

## LEADING WORLDWIDE EXPERTS PRESENT RESEARCH ON CHROMIUM SCIENCE AND DISEASE

**“Chromium in Health and Disease”  
A Council for the Advancement of Diabetes Research and Education (CADRE)  
Chromium Summit, held April 2003 in Boston**



The following is a summary of the presentations given at the “Chromium in Health and Disease” summit, held on April 1-2, 2003 sponsored by the non-profit organization The Council for the Advancement of Diabetes Research and Education (CADRE). The Summit was co-chaired by **William T. Cefalu, MD, University of Vermont** and **Frank Hu, MD, PhD, Harvard School of Public Health**. Attending the conference



were leading experts in chromium research, including academic and government scientists who have ongoing or recently completed studies on this topic.

### **Background**

Evidence of chromium’s impact on health and disease was first researched by Walter Mertz in the late 1950’s. Additional studies evaluating chromium’s relationship with impaired glucose tolerance were conducted in the 1960’s and 1970’s. However, significant interest in chromium research was initiated in 1997 when Dr. Richard Anderson (USDA) published the landmark study demonstrating the efficacy and safety of chromium picolinate supplementation in people with type 2 diabetes. Since then, the number of studies conducted on chromium and chromium picolinate has almost reached the total number of studies published in the previous 30 years. The recent Summit was designed to review and to engage in a scientific exchange about chromium research conducted or initiated over the past few years.

### **Chromium and Glucose Metabolism**

The effect of chromium on glucose metabolism has been studied in retrospective epidemiological studies and in prospective clinical studies. **Dr. Hu** presented on epidemiological research. **Dr. Cefalu**, and **Dr. Richard Anderson of the Beltsville Human Nutrition Research Center in Maryland** presented data from clinical studies.

**Dr. Hu** pointed out that several lines of evidence, from *in vitro* to epidemiological studies, suggest that inadequate intakes of trace minerals, such as chromium, could be risk factors for type 2 diabetes. Prior human studies have suggested that chromium picolinate improves glucose metabolism in obese people and people with type 2 diabetes. During the past two decades, there have been several studies of chromium picolinate involving human subjects with glucose intolerance or diabetes. One of the most notable was done in China, where researchers found 500 micrograms to 1,000 micrograms of chromium as chromium picolinate per day to be effective in improving glucose, insulin and lipid levels in people with type 2 diabetes.

**Dr. Cefalu** reported on an animal study, in which he found that chromium picolinate supplements given to obese rats resulted in a 50% improvement in insulin sensitivity and glucose tolerance, compared to controls. Chromium picolinate did not have a significant effect, however, in lean animals. He also discussed a new 6-month study of people with type 2 diabetes that is currently

underway in which he is seeing 100% response in obese subjects taking 1,000 micrograms of chromium as chromium picolinate per day.

**Dr. Anderson** pointed out that in his studies he has found that 200 micrograms of chromium as chromium picolinate per day, may not be enough to see an effect on insulin sensitivity. But he has observed a “nice effect” at 1,000 micrograms a day. Dr. Anderson also emphasized that chromium picolinate benefits people with hyperglycemia *and* hypoglycemia. If you give chromium to people with high blood glucose, then blood glucose will go down. If you give it to people with low blood sugar, both insulin and blood glucose improve. Moreover, he said that even people with type 1 diabetes show improvement with chromium supplementation. For people with type 2 diabetes, the improvement with chromium occurs even for those who are taking medication to control blood sugar levels i.e., the effects of chromium supplementation are in addition to medications.

### **Chromium and Coronary Heart Disease**

Two recent studies have been done to measure tissue levels of chromium and associate them with the risk of myocardial infarctions (MIs). Chromium levels in toenails are thought to be a possible indicator of chromium status in the body. **Eliseo Guallar, M.D., Dr.Ph., of Johns Hopkins University**, found an inverse relationship between toenail chromium concentration and risk of first, nonfatal MIs in men. The study collected data from men in eight European countries and Israel. He found that the lower the levels of toenail chromium, the greater the risk of MIs. **Dr. Guallar** concluded that the results add to a growing body of evidence pointing to the importance of chromium for cardiovascular health.

**Eric Rimm, Sc.D., of Harvard School of Public Health**, presented an abstract from his presentation at the 2002 American Heart Association Annual Convention that revealed the collection of chromium data from men in the Health Professionals’ Follow-Up Study. He also found a similar inverse relationship between chromium levels in toenails and risk of MI, including fatal MIs. The relationship was especially strong in subjects who were overweight.

**Gary Evans, Ph.D.**, formerly USDA and long-time chromium researcher, who consults for Nutrition 21, Inc., reviewed studies that showed 200 micrograms of chromium as chromium picolinate per day given to people with high cholesterol, decreased total cholesterol, LDL cholesterol and apolipoprotein B levels.

### **Chromium and Women’s Health**

A session of this Summit was focused on the benefits of chromium supplementation seen in women’s health. **Lois Jovanovic, M.D., of the Sansum Medical Research Center in Santa Barbara, CA**, and **Patty Trail, R.N.C., C.D.E., of Eastern Virginia Medical School in Norfolk**, presented research on gestational diabetes. **Michael L. Lydic, M.D., of the State University of New York at Stony Brook**, presented research on polycystic ovarian syndrome (PCOS).

According to **Dr. Jovanovic**, gestational diabetes is the most common problem complicating pregnancy today. An estimated 135,000 women have gestational diabetes, posing a risk to both the mother and the infant. High levels of blood sugar in the pregnant woman cross the placenta, triggering the beginnings of insulin resistance in utero. The child is then predisposed to overweight. If the child is female, she is more likely to develop gestational diabetes during her own pregnancy as an adult and pass it on to her child. A significant percentage of women with

gestational diabetes require insulin to manage blood glucose levels. Pregnancy is a normal state of chromium wasting, so it seems logical that intake should be increased. Most prenatal vitamins, however, contain no chromium. A clinical study was conducted in which 20 gestational diabetic women were given either chromium picolinate supplements or placebo. After eight weeks, those who were given chromium supplements had significantly lower glucose and insulin levels compared with their own baseline levels and with the placebo group.

**Dr. Jovanovic** concluded her presentation by saying that reduction of the severity of glucose intolerance in pregnancy by chromium supplementation might provide an easy and inexpensive means to reduce the problems related to maternal hyperglycemia and the devastating health effects on both mother and infant.

**Patty Trail** reported on six case studies in which women were at high risk for developing gestational diabetes and were given chromium picolinate supplementation throughout their pregnancy. The good pregnancy outcome that involved delivery of healthy full term babies observed in these test cases, she said, suggested the possible benefit of chromium supplementation in high-risk patients. Ms. Trail is currently initiating a randomized, placebo-controlled study to assess if dietary supplementation with chromium picolinate during pregnancy can decrease the incidence and severity of glucose intolerance in pregnancies at risk for gestational diabetes.

Both researchers concluded that chromium picolinate supplementation during pregnancy could provide an easy and inexpensive means to reduce the fetal and maternal problems related to hyperglycemia.

PCOS is associated with infertility, anovulation, obesity, hyperandrogenism, and insulin resistance. Affected women have increased risk for glucose intolerance, gestational diabetes and type 2 diabetes. **Dr. Lydic** presented information about a study, for which he is currently recruiting subjects, to investigate the effects of 1,000 micrograms of chromium as chromium picolinate on insulin sensitivity and levels of circulating androgens in women with PCOS. He has studied three patients so far and has found a trend of improvement in insulin sensitivity with chromium picolinate supplementation. Three more patients are currently being studied. **Dr. Lydic** plans to conduct an additional study in a larger group of women with PCOS, to confirm the positive results.

### **Chromium and Depression**

**Dr. Jonathan Davidson of the Duke University Medical Center in Durham, North Carolina**, presented his findings of a pilot study he completed, suggesting that chromium picolinate may be a promising new treatment for atypical depression. Atypical depression is a form of depression, characterized by symptoms of carbohydrate cravings, weight gain, and lethargy.

**Dr. Davidson's** study was conducted in 15 patients with atypical depression. Over the 8-week trial, patients received either a placebo or 400 micrograms of chromium as chromium picolinate a day; after two weeks, the dose was increased to 600 micrograms of chromium as chromium picolinate per day. **Dr. Davidson's** results suggest that chromium picolinate provides relief from symptoms, in some cases rapid relief, with relatively no side effects. Seventy percent of patients taking chromium picolinate in the study experienced relief from symptoms. None of the patients on placebo responded. The usual response to antidepressant medications is 40% to 50% remission rates.

Monoamine oxidase inhibitors (MAOIs), which are the drugs of choice for treating depression, frequently have side effects. Selective Serotonin Reuptake Inhibitors (SSRIs), which are also commonly prescribed to treat depression cause side effects as well. In fact, 44% of patients taking SSRI drugs stop within 4 to 6 weeks, due to side effects. A larger chromium trial for the treatment of depression is now in the planning stages. **Dr. Davidson** commented that if the findings can be replicated in this larger trial, chromium picolinate could be revolutionary for the treatment of depression.

### **Absorption of Chromium**

Chromium from foods and supplements is poorly absorbed. Certain exogenous factors have been found to effect absorption. And, various chelating agents have been used to enhance chromium absorption. **Dr. Anderson**, presented on this topic.

**Dr. Anderson** stated that the body's response to chromium is dependent on several factors, including the chromium status of an individual, the stage of glucose intolerance or diabetes, and absorption and stability of the chromium compound used. Stresses to chromium status include high sugar intake, acute exercise, pregnancy, lactation, infection and physical trauma. Chromium losses also increase with age, as does the risk for type 2 diabetes. Despite that fact, the most recent recommended intakes from the Food and Nutrition Board for people over age 50 were set at lower levels than for younger people.

Vitamin C and oxalate increase chromium absorption. Prostaglandins decrease chromium absorption, and aspirin and indomethacin, which inhibit prostaglandins, increase absorption. Components involved in formulating chromium capsules can also affect absorption. Carbohydrates used as fillers in supplement capsules have been shown to bind to several forms of chromium, including chromium polynicotinate and chromium chloride, making them essentially inert regarding absorption. Picolinic acid and histidine forms are stable complexes of chromium and allow them to be readily absorbed and are not affected by starch fillers. Even though one study shows chromium nicotinic acid to be better absorbed than chromium picolinate, this study used very low levels of radiolabeled chromium, which acts differently than the higher doses normally taken in supplement form. Because chromium absorption is increased at lower levels of intake, a greater absorption is seen. Chromium glutathione is also not absorbed and has no effects on glucose metabolism.

### **Mechanism of Action**

**Dr. Cefalu, John Vincent, Ph.D. from the University of Alabama, David Brautigam, Ph.D. of the University of Virginia School of Medicine and Dennis Mynarcik, Ph.D. of the State University of New York at Stony Brook**, presented theories and findings regarding the mechanism of action of chromium on insulin in cells.

The biochemistry of chromium has been poorly understood, until recently. **Dr. Brautigam** reported the results of a study on the effects of chromium on insulin receptors in cell culture. He concluded that chromium specifically interacts with insulin receptor tyrosine kinase, an important component in insulin signaling, and enhances insulin's activity.

**Dr. Mynarcik** studied individuals with and without HIV lipodystrophy, which is associated with loss of adipose tissue, insulin resistance and elevated tryglycerides, and supplemented them with 1,000 micrograms of chromium as chromium picolinate per day for 8 weeks. He found that insulin sensitivity improved in patients with and without lipodystrophy. He suggested that the

direct action of chromium at the site of insulin signaling initiation improves insulin sensitivity, rather than increasing activity of the activated insulin receptor.

**Dr. Cefalu** evaluated a potential cellular mechanism by assessing skeletal muscle PI-3 kinase activity (an enzyme involved in glucose metabolism) after insulin stimulation in obese and lean rats given chromium picolinate, and compared those findings to controls. Obese rats treated with chromium picolinate showed a significant increase in PI3KA after insulin stimulation, versus obese control. An increase in membrane-associated Glut-4, a glucose transporter protein, was also observed, compared with controls. These results suggested that reduced activity of PI3KA in obese states may be partially restored with chromium picolinate and that glucose transport across cells may be enhanced.

**Dr. Vincent** states that chromium is required for proper carbohydrate and lipid metabolism. Conditions that increase circulating glucose and insulin concentrations increase urinary chromium, in the form of the small peptide, chromodulin. **Dr. Vincent** believes that the mechanism of action for chromodulin may be the framework for future studies testing the role of chromium in metabolism.

### Safety

**John Hathcock, Ph.D., from the Council for Responsible Nutrition** and **Merlin Lindemann, Ph.D., from the University of Kentucky**, presented data on the safety of chromium and chromium picolinate.

**Dr. Hathcock** presented information regarding the safety of chromium picolinate. He emphasized that the Food and Nutrition Board did not find any toxicological basis for setting a tolerable upper level for chromium in their most recent report on Dietary Reference Intakes for the essential mineral. In addition, the United Kingdom's Expert Group on Vitamins and Minerals has found no credible evidence of adverse effects, but has identified a "guidance level" of 10,000 micrograms per day, based on extrapolation from animal research on chromium picolinate. The safety of chromium is also reflected in the high reference dose set by the Environmental Protection Agency.

In addition, the Food and Nutrition Board recently released a draft prototype monograph on the safety of chromium picolinate. Though the preliminary draft did not reach risk assessment conclusions (the full report is due out summer '03), the animal data show safety of very high intakes. **Dr. Anderson** also emphasized that findings of DNA damage from in vitro studies and studies with insects, can be over-interpreted and over-extrapolated to give false positive results i.e, they suggest DNA damage from chromium picolinate, where none exists.

**Dr. Hathcock** concluded that there is no recognizable pattern of adverse effects of chromium picolinate supplements in humans and that well-conducted clinical trials show no evidence of adverse effects at 1,000 micrograms of chromium as chromium picolinate per day.

Looking in more detail at animal studies, **Dr. Lindemann** presented several findings regarding the lack of negative effects and the observed beneficial effects of chromium picolinate supplementation in swine, poultry, dogs and cattle. Though the extent of positive results varied among species, he has found that chromium supplementation can benefit immunocompetence, cortisol levels and glucose metabolism, as well as milk production in lactating animals. In pigs, whose metabolic system most closely mirrors that of humans, he found improvements in several measurements of breeding, such as litter size, growth rate, increased ovulation rate and improved

embryo survival. Dr. Lindeman reported the beneficial effects were seen in one of the largest animal studies done to date, involving over 100,000 litters and 1,000,000 piglets. The conclusion from both experts was that the potential for toxicity of chromium and chromium picolinate is very low, and there have not been any confirmed studies documenting negative effects of nutritional levels of chromium in humans or farm animals.

### **Summary**

In summary, chromium research has grown considerably over the last few years. No longer are the only studies in weight loss and body composition. There is a clear link between chromium and insulin sensitivity. Chromium supplementation appears to be safe and beneficial in a number of conditions caused by insulin resistance. Epidemiological research is also beginning to further clarify the impact of chromium deficiency. It was encouraging to see the number of studies currently ongoing or planned that should continue to add to a large body of science demonstrating the benefits of chromium supplementation.