Title

A scientific review: the role of chromium in insulin resistance.

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Introduction

by Dr. Peter J. Havel

This in-depth scientific review presents the case for dietary chromium supplementation in the management of type 2 diabetes and other insulin resistant conditions. While its specific mechanism(s) of action are not well understood, it is clear that chromium has effects which potentiate the action of insulin to stimulate glucose transport into cells. Recent data suggests that chromium may facilitate insulin signaling by activating Akt, an intracellular protein involved in insulin signal transduction (Cefalu, EASD Abstract, 2003). Chromium is found in a number of foods, particularly in brewer's yeast, and is available as a supplement in several forms. Of these, chromium picolinate is considered to be the most bioavailable and therefore appears to be the most active form of chromium. The lack of clear standardized measures of chromium status has been an impediment to determining the impact of chromium supplementation on chromium levels and their relationship to glucose homeostasis. In most studies conducted in nondiabetic subjects with normal insulin sensitivity and glucose tolerance, chromium supplements have only modest or no effects on insulin and glucose levels. This is not surprising in that insulin sensitizers would not be expected to have more than modest effects in insulin sensitive subjects. In fact, plasma glucose levels are tightly regulated to protect against hypoglycemia such that it is very difficult to produce a sustained reduction in overall glucose concentrations in normoglycemic individuals.

In contrast, a significant number of randomized clinical trials (RCTs) have shown that chromium supplements lower circulating glucose and insulin levels in subjects with type 2 diabetes or other insulin resistant states. The lowering of fasting plasma insulin levels suggests that chromium supplementation improves systemic insulin resistance. Accordingly, chromium supplementation may be useful as an adjunct therapy to standard antidiabetic drugs such as insulin sensitizers (metformin and thaiazolidenediones) and insulin secretagogues (sulfonylureas and meglitinides) in the management of insulin resistance and type 2 diabetes. However, approximately one third of the RCTs (although only one utilizing chromium picolinate) did not report significant beneficial effects of chromium in patients with type 2 diabetes or glucose intolerance. Thus, while the present available data are intriguing, additional carefully designed and executed new clinical trials are needed to definitively establish the effectiveness of chromium supplementation in the management of insulin resistance and type 2 diabetes.

There are several additional points that should be considered in the design and implementation of new clinical trials:

1) Measures of chromium status and the impact of chromium supplementation on these indices need to be incorporated into the studies.
2) In addition to type 2 diabetes, it would be of interest to investigate the effects of chromium in patient populations with syndromes of insulin resistance such as polycystic ovarian syndrome, gestational diabetes, and lipodystropy disorders.
3) Because inflammation is implicated in both diabetes/insulin resistance and cardiovascular disease, inflammatory markers such as C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and plasminogen activator inhibitor-1 should be examined.
4) Since chromium may have beneficial effects on lipid metabolisms as well as on insulin sensitivity, cardiovascular risk factors such as apolipoprotein B, lipoprotein A, and LDL particle density should be measured.
5) The addition of biotin has been shown to increase the insulin sensitizing effects of chromium picolinate *in vitro* and in animals. Therefore, clinical trials with this combination supplement would appear to be warranted.

What is Chromium?

Chromium is an essential trace mineral required by the human body for normal carbohydrate and lipid metabolism.[1] Nutritional chromium, also known as Chromium III (III indicates the state of oxidation), is found in foods and supplements. It is the most stable form of chromium[2] and is considered one of the least toxic nutrients.[3,4] The normal range of chromium in whole blood is 0.12 to 0.67 mcg/L and it appears to be most concentrated in the liver, spleen, kidney and bone.[5,6]

Chromium is considered essential because, like all basic elements, it is not made in the body and a certain level is needed in the diet to maintain health.

Industrial chromium, also referred to as Chromium VI, is a by-product of manufacturing steel, pigments, chemicals and a variety of other products, and is toxic. Chromium VI can cause cancer if inhaled.[6] Chromium VI should not be confused with nutritional chromium, which is a safe and essential nutrient. Chromium III cannot be converted to Chromium VI in food or by the body.

Chromium's Functions in the Body

Chromium potentiates the biological actions of insulin,[7] a hormone that is critical for the normal regulation of carbohydrate, lipid and protein metabolism.[8] Evidence of chromium's role was first suggested in 1957 when a "glucose tolerance factor" (GTF), found in brewer's yeast, prevented an age-related decline of glucose tolerance in rats. Chromium III was identified shortly after as the active ingredient of GTF.[7] Chromium was declared an essential nutrient in 1977 after significant elevations in blood sugar levels were first observed in a hospitalized patient receiving total parenteral nutrition devoid of chromium.[6,9] Blood sugar levels returned to normal after the addition of chromium to her diet.

More recently, studies have begun to reveal the mechanism of chromium's actions. Research has suggested that after chromium is absorbed into the body, the chromium ions bind to an oligopeptide in order to become biologically active.[10] The chromium-bound peptide complex then binds to the insulin-receptor and activates the activity of the insulin receptor tyrosine kinase, thereby amplifying insulin action.[10] Chromium also has been shown to stimulate intracellular activity leading to enhanced glucose uptake in muscle cells.[10] As a cofactor of insulin, the actions of chromium are all consistent with enhancement in insulin sensitivity.

Insulin Resistance as a Disease Risk Factor

Impaired insulin function, or insulin resistance, is a common factor in a growing number of health concerns. It is well established that insulin resistance is the forerunner of elevated triglycerides, reduced HDL, hypertension, metabolic syndrome (also known as insulin resistance syndrome or Syndrome X)[11] and type 2 diabetes, all of which are associated with an increased risk of cardiovascular disease. Several factors underlie the development of insulin resistance, including obesity, physical inactivity, and genetic factors. Other factors that may affect the degree of insulin resistance include diet, aging, and hormones.

Insulin resistance is considered the common denominator in a cluster of metabolic markers that defines the condition known as metabolic syndrome.[12,13] Metabolic syndrome is a collection of risk factors that includes visceral obesity (central body fat distribution), elevated blood sugar, elevated triglycerides, low HDL and elevated blood pressure. When at least three of these factors are present, the diagnosis is metabolic syndrome.[14] Visceral obesity (central body fat distribution) and its consequences impose the greatest risk for insulin resistance and metabolic disease. More than one in five Americans have metabolic syndrome. The incidence increases with age, affecting more than 40% of people in their 60s and 70s.[15]

Research has found that coronary heart disease, myocardial infarction and stroke are two-to-three times more common in people with metabolic syndrome than in those who do not have the condition. Insulin resistance, without the other markers of metabolic syndrome, increases risk by 1.5-to 2-fold over that in subjects with normal insulin sensitivity as assessed by fasting insulin concentrations.[13]

Insulin resistance is often the forerunner of type 2 diabetes,[16] which has long been known to result from a combination of resistance to the actions of insulin and a relative deficiency of insulin secretion. The risk of diabetes rises relative to the degree of insulin resistance.[17]

In addition to diabetes and metabolic syndrome, a number of other conditions also have been associated with insulin resistance. Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder that interferes with ovulation and can cause infertility.[18] Insulin resistance affects about 50% to 70% of women with PCOS[19] and women with PCOS are at high risk of developing type 2 diabetes. The use of insulin-sensitizing agents for diabetes also have been an effective treatment for PCOS and its complications.[20]

Supplemental Chromium and Effects on Insulin Resistance and Type 2 Diabetes

Some investigators established correlations between low circulating ("body pool") levels of chromium and the presence, or incidence, of type 2 diabetes, and predict that large losses of chromium, over many years, "may exacerbate an already compromised chromium status in [non-insulin-dependent diabetes mellitus] patients and might contribute to the developing insulin resistance seen in patients with type 2 diabetes."[21]

continued

A number of human and animal studies have found that chromium supplementation can improve insulin sensitivity and blood sugar control in animals and humans with insulin resistance, elevated blood sugar levels, impaired glucose tolerance and diabetes. In one study, rats which were bred to become obese and insulin-resistant, and to develop elevated insulin and triglyceride levels, received supplementation with chromium picolinate. The supplemented rats demonstrated significantly lowered fasting insulin levels and significantly improved blood sugar levels.[5] Similar benefits have been reported in people with insulin resistance and diabetes.

Reviews evaluating the benefits of chromium supplementation have reported mixed conclusions.[22,23,24 25] One meta-analysis concluded that chromium supplementation had no effect in people with normal blood sugar levels and had inconclusive effects in people with diabetes.[25] However, this analysis has been criticized since it did not include most of the studies using chromium picolinate and focused on the studies with poorly absorbed forms of chromium. Another review also suggested limitations to the beneficial effects seen with chromium supplementation.[26]

The apparent inconsistency in effects may be attributed to the form of chromium used. While some studies utilizing less bioavailable forms of chromium have not shown significant benefits, almost all of the studies using chromium picolinate (considered more bioavailable) have demonstrated increases in insulin sensitivity and improved glucose control. A listing of chromium supplementation studies in people with insulin resistance or diabetes is shown in **Table 1**.

Nine of 15 randomized, controlled trials evaluating chromium's efficacy in people with diabetes or impaired glucose showed significant benefits in increasing insulin sensitivity and improving blood sugar control. Eight of nine open label (non-RCT) studies also indicated beneficial effects of chromium supplementation.

Studies using chromium picolinate as the source of supplemental chromium had a greater rate of success, with six of seven RCTs and 11 of 12 total studies showing significant positive effects.[26,27,28,29,30,31,32,33,34,35,36,37] Supplementation with 200-1,000 mcg of chromium per day, as chromium picolinate, has consistently improved glucose tolerance and lowered circulating insulin levels.[38]

In the largest clinical study testing chromium,[26] 180 diabetic patients received chromium picolinate (200 mcg or 1000 mcg Cr/day) or placebo for four months. Insulin sensitivity and blood sugar control improved significantly (assessed by FSIVGTT) with both chromium doses, but to a greater extent with the higher dose. Improvements were seen in fasting and two-hour blood glucose, fasting insulin and HbA1c levels.

In a study of 162 diabetic patients, supplementation with chromium picolinate (200 mcg of Cr/day) resulted in reduced need for insulin and glucose-lowering medications in 118 of the patients.[37] Two six-week, double-blind studies also found that chromium picolinate supplementation (200 mcg of Cr/day) resulted in significant decreases in fasting blood glucose and levels of glycosolated hemoglobin among volunteers with type 2 diabetes.[30] A double-blind, randomized, placebo-controlled 8-month trial of 29 subjects at risk for type 2 diabetes found that supplementing with chromium picolinate (1,000 mcg Cr/day) significantly improved insulin sensitivity compared to controls.[28] Chromium picolinate supplements also have been found to improve glucose tolerance and lower insulin levels in women with gestational diabetes.[32]

Table 1. Clinical Trials of Chromium Supplementation on Carbohydrate Metabolism in Subjects With Insulin Resistance/Type 2 Diabetes

Author	Year	Subjects	#	Design	Cr Form	Cr (mcg)	Results
Feng	2002	Type 2 DM	136	RCT	Cr Pic	500	↓ fasting & 2-hr glucose, ↓ insulin dose
Ghosh	2002	Type 2 DM	50	RCT, DB	Cr Pic	400	↓ fasting & postprandial glucose, ↓ HbA1c
Bahijiri	2000	Type 2 DM	76	RCT, DB	CrCl Cr Yeast	200 23	↓ fasting & 2hr glucose
Morris	2000	Type 2 DM	5	OL	Cr Pic	400	↓ insulin resistance (HOMA)
Rabinovitz	2000	Type 2 DM	39	OL	Cr Pic	400	↓ fasting glucose
Trow	2000	Type 2 DM	12	OL	Cr Yeast	100	No effects on fasting glucose & insulin
Bahadori	1999	Type 2 DM	16	OL	Cr Pic	1000	↓ fasting insulin
Cefalu	1999	Pre-diabetes	29	RCT, DB	Cr Pic	1000	↑ insulin sensitivity (FSIVGTT)
Cheng	1999	Type 2 DM	833	OL	Cr Pic	500	↓ fasting glucose
Jovanovic	1999	Gestational	20	RCT, DB	Cr Pic	300 - 800	↓ fasting & postprandial glucose & insulin, ↓ HbA1c
Ravina	1999	Steroid-Induced	44	OL	Cr Pic	300 - 600	↓ fasting glucose*
Anderson	1997	Type 2 DM	180	RCT, DB	Cr Pic	1000	↓ fasting glucose & insulin, ↓ HbA1c
Thomas	1996	Type 2 DM	5	RCT, DB	Cr Nic	200	No effect on fasting & postprandial glucose
Ravina	1995	Type 1 & 2 DM	162	OL	Cr Pic	200	↓ fasting glucose ↑ insulin sensitivity (glucose/insulin response)
Lee	1994	Type 2 DM	30	RCT, DB	Cr Pic	200	No effect on fasting glucose & HbA1c
Abraham	1992	Type 2 DM	25	RCT, DB	CrCl	250	No effect on fasting glucose
Uusitupa	1992	IGT	26	RCT, DB	Cr Yeast	160	No effect on fasting glucose & insulin
Evans	1989	Type 2 DM	11	RCT, DB	Cr Pic	200	↓ fasting glucose & HbA1c
Mossop	1983	Type 2 DM	26	OL	CrCl	600	↓ fasting glucose
Rabinowitz	1983	Type 2 DM	43	RCT, DB	CrCl Cr Yeast	150 13	No effect on fasting glucose
Uusitupa	1983	Type 2 DM	10	RCT, DB	CrCl	200	↓ 1-hr insulin
Offenbacher	1980	Type 2 DM	8	RCT, SB	Cr Yeast	10.8	↑ glucose tolerance, ↓ insulin levels
Sherman	1968	Type 2 DM	7	RCT, DB	CrCl	150	No effect on fasting and postprandial glucose
Glinsmann	1966	Type 2 DM	6	OL	CrCl	180 - 1000	↑ glucose tolerance

Table 1 Legend: RCT = randomized controlled trial; DB = double blinded; SB = single blinded; OL = open label
Cr Pic = chromium picolinate; CrCl = chromium chloride; Cr Yeast = chromium yeast;
Cr Nic = chromium nicotinate
HbA1c = glycosylated hemoglobin; HOMA = homeostasis model assessment;
FSIVGTT = frequently sampled intravenous glucose tolerance test
- Tabular references follow main bibliography.
- *Ravina citing unpublished data within manuscript.

Chromium's Role in Insulin Resistance and Cardiovascular Disease

As part of the long, ongoing Health Professionals Follow-up Study, researchers recently found an inverse relationship between toenail chromium levels and cardiovascular disease, particularly with myocardial infarction.[39] The relationship was especially strong in subjects who were overweight. Toenail chromium may reflect long-term chromium status in the body.

Several studies now have demonstrated that chromium supplements, particularly chromium picolinate, enhance the metabolic action of insulin and lower some of the risk factors for cardiovascular disease. Supplementation with chromium picolinate may help to reduce the risk of early onset of coronary heart disease (CHD) by reducing the associated coronary risk factors (e.g., Apo-lipoprotein-B, LDL particle size, C-reactive protein, intreleukin-6, PAI-1).

Of five randomized, placebo-controlled, double-blind clinical trials, four found supplementation with chromium picolinate (200 to 1,000 mcg Cr/day) decreased total cholesterol and/or LDL cholesterol.[40] The one study that failed to demonstrate a similar outcome did show a reduction in serum triglycerides.[40] The average improvement in total cholesterol levels could, theoretically, provide a 15% reduction in CHD. The average increase in HDLs could be predicted to decrease risk by 2%-3%.[40]

Recommended Intakes of Chromium

A recommended range of intake for chromium was first set by the National Academy of Sciences in 1980.[41] The most current recommended intakes were issued by the Institute of Medicine (IOM) in 2001.[6] The Institute concluded that there was not enough existing evidence to set Recommended Dietary Allowances (RDAs) for chromium and, instead, set Adequate Intakes (AIs) based on limited information regarding the amount of chromium that normal, healthy people currently consume. Based on that information alone, the AIs set by the IOM are 35 mcg of chromium a day for men and 25 mcg a day for women, 19 to 50 years of age. Based on the third National Health and Nutrition Examination Survey data, the median supplemental intake of chromium is 23 mcg/day, which is similar to the AI for the mineral.[6] The IOM set a lower AI for chromium for people over 50 years of age, 30 mcg a day for men and 20 mcg a day for women.[6]

A Daily Value (DV) for food and supplement labels was set in 1997. The current DV for chromium is 120 mcg per day, significantly more than the current AI.

Few serious adverse effects have been associated with excess intake of chromium in food or supplements.[4,6] Therefore, a tolerable Upper Intake Level (UL) was not established by the IOM.[6]

Food Sources of Chromium

Chromium is widely distributed throughout the food supply, but most foods with chromium only supply less than 1 to 2 mcg per serving (Table 2). Determining the exact chromium content in foods has proven to be difficult, in part because of a lack of standardized analytical methods. In addition, the chromium content of foods may increase or decrease with processing. Consequently, dietary chromium intakes cannot be accurately determined from any currently existing databases.[6]

Table 2. Chromium Content of Foods

Food	Serving size	Chromium per serving (mcg)
GRAINS		
Bagel	1	2.6
Corn flakes	1 cup	1.8
Whole wheat bread	1 slice	0.8-1.0
White rice	1/2 cup	0.6
Oatmeal	1/3 cup	0.3-0.4
MEAT, FISH, POULTRY		
Beef	3 oz	2
Turkey (light and dark)	3 oz	0.9-1.7
Baked fish (haddock)	3 oz	0.6-0.9
Chicken breast	3 oz	0.5
Eggs	1	Less than 0.5
DAIRY PRODUCTS		
American cheese	1 oz	0.6
Skim milk	1 cup	Less than 0.5
Butter	1 pat	0.1-0.3
Whole milk	1 cup	0.1
Margarine	1 pat	0.02-0.1
FRUITS AND FRUIT JUICES		
Apple, unpeeled	1 medium	1.4-7.5
Orange juice	1/2 cup	1.1
Banana	1 medium	1.0
Orange	1 medium	0.5
VEGETABLES		
Broccoli	1/2 cup	0.9-11.0
Green beans	1/2 cup	1.1
Tomato	1 medium	0.9
Carrots	1 medium	0.5
Celery	1 stalk	0.5
MISCELLANEOUS		
Red wine	3.5 oz	0.6-8.5
Champagne	3 oz	1.0-3.3
Tea and coffee	1/2 cup	4.0
Brewer's yeast	1 oz	3.3
Chocolate chip cookies	4 each	3.4

Chromium Absorption

Absorption of chromium has been shown to be inversely proportional to chromium intake, although, at any intake the body absorbs dietary chromium poorly.[10] Only about 0.4% to 2.5% of chromium taken in is actually absorbed.[6] The mechanisms of absorption and transport of chromium in the body are not completely known.

High fiber intake has been debated as a cause of decreased absorption of some nutrients, including chromium, but the effect of a high fiber intake on nutrient absorption has not been thoroughly investigated.[6]

Citing the work of Kamath and colleagues (1997), the Food and Nutrition Board has remarked that certain medications, such as aspirin or antacids, if taken on a regular basis, may also negatively impact chromium absorption and retention by altering stomach acidity or inhibiting the production of gastrointestinal prostaglandins.[6]

Total body chromium concentrations decrease with age,[41] dropping by 25% to 40%, depending on the tissue being analyzed.[5] The increased incidence of impaired glucose tolerance with age suggests that the elderly might be more vulnerable to chromium depletion than younger adults.

A number of other factors affect how well chromium will be absorbed. Intakes of vitamin C, amino acids (the building blocks of protein) and oxalate (found in some vegetables and grains) have been found to enhance chromium absorption, while a diet high in phytate (found in cereals, legumes and vegetables) and simple sugars[42] appear to decrease chromium absorption. A 28% documented increase in consumption of added sugars (i.e., white sugar, brown sugar, etc.) from 1982 to 1987 could translate into an increased need for chromium because of this possible decrease in chromium absorption.

Chromium Supplementation Doses

The response of glucose, insulin and lipid levels to chromium supplementation is related to the amount and form of supplemental chromium, the degree of glucose intolerance, and the duration of the study.[3] Chromium supplements are generally available in a picolinate or chloride salt form or in a complex with nicotinic acid and amino acids.[5] The most stable and most bioavailable form of supplementation available appears to be chromium picolinate.[43] Nearly all of the studies using the more bioavailable chromium picolinate have reported positive effects in lowering elevated blood glucose, insulin or lipid levels in subjects with insulin resistance and type 2 diabetes.[3]

For people with glucose intolerance, the requirement for chromium may be related to the degree of glucose intolerance. An intake of 200 mcg per day of supplemental chromium has been found adequate to improve glucose variables in those who are mildly glucose intolerant. However, people with more overt impairments in glucose tolerance and diabetes usually require more than 200 mcg per day.[3] In most studies, chromium picolinate supplementation has had the most dramatic impact on risk factors in overweight subjects, who would be expected to be insulin resistant, suggesting that chromium supplementation will have the greatest benefit in overweight, insulin resistant individuals.

Chromium Safety

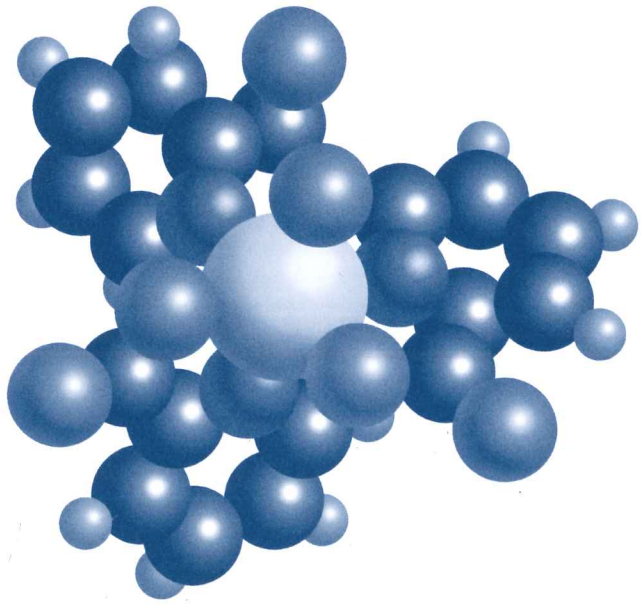
The safety margin for nutritional chromium is set at 350.[44] This indicates that a person would have to take approximately 350 times the common supplemental dose (200 mcg) of chromium before any harmful effects would be expected. Typical amounts of chromium picolinate used in multi-vitamin, multi-mineral dietary supplements range from 50 to 400 mcg Cr/day. Specialty dietary supplements may contain much more and may include other forms of chromium.[6] Chromium picolinate has been the subject of more than 30 clinical trials and 100 published research reports. However, there is limited safety information available on other chromium complexes.

Numerous studies have established that chromium is one of the least toxic trace elements and laboratory and animal studies support the safety of chromium picolinate,[45] even in animals fed levels several thousand times the upper limit of the safe intake for humans, relative to weight.[47]

The reproductive effects of chromium picolinate in swine have also been investigated, since their metabolic systems closely mirror those of humans. The researchers found that animals fed chromium picolinate (200-1000 ppb) experienced no negative effects. In addition, supplementation resulted in greater litter size and weight compared to controls.[47] In a twelve month study of 48,000 pigs having 100,000 litters with an average litter size of 10 piglets per litter, chromium picolinate significantly increased litter size compared to untreated pigs, with no reported adverse events to the sows or piglets.[48]

In more than 30 clinical trials with more than 2,000 subjects tested, there have been no reported adverse events related to chromium picolinate supplementation. The safety of chromium picolinate has been demonstrated in these clinical trials lasting up to 8 months.[49] There have been isolated case reports of liver damage and one case of kidney damage in people taking products that contained chromium picolinate,[50] but there was no conclusive evidence that the chromium picolinate was the direct cause of either event.

Although chromium picolinate has not been shown to be mutagenic or carcinogenic in human or animal trials, it has been suggested to be mutagenic in cell cultures in *in vitro* studies and in fruit flies.[51,52,53] However, a study that examined the effect of chromium picolinate supplements on the bone marrow cells of rats, using a sensitive test for chromosomal damage, found no induction of chromosomal damage.[54] A clinical trial of ten obese volunteers taking 400 mcg a day for eight weeks found no oxidative DNA damage, suggesting that the dose typically used for supplementation is safe.[55]



Chemical structure of the chromium picolinate molecule. The combination of chromium with picolinic acid plays a key role in its high degree of bioavailability.

Summary

- Chromium is an essential mineral that appears to have a beneficial role in the regulation of insulin action and its effects on carbohydrate, protein and lipid metabolism.
- Chromium is an important factor for enhancing insulin activity.
- Studies show that people with type 2 diabetes have lower blood levels of chromium than those without the disease.
- Insulin resistance is the common denominator in a cluster of cardiovascular disease risk factors.
- One out of every five Americans has metabolic syndrome. It affects 40% of people in their 60s and 70s.
- Insulin resistance, with or without the presence of metabolic syndrome, significantly increases the risk of cardiovascular disease.
- Insulin resistance is present in two serious health problems in women; polycystic ovarian syndrome (PCOS) and gestational diabetes.
- Several studies have now demonstrated that chromium supplements enhance the metabolic action of insulin and lower some of the risk factors for cardiovascular disease, particularly in overweight individuals.
- Chromium picolinate, specifically, has been shown to reduce insulin resistance and to help reduce the risk of cardiovascular disease and type 2 diabetes.
- Dietary chromium is poorly absorbed.
- Chromium levels decrease with age.
- Supplements containing 200-1,000 mcg chromium as chromium picolinate a day have been found to improve blood glucose control.
- Chromium picolinate is the most efficacious form of chromium supplementation.
- Numerous animal studies and human clinical trials have demonstrated that chromium picolinate supplements are safe.

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Biography

Dr. Peter J. Havel

Peter J. Havel, D.V.M., Ph.D. is a Research Endocrinologist in the Department of Nutrition at the University of California, Davis. He received a B.S. in Zoology from the University of Washington, Seattle, WA, a D.V.M in Veterinary Medicine and Ph.D. in Endocrinology from the University of California, Davis.

Dr. Havel's research is focused endocrine regulation of energy homeostasis, adipocyte metabolism, and the pathophysiology of two interrelated diseases of major medical and economic importance, diabetes and obesity. His previous work investigated the role of the nervous system in regulating pancreatic hormone (insulin and glucagon) secretion and examined the mechanisms responsible for impaired defenses against hypoglycemia in humans and animals with diabetes. Hypoglycemia limits the ability to control blood sugar and reduce the long-term complications of diabetes.

Dr. Havel currently has several projects investigating the regulation of secretion and the actions of the adipocyte hormones, leptin and adiponectin, and gastrointestinal hormones such as ghrelin which are involved in the regulation of feeding behavior, energy metabolism, insulin sensitivity, and lipid metabolism. His work in this area includes nutritional studies in humans and animals as well as *in vitro* experiments. His current research focuses on the molecular and biochemical mechanisms regulating leptin and adiponectin production and the role of endocrine and dietary factors in the control of energy homeostasis, insulin action and in the development of obesity and type 2 diabetes.

Research conducted in Dr. Havel's laboratory demonstrated that leptin production by adipose tissue is regulated by glucose metabolism. Studies from his laboratory have shown that high fat or high fructose diets reduce circulating leptin concentrations in humans, a finding that has implications for the development of obesity and diabetes in animals and humans consuming diets high in fat and fructose. In addition, fructose increases circulating lipids and could increase the risk of cardiovascular disease.

Dr. Havel has published over 70 peer-reviewed articles related to diabetes and obesity in journals such as *Journal of Clinical Endocrinology and Metabolism, Endocrinology, Diabetes*, and *American Journal of Clinical Nutrition*, as well as a number of scientific reviews and book chapters. He has been awarded several honors including the Academic Federation Award for Excellence in Research, University of Davis, 2003, Shih-Chun Wang Award for Physiology Research from the American Physiological Society, 2000 and Outstanding Investigator Award from the American Federation for Medical Research, 1999.