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Review Article

EVIDENCE FOR USE OF CHROMIUM IN TREATMENT OF PRE-DIABETES

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ABSTRACT
Chromium supplements are widely used for the prevention and treatment of type 2 diabetes. Recent conflicting reports on its varying effects across different patient demographics calls for a review of the evidence to clarify the role of chromium supplementation in the prevention and management of elevated fasting glucose levels. A search of the literature performed with the terms chromium, pre-diabetes, type 2 diabetes continues to yield conflicting results due to small sample sizes, heterogeneous subjects and different forms and doses of chromium supplementation used. There is still scientific evidence that in specific patient populations, chromium supplementation is clinically relevant. Until further clinical trials provide a definitive answer, the risk-benefit ratio is in favor of possible benefit.
Keywords: Chromium, pre-diabetes, type 2 diabetes, dietary supplement, blood glucose.

INTRODUCTION

Diabetes (Types 1 and 2) now affects 366 million people worldwide and is responsible for about 4.6 million deaths annually. According to the American Diabetes Association, 29.1 million or 9.3% of the US population over 20 years of age have diabetes.[1] It remains the 7th leading cause of death in the US. Type 2 diabetes (T2D), a chronic metabolic disorder, results from an insulin secretory defect in the context of insulin resistance and relative insulin deficiency.[2] It is characterized by high blood glucose. The disease is usually linked to obesity, lack of physical activity and/or a family history of the disease.

According to the CDC's 2014 report, an additional 86 million American adults have "pre-diabetes" meaning that their blood sugar levels are higher than normal, but not yet meeting the threshold of diabetes as defined. Worldwide, the number of people with pre-diabetes is estimated to exceed 300 million and is projected to be 418 million by 2015 according to the International Diabetes Federation. Pre-diabetes is differentiated from T2D but the two are interlinked. Pre-diabetes can progress to T2D; 90% of the estimated 86 million Americans do not know they are cascading toward this chronic metabolic disorder. The CDC estimates that 15 to 30% of people with pre-diabetes will develop T2D within five years if they do not adopt healthier lifestyles and lose weight.[3] Pre-diabetes has been recognized since the late 1990s as a marker denoting a relatively high risk for the future development of T2D. The Expert Committee on Diagnosis and Classification of Diabetes Mellitus labeled an intermediate group of individuals whose glucose levels did not meet the criteria for diabetes but were still above what was considered normal.[4,5] These persons were described as having impaired fasting glucose (IFG). Laboratory tests indicating IFG are a fasting plasma glucose (FPG) level between 100mg/dL [5.6mmol/L] and 125mg/dL [6.9 mmol/L]) or an impaired glucose tolerance (IGT) measured by a 2-hour oral glucose tolerance test (OGTT) resulting in a blood sugar level between 140mg/dL [7.8mmol/L] and 199 mg/dL [11.0mmol/L]). There is no universal agreement on the cutoff point for impaired fasting glucose; the World Health Organization (WHO) and other diabetes organizations suggest IFG of 110mg/dL (6.1mmol/L).

Elevated IFG and IGT are not clinical conditions but are best regarded as risk factors for diabetes as well as for cardiovascular disease (CVD). Individuals with pre-diabetes often have other cardiovascular risk factors, such as obesity (especially abdominal or visceral obesity), hypertension, and dyslipidemia with high triglycerides and/or low HDL cholesterol. Assessing and treating these risk factors is an important aspect of reducing cardiac risk. Numerous studies have similarly shown that T2D can indeed be prevented or delayed in people with IFG or IGT through physical activity, various drugs and a healthy diet. Researchers from the recent Diabetes Prevention Program Outcomes Study (DPPOS) reported that recovery from pre-diabetes to euglycemia, even if only transiently, significantly reduces the risk for future diabetes mellitus.[6] Published in the June, 2012 Lancet, this landmark study showed that significant long-term reduction in diabetes risk can be achieved by aggressive early intervention to lower blood glucose levels in patients with pre-diabetes.

DPPOS findings revealed that people who had at least one normal OGTT following an intervention had a lower relative risk of developing diabetes than people with pre-diabetes who never achieved a normal glucose measurement. The decrease in risk was significant, 56% measured at hazard ratio (HR), 0.44; 95% confidence interval (CI), 0.37 - 0.55; P < .0001. Further, risk of developing diabetes was reduced by 61% if normal glucose regulation was reached twice and by 67% if it was reached 3 times during the study (Respectively, HR, 0.39; 95% CI, 0.28 - 0.56; P < .0001 and HR, 0.33; 95% CI, 0.19 - 0.58; P = .0001). The bottom line is that for lowering the risk for diabetes, achieving normal glucose levels is the target goal. The DPPOS researchers noted that it did not matter which method was used to achieve normal glucose regulation so long as it was accomplished. The ACE and AACE (The American College of Endocrinology and the American Association of Clinical Endocrinologists) consensus statement recommends a two-pronged approach to treating pre-diabetes: intensive lifestyle intervention, followed by the prevention of cardiovascular complications

using CV risk reduction medications for abnormal blood pressure and cholesterol, independent of glucose control medication.[7] Guidelines from the ADA suggest that patients who are diagnosed with pre-diabetes be referred to an ongoing support program, achieve a weight loss of 5 % to 10 % of their current body weight, as well as to increase their physical activity to at least 150 minutes per week of moderate activity.[8] According to DPP findings, patients who lose weight often regain normal glucose regulation. However chromium supplementation was not mentioned in the DPPOS or guidelines.

The goals of pre-diabetic therapies are to normalize glucose levels, prevent or delay progression to diabetes, prevent micro vascular complications, and modify other risk factors such as obesity, hypertension, and dyslipidemia. Therapeutic lifestyle management is the cornerstone of all prevention efforts. No pharmacologic agents are currently approved for the management of pre-diabetes. Pharmacotherapy targeted at lowering glucose may be considered in high-risk patients after individual risk-benefit analysis. Converging evidence strongly suggests that an array of nutritional interventions including herbs in combination with optimal levels of vitamins and minerals not reflected in current guidelines can successfully contribute to normal glucose management in the pre-diabetic population. This paper explores the controversies with one of the most popular nutrients, chromium.

Nutritional intervention with Chromium

Chromium, a micronutrient, is an essential element required for normal carbohydrate and lipid metabolism. Studies have shown that a deficiency in chromium is related to early-stage diabetic complications and hastens the onset of overt diabetes mellitus. Low serum chromium levels are associated with increased glucose, triglycerides and decrease high density lipoprotein (HDL) and cholesterol levels, both critical markers in pre-diabetes and T2D. Trivalent chromium (Cr^{3+}) supplements are widely promoted for use in pre-diabetes and T2D based on the physiologic function of chromium in glucose and insulin homeostasis. In addition to proper carbohydrate and lipid metabolism, chromium is beneficial in reducing carbohydrate cravings and appetite, preventing insulin resistance and glucose intolerance and potentially regulating body composition. Sales of vitamins, minerals and supplements totaled nearly $23 billion in the U.S. in 2012, according to Euro monitor International and the Wall Street Journal[9] and are growing at 5% to7 % annually. Current retail sale numbers are proprietary but retail sales for all dietary forms of chromium were reported to be $106 million in 2003, an increase of 25 per cent over 2002, with about $92 million of that total being for chromium picolinate.[10] Chromium is available as a single-ingredient supplement as well as in combination formulas marketed for weight loss and performance enhancement. Supplement doses typically range from 50 to 200 mcg.

A meta-analysis of the use of chromium in pre-diabetes and T2D conducted by Althuis *et al* in 2003 found inconclusive results but a systematic review of randomized controlled trials by Balk *et al*[11] in 2007 came to the following conclusion. After reviewing randomized controlled trials of chromium supplements they state that no significant effect of chromium on lipid or glucose metabolism was found in people without diabetes: however a modest beneficial effect on glycemia and dyslipidemia was found in people with T2D. Interestingly they reported that studies with brewer's yeast had more favorable results over the single entity chromium picolinate or chromium chloride. Clearly, such studies warrant consideration. This paper reviews the literature and examines the underlying science and evidence pertaining to the form of chromium used and patient populations.

Mechanism of Action

Chromium was first suggested by Mertz and Schwarz to play a role in regulating blood glucose levels in the 1950's.[12] Before chromium was commonly added to total parenteral nutrition (TPN) solutions, glucose intolerance reversed by supplemental Cr was reported in patients on TPN.[13,14] Discovering this relationship lead to elevating chromium's status to that of an essential trace element. Today, 50 years later, whether it's essential status is being debated as Cr appears to have a low dietary requirement and may only enhance the actions of insulin in people with T2D.[15]

However, diabetics may have a higher requirement for chromium and have impaired mechanisms to convert the mineral into a usable form.[16,17] In the 1990's the bioactive form of chromium bound to chromodulin was shown to have a low serum concentration in study patients with diabetes.[18,19] In people with diabetes, chromium metabolism, may differ in both absorption and excretion.[20,21] Ding reported finding that chromium levels were reduced by more than half in both diabetic men and women compared with control subjects.[22] Other research supported this finding. Mean levels of plasma chromium were found to be about a third lower in 93 T2D subjects compared with control subjects.[18] Another study reported significantly lower chromium levels in the plasma of T2D individuals compared with non diabetic healthy control subjects. But other small studies found no alteration of chromium levels in T2D.[23] To date, no chromium-specific enzyme or biomarker reliably assess chromium status.[24]

In order to understand how chromium enhances insulin's actions it is useful to briefly review the mechanisms whereby insulin normally lowers blood glucose in skeletal and adipose tissues. Insulin is recognized extracellularly by receptor tyrosine kinases which transduce signals intracellularly via various kinase cascades with or without the involvement of low molecular weight G-proteins (LMWGPs). The insulin receptor (IR) in skeletal muscle binds insulin allowing auto phosphorylation of its intracellular subunit that in turn activates its function as a tyrosine kinase. Various so-called docking or adapter proteins are subsequently recruited and phosphorylated on multiple specific tyrosine residues. These include the insulin receptor substrates 1 and 2 (IRS-1 and IRS-2 respectively) which once phosphorylated, appropriately bind Src-homology 2 domains (SH2) on target proteins. The regulatory subunit of phosphatidylinositol 2-kinase (p85 of PI3K) has an SH2 domain and the interaction recruits the catalytic subunit of PI3K (p110) to the cell membrane allowing it to convert phosphatidylinositol-4,5-bisphosphate to phosphatidylinositol-3,4,5-triphosphate which in turn activates phosphoinositide-dependent kinases finally resulting in the activation of protein kinase B (Akt).

Akt phosphorylates many targets including the GTPase activating protein (GAP) for the LMWGP Rab resulting in the insertion of vesicles containing the glucose transporter GLUT4 into the cell membrane. This then allows facilitated diffusion of glucose into the cell down its concentration gradient. It should also be noted that Akt activates glycogen synthase kinase-3 by phosphorylation so stimulating glycogen synthesis from the influx of glucose[25] (see Figure1).

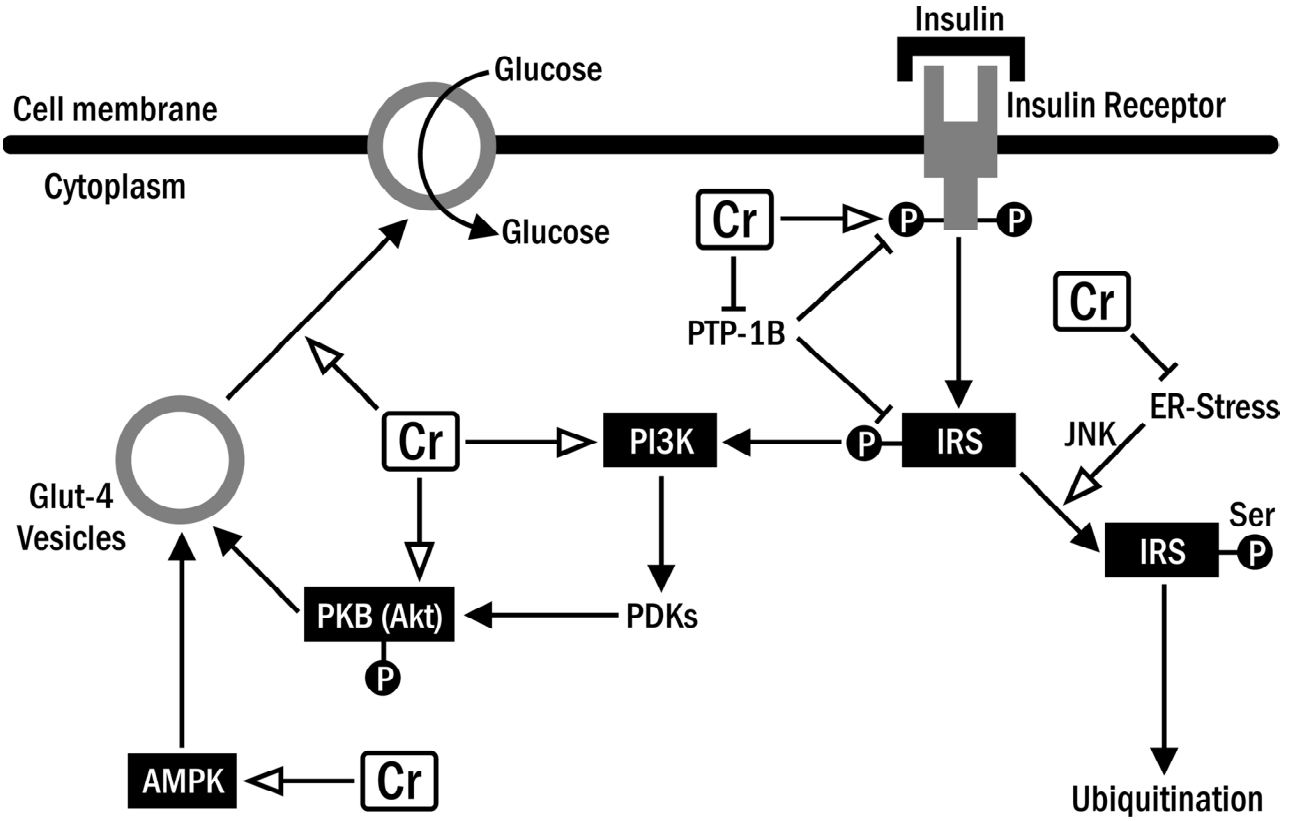

Figure 1: Model showing the principal sites whereby chromium is thought to directly enhance insulin signaling

Chromium (Cr) has been shown to enhance the kinase activity of the insulin receptor itself and increase phosphorylation and activation of insulin receptor substrate 1 (IRS), protein kinase B (PKB, also known as Akt) and phosphatidylinositol 2-kinase (PI3K, via phosphoinositide-dependent kinases/PDKs). In addition, Cr has been reported to increase the phosphorylation of AMP-activated protein kinase (AMPK); all of these interactions lead to increased glucose uptake by increasing transporter insertion via Glut-4 (insulin-sensitive glucose transporter) vesicles. Cr also seems to inhibit 2 mechanisms that usually reduce increased glucose uptake. These include inhibition of protein tyrosine phosphatases (PTPs) that dephosphorylate the insulin receptor therefore inactivating it and endoplasmic reticulum (ER) stress, mediated via various inflammatory cytokines, that acts via Jun NH(2)-terminal kinase (JNK). IRS can be phosphorylated on a specific serine (Ser) residue which makes it a substrate for JNK and increased degradation by a ubiquitin-proteosome-mediated process so making it unavailable to activate PI3K. Adapted from Hua *et al*.[116]

Insulin has other actions including effects on gene transcription and these will be discussed subsequently only if relevant.

Before discussing the effects of chromium on insulin signal transduction its sources in the diet and supplement form, uptake, transport and bioactive form should be considered. Good sources of dietary Cr include meats such as beef, fish, poultry, whole grains, cheese, peanuts, dark chocolate, some vegetables and fruits, some spices, brewer's yeast, tea, beer and wine.[30] Chromium is typically consumed as Cr^{3+} or Cr^{6+}. The hexavalent form (also written CR (VI)) is a toxic form that rarely occurs in significant amounts naturally. If ingested in small amounts together with other foodstuffs it tends to be reduced to Cr^{3+}.[26,27] Chromium (VI) is formed as an industrial by-product of the welding and chemical industries. Ingesting large amounts of chromium (VI) can cause stomach ulcers, convulsions, kidney and liver damage and even death. It is also a carcinogen and is the form implicated in causing cancers in the movie Erin Brockovich. This form is a known contaminant in supplements.[28,29] Trivalent chromium is 10-100x less toxic than the hexavalent form.[30] In 2002 the EPA suggested a daily dose of chromium of ~70 mg for adults which is much greater than the proposed safe adequate dietary intake which may suggest that typical recommended supplement dosing is inadequate.[31,32] There exists very little evidence that Cr^{3+} is toxic in humans at typical recommended doses but there do exist a few isolated, anecdotal reports of toxicity at doses between 200 mcg and 2400 mcg but most of these can be explained by other factors.[33-37]

Chromium is poorly absorbed from the GI tract with typically only 0.5 to 2 % of that ingested being absorbed: interestingly high amounts of chromium in the diet tend to decrease absorption.[38] To enhance uptake from oral supplements, Cr is typically combined with molecules known to be well absorbed in the GI tract including polynicotinate (niacin), picolinate (picolinic acid derived from tryptophan), phenylalanine, dinicocysteinate, biotin and the inorganic salt Cr chloride.[41]

After absorption from the digestive system Cr binds to transferrin (better known for the transport of iron) in the blood and is transported to the tissues. Currently, Cr is only known to bind to 2 molecules, namely transferrin and low-

molecular weight chromium-binding substance (LMWCr) also known as chromodulin (analogous in function to calmodulin with respect to calcium).[42] Insulin appears to stimulate the expression of transferrin receptors on the cell membrane so allowing Cr uptake by endocytosis, suggesting a functional link which due to their synergistic effects, is logical. Transferrin can normally bind 2 Fe^{3+} but is typically only ~30 % occupied with iron so it is thought that it is also used to transport other metal ions in the body. Injected Cr^{3+} and *in vitro* studies support the concept that in the blood Cr^{3+} binds principally to transferrin although this has not been confirmed *in vivo*.[43-45] However the transfer of Cr^{3+} from transferrin to chromodulin has been demonstrated *in vitro*.[46] In elderly T2D sufferers chromium levels may be low possibly due to hepatic iron overload which is frequently associated with T2D: Fe-transferrin occupancy is very high so possibly resulting in inadequate chromium transport resulting in insulin resistance.[47]

Significantly, Cr picolinate, the most popular supplement form, is not apparently absorbed via endocytosis, meaning its uptake will not be coordinated with insulin release.[46] Vincent (2010) states that this difference in uptake may be crucial to efficacy.[48] In fact *in vitro* studies indicate that Cr ingested in this form can be reduced and interact with oxygen to generate the hydroxyl radical which may cause DNA cleavage.[49] Once internalized the pH in the endocytotic vesicle decreases causing the release of the Cr ions from transferrin which then bind to LMWCr. LMWCr is a small oligopeptide that can bind up to 4 Cr^{3+} ions. It is thought that Cr acts mainly in this form and that it is also excreted in this form both in urine and feces.[50-52] Vincent *et al*. showed that LMWCr with bound Cr increased insulin-dependent tyrosine kinase activity of the IR by x3 to x8 *in vitro.* In these studies he also showed that if Cr was removed, the increase was eliminated.[53] Subsequently, it was found that increased kinase activity was proportional to the amount of Cr bound to LMWCr and that other metal ion complexes (such as Mn, Fe or Co) did not augment insulin function.[54]

However, other studies did not observe increases in IR phosphorylation either at basal levels or following insulin treatment.[55,56] Looking further down insulin's signal transduction pathway yields more reliable results with Cr treatment. In several cellular and animal models of insulin resistance Cr treatment produced increased phosphorylation and therefore activation, of IRS-1, Akt and increased activity of PI3K (see Figure 1).[57] Using a triphenylalaninate Cr complex Yang *et al*. enhanced insulin-stimulated glucose uptake in adipocytes *in vitro* via increased insulin-stimulated phosphorylation of Akt.[16] This complex was also fed to leptin-deficient obese mice where it improved glucose tolerance, helped correct lipid metabolism and enhanced insulin-stimulated IR phosphorylation in muscle and liver.[58,59] Studies on the skeletal muscle of high-sucrose-diet-fed mice and diabetic rats showed increased translocation of GLUT4 transporters into the cell membrane with Cr supplementation.[60,61] To see if this effect was due to the previously described effects on the insulin signal transduction pathway or a separate, possibly direct effect, Chen *et al*., using adipocytes *in vitro*, studied insulin-stimulated GLUT4 translocation. They found Cr treatment increased GLUT4 at the cell membrane independent of insulin signaling molecules (IR, IRS-1, PI3K and Akt) and proposed that this is due to an increase in membrane fluidity by decreasing the membrane's cholesterol content.[62]

Although a discussion on the various chromium supplements' chemistry is beyond the scope of this article, we should discuss the efficacy, if known, of the different dietary supplements available. It appears that organic forms or complexes of chromium are better absorbed than inorganic ones such as chloride, carbonate or phosphate.[63-65] In addition some dietary factors are thought to increase absorption, resulting in increased blood levels, including starch, ascorbic acid and oxalates (chelator).[66-68] Whereas a zinc deficiency can actually increase chromium levels,[69] iron, manganese, calcium and titanium can all decrease chromium uptake from the GI tract.[70] Chromium absorption can be affected by a number of drugs: aspirin and indomethacin both increase absorption whereas antacids (possibly due to competition with metal ions in the antacid) can decrease absorption.[71,72]

Many forms of chromium supplement have been marketed with varying success and much of this is due to the paucity of real data not only on efficacy of restoring glucose homeostasis but even on absorption. A review by Lamson and Plaza published in 2002 actually compiled results comparing absorption of inorganic chromium chloride to several organic forms including nicotinate, picolinate and chromium from the diet and brewer's yeast in various animals and human studies.[73] They concluded that, after diet and brewer's yeast as sources, the best supplement was picolinate. DiSilvestro and Dy[74] in 2007 found picolinate was better absorbed than nicotinate and chloride while Preuss *et al.*[75] in 2008 compared five different organic forms of chromium and found only 2, an amino acid chelator and polynicotinate, produced a significant decrease in the insulin challenge test. These authors also noted that polynicotinate produced less liver and kidney damage than picolinate. Picolinate is very popular although there have been some questions raised concerning its safety as mentioned previously. Currently the supplement of choice may be chromium dinicocysteinate which attempts to partially mimic chromodulin. In diabetic rats compared to dinicotinate and picolinate, dinicocysteinate was best overall at lowering blood glucose, A1C and vascular inflammation markers[76] while in a recent study in humans with T2D dinicocysteinate was clearly superior to picolinate in decreasing insulin levels and resistance.[77]

As with any signaling pathway activated by phosphorylation, it is invariably balanced by the action of de-phosphorylating protein tyrosine phosphatases (PTBs). As shown in Figure 1, PTB-1B is implicated as a negative regulator of both the phosphorylated forms of IR and IRS-1 and therefore contributes to insulin resistance.[78-80]

Studies with Cr in this area have yielded mixed results. Vincent's group found that LMWCr (complete with Cr) enhanced phosphatase activity (although not necessarily PTP-1B) in adipocyte membranes but did see a significant reduction in activity with Cr in PTP-1B in rat hepatoma cells.[81,82] In addition, Wang *et al* saw reductions in both expression and activity of PTP-1B in the skeletal muscle of obese rats treated with Cr picolinate.[17] Insulin Receptor Substrate 1 (IRS-1) can also be phosphorylated on a specific serine residue which prevents it from activating PI3K so reducing insulin signaling.[83,84] Once phosphorylated on this specific residue IRS-1 becomes a substrate for Jun NH(2)-terminal kinase (JNK) and increased degradation by a ubiquitin-proteasome-mediated process.[30,85,86]

Studies on various obese insulin-resistant mice models have shown elevated levels in the liver and skeletal muscle of both

serine phosphorylated JNK and IRS-1 that was reduced by Cr treatment.[19,87] Endoplasmic reticulum (ER) stress has been implicated in the development of insulin resistance and this stress has been shown to activate JNK so attenuating insulin signaling (see Figure 1).[88-90] Again, Cr treatment appeared to reduce ER stress and other pro-inflammatory cytokines which can all enhance the development of insulin-resistance.[91,92] Studies on human keratinocytes indicated Cr may up-regulate certain antioxidant and DNA-repair genes and this was also observed in diabetic patients and obese mice.[93-96] Finally it should be noted that Cr has also been reported as stimulating the phosphorylation of AMP-activated protein kinase (AMPK) which is thought to be important as a regulator of glucose metabolism.[97,98] Cr-mediated up-regulation of AMPK produces increased glucose uptake.

To summarize, Cr appears to enhance several of the actions of insulin, including increased activation of both IR and its targets, to increase glucose uptake. In addition it appears to reduce oxidative stress which is also a contributor to the development of diabetes. Apart from these positive effects on insulin signaling Cr has also been reported to reduce triglyceride levels and stimulate β-oxidation.[99,100]

Supporting Evidence

In a 2009 randomized multicenter trial, diabetic patients given chromium experienced reductions in their total insulin requirements, along with reductions in fasting and afternoon glucose levels.[101] Other older studies show that supplementation with chromium improved glycemic control in overweight to obese diabetic patients when taken along with their regular medication.[102-104] It's possible that chromium helps control glycemic status and reduces the risk of insulin resistance via lowering plasma membrane cholesterol. Related studies showed that a loss of plasma membrane phosphatidylinositol 4,5-bisphosphate-regulated filamentous actin structure contributes to insulin-induced insulin resistance.[105,106] A 2010 Louisiana State University investigation also concluded that modulation of lipid metabolism by Cr in peripheral tissues may represent a novel mechanism of action for combatting the insulin resistance that characterizes pre-diabetes and T2D.[107] The objective of their study was to provide a comprehensive evaluation of chromium supplementation on metabolic parameters in a cohort of T2D subjects representing a wide phenotype range. To do so, they measured changes in "responders" and "non-responders." After establishing baseline levels of glycemia, insulin sensitivity (assessed by euglycemic clamps), Cr status and body composition, subjects were randomized in a double-blind fashion to placebo or 1 mg chromium supplementation. These researchers found the clinical response to chromium supplementation was more likely in insulin-resistant subjects who have more elevated fasting glucose and A1c levels. In subjects with T2D who do respond clinically independent of effects on weight or hepatic glucose production, chromium may reduce myocellular lipids and enhance insulin sensitivity. The outcomes of this study imply patient selection is important and that modulation of lipid metabolism by Cr in peripheral tissues may be a novel mechanism of action for treatment.

Some evidence supports chromium specifically as a prevention for advancing from the pre-diabetic state to T2D. Studies involving subjects not yet meeting the full diabetes diagnostic criteria also showed improved blood lipids following Cr treatment. Improvements were typically greatest in subjects with the highest blood lipid levels.[108] However, in some investigations clinically significant improvement took several months to appear. Abraham, *et al*. found that treatment with 250mcg Cr chloride over 6 to 16 months both increased HDL cholesterol and decreased triglycerides levels.[109] Other studies such as one by Anderson reported beneficial effects of on blood lipids after only 3 or less months of supplementation.[110] In one of the earliest studies involving chromium picolinate, 180 people with T2D were randomly assigned to receive either 100 mcg chromium picolinate, 500mcg chromium picolinate, or a placebo.[111,112] Subjects receiving the chromium supplement had significantly lower fasting insulin levels after two months, and at four months both groups actually had identical values for fasting insulin levels. After four months, insulin levels (after a 2 hour glucose challenge) were also significantly lower and similar in both groups. In this study, subjects taking the higher dose of chromium were found to have lower total cholesterol levels and scored significantly lower on their fasting and two-hour insulin level tests, indicating improvement. A1C levels were also significantly lower after four months in both groups receiving chromium supplementation. The group receiving 100 mcg/day demonstrated a quicker drop in A1C and also showed a significantly lower A1C after two months, which remained significant at four months. It also should be noted that this study was not included in the meta-analysis by Althuis as inclusion would have introduced heterogeneity into the data.[113]

As mentioned previously newer forms of chromium are being tested in T2D patients. Jain who did earlier mechanistic work developed a chromium dinicocysteinate supplement and ran a double-blind placebo-controlled study with 74 T2D patients. His team looked at TNF-α, oxidative stress, and insulin resistance. His new formulation appeared to produce significantly reduced levels of the inflammatory cytokine, TNF-α, and about a 30% reduction in both fasting insulin levels and insulin resistance.[114] Chromium has been studied in people without pre diabetes or T2D. A double blind placebo-controlled randomized trial was conducted on 31 non-obese, normoglycemic subjects. After baseline studies, the subjects were randomized to placebo or chromium picolinate 500mcg twice a day. The primary endpoint was the change in insulin sensitivity as measured by euglycemic hyperinsulinemic clamp. Pre-specified secondary endpoints included fasting lipids, blood pressure, weight and body composition measured by Dual-energy X-ray absorptiometry (DXA) scan. After 16 weeks of chromium picolinate therapy there was no significant change in insulin sensitivity between groups ($p = 0.83$). There was, unexpectedly, an association between serum chromium and change in insulin resistance ($\beta = -0.83$, $p = 0.01$). Subjects with the highest serum chromium experienced a worsening of insulin sensitivity. This effect could not be explained by changes in physiological parameters such as body weight, truncal fat and serum lipids. Chromium supplementation did not improve insulin sensitivity in non-obese normoglycemic individuals. Further, subjects who have high serum chromium levels paradoxically had a decline in insulin sensitivity. This finding warrants further study due to the wide spread use of this supplement in the general population.[11]

CONCLUSION

After reviewing the literature and examining the underlying science pertaining to chromium supplementation in people with impaired glucose levels, the evidence still is contradictory. Additional clinical trials on the form of chromium used and performance in specific patient populations needs to be performed; however, chromium is a relatively safe and inexpensive supplement that may have clinical utility in selected populations. Newer compounds such as chromium dinicocysteinate hold promise for achieving the maximum potential benefit of chromium supplementation. There seems to be no reason for it not to be used in people who have impaired glucose control or insulin resistance. The benefit-to risk-ratio favors benefit. Research on the effects of various forms of chromium on biomarkers of T2D and characteristics of patients who most benefit from supplementation is needed.

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