Chromium and polyphenols from cinnamon improve insulin sensitivity

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Naturally-occurring compounds that have been shown to improve insulin sensitivity include Cr and polyphenols found in cinnamon (*Cinnamomum cassia*). These compounds also have similar effects on insulin signalling and glucose control. The signs of Cr deficiency are similar to those for the metabolic syndrome and supplemental Cr has been shown to improve all these signs in human subjects. In a double-blind placebo-controlled study it has been demonstrated that glucose, insulin, cholesterol and HbA1c are all improved in patients with type 2 diabetes following Cr supplementation. It has also been shown that cinnamon polyphenols improve insulin sensitivity in *in vitro*, animal and human studies. Cinnamon reduces mean fasting serum glucose (18–29%), TAG (23–30%), total cholesterol (12–26%) and LDL-cholesterol (7–27%) in subjects with type 2 diabetes after 40 d of daily consumption of 1–6 g cinnamon. Subjects with the metabolic syndrome who consume an aqueous extract of cinnamon have been shown to have improved fasting blood glucose, systolic blood pressure, percentage body fat and increased lean body mass compared with the placebo group. Studies utilizing an aqueous extract of cinnamon, high in type A polyphenols, have also demonstrated improvements in fasting glucose, glucose tolerance and insulin sensitivity in women with insulin resistance associated with the polycystic ovary syndrome. For both supplemental Cr and cinnamon not all studies have reported beneficial effects and the responses are related to the duration of the study, form of Cr or cinnamon used and the extent of obesity and glucose intolerance of the subjects.

**Chromium:** Chromium is essential for the metabolism of carbohydrates, lipids, and proteins. It plays a role in the production of insulin and glucose utilization. Cr deficiency can lead to impaired glucose tolerance and insulin resistance, characteristic of the metabolic syndrome. Cr supplementation has been shown to improve insulin sensitivity and glucose control in patients with type 2 diabetes. The optimal dose and duration of Cr supplementation vary, and individual responses may differ.

**Cinnamon polyphenols:** Cinnamon polyphenols, specifically the compound eugenol, have been shown to improve insulin sensitivity and glucose control in various studies. Ingestion of cinnamon, either as an aqueous extract or whole spice, has been associated with decreased fasting glucose and insulin levels, improved glucose tolerance, and reduced incidence of type 2 diabetes. The effects of cinnamon polyphenols are thought to be mediated through their antioxidant and anti-inflammatory properties. The mechanism of action involves modulating insulin signaling pathways and improving beta-cell function.

**Insulin sensitivity:** Insulin sensitivity is a key factor in the development of the metabolic syndrome and type 2 diabetes. Insulin resistance, characterized by decreased ability of insulin to stimulate glucose uptake, is a hallmark of the metabolic syndrome. Improving insulin sensitivity through lifestyle interventions, such as increased physical activity and dietary changes, or pharmacological interventions, such as Cr and cinnamon polyphenols, can help mitigate the risk of developing diabetes and other metabolic disorders.

**Metabolic syndrome:** The metabolic syndrome is a multi-factorial disorder characterized by a cluster of risk factors that increase the risk of developing cardiovascular disease (CVD) and type 2 diabetes. The syndrome includes elevated blood pressure, increased waist circumference, increased fasting glucose, impaired fasting glucose, and elevated triglycerides and low HDL cholesterol. The metabolic syndrome is often a precursor of type 2 diabetes and CVD. Effective interventions to improve insulin sensitivity can lead to improvements in risk factors associated with the metabolic syndrome, diabetes, and CVD.
Cr also decreases cortisol concentration in human subjects, which is important in relation to weight control because cortisol increases circulating insulin and increases fat accumulation. Adrenalectomy of obese rats leads to a normalizing of insulin and decreased fat accumulation, and after glucocorticoid administration there is a return to elevated insulin levels and accumulation of fat.

Studies involving improved lean body mass as a result of supplemental Cr in human subjects are supported by animal studies conducted mainly using pigs; Cr increases longissimus muscle area and decreases percentage fat in pigs. Following the original studies showing beneficial effects of Cr on lean body mass, pig producers started adding Cr to the feed of sows, which would also affect the Cr status of the young pigs. Goats fed a high-refined-carbohydrate low-Cr diet also have increased feed consumption and corresponding weight gain compared with animals consuming the same diet with added Cr. The increases in weight gain are attributed to the antilipolytic effects of increased insulin leading to accumulation of TAG in the adipose tissue. Elevated insulin levels in the animals receiving the low-Cr diet would also lead to decreased glucagon. As glucagon stimulates lipolysis, decreased glucagon may lead to decreased lipolysis and subsequent accumulation of body fat and weight gain.

There were no effects until after 28 weeks on the low-Cr diet of low nutritional quality. If it takes >28 weeks to detect significant changes in body weight in rapidly-growing goats, it is not surprising that most of the human studies, which are usually ≤12 weeks in duration, are also unable to detect significant changes in individuals consuming conventional diets.

A meta-analysis of several human studies has reported that there is a significant reduction in body weight caused by Cr, but it states that ‘a body weight reduction of 1-1.2 kg during an intervention period of 10 to 13 weeks (i.e. 0.08 to 0.1 kg/week) seems too small to be clinically meaningful’. Improvements in this range, if sustained, could lead to a loss, or prevention of gain, of approximately 4 kg/year, which certainly could lead to large changes over time. Even if Cr only prevents the increase in body weight of 0.5–1 kg/year, it becomes consequential with time. Improvements in insulin-related variables that affect body weight and lean body mass are a result of changes in metabolism and should not be confused with those associated with changes in dietary intake and energy expenditure. Lasting changes in insulin sensitivity and changes in metabolism could lead to lasting changes in body weight and composition. Additional long-term studies in this area are needed.

Increased insulin resistance also leads to an increased incidence of CVD. It has been shown that improvements...
in risk factors associated with the metabolic syndrome also lead to improvements in heart function (Fig. 2)(22). Sixty patients with type 2 diabetes were randomly assigned to two groups and one group was given 1000 μg Cr/d and the other the placebo. After 3 months, QT interval (a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle) corrected for heart rate (QTc interval) decreased. The rate-corrected QT interval is a powerful predictor of total mortality, cardiac death and future stroke in patients with type 2 diabetes mellitus, and is inversely related to insulin sensitivity. BMI was found to be the only variable predictive of the shortening of the rate-corrected QT interval(22).

The effects of Cr on lean body mass, blood lipids, glucose, insulin and related variables vary among the studies and a large number of studies do not report beneficial effects of supplemental Cr. The fact that not all studies show beneficial effects of supplemental Cr is consistent with the expected observations that not all individuals are marginally or overtly deficient in Cr. In addition to the selection of subjects, duration of study and form of Cr, the effects of Cr may be masked by poor diets and a sedentary lifestyle. Cr should be considered as one factor that affects insulin sensitivity and related lean body mass but is certainly not, for most individuals, the one factor that affects insulin sensitivity and related lean and a sedentary lifestyle. Cr should be considered as an additional factor to the selection of subjects, duration of study and form of Cr.

Another possible reason for the variable response to Cr may be combined altered glucose and cholesterol metabolism(25). Cr added to adipocytes (3T3-L1 cells) induces a loss of plasma membrane cholesterol that is linked to GLUT4 translocation. GLUT4 redistribution in cells treated with chromium picolinate occurs only in cells treated with high glucose, conditions that resemble the diabetic state, and not in cells cultured under normal conditions. There may need to be both impaired glucose and cholesterol homeostasis for supplemental Cr to be beneficial(25).

Cinnamon

In 1990 it was reported that compounds found in cinnamon (Cinnamomon cassia) have insulin-potentiating properties and may be involved in the alleviation of the signs and symptoms of diabetes and CVD related to insulin resistance(26). Aqueous extracts of cinnamon have been shown to potentiate insulin activity >20-fold, higher than any other compound tested at comparable dilutions, in an in vitro assay of the insulin-dependent utilization of glucose(27). Water-soluble cinnamon compounds also stimulate the autophosphorylation of the insulin receptor(28) and inhibit phosphotyrosine phosphatase, an enzyme functioning in the dephosphorylation of the insulin receptor(28). This inhibition is specific since there is no inhibition of alkaline phosphatase. The activation of the phosphorylation and the inhibition of the dephosphorylation of the insulin receptor leads to increased phosphorylation of the insulin receptor, which is associated with increased insulin sensitivity. Subjects with type 2 diabetes mellitus have reduced phosphorylation of the insulin receptor(29).

In rats fed a control diet, the administration of aqueous extracts of cinnamon improves glucose metabolism and potentiates the action of insulin(30). Euglycaemic clamp studies have shown that after 3 weeks of oral administration of an aqueous cinnamon extract at 30 and 300 mg kg/body weight there is greater glucose utilization. Skeletal-muscle insulin-stimulated insulin receptor-β and insulin receptor substrate-1 tyrosine phosphorylation levels and insulin receptor substrate-1: phosphoinositide 3-kinase are also increased. These results suggest that increased glucose uptake is a result of enhancing of the insulin-signalling pathway(30). Cinnamon extract fed to animals consuming a high-fructose diet also prevents the development of the metabolic syndrome(31).

Following the observations that cinnamon potentiates insulin action in vitro, a human study was conducted involving sixty subjects with type 2 diabetes (thirty males and thirty females) who were taking sulfonylurea drugs(32). The subjects were divided randomly into six groups. Groups 1, 2 and 3 received 1, 3, or 6 g cinnamon/d for 40 d. From day 40 to day 60 there was a washout period in which subjects did not receive capsules. Groups 4, 5 and 6 received the same number of placebo capsules as the corresponding cinnamon groups. After 40 d all three levels of cinnamon were found to have reduced mean fasting serum glucose (18–29%: three groups, each of ten subjects), TAG (23–30%), total cholesterol (12–26%) and LDL-cholesterol (7–27%). Values after the 20 d washout period were returning to baseline but were still lower than the values at the onset of the study. In a separate study involving twenty-two subjects with the metabolic syndrome, subjects were divided into two groups and given daily either 500 mg commercially-available aqueous extract of cinnamon (Cinnulin PF®; Integrity Nutraceuticals, Sarasota, FL, USA) or a placebo for 12 weeks. Subjects in
the group receiving the capsules containing the aqueous extract of cinnamon were reported to display decreases in fasting blood glucose (–8.4%) and systolic blood pressure (–3.8%) and increases in lean mass (+1.1%) compared with the placebo group. There were also significant decreases in body fat (–0.7%) in the cinnamon-treatment group (33).

Oxidative stress, which is increased in obesity, plays an important role in the development of diabetes and CVD in obese individuals (34). Hyperglycaemia causes the auto-oxidation of glucose, glycation of proteins and the activation of polyol metabolism (35). Cinnamon has been reported to improve the antioxidant status of subjects with the metabolic syndrome (36). Plasma malondialdehyde levels were found to be reduced by the aqueous extract of cinnamon, indicating decreased lipid peroxidation, while plasma SH groups were increased, indicating a protection of antioxidant SH groups against oxidation. In the group receiving cinnamon, plasma SH groups were found to be increased after 12 weeks of supplementation, suggesting that cinnamon acts in protecting both lipids and proteins against oxidation. In parallel, the ferric-reducing ability of plasma, was shown to be increased, thereby providing a contributory factor to the protective effects of cinnamon supplementation (36).

Polycystic ovary syndrome is one of the most common endocrinopathies among women of child-bearing age, affecting 5–10% of the population (37). Insulin resistance and the compensatory hyperinsulinaemia are present in 50–70% of the women with polycystic ovary syndrome and maybe as high as 95% in overweight women. Excess insulin secretion may also be implicated in the increased metabolic and cardiovascular risks reported in this disorder. Since insulin-sensitizing agents such as Cr (38) and troglitazone (39) have been shown to be beneficial in the treatment of polycystic ovary syndrome, it has been postulated that the insulin-potentiating water-soluble polyphenolic compounds found in cinnamon may also be beneficial for women with polycystic ovary syndrome (37).

During an 8-week treatment period oral cinnamon extract (500 mg/d) was shown to reduce fasting glucose as well as insulin resistance, with oral glucose tolerance tests also showing a 21% reduction in mean glucose and an increase in Matsuda’s insulin sensitivity index (40). The cinnamon extract was found to improve insulin resistance of the
women with polycystic ovary syndrome compared with the control women.

The beneficial effects of cinnamon were greater in the study of Khan et al.\(^{(32)}\) than those observed in the studies of Ziegenfuss et al.\(^{(33)}\), Mang et al.\(^{(41)}\) and Wang et al.\(^{(37)}\), but the subject populations were very different. Subjects in the Khan et al.\(^{(32)}\) study had type 2 diabetes and were taking sulfonylurea drugs that increase insulin secretion. Since compounds found in cinnamon increase insulin sensitivity, they are likely to have larger effects in subjects taking sulfonylurea drugs. Insulin resistance would also be larger in subjects with type 2 diabetes than in subjects who are still prediabetic. The duration of the supplementation is also important to consider, since in the studies of Ziegenfuss et al.\(^{(33)}\) and Roussel et al.\(^{(36)}\) no effects on blood glucose were found after a 6-week intervention of supplementation with an aqueous cinnamon extract (500 mg/d), but were found after 12 weeks. Similarly, no beneficial effects were found in post-menopausal women with type 2 diabetes after only 6 weeks\(^{(44)}\). Antioxidant effects were also not found to be significant after 6 weeks but were significant after 12 weeks in the study of Roussel et al.\(^{(36)}\). Whether differences in hormonal milieu affect the potential interaction between cinnamon supplementation and glucose control is unknown at this time. In all the human studies involving cinnamon, or aqueous extracts of cinnamon, there have been no reported adverse events and subjects with the poorest glycemic control appear to benefit the most.

**Model of cinnamon effects**

A model of the potential diverse effects of cinnamon is depicted in Fig. 3\(^{(43)}\). Cinnamon polyphenols (CP) affect multiple steps related to glucose and insulin function. CP activate insulin receptors by increasing their tyrosine phosphorylation activity and by decreasing phosphatase activity that inactivates the insulin receptor\(^{(28)}\). CP also increase the amount of insulin receptor β and GLUT4 protein\(^{(43)}\). CP increase glycogen synthase activity and glycogen accumulation\(^{(44)}\), with decreased glycogen synthetase kinase-3 β activity\(^{(44)}\). CP also increase the amount of the early-response anti-inflammatory protein, tristetraprolin\(^{(43)}\). All these activities and other potential activities may eventually lead to more efficient glucose transport and utilization. In addition, CP-induced tristetraprolin accumulation may provide one of the molecular bases for the beneficial effects of cinnamon in improving the conditions of individuals with metabolic syndrome and insulin resistance by down regulating the synthesis of pro-inflammatory cytokines. It has also been reported that improvements in postprandial blood glucose response are related to gastric emptying rate but that the effects on postprandial glucose are greater than those on gastric emptying rate\(^{(45)}\).

**Conclusions**

In summary, naturally-occurring insulin-potentiating compounds such as Cr and CP lead to increased insulin sensitivity characterized by improvements in characteristics of the metabolic syndrome and decreases in risk factors associated with diabetes and CVD. Individuals with metabolic syndrome, and the subsequent diabetes and CVD, have both decreased insulin sensitivity and decreased antioxidant status. Animal and human studies involving subjects with the metabolic syndrome, type 2 diabetes and polycystic ovary syndrome show beneficial effects of Cr, whole cinnamon and aqueous extracts of cinnamon on glucose, insulin, lipids and antioxidant status. There also may be effects on lean body mass and body composition, and inflammatory response. All these effects would lead to decreased risk factors associated with diabetes and CVD and improvements in the metabolic syndrome leading to decreased incidences of these diseases.

**References**


