr has been shown to help in increasing insulin sensitivity and alleviate cardiovascular functions, therefore giving credit to those work under argument which were saying Cr has health benefits toward diabetes mellitus and cardiovascular performance by having great role in lipid metabolism [7]. Insulin is a hormone that is pleiotropic with mitogenic and metabolic functions [7]. It is well understood and clear that insulin's first and primary role in metabolism and regulating blood sugar level.

Effects of chromium on insulin receptors

many studies have been conducted by focusing on how Cr alter and affect insulin signaling. These studies worked on cell bases or cell-free systems at basal or insulin stimulating levels. The study model system was exposed to the desired Cr compound (Cr salts or potassium chromate or well-known dietary supplement Cr picolinate and desired compound which thought might be helpful such as Triphenylalaninate Cr complex [$Cr(phe)_3$] which designed and synthesized recently. Furthermore, different ligands have been used. These studies in terms of variables were so unique and focused on many details from dose to methods used and etc. which can explain some differences in outcomes and results [7].

Effect of Cr on IRS, Akt, and PI3-kinase

Yinan Hua and co-workers, school of Pharmacy-University of Wyoming, reported on their paper (7) that Cr is capable of upregulating insulin-stimulated insulin signal transduction by affecting actuator molecules downstream of the IR, as proof by increased level of tyrosine phosphorylation of IRS-1, raise thr308 and ser473 phosphorylation of Akt and elevated PI3-kinase activity in a different insulin resistance cells and animal models.

Effect of chromium on Glucose transporters (Glut)

The effects of Cr on proximal insulin-signaling molecules affected far functional imminent events such as normal insulin-stimulated translocating of Glut 4 vesicles into the cell membrane. In skeletal muscles of ice which was under high sucrose diet, insulin-stimulated membrane-associated Glut 4 levels were significantly weakened and diminished compared to those thin mice [7].

Effect of Cr on insulin signaling's negative regulators: PTP- 1B, JNK, IRS- 1 serine phosphorylation

considering Cr modified insulin signaling under insulin-resistant conditions in cell cultures and animal models, Cr did not affect insulin-signaling in thin or control mice, suggesting that under normal condition, Cr is not effective on regular insulin-signaling [23].

Chromium, high oxidative stress and inflammation

The high oxidative stress and inflammation role in diabetes mellitus and its concurrent conditions are well established and the beneficial effect of Cr in oxidative stress and inflammation as the regulator has been said in detail in Rains and Jain [24] and briefly discussed as below:

Effect of chromium on AMP-activated protein kinase (AMPK)

The amp-activated kinase is a threonine-serine kinase that has come to light and got attention for its regulatory effect on energy homeostasis of cells [7, 25–27]. AMPK usually activating by the elevated ratio of AMP: ATP was primarily discovered as a switch that regulates oxidation of fatty acids in the heart [28] and skeletal muscles [29]. Recently has been found out that its key factor in the metabolism of glucose [30]. Dual-adjustment and controlling of TSC – mTOR – S6Kinase pathway via AMPK and in collaboration with insulin – PI3K signaling. Key role insensitivity to insulin and an important risk factor for obesity and also T2DM is the activation of TSC – mTOR – S6Kinase pathway which is the result of embedding the activating

signals of PI3K / Akt signaling which is insulin and activation of AMPK pathway including hypoxia or exercise or etc. TSC manages the mTOR – S6Kinase signaling activity via working as GTPase initiating protein for other proteins like Ras – Like GTPase Rheb which is Ras homolog enriched in the brain. Once it gets active, TSC elevates Rheb – GDP thresholds, this downregulates the activity of mTOR activity. The activity of TSC adjusts and managed inversely via AMPK and PI3K / Akt bio pathways. PI3K / Akt pathway activation results in suppression of TSC activity and then, reactivation of the mTOR pathway. On the other hand, AMPK initiation activates TSC, so suppressing the mTOR bio pathway. Anyhow, activation of mTOR can be suppressed by AMPK. Adjustment of the mTOR – S6K1 bio pathway via AMPK shall affect the sensitivity of insulin by altering the phosphorylation and the amount of IRS. In fact, by inactivation of mTOR, S6K1 activity downregulating, that causes a decrease in serine phosphorylation of IRS and elevating in IRS – dependent signaling. These modifications can alter insulin signaling and the transcriptional and metabolic effects of insulin. These types of changes increase the risk of T2DM and obesity and also comorbid conditions like hyper lipid profile and in some cases depression, which we will discuss later (pathway description – courtesy Patti and Kahn, 2004) [31].

Biochemistry and toxicology

How Cr work as co-factor for insulin action is incompletely understood. From several *in-vivo* and *in-vitro* studies, it was first thought Cr has potential role inaction of insulin as part of an organic complex, glucose tolerance factor. More recent studies proven that Cr may work and help as oligopeptide low molecular weight chromium binding substances (LMWCr MW~1,500 Da) [32]. Which are consists of cysteine, glycine, glutamic acid, and aspartic acid. Very less amount of Cr which is less than 2% in the form of inorganic compounds is being absorbed but with the help of little organic formulation, modification can be increased [33]. While absorbed it can be delivered into various organs and tissues in the body but seems to be mainly concentrated in the liver, muscles, and kidneys [34]. The main glycoprotein to control the level of free iron is transferrin, which also plays a crucial role in the movement of Cr from blood to the cells. Transferrin includes the plasma bound Cr postulated to bind to the transferrin receptors and is taken into the cell by endocytosis. The pH of the now internal vesicle is decreased by an ATP driven proton pump, Cr is released from transferrin, and the result will be free Cr assumed to be broken by LMWCr [5].

Safety/toxicity of Chromium supplementation:

Most concern issue regarding Cr compound supplementation is its long term safety, where few studied in cell culture level using a greater amount than the body usually can tolerate can lead to DNA damage. Some studied conducted on Cr picolinate (CrP) proving this hypothesis. However, there is no *in-vivo* or human trial in favor of such a claim. There are also a few isolated reports of kidney failures on a patient who was under treatment with CrP, but no evidence on the relationship between Cr and kidney failure has been ruled out [35]. Much reliable and trusted trials conducted by the Institute of Medicine (IOM) done by Berner et al. have concluded that Cr picolinate is absolutely safe [36]. Decades ago Jeejeebhoy and team believed that Cr on its inorganic state has poor absorption and is potentially toxic agent [37]. Results from other much referred clinical controlled trial for more than 5 years (64 months study) has also suggested that treatment with Cr compounds such as picolinate till up to 1000 μg/day is safe and does not show any toxicity [38]. On other side Cr toxicity which may define as exposure of a cell or living organism to usually Hexavalent Cr. Hexavalent Cr is toxic when ingested or even inhaled.

Clinical trials

For the first time in the modern history effect of Cr supplementation discovered and documented in the year 1977 when a female patient on TPN (total parenteral nutrition) developed severe hyper glycaemic-like symptoms that rejecting insulin therapy. Before that Cr supplementation administered, doctors recorded weight loss comorbid with glucose intolerance and neuropathy, even after 50 mg/dl. After 200 mg of Cr in the form of Cr chloride was added to her TPN for the next 21 days, her diabetes mellitus-like conditions subsidized and she was in no need of insulin any more [39, 40]. Gröber and team in their 2014 comprehensive paper claimed that lots of evidence show the positive influence of micronutrients such as Vit C, D, K, and B group of vitamins along with chromium, copper, and zinc beside Co-Enzyme Q-10 and magnesium on diabetic control and prevention such as comorbid conditions and consequences [41]. Result of one new double-blind placebo-controlled randomized human trial on people with T2DM revealed that a potential mechanism may increase the ability of Cr picolinate to improve insulin resistance in skeletal muscles in humans which is the primary site for glucose metabolism. These data suggest that if Cr picolinate added to a daily diet, insulin sensitivity improves for diabetic people, the chronic disease that affect 422 million worldwide in 2014 compare to 108 million people in 1980 (WHO). The above finding of an effect of Cr picolinate was presented by Dr. William T. Cefalu from the University of Vermont College of Medicine, USA at the 18th International Diabetes Federation Congress [5].

The World Health Organization (WHO) estimates that 4-5% of health budgets in developed countries are spent on diabetes mellitus or related illnesses and the people who suffer from this illness incur medical 2-5 times higher than healthy

and normal people [2]. For example, Germany one of the most developed countries spending 10% of its health bill (which is >16 Billion euros) [42]. Cr is an essential micronutrient and a very helpful co-factor of insulin. "By applying rigorous science, we hope to show it's potential to improve the quality of patient care for people with T2DM and reduce the cost of therapy", said Broc Komorowsky, vice president of Nutrition 21, Inc [5]. In the recent USA, a government-funded clinical trial which the result published in May 2013, announced that evidence is in favor of the effectiveness of Cr in diabetic patients and additionally improves lipid profile's parameters such as triglycerides ad HDL levels [43].

Chromium's effect on serum lipid profile

William Cefalu's paper which included more than 18 clinical trials, mentioned that in more than half of the trials the beneficial effects of Cr on lowering the lipid profile index in a patient with diabetes or healthy individuals have been observed (Table 1). In other trial which is conducted by Rotter and team on all kind of heavy trace elements found in our body including Lead Pb, cadmium Cd, mercury Hg, arsenic As, tungsten W, and macro elements such as magnesium Mg and calcium Ca and microelements like iron Fe, zinc Zn, copper Cu, Cr, molybdenum Mo, selenium Se, and manganese. they found there is a positive correlation between tungsten as heavy trace elements and lipid disorders; patients who had high total cholesterol and high LDL interestingly had a higher serum level of tungsten. They also find out that manganese, chromium, and selenium playing an intensifying role in metabolic syndromes such as diabetes mellitus [44]. In other trials done in India in the year 2011, Sharma S. and team reported that group of patients who were under yeast supplemented Cr was showing significant improvement in glycaemic index (HbA1c by almost 2.7 mg/dL and FBS reduced by 94 gm/dL) and in terms of lipid profile they showed reduction in triglyceride and LDL by 10 mg/dL. [45]. On almost all registered clinical trials on Lipid-lowering properties of Cr and its compounds (on diabetic and non-diabetic population), as shown in Table 1, out of 11 clinical trials which included partly or fully diabetic individuals, 4 studies suggested no change in lipid profile index. The other 7 trials showed

Table 1 Clinical trials performed on Chromium and its compounds to evaluate its beneficial effects on lipid profile (HDL, LDL, cholesterol and TG)

Study	Design	No. of subjects	Chromium supplement (dose)	Key result
Patients with diabetes or IGT				
Abraham, Brooks, and Eylath (69)	R,PC	76 (25 with diabetes)	$CrCl_3$(250 μg/day)	TG↓, HDL cholesterol↑
Bahijri et al. (70)	R,DB,PC,CO	78 (type 2 diabetes)	$CrCl_3$(250 μg/day),brewer's yeast (23.3 μg/day Cr^{3+})	TG↓, HDL cholesterol↑
Lee and Reasner (71)	DB,PC,CO	30 (type 2 diabetes)	CrP(200 μg/day)	TG ↓
Anderson et al. (72)	R,PC	180 (type 2 diabetes)	CrP(200 or 1000 μg/day)	Total cholesterol ↓
Ghosh et al. (73)	DB,PC,CO	50 (type 2 diabetes)	Cr_3 (200 μg/day)	Nochange
Chen S, Sun, and Chen X (74)	R	188 (type 2 diabetes)	JKT	TG ↓
Uusitupa et al. (75)	DB,PC,CO	10 (type 2 diabetes)	Cr_3(200 μg/day)	Nochange
Rabinowitz et al. (76)	R,DB,PC,CO	43	Brewer's yeast	Nochange
Uusitupa et al. (77)	R,PC	26 (all with IGT)	Brewer's yeast (160 μg/dayCr^{3+})	Nochange
Offenbacher and Pi-Sunyer (78)	R	24 (8 with type 2 diabetes)	Brewer's yeast	Total cholesterol ↓
Evans (79)	DB	11 (type 2 diabetes)	CrP (200 μg/day)	LDL cholesterol ↓, apoB ↓, HDL cholesterol ↑, apoA-I ↑
Individuals without diabetes				
Roeback et al. (80)	R,DB,PC	72	GTF-Cr(600 μg/day)	HDL cholesterol ↑
Riales and Albrink (81)	R,DB,PC	23	$CrCl_3$(200 μg/day) $CrCl_3$	HDL cholesterol ↑
Press,Geller,andEvans (82)	DB,PC,CO	28	CrP(200 μg/day)	Total cholesterol ↓, LDL cholesterol ↓, apoB ↓, apoA-I ↑
Preuss, Wallerstedt, and Talpur (83)	R,DB,PC	40	CrP(400 μg/day)	LDL cholesterol ↓
Volpe et al. (84)	R,PC	44	CrP(400 μg/day)	Nochange
Wilson and Gondy (18)	R,DB,PC	26	CrN(220 μg/day)	Nochange
Amato, Morales, and Yen (85)	R,DB,PC	19	CrP(1000 μg/day)	Nochange
Cefalu et al. (86)	R,DB,PC	29	CrP(1000 μg/day)	Total cholesterol ↓

↑, Increased: ↓, decreased: apo, apolipoprotein: CO, Crossover, Cr, trivalent chromium, CrN, chromium nicotinate: DB, Double Blind: JKT, jiangtangkang: PC, Placebo Controlled: R, Randomized: TG, Triglyceride

lowering in triglyceride and increase and improvement in HDL and even lowering total cholesterol. On clinical trials conducted on nondiabetic population, out of 8, 3 clinical trials didn't notice any significant changes, but rest showed satisfactory results such as enhancement and improvement of HDL, decrease in LDL and as well total cholesterol.

Chromium as a cancer fighter

Ya Li and colleagues on a very comprehensive latest review which published less than a year ago on anti-cancer (with focus on breast cancer) properties of fruits/vegetables and spices greatly mentioned orange and grape in fruits, cereal in vegetables and black peppers along with many other vegetables and fruits, has great impact on breast cancer both *in vivo* and *in vitro* [46]. But the very interesting fact that they didn't mention or noticed is that above-listed fruits and vegetables are sources of Cr which are reporting for the very first time. And suggest further *in vitro* and *in vivo* for evaluating their effects on other types of cancers.

The relation between Cr level and cardiovascular diseases (CVD)

Decades of studies and trials have been included, findings are compared and the results showing that advised daily dose of Cr has an important role for coronary heart disease and CVD in diabetes patients [5].

Chromium supplementation on depression treatment

In a clinical trial which its result published recently in the year 2015, Brownley KA and co-workers found that Cr beside increases cell's sensitivity towards insulins can also improve serotonin and dopamine's function's too which can be very helpful and effective in the treatment of neurobehavioral processes like depression and comorbid conditions [47]. A later study in the same year suggests that many foods and dietary compounds such as trace elements with nutritional value like Zinc, Magnesium, and Chromium are involved in the onset, symptomatic management or maybe even treatment of depression. Recent studies demonstrate new mediators of mood change factors and energy homeostasis like Insulin-like growth factor (IGF-1), Neuropeptide Y (NPY), Brain-derived neurotrophic factor (BDNF), Leptin, Ghrelin, Glucagon-like peptide-1 (GLP-1), Cholecystokinin (CCK), and metabolism of glucose acting in brain circuits. Many unhealthy western food pattern like high consumption of sweetened beverages, fried items like French fries or fried chicken and etc. refined foods like processed meats and can foods, high-fat dairy products, refined grain, like in biscuits and snacks and pastries shows associates with an elevated risk of depression; but in contrast healthy food such as white meats like fish and poultry, olive oil, fresh vegetables and fruits, nuts and dry fruits, legumes, low-fat dairy products and unprocessed meat showing anti-depressant effect and work in a positive mood change mechanism. In the same trial, they found that calcium, chromium, Polyunsaturated fatty acids

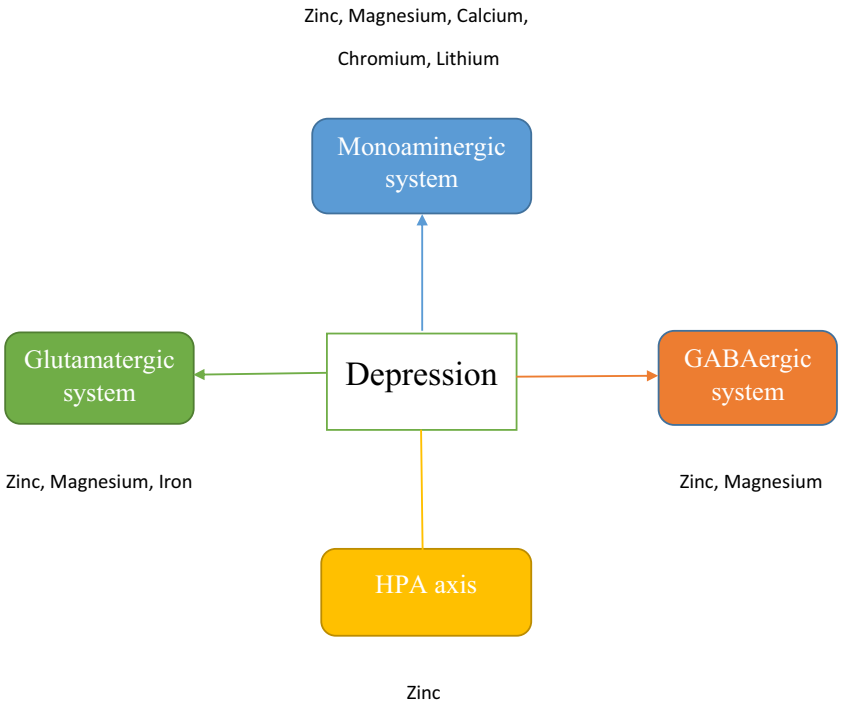


Fig. 2 Depression Diagram, different elements affecting Monoaminergic system, Glutamatergic system, GABAergic system and HPA axis which may cause depression

(PUFAs), folate and vitamins like B12 and D minerals like zinc, magnesium, and D-serine have been hypothesized o be used as an add on strategy in depressant therapies. In this circumstance, dietary and healthy lifestyle interventions have the utmost importance. In first randomized clinical controlled trials conducted by Lang UE and colleagues several medications which mostly used to treat metabolic disorders such as metformin, atorvastatin, and antibiotics which works against gram-negative bacteria, shown a clear and undisputed potential effect to treat depression [48].

Based on a mechanism and clinical trials reported in one the latest systemic review on nutrient-based depression therapy by Louisa G. Sylvia and the team from Harvard Medical schools; Cr has an effect on monoamine neurotransmitter system and plays a vital and key role in fat and glucose metabolism [49]. Louisa G. also reported on a first open pilot study for evaluating the effects of Cr on bipolar disorder on study population on 30individual for the period of over 2 years, almost one-third of patients report a great decrease in depressant symptoms [50]. Many clinical trials on rats and humans on Cr salts such as Cr picolinate and Cr yeast and Cr chloride are in favor of enhancing and serotonergic pathways as part of antidepressant action [51, 52]. As previously said Cr has an important role in glucose and fat metabolism which include enhancement of functions of the hypothalamus by elevating glucose metabolism and intake which consequently results in serotonin, norepinephrine, and melatonin synthesis [53]. In short, the conclusion of all above trials and research can be seen on below diagram (Fig. 2), as it is self-explanatory; trace elements like zinc, magnesium, calcium, chromium, and lithium by affecting on monoaminergic pathway, zinc and magnesium on GABAergic pathway, zinc, magnesium, and Iron on Glutamatergic pathway and zinc on HPA may cause depression.

Chromium and Diabetes Mellitus

Let's back to diabetes control, here we going to talk about a very unique method that went on a clinical trial in the year 2016 by formulating Cinnamon-chromium-magnesium honey and observing its effect on the diabetic patient and compare it with control group and results were so interesting. Formulating Kanuka honey by adding cinnamon, chromium and magnesium had not so significant improvement in lowering glycaemic index but very well associated with weight loss and decreasing lipid profile parameters; which need further trials [54]. Also, it may reduce the risk of retinopathy and kidney disease when they caused by abnormality high glycaemic index [55]. The other naturally-occurring compound that improves insulin sensitivity has been proofed in DM is polyphenols found and extracted from cinnamon [56, 57]. In another clinical trial conducted by Liu Y and tam in the year 2015 on 60 individual which based on teams criteria selected out of 220 primary enlisted patients, results of double-blind treatment with combination of cinnamon and chromium and carnosine showed decreased in FPG points and at same time observed increase in fat-free mass, which they concluded this dietary supplement can be used in overweight patients/individuals with elevated FPG who is at risk of type diabetes as they can gain fat-free muscle mass and decrease lipid deposition [58]. The suggested amount in this study for cinnamon intake was 500mg/day to increase fat-free lean muscle. McIver DJ and colleagues in the year 2015 reported that more than 150 million people (> half of US population) taking nutritional supplementation and near 50 million of them consume Cr separately or included in their multivitamins capsules. Their study found that the rate of type 2 DM was lower in those individuals who were under Cr (solo/multivitamin). This study suggests the role of Cr in the form of picolinate as one of preventive care in healthy or pre-diabetic individuals [59]. In the same year as McIver's trial Peruzzu A and team conduct a trial to see the effectiveness of trace elements such as Zinc, selenium, chromium, and iron on lipid parameters and glucose level in type I diabetes in Sardinia, Italy. They found Cr positively effect on lipid parameters like HDL and selenium in female patients effectively work with triglyceride. And also findings suggest that Cr was showing a decline in FBS, especially in male patients. Overall they found trace elements such as zinc, iron, and selenium have a correlation with lipid profile and chromium and copper associated with glycated hemoglobin or HbA1c percentile [60]. In Paiva and colleagues study in the same year of 2015 on 198 shortlisted patients, she found interesting result that besides taking Cr supplementation for individuals with deficiency of Cr in their serum still some of them could not reach desired level of Cr in their blood which later found out to be due to excessive use of process, fast food, and fried items in their daily diet and smoking [61]. As everybody knows HUNT is one of the world's largest country-wide population health studies conducted by the health department of the government of Norway for decades. In their 2016 study, they considered 26 elements and observe their effect on type 2 pre-diabetic individuals report suggests out of 26 trace elements they found a correlation between only 7 elements and developing of type 2 diabetes mellitus which include bromine, cadmium, chromium, iron, nickel, silver and zinc [62]. In their 2017 study report when they evaluate diabetic patients this time; unlike the first time that they considered pre-diabetic individuals; they didn't find any significant statistical evidence correlating deficiency of Cr and high glycaemic index [63]. In one clinical trial which conducted in 2012 in the northern African country of Algeria, results suggesting Cr has a determinant role in metabolic disorders especially diabetes mellitus by showing better acceptable HbA1c results on a study population of 278 individuals [64]. In the same year, a similar study has been conducted in another side of the world, and they monitored the effect of concentration of trace elements like copper, zinc, iron, and chromium in diabetic patients and found that type 2 diabetes mellitus patients

have significantly lower serum level of copper, chromium, and zinc. It suggests that deficiency of the above trace elements plays a crucial role in developing diabetes mellitus [65]. Cr role in prevention or delay in the steady progress of pre-diabetes to diabetes, multivitamin intake which contains Cr picolinate or brewer's yeast will reduce or delay diabetic onset. By prohibiting or postponing diabetes invasion we can reduce the risk of other comorbid diseases and conditions where prediabetes or diabetes itself is causative. In Adam and colleagues' study on Cr bind metformin and its postulated antimicrobial activity, after tests and trials they found, moderate antimicrobial recorder against gram-negative and positive and even different fungal strains [66, 67].

Chromium and healthful diet

As previously stated based numerous research and clinical trials Cr has the key in the prevention or alternative therapy in treating diabetes or as vital elements in lowering hyperlipidemia. The Dietary Guidelines for Americans which is published by FDA-USA for the following 5 years from 2015-2020 describes a healthy eating pattern as one that includes a:

- variety of vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, and oils.
- Whole grain products and certain fruits and vegetables like broccoli, potatoes, grape juice, and oranges are sources of Cr. Ready-to-eat bran cereals can also be a relatively good source of Cr.
- Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.
- Lean beef, oysters, eggs, and turkey are sources of Cr.
- Limits saturated and trans fats, added sugars, and sodium.
- Stays within your daily calorie needs (Table 2) [55, 68].

Table 2 Natural sources of Chromium

Food	Size	Ch./Serving
Broccoli	½ cup*	11 mcg
Grape juice	1 cup	8 mcg
Mashed potato	1 cup	3 mcg
Dried garlic	1 teaspoon	3 mcg
Orange juice	1 cup	2 mcg
Whole wheat bread	2 slices	2 mcg
Unpeeled apple	1 medium	1 mcg
Banana	1 medium	1 mcg

*Cup: 150 ml

Natural sources of chromium which can include in daily diet

Conclusion

It is possible that ethnic or genetic factors impact the clinical effects of Cr, including trials conducted on Indian, Chinese and western populations. Many may show in favour of positive effects of Cr compounds on DM and lipid profile and very few may show no effect, but none of the trials showed a negative effect on DM. Numerous literature in both the field of animal and human experiments and trials shows and support hypothesis that Cr is an essential micronutrient involved in insulin metabolism as find out trials on type 2 diabetes mellitus patients with Cr deficiency. Nowadays studies and trials have been increased to deepen our knowledge toward Cr and its interesting and vast beneficial effects. Further studies have been suggesting to confirm and may find other beneficial properties of Cr compounds.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

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