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Review

Clinical Studies on Chromium Picolinate Supplementation in Diabetes Mellitus—A Review

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ABSTRACT

Chromium (Cr) picolinate (CrPic) is a widely used nutritional supplement for optimal insulin function. A relationship among Cr status, diabetes, and associated pathologies has been established. Virtually all trials using CrPic supplementation for subjects with diabetes have demonstrated beneficial effects. Thirteen of 15 clinical studies (including 11 randomized, controlled studies) involving a total of 1,690 subjects (1,505 in CrPic group) reported significant improvement in at least one outcome of glycemic control. All 15 studies showed salutary effects in at least one parameter of diabetes management, including dyslipidemia. Positive outcomes from CrPic supplementation included reduced blood glucose, insulin, cholesterol, and triglyceride levels and reduced requirements for hypoglycemic medication. The greater bioavailability of CrPic compared with other forms of Cr (e.g., niacin-bound Cr or $CrCl_3$) may explain its comparatively superior efficacy in glycemic and lipidemic control. The pooled data from studies using CrPic supplementation for type 2 diabetes mellitus subjects show substantial reductions in hyperglycemia and hyperinsulinemia, which equate to a reduced risk for disease complications. Collectively, the data support the safety and therapeutic value of CrPic for the management of cholesterolemia and hyperglycemia in subjects with diabetes.

THE DIABETES EPIDEMIC

DIABETES IS A GROUP of chronic diseases marked by high levels of blood glucose that result from defects in insulin production and/or function. Type 1 diabetes mellitus (T1DM) is an insulin deficiency disease resulting from autoimmune destruction of pancreatic beta cells. It accounts for 5–10% of all diagnosed cases of diabetes. Type 2 diabetes mellitus (T2DM) begins with insulin resistance followed by reduced insulin production as the disease progresses, and makes up 90–95% of all diagnosed cases. Type 2 diabetes is associated with older age and obesity. A small percentage of diabetes (1–5%) occurs during pregnancy (gestational diabetes), following corticosteroid and other drug use, or following surgery or illness. Diabetes is the sixth leading cause of death in the United States, mostly from associated cardiovascular complications. Diabetes is also one of the leading causes of blindness, kidney failure, dental disease, lower-limb amputation, and complications of pregnancy. The es-

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timated cost of diabetes in the United States is $132 billion.[1]

Diabetes is a progressive disorder that affects an estimated 20.8 million Americans,[1–3] with over 200 million cases worldwide.[4] Since the vast majority of these cases are T2DM, managing their disease can involve a number of options. Most can control their blood glucose with diet and exercise, though some may require medications for hyperglycemia or concomitant cardiovascular disease. The question arises as to whether dietary supplements can provide nutritional support, in conjunction with other modalities, to improve glycemic and lipidemic control in diabetes.

THE CHROMIUM (CR) CONNECTION

Cr is a trace element essential in carbohydrate, lipid, and protein metabolism.[5,6] Cr is a cofactor for insulin function that increases insulin binding,[7] the number of insulin receptors,[8,9] and insulin receptor phosphorylation,[10] resulting in enhanced glucose transport into liver, muscle, and adipose tissue.[6] Since Cr is required for normal glucose and lipid metabolism, low Cr status can adversely affect blood glucose, insulin, total cholesterol, triglycerides, and high-density lipoprotein cholesterol.[6,9,11–15]

Although the minimum estimated safe and adequate daily dietary intake for Cr is 50–200 μg/day for persons 7 years and older, typical Western diets do not meet these requirements.[16–18] Anderson and Kozlovsky[16] reported that 90% of the U.S. population does not meet the estimated safe and adequate daily dietary intake. Similar studies have been documented in Canada,[19] Britain,[20] and Finland.[21] A more recent report found that U.S. adults are consuming less than the established adequate intakes of 25–35 μg of Cr/day.[22]

Dietary sources of Cr include brewer's yeast, beer, whole grains, cheese, liver, and meat; however, Cr content in foods varies widely.[18,23] In addition, the refining of grains and sugars and the processing of foods remove most of the absorbable Cr.[24] Much of the Cr measured in foods may originate from contamination from food-processing equipment and thus is not bioavailable.[23]

Both reduced Cr status[13,24] and overconsumption of refined carbohydrates[24,25] have been positively correlated with an increased prevalence of T2DM. High-sugar diets have been shown to increase urinary Cr losses 10–300%.[24] Relative Cr deficiency is further exacerbated with age,[26,27] illness,[28] pregnancy,[29] burns,[30] and stress.[31] One epidemiological study based on hair analysis showed low Cr status in over 50% of >2,000 Canadian subjects.[19]

In subjects with T2DM, Cr metabolism is altered by inadequate intake, decreased absorption, and increased loss, which is exemplified by abnormal blood, tissue, and urine Cr levels.[14,15,32] Current data strongly suggest that low levels of Cr in serum,[26,33] hair,[34] and toenail tissues[13] are significantly correlated with diabetes. However, people with diabetes show high urine Cr levels, which indicates that mobilized Cr was not reabsorbed by the kidneys.[13,35] For these reasons, Cr supplementation on the order of 1,000 μg/day has been recommended to provide significant clinical benefit in T2DM.[36]

GLYCEMIC RESPONSES TO CR PICOLINATE (CRPIC)

Methodology

Fifteen clinical studies on CrPic supplementation for diabetes mellitus were identified from a number of sources, including a recent meta-analysis,[37] a review of Cr effects on glycemic control,[38] literature searches retrieved from PubMed, Embase, *Current Contents*, *Ingenta*, *Science Direct*, journals, and abstracts from proceedings.

The study designs are summarized in Table 1. A total of 1,690 subjects, including 1,505 receiving CrPic, completed the trials. Twelve of the 15 studies were randomized, controlled trials. Three were open-label trials. Fourteen studies focused on T2DM, and one each on T1DM, corticosteroid-induced, and gestational diabetes. CrPic dosages ranged from 200 to 1,000 μg of Cr/day, and the duration of supplementation ranged from 1 week to 10 months.

Although measures of glycemic control varied, all 15 trials shared one or more measure-

Table 1. Clinical Studies Evaluating CrPic in Subjects with Diabetes

Investigator	*RCT*	*Form of diabetes*	*Number of subjects (number with CrPic)*	*CrPic (μg of Cr)*	*Study duration*	*Concomitant medication*
Anderson et al.[15]	Yes	Type 2	155 (105)	200, 1,000	4 months	Glibenclamide or glipizide
Bahadori et al.[39] (abstract)	No	Type 2	16 (16)	1,000	4 months	Sulfonylurea and metformin
Cheng et al.[40]	No	Type 2	833 (833)	500	9 months	Hypoglycemic medications
Evans[5]	Yes	Type 2	11 (6)	200	1.5 months	Hypoglycemic medications
Feng et al.[41] (abstract)	Yes	Type 2	136 (104)	500	3 months	Insulin
Ghosh et al.[42]	Yes	Type 2	43 (43)	400	3 months	Hypoglycemic medications
Kleefstra et al.[43]	Yes	Type 2	46 (29)	500, 1,000	6 months	Insulin >50 U/day
Lee and Reasner[44]	Yes	Type 2	28 (28)	200	2 months	Insulin, oral medications, diet
Martin et al.[45]	Yes	Type 2	27 (16)	1,000	6 months	Sulfonylurea
Morris et al.[46]	No	Type 2	5 (5)	400	3 months	None
Jovanovic et al.[47]	Yes	Gestational	30 (20)	300–800	2 months	Insulin or none
Rabinovitz et al.[48]	Yes	Type 2	78 (39)	400	3 weeks	Hypoglycemic medications, insulin
Ravina et al.[49]	No	Steroid-induced	54 (44)	600	1–2 weeks	Glibenclamide, metformin, or insulin
Ravina et al.[50]	Yes	Types 1 and 2	172 (162)	200	3 months	Sulfonylurea, metformin, or insulin
Vrtovec et al.[51]	Yes	Type 2	56 (56)	1,000	24 weeks	None
Totals	11		1,690 (1,505)	200–1,000	3 weeks–9 months	

ments of glycemic control, including fasting glucose (FG), postprandial glucose (PPG), fasting insulin (FI), postprandial insulin (PPI), glycated hemoglobin (HbA1c), or insulin sensitivity. Mean differences from baseline are summarized in Table 2. Some studies measured other aspects of metabolic dysfunction (i.e., blood lipids, microalbuminuria, apolipoprotein A1, or C-reactive protein) or body composition (i.e., body mass index, body fat, lean body mass). One study measured QTc interval prolongation on a standard electrocardiogram, which is a powerful predictor of mortality, cardiac death, and stroke in patients with T2DM.[52]

T2DM: summary of responses

Anderson et al.[15] conducted a landmark, randomized controlled trial (RCT) evaluating CrPic in subjects with T2DM. Sixty Chinese subjects received 200 μg/day, and 60 subjects received 1,000 μg of Cr/day as CrPic for 4 months. Supplemental CrPic led to significant improvements in FG, PPG, FI, PPI ($P < 0.05$), and HbA1c ($P < 0.01$) levels. Significance was achieved as early as 2 months, especially at the higher dose. Subjects receiving the 1,000 μg of Cr dose showed near 30% reductions in FG, PPG, FI, and HbA1c (Table 2).

A follow-up, open-label study was conducted in 833 Chinese subjects with T2DM taking insulin or hypoglycemic drugs.[40] All patients received 500 μg of Cr/day as CrPic for 10 months. Again, FG and PPG were significantly lowered ($P < 0.05$) after the first month of therapy and remained so in the following 9 months (Table 2). Close to 90% of subjects experienced marked relief from fatigue, thirst, and frequent urination. No confirmed side effects were reported.

Another RCT study[41] involving 136 Chinese subjects on insulin therapy taking 500 μg of Cr/d as CrPic for 3 months showed significant reductions in FG and PPG ($P < 0.01$). Three other studies, supplementing with 200–1,000 μg of Cr/day as CrPic from 3 weeks to 6 months (Table 1), reported significant improvement in both FG and HbA1c levels.[5,45,48] In two of those studies, the mean reduction in FG was highly significant ($P < 0.001$) (Table 2).

An RCT study on elderly subjects with T2DM recovering from stroke or hip fracture involved supplementation with 400 μg of Cr as CrPic over 3 weeks in addition to their normal

Table 2. Effect of CrPic on Glycemic Parameters in Subjects with T2DM

	FG (mmol/L)		*PPG (mmol/L)*		*FI (pmol/L)*		*PPI (pmol/L)*		*HbA1c (%)*	
Study	Δ	%	Δ	%	Δ	%	Δ	%	Δ	%
Anderson et al.[15]										
200 μg Cr/day	−1.1	−10.8	−2.3	−13.9	−35.0[a]	−25.5	−117.0[a]	−18.2	−2.3[a]	−24.5
1,000 μg Cr/day	−2.7[a]	−27.6	−4.5[a]	−30.4	−48.0[a]	−33.1	−103.0[a]	−15.6	−3.2[b]	−34.0
Bahadori et al.[39]	—	—	−0.7	−5.0	−60.4[a]	−38.5	−75.0	−13.6	−0.2	−2.4
Cheng et al.[40]	−2.0[a]	−20.0	−2.1[a]	−17.5	—	—	—	—	—	—
Evans[5]	−2.5[a]	−24.3	—	—	—	—	—	—	−1.9[a]	−16.0
Feng et al.[41]	−1.6[b]	−16.2	−3.2[b]	−20.8	—	—	—	—	—	—
Ghosh et al.[42]	−0.5[c]	−7.2	−2.0[c]	−16.4	−50.0[a]	−19.5	—	—	−0.01[d]	−0.1
Kleefstra et al.[43]	—	—	—	—	—	—	—	—	−0.4	−4.2
Martin et al.[45]	−1.7[c]	—	—	—	—	—	—	—	−1.16[b]	−11.9
Morris et al.[46]	−0.1	−1.3	—	—	—	—	—	—	0.1	1.5
Rabinovitz et al.[48]	−2.2[c]	−21.0	—	—	—	—	—	—	−0.6[b]	−7.3
Vrtovec et al.[51]	−0.2	−1.7	—	—	−27.8[a]	−28.4	—	—	0.2	2.9
Mean ± SD	−1.5 ± 0.9	−15.3 ± 9.7	−2.7 ± 1.4	−18.9 ± 8.4	−45.2 ± 12.2	−29.8 ± 7.0	−92.7 ± 16.6	−15.0 ± 1.5	−0.95 ± 1.1	−9.6 ± 12.1

A dash indicates no data are available. Δ, change from baseline; %, percent from baseline.
[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ from baseline; [d]$P < 0.05$ compared with control.

hypoglycemic and/or insulin medication.[48] These rehabilitating patients showed a significant decrease in FG and HbA1c levels. Blood glucose levels decreased from 10.5 mmol/L (190 mg/dL) at baseline to 8.3 mmol/L (150 mg/dL) at the end of the study ($P < 0.001$), and HbA1c improved from 8.2% to 7.6% ($P < 0.01$) (Table 2).

An RCT study on Asian Indian subjects taking CrPic (400 μg of Cr/day for 12 weeks) showed highly significant improvements in most measures of glycemic control (FG, PPG, and FI). Though the mean change in HbA1c was not different from baseline, it was significantly better than placebo ($P < 0.05$) (Table 2).[42]

Two studies on Caucasian subjects with T2DM either diet-treated[51] or on hypoglycemic drugs[39] showed that 1,000 μg of Cr/day as CrPic for 3 or 4 months, respectively, reduced FI significantly ($P < 0.05$, mean reduction between 28.4% and 38.5%) (Table 2). In the diet-treated study, a significant decrease in FI was associated with a shortened QTc interval in 62% of subjects, especially those with high body mass index.[51]

Insulin sensitivity was also significantly increased in three studies with CrPic[45,46,50] after 3–6 months of supplementation, with improvements as great as 72.5%.[50]

Two of the 15 studies did not show significant benefit on glycemic markers with CrPic intervention. One 6-month study examined obese patients, who exhibited poorly controlled T2DM (mean HbA1c >9.4%) despite receiving oral antidiabetic medications and high-dose insulin (mean >75 IU/day).[43] Thus, subject selection did not favor a positive outcome, particularly with single-nutrient intervention. The other negative study[44] employed 200 μg of CrPic for 2 months, which may have been an insufficient dose and duration to see positive results. Nevertheless, both studies reported a significant impact on blood lipid risk factors (see Nonglycemic parameters).

Other types of diabetes

CrPic may also improve insulin function in T1DM. Supplementation of 200 μg of Cr/day as CrPic to 48 patients with T1DM led to a 30% decrease in circulating insulin and improved blood sugar stabilization. The number of hypoglycemic episodes was also reduced. Over 70% of T1DM patients responded to CrPic therapy ($P < 0.05$).[50]

Supplementation with CrPic may be considered a safe and inexpensive way to improve glucose intolerance in gestational diabetes, the most common medical complication of pregnancy.[47] Gestational diabetes requires insulin therapy when diet does not prove effective. In a study involving 30 patients with gestational diabetes, those taking CrPic (4 or 8 μg of Cr/kg of body weight/day; 300–800 μg of Cr/day) for 8 weeks showed significantly improved glucose tolerance and reduced hyperinsulinemia compared with controls (Table 2). The 8 μg/kg/day group exhibited the lowest postprandial glucose levels.[47]

Diabetes can also result from corticosteroid treatment. Corticosteroid therapy is known to increase urinary Cr loss. Corticosteroid-induced diabetes is characterized by insulin resistance, ketosis, and acidosis—also symptoms of Cr deficiency.[49] Supplementation with CrPic has been shown to reverse corticosteroid-induced diabetes. Within 1 week, administration of 600 μg of Cr/day as CrPic significantly decreased FG values from 13.9 to 8.3 mmol/L (from 250 to 150 mg/dL, respectively) in one patient, while a maintenance dose of 200 μg of Cr/day kept glucose in the normal range. Corticosteroid-induced diabetes was ameliorated in 41 of 44 patients treated with CrPic. Hypoglycemic drugs were also reduced 50% in all patients who received CrPic supplementation.

Reducing drug requirements

CrPic supplementation reliably reduced antihyperglycemic medication requirements in several trials. In a 3-month study involving 136 patients, 81% of those in the CrPic (500 μg of Cr/day) group reduced their exogenous insulin dosage by an average of 19.4% ($P < 0.001$).[41] In a 3-week study of elderly patients with diabetes rehabilitating from stroke or hip fracture, CrPic (400 μg of Cr/day) decreased and often eliminated their need for antihyperglycemic medication.[48] Supplementation with CrPic (200 μg of Cr/day for 3 months) in 114

patients with T2DM and in 48 patients with T1DM led to a significant decrease in the insulin, sulfonylurea, or metformin requirements in >70% of patients as a result of significantly enhanced insulin sensitivity.[50]

Prediabetes

From a regulatory perspective, treatment claims for a disease like diabetes are not permissible with a dietary supplement. Thus, none of the above-cited clinical papers on diabetes and CrPic intervention can support a petition for a qualified health claim (QHC). A QHC for diabetes prevention was nevertheless issued by the Food and Drug Administration.[53] This QHC is the first for insulin resistance and was specific for CrPic. The QHC was based largely on one study by Cefalu et al.,[54] which showed that a dose of 1,000 μg of Cr as CrPic for 8 months had a significant impact on insulin resistance in obese subjects. In contrast, a recent 3-month study by Gunton et al.[55] did not show efficacy in insulin-resistant subjects. These researchers had reported using a daily dose of 800 μg of Cr, but it was later determined that only 100 μg of Cr/day (800 μg of CrPic) was provided,[56] suggesting the need for higher CrPic doses.

POOLED ANALYSES OF GLYCEMIC CONTROL

Given that virtually all studies employing CrPic supplementation for T2DM subjects showed improved glucose or insulin control, an attempt was made to express the combined effects of these changes. This analysis was conducted despite the diversity of demographics, doses, and durations in these studies. Pooled mean differences, pooled percent changes, and their standard deviations were determined for FG, PPG, FI, PPI, and HbA1c and are presented in Table 2.

FG and PPG

Six of 10 evaluable studies reported significant improvement in FG from baseline, with a mean reduction of 1.5 mmol/L (27.0 mg/dL), or 15.3%. Several studies have suggested that it is possible to decrease FG by 1.7–2.2 mmol/L (30–40 mg/dL). This change is comparable to that seen with intensive control using sulfonylureas or insulin.[57] Four of six studies measuring PPG showed significant results compared with baseline, with a mean reduction of 2.7 mmol/L (48.6 mg/dL), or 18.9%. In a study using two CrPic doses, the lower dose (200 μg of Cr/day) was ineffective, but the higher dose (1,000 μg of Cr/day) dose showed significant reductions in FG and PPG (Table 2).[15]

FI and PPI

There were four studies that evaluated FI after CrPic supplementation, one of which employed two different doses of CrPic. All trials reported significant improvements in FI from baseline regardless of CrPic dose, with an average reduction of 45.2 pmol/L (6.5 mU/L), or 29.8%. Two of three evaluable studies reported improvements in PPI from baseline, with an average reduction of 92.7 pmol/L (13.3 mU/L), or 15.0% (Table 2).

HbA1c

Of nine studies that measured HbA1c, four were significant with respect to change from baseline, and one was significant compared with placebo. One study[50] reported no difference in HbA1c between experimental and placebo groups, but did not disclose baseline data. This study also used a relatively low dose of CrPic (200 μg of Cr/day) for a short duration (2 months). In the study comparing two doses (200 vs. 1,000 μg of Cr/day), a greater reduction in HbA1c occurred with the higher dose.[15] The average reduction in HbA1c for all nine studies was -0.95, which was a 9.6% reduction from baseline (Table 2). A chart of these mean differences in ascending order shows the trends for HbA1c with CrPic intervention (Fig. 1).

NONGLYCEMIC PARAMETERS

Hyperlipidemia

CrPic supplementation also improves lipid profiles in subjects with diabetes. In a study T2DM patients, 200 μg/day Cr as CrPic for 1.5

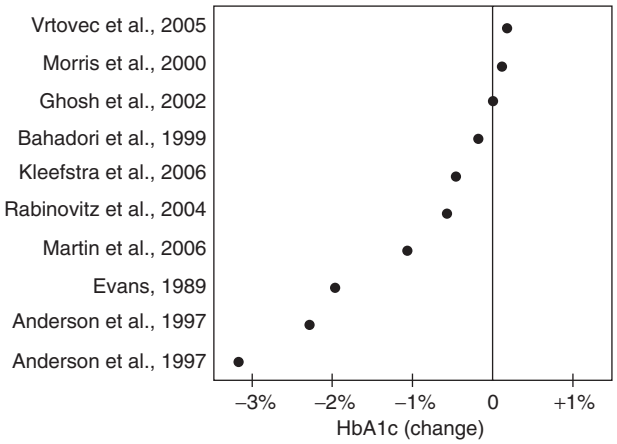

FIG. 1. Mean differences in HbA1c. The mean difference in HbA1c from baseline for the CrPic arm in each clinical study (nine studies total) is shown in ascending order: Anderson et al.,[15] Evans,[5] Martin et al.,[45] Rabinovitz et al.,[48] Kleefstra et al.,[43] Bahadori et al.,[39] Ghosh et al.,[42] Morris et al.,[46] and Vrtovec et al.[51] A negative number represents an average decrease in HbA1c.

months decreased total cholesterol and low-density lipoprotein cholesterol by 13% and 11%, respectively.[5] CrPic supplementation significantly improved total cholesterol, high-density lipoprotein cholesterol, and triglycerides in subjects with insulin-treated T2DM.[15,40,58] Rehabilitating, elderly patients with diabetes showed significant improvement in total cholesterol ($P < 0.02$) and a trend toward reduction in triglycerides.[48] Lee et al.[44] demonstrated a significant (17.4%) reduction in triglycerides in Hispanic subjects with diabetes after 2 months of CrPic supplementation (200 μg of Cr/day). Martin et al.[45] reported significant reductions in plasma free fatty acids after 6 months for T2DM subjects taking sulfonylurea and 1,000 μg of Cr/day as CrPic. Kleefstra et al.[43] showed a trend toward improvement in blood lipid profile with increasing blood Cr concentration, which became significant after 6 months for low-density lipoprotein, total cholesterol, and total-to-high-density lipoprotein cholesterol ratio.

Body composition

Improved insulin sensitivity and glucose control often result in improved body composition. This was supported in a recent study in which 27 subjects with diabetes on sulfonylurea received CrPic supplementation (1,000 μg of Cr/day) or placebo for 6 months. Those on placebo showed a significant increase in body weight, percent body fat, and total abdominal fat. Subjects randomized to sulfonylurea + CrPic experienced significant improvements in insulin sensitivity, HbA1c, and free fatty acids, which resulted in significantly attenuated body weight gain and visceral fat accumulation compared with placebo.[45]

CONCLUSIONS

The data indicate that CrPic supplementation represents a uniquely efficacious modality for glycemic control in subjects with diabetes. Indeed, 13 of 15 clinical studies reported significant improvement in at least one outcome of glycemic control. All 15 studies showed significant benefits in a least one parameter of diabetes management, including blood lipid control. Other positive outcomes linked to CrPic therapy included improved electrocardiograms, reduced need for hypoglycemic medications, and no reported adverse effects.

In contrast, a recent review[38] and meta-analysis[37] were less than positive about the effects of dietary Cr on glucose and insulin responses, in either T2DM or normoglycemic subjects. There are several reasons why these earlier reviews failed to support Cr supplementation for T2DM. First, distinguishing among the different forms of Cr appears crucial to the analysis. Other Cr complexes do not show the same consistent benefits.[59–63] Second, subjects with T2DM may require much higher Cr intakes than normal subjects to demonstrate significant benefits.[15,64] Third, in earlier reviews,[37,38] arbitrary dismissal of important CrPic clinical studies weakened the analysis. In this review, all trials using CrPic were considered, and most of those were RCTs.

A review that pools all Cr complexes fails to account for differences in their bioavailability. Several studies have shown CrPic to be significantly better absorbed than other Cr complexes.[15,65–68] In animal studies, CrPic reached significantly higher tissue concentrations in muscle, liver, and heart than Cr chloride ($CrCl_3$), Cr polynicotinate, or Cr histidinate.[66]

CrPic has also demonstrated higher absorption and insulin internalization rates compared with Cr polynicotinate.[65,68] Only one animal study reported greater bioavailability of Cr polynicotinate over CrPic, but based their analysis on a relative (percent Cr retained) rather than absolute (total Cr absorbed) scale.[69] The available data indicate that Cr polynicotinate is poorly absorbed.[65,68] Inorganic forms of Cr (e.g., $CrCl_3$) have never demonstrated consistent efficacy because of both limited intestinal absorption and intracellular uptake.[42,65,68] The addition of starch can further inhibit $CrCl_3$ but not CrPic absorption, suggesting that certain foods can interfere with bioavailability of inorganic Cr.[65]

Anderson et al.[65] have developed another Cr complex, Cr histidinate, which shows enhanced Cr bioavailability. However, this supplement does not yet have clinical or preclinical data supporting its efficacy or safety, and is not readily available in the marketplace.

There are several lines of evidence suggesting that CrPic supplementation reduces risk factors for diabetes and cardiovascular disease. According to the landmark Diabetes Control and Complications Trial[70] and UK Prospective Diabetes Study[71] trials, the risk for chronic disease complications of diabetes is closely related to the degree of glycemic control, as measured by HbA1c. In the current review, a pooled mean HbA1c change of −0.95% from 10 trials may represent substantial risk reduction, since a 1% drop in HbA1c equates to a 37% reduction in risk of microvascular complications and a 21% reduction in risk for diabetes-related mortality.[72] Cr deficiency is also associated with lipid abnormalities and an increased risk of atherosclerotic disease.[73] Given the known predisposition for coronary heart disease in diabetes, improving glycemic and lipidemic control with CrPic may translate to reduced risk. However, to substantiate real reductions in morbidity and mortality using CrPic supplementation, prevention trials will be required.

Several CrPic clinical trials in this review reported significant reductions in blood lipids.[15,44,58,74] Supplementation with CrPic may also reduce side effects (e.g., weight gain, elevated liver enzymes) associated with high sulfonylurea intake[75] by reducing the requirement for this medication.[49,50] Further risk reduction from CrPic supplementation is suggested by shortening of QTc intervals. QTc prolongation is a powerful predictor of total mortality, cardiac death, and future stroke in patients with T2DM.[51,52] Prolonged QTc in T2DM is related directly to impaired glucose tolerance and FI levels, and inversely with insulin sensitivity.[76]

Insulin resistance is an important risk factor for the development of diabetes and cardiovascular disease.[77] Up to 80% of Americans with T2DM are insulin-resistant.[78] Insulin resistance can affect a host of metabolic and mitogenic processes.[79] Chronic hyperinsulinemia is associated with hypertriglyceridemia, which is an atherogenic risk factor.[80,81] Hyperinsulinemia is also associated with an altered, proinflammatory fatty acid pattern in plasma.[82] High insulin levels also inhibit fatty acid oxidation and the regulation of body fat distribution, which can promote obesity.[83] Lowering the FI is associated with decreased risk of obesity, diabetes, and heart failure.[84]

The marked and consistent reduction in FI seen with CrPic supplementation in T2DM subjects (mean −29.8%) indicates improvements in insulin sensitivity. Insulin sensitivity was also shown directly in three other studies using CrPic supplementation. Since Cr helps improve insulin function and stabilizes blood glucose levels, less insulin is required.[41] Cr has been shown to reduce plasma triglycerides in T2DM patients.[44] Furthermore, body weight, body fat, and fat distribution may be positively impacted with CrPic supplementation.[45]

In conclusion, a significant body of clinical evidence supports the use of CrPic supplementation for treating hyperglycemia, hyperinsulinemia, and dyslipidemia in diabetes. Supplementation with CrPic, particularly at higher doses, may improve insulin sensitivity and glucose metabolism in gestational diabetes, corticosteroid-induced diabetes, and T1DM and T2DM patients. This review also underscores the importance of distinguishing CrPic from other forms of Cr based on bioavailability. Considering its compelling safety profile, as recently affirmed by the Food and Drug Administration,[53] CrPic is an inexpensive and efficacious modality with which to control

the high costs associated with diabetes treatment.[85] It could also prove useful as a nutritional adjunct to existing pharmacotherapies, corticosteroid use, and hypoglycemic drugs,[45] and may help reduce the requirement for these medications. Though the data supporting the benefits of supplemental CrPic for subjects with diabetes are strong, future studies may require a more careful selection of subjects to pinpoint its usefulness.

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