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# Effects of Chromium Picolinate Supplementation on Control of Metabolic Variables: A Systematic Review

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**Abstract** Chromium picolinate is widely used as a supplement to improve glucose metabolism, insulin sensitivity and lipid profile. Its actions, however, extend beyond these metabolic changes, as it has positive effects in the clinical setting of cardiovascular disease, shows anti-inflammatory and antioxidant properties, and even modulates behavior patterns, such as in depression and anxiety. In view of the numerous possible applications of chromium picolinate, understanding the therapeutic properties of this supplement becomes necessary. Thus, the aim of this review is clarify and identify the applications of chromium picolinate, as well as its effectiveness under several clinical conditions. A systematic review was performed during July and September of 2015 through a search on PubMed, Web of Knowledge and SciElo databases using the keywords 'chromium picolinate' and 'supplementation'. Articles selected were published between 2005 and 2015 and written in English, Portuguese and Spanish. The search resulted in 361 articles (Web of Knowledge: 245, Pubmed: 115, SciElo: 1) and after inclusion and exclusion criteria was applied, 12 articles were selected to analyze by reading the full text. Articles reviewed demonstrate that chromium picolinate has a positive action in glucose control, oxidative stress, lipid profile, protein synthesis, binge eating disorder and cognitive decline, although some studies showed absence of effect. Also, a difference was observed in dosage of the supplementation among different samples and there was a largely variable time of treatment. Chromium picolinate supplementation appears to positively contribute to the improvement of metabolic control and health, and could potentially be used as an auxiliary therapy in several diseases.

***Keywords:*** *chromium tripicolinate, dietary supplement, glucose metabolism, lipid metabolism, oxidative stress, behavior control*

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## 1. Introduction

Chromium (Cr) is a trace element, largely used to control glucose and improve insulin sensitivity, especially in diabetes [1,2,3,4]. This mineral is present in two different valence statuses: a toxic hexavalent form and an organic trivalent form. Chromium supplements usually consist of the trivalent form of chromium combined with ligands like picolinic acid, resulting in a chromium picolinate compound [1,2].

Chromium picolinate (CrPic), as a trivalent chromium complex, is a less toxic form than its hexavalent form, shows high bioavailability and is widely used in populations with carbohydrate metabolism disorders, such as insulin resistance and diabetes mellitus type 2 (DM2) [3,5,6]. The dosage of CrPic used varies greatly, ranging from 25 µg/kg to 1000 µg/kg [6], and it is estimated that 0.4 to 2.5% of the total amount of chromium ingested is absorbed, although absorption of chromium is greater from CrPic than from other forms of chromium compounds (0.7 to 5.2%) [5,6].

The most widely recognized role of chromium is in relation to glucose modulation, which occurs via the activation of apochromodulin to chromodulin. CrPic also, however, shows positive effects on cholesterol levels, cardiovascular diseases, and antioxidant and anti-inflammatory capacity, as well as modulating behavioral patterns like depression and anxiety, beyond physical changes (e.g., modified body composition, improvement in training performance) [7,8,9,10].

The effectiveness of CrPic is controversial in the literature, however, due to a great variety of factors, most of which are caused by heterogeneity of methodology. The outcomes investigated are also distinct, including glucose tolerance, glycated hemoglobin, lipid profile, blood pressure, antioxidant capacity, depressive behavior, changes in body composition and exercise performance [6].

CrPic supplements are considered to be the most studied chromium complex [4,11] and have demonstrated several possible applications. More studies therefore need to be carried out to identify their principal and effective properties. Thus, we performed a systematic review to elucidate the mechanisms of action of chromium

picolinate and its benefits in populations with different health conditions.

## 2. Aim

The aim of this systematic review was to elucidate the actions of chromium picolinate and its effects in different clinical conditions.

## 3. Methods

In this study, we performed a systematic review of the literature regarding the supplementation of CrPic and its effects. A search was performed during July and September of 2015 on the Public Medline (PubMed), Scientific Electronic Library Online (SciELo) and Web of Knowledge databases using the keywords 'chromium picolinate' and 'supplementation'.

Articles that were selected included only those: 1) published between 2005 and 2015, so that data included were recent; 2) written in English, Portuguese or Spanish; 3) based on randomized clinical trials with adults and elderly (18 – 75 years); 4) based on experimental studies performed with rats or mice; 5) investigating supplementation of chromium picolinate; 6) implementing supplementation doses between 100 and 1000 µg/kg/day; and 7) with a therapy period of at least four weeks. An article was not selected if it: 1) had no abstract; 2) included patients using medications for glucose control; or 3) involved CrPic supplementation administered by methods other than gavage.

Articles that were selected underwent full-text analyses. The analyses consisted of reading the article and drafting a table with data collected from each study, showing authors/date, sample, methodological aspects and main results. It was thus possible to identify the main outcomes of the studies.

## 4. Results and Discussion

The search found 361 articles (Web of Knowledge: 245, Pubmed: 115, SciElo: 1). Only 12 articles met the selection criteria (Figure 1). The data collected are described in Table 1 and Table 2.

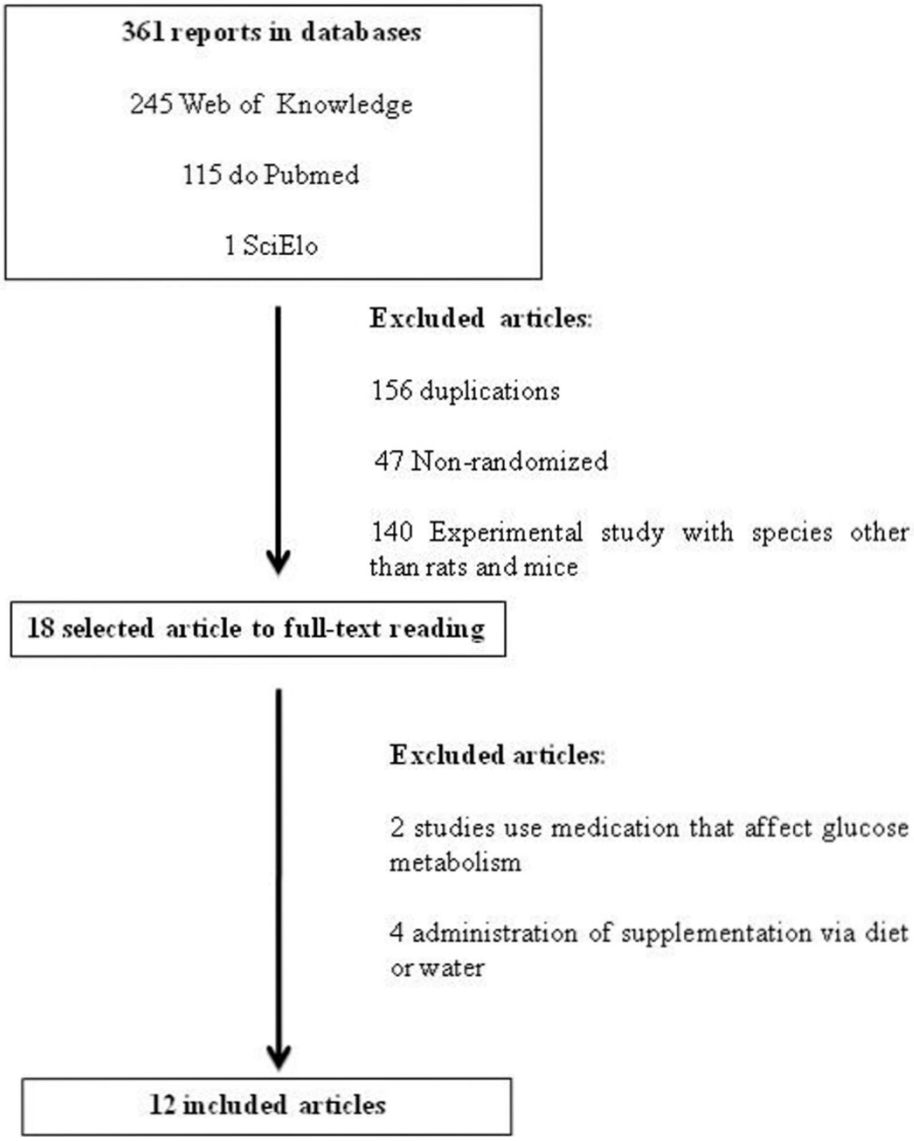


**Figure 1.** Selection of articles through the inclusion and exclusion criteria application

**Table 1. Controlled clinical trial selected to review**

| Author/year | Intervention | Main Outcome |
|---|---|---|
| **Brownley *et al.*, 2013** | Receive placebo or 600 and 1000µg/day of CrPic for 6 months | ↓fasting plasma glucose<br>↓binge eating<br>↓weight<br>HbA1c normalized in 86% of patients under CrPic treatment |
| **Masharin *et al.*, 2012** | Received 500µg 2x/ day for 16 weeks | ↑ serum chromium levels and urinary<br>↔ insulin sensitivity, body composition, muscle biopsies, PCR analyses, BMI, truncal fat or lipid levels |
| **Ali *et al.*,2011** | Offered 2 dosages (500 or 1000 µg/day) for 6 months | ↔ glucose and insulin levels, insulin resistance |
| **Krikorian *et al.*, 2010** | Received 1000 µg/day of CrPic for 12 weeks | ↑ cognitive control and cerebral function<br>↔ depressive symptoms<br>↑ brain activation |
| **Cefalu *et al.*, 2010** | Offered 1000µg/day CrPic for 24 weeks | ↔body fat and composition measures of "responders" and "nonresponders"<br>↓myocellular and intrahepatic lipid in "responders" and "nonresponders" |
| **Iqbal *et al.*, 2009** | Offered 1000µg/day CrPic for 16 weeks | ↑acute insulin response to glucose<br>↔ glucose metabolism, body weight, serum lipids, inflammation and oxidative stress |
| **Wang *et al.*, 2007** | Received 1000 µg/day of CrPic for 6 months | ↑ response to chromium treatment in insulin resistant patients |
| **Vrotvec *et al.*, 2005** | Received 1000µg CrPic for 3 months | ↓ QTc interval of diabetic patients |

BED: binge eating disorder; BMI: body mass index; CrPic: chromium picolinate; DM: diabetes mellitus; HbA1C: glycated hemoglobin; PCR: protein C reactive.

**Table 2. Experimental research selected to review**

| Author/year | Intervention | Main Outcome |
|---|---|---|
| **Seif *et al.*, 2014** | Received 200µg/day of CrPic via gavage for 10 weeks | ↓Platelet hyperaggregability<br>↓Risk of cardiovascular disease<br>↑Improve lipid profile<br>Normalize ADP, collagen-induced hyperaggregability and levels of TX B2 |
| **Huang *et al.*, 2014** | Offered three concentrations of CrPic (25, 50, 100 µg/kg) for 15 weeks | ↓Macroangiopathy<br>↓mRNA expression levels of APN and apelin (100 µg/kg CrPic)<br>↓Levels of HbA1C, AGES, APN, and apelin (100 µg/kg CrPic)<br>↑NO and insulin levels and recover β cells function (100 µg/kg CrPic) |
| **Sundaram *et al.*, 2013** | Received 1000µg/kg of CrPic for 4 weeks | ↑GSH levels and activity of antioxidant enzymes and plasma antioxidants in DM<br>↓Plasma glucose in DM<br>↓Lipid peroxidation in DM<br>↓Activity of AST and ALT in DM |
| **Refaie *et al.*, 2009** | Received supplementation in low (23µg/kg/day) and high doses (100 µg/kg/day) of CrPic for 4 weeks | ↓FBG in diabetic in dose depend.<br>↔ FBG in normal rats<br>↑Mitochondrial β-oxidation of FFA<br>↑Oxidative stress in liver and brain of normal rats<br>↑Antioxidant system in diabetic rats<br>↑Total protein and [RNA] in brain and liver of normal rats with high dose of CrPic<br>↑Total protein in brain and liver of diabetic rats with low dose of CrPic |

ADP: adenosine diphosphate; AGES: advanced glycation end products; ALT: alanine transaminase; APN: adiponectin; AST: aspartate transaminase; CrPic: chromium picolinate; DM: diabetes mellitus; FBG: fasting blood glucose; FFA: free fatty acids; HbA1C: glycated hemoglobin; NO: nitric oxide; TX B2: thromboxane B2.

## 4.1. Glucose Control

Studies that focused on effects of CrPic in diabetes showed an improvement of evaluated parameters. Decreases were observed in plasma glucose, fasting blood glucose (FBG), advanced glycation end products (AGES), glycated hemoglobin (HbAc1), and glucose area under the curve (AUC), while an increase in insulin sensitivity level was observed, demonstrating a recovery of function for hepatic β cells. A reduction in macroangiopathy was also observed after CrPic supplementation [12,13]. In a study by Cefalu and colleagues [12], patients with DM2 were classified as 'responders' and 'non responders' to CrPic treatment. Interestingly, subjects classified as responders had significantly lower levels of HbAc1, fasting glucose and glucose AUC in supplemented groups. Wang and colleagues [14] verified that insulin resistance is the major factor in determining whether a patient may respond on a clinical level to supplemental Cr, with insulin resistance representing approximately 40% of the variance in insulin sensitivity response to Cr after the treatment period.

CrPic was found to be related to improvement of glucose levels, including an increase in numbers of insulin receptors. Moreover, the influx of Cr in the cell activated apochromodulin, through biding with Cr, producing chromodulin. The chromodulin stimulated insulin signaling and consequentially improved translocation of GLUT-4 to the membrane. Chromodulin also induced the activation of substrates such as insulin receptor substrate (IRS) and phosphoinositide-3-kinase (PI-3K) in skeletal muscle and reduced protein tyrosine phosphatase 1B (PTP1B), leading to an increase in insulin sensitivity [1,2].

Furthermore, Suksomboo and colleagues [6] found an important reduction of HbA1c with CrPic that was similar to reductions exerted by antidiabetic agents. Thus, insulin stimulation and increase of glucose cellular uptake were promoted by CrPic supplementation, contributing to an

improvement in glucose control and insulin sensitivity in diabetic subjects [6]. Also, treatment with CrPic demonstrate improvement trend in diabetic indicators, which is maintained by the end of the intervention and the washout period in groups with DM2 compared to placebo, according to Ahmad study [15]. Another study compared the odds of obtaining a higher HbA1c value between subjects taking general supplements and those taking supplements containing chromium and concluded that intake of supplements containing chromium is associated with a lower chance of having DM2 [16].

Huang and colleagues [12] observed that CrPic supplementation was able to reduce macroangiopathy, which is one of the main causes of comorbidity in DM2. This effect may be attributed to nitric oxide (NO) level increases, as these have been reported in others studies of CrPic supplementation. An increase in aortic relaxation mediated by endothelial NO was observed in chronically hypertensive rats that were supplemented with CrPic for 15 weeks, which resulted in an improvement of circulation and recovery after ischemia/reperfusion insult, suggesting that chromium may improve endothelium function and increase vasodilatation mediated by the endothelium. These results indicated a positive effect of CrPic on macroangiopathy in DM2 [17].

## 4.2. Oxidative Stress

Sundaram and colleagues [18] performed a study using diabetic rats which found an antioxidant activity of CrPic. The results showed increases in glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels, as well as no enzymatic plasma antioxidants. Moreover, decreases in lipid peroxidation were found, as evaluated by malondialdehyde (MDA) concentrations. Likewise, Refaie and colleagues [19] demonstrated an antioxidant role of CrPic supplementation through a decrease in hepatic and cerebral MDA concentrations, similar to hepatic and cerebral SOD, GPx and CAT activity in diabetic rats [18]. These findings indicate a preventive capacity of CrPic for oxidative damage induced by hyperglycemia, which is corroborated by both Al-Rasheed and colleagues [9] and Sahin and colleagues [20], who demonstrated a reduction in blood and kidney MDA concentration and increases in GSH, SOD, GPx and CAT activity in myocardium, respectively. Moreover, this improvement in oxidative stress has been related to decreases in tumor necrosis factor alpha (TNF-α) levels and nuclear factor-κB (NF-kB) inhibition [9,18,20]. The antioxidant and anti-inflammatory action of CrPic has been observed in a number of studies and can be explained through multiple mechanisms, among them one which promotes the reduction of nitrite serum levels, leading to blocking the reaction of nitrite with superoxide (O−2•) and then decreasing peroxynitrite production [12,21]. In summary, CrPic may ameliorate oxidative stress and inflammatory response in patients with a pathologic status established [19].

## 4.3. Protein Synthesis

Refaie and colleagues [19] demonstrate an elevation in total protein and RNA concentration in the brain and liver of normal rats subjected to a high dose of CrPic over four weeks. No changes in DNA concentration or protein/DNA and RNA/DNA ratios were identified with this dose. A low dose of CrPic in diabetic rats was able to increase total protein in the brain and liver, but had no effect on protein/DNA and RNA/DNA ratios. In diabetic rats that received a high dose of CrPic, there was an increase in hepatic and cerebral RNA concentration, as well as protein/DNA and RNA/DNA ratios, whereas DNA concentration remained unchanged.

Ratios of protein/DNA and RNA/DNA reflect protein synthesis per cell. These parameters were assessed in the liver and brain in a study by Refaie and colleagues [19], where it was shown that CrPic does not exert an effect on protein synthesis since these ratios were not altered [19]. Diabetic rats that received a high dose of CrPic, however, showed an increase in protein concentration levels, but not in ratios. This finding is likely related to an improvement in glycemic control and cannot be attributed to a direct effect of CrPic. In fact, improvement in glucose metabolism can promote better cellular activity and consequently cause an increase in protein synthesis. In this way, CrPic may exert an indirect positive effect on muscle mass increases [22].

## 4.4. Lipid Profile

Lipid profile was assessed by Seif and colleagues [21] in hypercholesterolemic rats that were fed a hyperlipidic diet. A decrease in platelet hyperaggregability and risk of cardiovascular disease was observed when CrPic supplementation was used, and an improvement in lipid profile was also detected. Similarly, Cefalu and colleagues [12,21] demonstrated a decrease in myocellular and intrahepatic lipid levels in groups that received CrPic supplementation. In this way, CrPic appears to possess a property for lowering the risk of cardiovascular diseases, due to an enhancement in mitochondrial β-oxidation of free fatty acids (FFA), and may indirectly contribute to minimizing esterified cholesterol, which is responsible for the formation of atherosclerotic plaque [12,19,21,23]. Additionally, the findings of Vrotvec and colleagues [23] suggest that intake of CrPic may lower cardiovascular risk in DM2, as a result of the potential function of CrPic in shortening the QTc interval of diabetic patients. CrPic therefore appears to be associated with a decrease of mortality in DM2.

The mechanism involved in lipid profile modifications is not clear and is speculated to occur based on CrPic improving the activity of protein kinase 5'-AMP-activated (AMPK). The increase in AMPK results in suppression of sterol regulatory element binding protein (SREBP-1), which contributes to synthesis of cholesterol, triglycerides, fatty acids and phospholipids. CrPic also inhibits acetyl-CoA carboxylase (ACC) by reducing malonyl-CoA, an enzyme involved in the synthesis of cholesterol, which increases fatty acid (FA) oxidation, leading to degradation of FFA. Likewise, a reduction in the synthesis of FA leads to a decrease in triglycerides (TG) [21,24].

Insulin sensitivity could be related to a modification of content of lipid in tissues, considering that an accumulation of lipids in muscle and liver impaired the signaling of insulin receptors. The beneficial effect found on lipid content analyses could be due to a cholesterol-dependent mechanism exerted by CrPic that activates

GLUT-4 trafficking. CrPic supplementation may therefore lower blood glucose by altering the plasma membrane composition of cholesterol, thereby improving fluidity of the membranes of fat and muscle cells [12,25,26,27].

## 4.5. Binge Eating Disorder

Effects of CrPic supplementation were also investigated in a study by Brownley and colleagues [13], which demonstrated a reduction in episodes of binge eating in patients diagnosed with binge eating disorder (BED). A normalization of HbA1c was also detected in 86% of patients receiving CrPic treatment. The decline of binge episodes could be related to a possible action of CrPic involved in enhancing serotonin synthesis due to an improvement in insulin activity, which promotes an increase of tryptophan brain input, which is a precursor of serotonin. In addition, based on reciprocal the interaction between serotonin and dopamine through a directly synaptic connection, is possible that CrPic indirectly exerts an influence on dopamine function via serotonin receptors, 5-hydroxytryptamine receptors (5-HT) [28].

Since these neurotransmitters are involved in the central control of food intake and energy homeostasis, abnormalities of pathways can be observed in individual diagnoses of BED [29,30]. CrPic normalized HbAc1, indicating an improvement in insulin action, which could indirectly influence serotonin synthesis and dopamine function. Additionally, effects of CrPic on the serotonin pathway were evaluated by a test of stress behavior in an experimental study. The results showed an antidepressant action of supplementation, and CrPic also increased the concentration of 5-HT in brain regions, which may improve expressed symptoms of depression and anxiety [10].

## 4.6. Cognitive Decline

In a study by Krikorian and colleagues [31], it was demonstrated that CrPic could enhance cognitive inhibitory control and cerebral function, indicating an increase in brain activation in a sample of older adults with early cognitive decline. The beneficial cognitive and neural actions were attributed to CrPic supplementation and appeared to be independent of metabolic functions modification because the absence of metabolic effect was detected. CrPic therefore improved brain activation and suppressed indicators of neurodegeneration, reducing the risk of developing dementia [31].

Generation of β-amyloids, pro-inflammatory cytokines and cognitively impaired performance are related to neurodegeneration and Alzheimer's disease. Despite the capacity of CrPic to improve insulin metabolism and consequently attenuate the degeneration process, the mechanism of action is still unknown and further investigation is necessary to elucidate this topic [32,33].

## 4.7. Absence of Effect

Some studies controversially show no effects of CrPic supplementation. Masharani and colleagues [34] demonstrated that CrPic does not exert beneficial effects in glycemic control and does not change sensitivity of insulin parameters in body composition, muscle biopsies, PCR analyses, body mass index (BMI) or truncal fat and lipid levels. Ali and colleagues [35] demonstrated no changes in glucose level, insulin level, or insulin resistance, and even found a slight impairment in glucose metabolism. Both studies were performed on normoglycemic, non-obese samples and on patients with high risk of DM [34,35], and the measures of body composition and weight remained unchanged after CrPic supplementation. In contrast, a study by Brownley and colleagues [13] that was performed with pre-diabetic and overweight subjects demonstrated a reduction in body weight after 6 months of CrPic supplementation with one of two doses, 600 µg/day or 1000 µg/day [12,13,34,36].

When investigating metabolic syndrome, Iqbal and colleagues [36] found no change in measures of glucose metabolism, body weight, serum lipids or measures of inflammation and oxidative stress with CrPic supplementation. Despite the apparent lack of effects, an increase in acute insulin response to glucose was detected. The lack of effects was attributed to a heterogeneous population, which did not include patients with diabetes. Kleefstra and colleagues [37] also detected no significant effects on any variables and attributed this fact to a possible deficiency of Cr in patients, when compared to a previous study in China with patients without Cr deficiency.

A decrease in serum levels of Cr reported in studies may be related to an impaired metabolic function [9,38,39]; however, Cr consumption in the diet was not measured in these studies and thus there could be a bias in supplementation response. The lack of insulin resistant patients could also be a key factor in the absence of results in these studies [40]. In addition, recent reviews have concluded that chromium supplementation in patients with type 2 diabetes should not be recommended, in view of inconsistence in estimated chromium status and rare chromium deficiency [41,42,43,44,45].

The beneficial effect of Cr could depend on physiologic and metabolic conditions of the population studied. Supplementation is unlikely to attenuate diabetes risk or modulate lipid and glucose metabolism in normoglycemic patients with normal lipid levels, or have an antioxidant effect on control groups. This indicates that the action of CrPic depends on the glucose tolerance of the sample, which corroborates findings that showed that insulin sensitivity was a determinant factor in response to CrPic treatment [12,40].

## 4.8. Side Effects, Interactions and Toxicity

Studies Regarding the side effects, interactions and toxicity of CrPic, Iqbal and colleagues [36] highlighted that CrPic was well tolerated and there were no adverse events. Refaie and colleagues [19], in its experimental study, adopted a loss in 20% of body weight as toxic, and CrPic treatment showed a much less body weigh changes and was considered no toxic. As well as, other studies does not associate CrPic with any toxic effects [13,15,17,18,21,23,31,34,35,40].

The adverse effects of CrPic were not convincingly associated with the excess intake of chromium from food or supplements. However, data suggest that people with renal and liver disease may be susceptible to the adverse effects of excess levels of chromium. Moreover, it was not stipulated chromium Tolerable Upper Intake Level (UL), which is the highest level of daily nutrient intake, due to

insufficient data, the intake of doses higher than the studies use with any adverse effect require more studies [46,47].

In the literature, there is evidence that Chromium may interact with other nutrients, dietary substances and medications. It may has its absorption improved when was given with ascorbic acid, however only one study demonstrate that association. High percent of simple sugars in diet may increase chromium urinary excretion. Phytate interaction role in chromium is controversy, apparently phytate at high doses present adverse effect on chromium absorption, while phytate in low doses do not have negative effects on chromium. Concerning to medicines, antacids, other drugs that alter acidity of stomach and gastrointestinal prostaglandins may affect absorption of chromium. Association of chromium with prostaglandin inhibitors result in the increase of chromium levels in the blood, tissues and urine, while the use of antacids reduces chromium absorption and retention [46].

In relation of CrPic toxicity, articles that evaluate it do not detect any tissue lesion, neither DNA damage, in liver or kidney in *in vitro* and *in vivo* tests using the same supplement range dose of 300 to 1000µg/kg. In addition, National Toxicity Program shows no evidence of CrPic induces any carcinogenesis. This low level of toxicity probably occurs due to poor chromium absorption [4,46,47].

### 4.9. Application, Dose, Time and Sample of Supplementation

Most studies reviewed used subjects with diabetes or pre-diabetes, or subjects with high risk for DM, and aimed to investigate outcomes such as glucose and insulin sensitivity, related comorbidity risk, oxidative challenge and factors influencing the clinical response of chromium treatment. Other studies investigated the properties of CrPic in relation to hypercholesterolemia, binge eating disorder, cerebral cognitive control and metabolic syndrome. Overall, studies showed a variance in treatment duration from 4 weeks to 6 months and used doses ranging from 25 to 1000 µg/kg. Most samples selected for studies presented impaired glucose metabolism and showed a beneficial effect of supplementation, independent of the duration of the study.

In relation to the dosage used and study duration, the dosage appears to be the most determinant aspect of the success of CrPic therapy, based on the studies that found a dose-dependent response in all parameters. Duration of therapy seems not to be an important aspect of CrPic results, since no effects of supplementation, as well as occasionally conflicting results, were observed. Beneficial effects of CrPic supplementation over four weeks were found, but absence of effects over six months of supplementation was also found [18,19,35]. Healthy individuals showed no difference in any analyses. When the individuals presented some metabolic disorder, a potential restoration of parameters was observed after supplementation protocol [13,17,35,48].

## 5. Conclusion

The supplementation of CrPic appears to contribute to the improvement of metabolic control and impaired health condition. More studies are required, however, to better define proper dosage and length of time for supplementation and to evaluate the possible beneficial effects in different clinical conditions. Thus, this review was able to conclude that CrPic benefits patients with pathological alterations and could be used as an auxiliary therapy for many diseases.

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## Statement of Competing Interests

The authors declare that they have no conflict of interest.

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