The Effect of Chromium supplementation on Glucose and Lipid Metabolism in Type II Diabetics

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A. Background

Animal studies conducted in the 1950's, first suggested that chromium played a role in glucose metabolism. Experiments that restricted chromium intake in monkeys and rats were able to induce a state of glucose intolerance. This condition, similar to diabetes, was readily reversible with chromium supplementation.

Clinical relevance were reported in the late 1970's when several cases of patients receiving long term hyperalimentation developed poor glucose tolerance with pronounced insulin resistance. Intravenous supplementaion with chromium almost immediately restored normal insulin sensitivity and action.

The exact mechanism of chromium's action is unknown. It is proposed that chromium potentiates the action of insulin. Some studies have suggest that chromium increases the number of insulin receptors, others proposed that chromium enhances the affinity of insulin for its receptors. In one study, chromium was also seen to increase the volume of pancreatic Beta cell. This implied that chromium may increase insulin secretion.

Chromium's function in lipid metabolism was observed in animal studies during the same time. Animals deficient in chromium exhibited abnormal lipid profiles. Several animal studies linked chromium deficiency to development CAD. One study even found that chromium supplementation in rabbits was able to reverse formed atherosclerotic plaques.

Early clinical correlation came from several human autopsy series that linked low chromium level with death from heart disease. The mechanism behind chromium's effect on lipids is even less well defined. Again it is thought to be mediated by chromium's action on insulin sensitivity.

Human studies since the afore mentioned studies have been carried out by a small group of investigators. Most were observational trials with optimistic results but inadequate controls. The few randomized trials published have shown more equivocal results; however, some have documented significant increases in HDL, improvement in total cholesterol, and improved response to oral glucose tolerance test. Beneficial evidence for improvement in triglyceride value and fasting glucose values has been weaker.

Many factors have made the interpretation of the data from these trials difficult. These trials are usually composed of a small group of patients, most averaging less than 30 patients. Different chromium formulations at different doses were used. Very different population of patients were also studied. Typically the duration of these trials generally were short; most less than 3 months.

An agent like chromium that may improve both glucose metabolism and lipid profile deserves further investigation. Diabetic dyslipidemia is felt to be a major risk factor for early morbidity and mortality from the disease. Atherosclerotic disease in NIDDM is responsible for over 50% of hospital admissions and 80% of all mortality. If proven even to be mildly efficacious, the low cost and benign nature of chromium would make it an ideal adjuvant therapeutic agent.

B. Hypothesis

The objective of this study is to further define the effect of chromium on glucose and lipid metabolism in Type II diabetics. If efficacious, chromium treatment should decrease total cholesterol, increase HDL, and decrease triglyceride. It's action on glucose metabolism should cause decrease in Hgbalc.

C. Methods

A double blinded randomized placebo controlled crossover study is planned. The crossover component is important due to the expected variability in our patient population. Not only will they have large differences in lipid and glucose metabolism, but it is also expected that their diet and exercise patterns will differ. Given that these are very difficult factors to control a crossover study will be most ideal.

The time period of study will be composed of 6 month of drug with 2 months of washout and then 6 months of placebo. Prior studies have shown that the beneficial effect of chromiumB will resolve after about one month of washout period.

To control for intra-subject variation, the time course of the study will try to account for seasonal variation in diet and exercise. Both time periods of treatment will be composed of equal number of warm and cold months. To further control for intra-subject variation, the diet, exercise, alcohol history will be recorded and compared through out study to detect changes in behavior. Patients will be counseled to maintain their usual dietary intake and exercise. Changes in weight will be also recorded.

D. Power

The subject number of 80 is chosen based mainly on power calculation allowing 0.05% type I error and 20% type II error. The power calculation in this study is based on prior studies measuring chromium's effect on HDL. two trials provided adequate data for this power calculation. Power calculation is based solely on HDL because no values has been reliably established for expected changes in triglyceride or Hgbalc.

From this calculation, it is seen that about 60 patients are required for the crossover study. An extra twenty are added on to account for drop outs. It is also hoped that the additional subjects will provide more power to assess the other parameters.

E. Study subjects

Eighty subjects will be recruited by physician referral (from Atchley pavilion and AIM clinic) and flyers posted around the medical center. Female and male patients over the age of 18 that have been diagnosed to be type II diabetics on the basis National Diabetes Data Group criteria are eligible. Subjects should be only on diet control or oral hypoglycemics. Type I patients are excluded based on their lack of response to chromium in previous studies.

Subjects with poorly controlled diabetes (hgbalc>11) will be excluded. From past studies, we don't expect chromium to significantly impact this population of patients. This exclusion criteria will also prevent extreme results that may interfere with the power of the study. Also, poorly controlled diabetics tend to have a complex and constantly changing medication regimen, this will clearly add further noise to our results.

Other exclusion conditions include pregnancy, acute medical or psychiatric illness, renal insufficiency (creatine >2.5) untreated thyroid dysfunction, steroid use, excessive alcohol use (> 5 drinks/wk), and liver dysfunction.

The recruitment method of patients is aimed at obtaining a sample that would give a good representation of minorities. Therefore of the eighty patients approximately thirty patients will be chosen from the clinic population. We also aim for a population consisting of equal numbers of female and male subjects if possible.

F. Measurements

Hgba1c, total cholesterol, triglyceride, and HDL will be measured at 0, 3, and 6 months after initiation of study. Subjects will be informed to present for AM blood draw following 12 hrs of fasting. For each value, 3 consecutive weekly measurements will be taken to minimize variability in these values. Number coded bloods will be drawn and sent to the hospital chemistry lab where results will be recorded in blinded fashion. These values will be made available to subject's primary medical doctor upon request.

G. Study drug

Chromium picolinate is an organic formulation of chromium. It is chosen for this study due to past study's suggestion that it may provide better bioavailability. It has also been linked to several studies with positive findings.

The dose of chromium is chosen after analyzing the range of doses previously used. older trials used lower doses of 200ug/d to study the physiologic action of chromium. Newer studies suggest that there may be pharmacologic activity at higher doses. Two newer studies using doses above 600ug/d have seen positive results. we will use a dose of 800ug/d. This regimen is expected to provide good patient compliance due to its benign adverse effect profile and its bid dosing.

The placebo will be calcium carbonate. The active and placebo drugs will be donated by drug manufacturers in powder form. This powder form will be prepared by our investigational pharmacy into identically appearing capsules.

H. Side Effects

Chromium has been long available in the health food stores. There have been no severe adverse effects reported. Clinical trials in the past have reported minimal GI discomfort. Doses of up to 2000ug/d have been taken by human subjects without adverse effects.

It must be noted that chromium is present in two oxidation states. The inorganic non medicinal hexavalent state of chromium has been shown to have carcinogenic potential in animals when given in high doses. Trivalent forms of chromium are thought not to be carcinogenic.

I. General Procedure

At the initial study seminar, the study procedure, subject obligation, and consent process will be explained to potential subjects. After the consent form are completed, patients will be randomized into the 2 treatment groups.

On initial visit patients will fill out a questionnaire that will record their baseline exercise routine, alcohol intake, and usual weight. A four day diet diary will also be obtained. A brief history including medications regimen will be obtained. Physical exam will include weight and height.

Pt will then consult with a study dietitian who will advise them to maintain their usual dietary and activity habits. They will be given a three month supply of medication. Instructions on dosing will be provided at that time. Date and time of subsequent blood draws will be given to patients. They will be reminded by telephone 1 week and 1 day prior to each blood sampling.

Diet records, medication regimen, exercise amount, weight, and alcohol intake will be recorded on subsequent visits, at 3 and 6 months. These records will be compared to previous baseline behavior. Subjects will again discuss with study dietitian the need to maintain their baseline dietary habits.

J. Compliance

Study medication compliance will be assessed by periodic capsule counting and measurement of serum chromium levels on the first and one mid-treatment blood draw. From past studies, a four fold increase in serum chromium suggests compliance.

K. Statistical Analysis

This crossover study of 2 treatment groups will be analyzed by the analysis of covariance. This model will allow us to make adjustment for certain baseline values.

L. Funding

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