The Effect of Chromium Supplementation On Blood Glucose Control In Individuals with Type 2 Diabetes

Denis J. Collier©
Lakehead University
Thunder Bay, Ontario

A Thesis
Submitted to the School of Graduate Studies and Research
In Partial Fulfilment of the Requirements for the Degree
Master of Science
(Kinesiology)

December 1, 2003

Your file Votre référence
ISBN: 0-612-92232-4
Our file Notre référence
ISBN: 0-612-92232-4

ACKNOWLEDGEMENTS

They say the writing of a Master's thesis can be a stressful endeavour. For me, this was largely untrue because I was fortunate enough to have an advisor with a temperament very similar to my own. Thanks to Ian Newhouse, who over the course of two years taught me about exercise physiology, research design and how to drive a standard.

He is one of the many people for whom thanks are in order: To all the Kinesiology profs who helped me during my tenure at Lakehead, especially Jim McAuliffe and Norm Lavoie who graciously agreed to be on my thesis committee. To Sandra Blackburn for her patience with my requests for photocopies and faxes. To Janine Veniot, Cheryl Graham and Liz Teskey at MDS Laboratories who helped organize the blood testing. To Jamieson's Laboratories for donating the chromium and placebos free of charge, and particularly Marion Bruinsma for her assistance with the ordering process. To Kris Ketonen whose article in the Chronicle Journal was the vehicle of recruitment for every subject in the study. To Tracey Muldoon and Nancy Pazianos in the interlibrary loan office, who took the time to learn my name when it really wasn't part of their job. To my friends in Marathon House, who helped to make these last two years the most enjoyable of my University career.

And finally the biggest thanks of all go to the 12 subjects. Every other aspect of the study was a given. In one way or another, it would all eventually come to fruition. But for six months I worried about the subjects. I was plagued by the notion that on any given day, you all could call me and say that you were dropping out of the study, leaving me with no thesis. I should never have worried. Without you guys, there would be nothing.

ABSTRACT

The purpose of this study was to determine the effect of chromium supplementation on the blood glucose control of individuals with type 2 diabetes. A positive finding would result in substantial health and financial benefits for individuals with this disease. In the previous literature, some studies have found that supplementation with chromium improves blood glucose control, while others have reported no effect; hence the need for more research. This study utilized a repeated measures, double-blind, cross-over design, consisting of two study periods separated by a washout period. Both study periods, as well as the wash-out period, were two months in duration. The sample used in this study was comprised of 12 individuals (9 men and 3 women). Each study period saw half the subjects taking a 400 μg glucose tolerance factor (GTF) chromium supplement per day while the other half received a placebo. The dependent variable, or primary outcome measure of blood glucose control, was haemoglobin A1c (HbA1c). Analysis revealed no evidence of a carry-over effect between periods, so data could justifiably be pooled into change scores from pre to post. Analysis of this data using a repeated measure, within-subjects t-test found no significant differences in HbA1c after treatment with chromium as compared to the placebo. These findings support those previous studies that have found no effect of chromium supplementation on blood glucose control.

TABLE OF CONTENTS

Appendices

Tables

Figures

CHAPTER 1: INTRODUCTION

1.1: PURPOSE

The purpose of this study was to determine the effects of chromium supplementation on the blood glucose control of individuals with type 2 diabetes. Blood glucose control was measured using haemoglobin A1c (HbA1c).

1.2: IMPORTANCE OF STUDY

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes mellitus is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidney, eye, nerves, heart and blood vessels (Meltzer et al., 1998).

Type 1 diabetes (also commonly inappropriately referred to as insulin-dependent diabetes mellitus or IDDM) encompasses diabetes that is primarily a result of pancreatic beta-cell destruction and that is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta-cell destruction is unknown (Meltzer et al., 1998).

Type 2 diabetes (also commonly inappropriately called non-insulin-dependent diabetes mellitus or NIDDM) may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance (Meltzer et al., 1998). It is within this disease-state where chromium's role as an insulin potentiator (Vincent, 1999) may prove particularly beneficial. If supplemental chromium could be used to help insulin-resistant individuals utilize their insulin more efficiently,

the characteristic hyperglycemia of diabetes mellitus could be lessened or avoided. Some, but not all, previous studies have confirmed this speculation.

Currently, approximately 5% of Canadians or 1.5 million people have been diagnosed with diabetes mellitus (Tan & McLean, 1995). Although the distinction is often unclear, type 2 diabetes may account for 90% to 95% of all cases (Mahan & Escott-Stump, 2000). There is no data available as to the exact cost of diabetes treatment in Canada, however, data from the United States suggest that diabetes and its management consume approximately one in seven health care dollars (Rubin, Altman & Mendelson, 1994). It stands to reason that an inexpensive mineral supplement, if found to be effective, would ease this financial burden.

1.3: DEFINITIONS

Ataxia – an inability to coordinate muscle activity during voluntary movement; most often due to disorders of the cerebellum or the posterior columns of the spinal cord; may involve the limbs, head or trunk (Barlow-Pugh, 2000).

Encephalopathy – any abnormal condition of the structure or function of brain tissues, especially chronic, destructive, or degenerative conditions such as Wernicke's encephalopathy or Schilder's disease (Anderson, K.N. & Anderson, L.E., 1998).

Glycosuria – urinary excretion of carbohydrates (Barlow-Pugh, 2000).

Haemoglobin A1c - a haemoglobin A molecule with a glucose group on the N-terminal valine amino acid unit of the beta chain. The HbA1c concentration represents the average blood glucose level over the previous several weeks (Anderson K.N. & Anderson L.E., 1998).

Interstitial Nephritis –encompasses a group of clinical disorders that affect principally the renal tubules and interstitium, with relative sparing of the glomeruli and renal vasculature. Most cases of interstitial nephritis can be classified into one of two types: acute causes a rapid decline in renal function, characterized by an acute inflammatory infiltrate; chronic causes a progressive deterioration in renal function, characterized by interstitial scarring and fibrosis (Andreoli, 2001).

Ketoacidosis – acidosis accompanied by accumulation of ketones in the body, resulting from extensive breakdown of fats because of faulty carbohydrate metabolism. It occurs primarily as a complication of diabetes mellitus and is characterized by a fruity odour of acetone on the breath, mental confusion, dyspnea, nausea, vomiting, dehydration, weight loss and, if untreated, coma (Anderson, K.N. & Anderson, L.E., 1998).

Peripheral Neuropathy – any disorder affecting the peripheral nervous system (Barlow-Pugh, 2000).

Sequelae – a condition following as a consequence of a disease (Barlow-Pugh, 2000).

Thrombocytopenia – reduction in the number of platelets. There may be decreased production of platelets, decreased survival of platelets, and increased consumption of platelets or splenomegaly. Thrombocytopenia is the most common cause of bleeding disorders (Anderson, K.N. & Anderson, L.E., 1998).

Total Parental Nutrition – the administration of a nutritionally adequate hypertonic solution consisting of glucose, protein hydrolysates, minerals and vitamins through an indwelling catheter. The procedure is used in prolonged coma, severe uncontrolled malabsorption, extensive burns, gastrointestinal fistulas, and other conditions in which feeding by mouth cannot provide adequate amounts of the essential nutrients (Anderson, K.N. & Anderson, L.E., 1998).

1.4: ABBREVIATIONS

AI = adequate intake

DNA = deoxyribonucleic acid

DRI = dietary reference intake

GTF = glucose tolerance factor

HbA1c = haemoglobin A1c (or glycosylated haemoglobin)

IDDM = insulin-dependent diabetes mellitus

NIDDM = non-insulin dependent diabetes mellitus

RDA = recommended dietary allowance

TPN = total parental nutrition

UL = upper limit

μg = microgram

1.5: LIMITATIONS

Some limitations of the study include the following:

1) Eight week test periods – Neither the time required for chromium to begin working or the period of blood glucose control reflected by HbA1c are known precisely. If either of these time periods is longer than eight weeks, then the length of test periods used in this study could be a limitation. However, on both counts, enough evidence was found to justify using test periods of eight weeks duration. Also, shorter rather than longer test periods were chosen to minimize subject burden.
2) No reliable way to assess chromium status – As is common with other trace minerals, extra chromium will be of no benefit to a person who already has ample stores. Although previous research has provided evidence that diabetics excrete more chromium than healthy controls (Morris et al., 1999), leading to speculation that they may be prone to chromium deficiency, it was impossible to determine the actual chromium status of the subjects in this study. Presently, there is no universally accepted measure of clinical chromium status (Hellerstein, 1998; Mertz, 1993). What this means is that it is not possible to pinpoint whether any beneficial effects of chromium would be nutritional or pharmacological in nature. However, regardless of the means, any finding of a treatment improving blood glucose control in a sample of diabetics would still be important. Until a means of gauging an individual's stores of biologically important chromium is found, all chromium researchers will face this limitation.
3) Geographically dispersed sample – Three subjects lived in Dryden, Ontario and another who did live in Thunder Bay had no means to get to the Lakehead University

Campus. Because one third of the subjects in the study were never seen by the researcher, measurements such as body weight, body composition and pill count were not taken. In order to monitor body weight changes and compliance to pill-taking, the subjects were periodically contacted and questioned regarding these issues. One measure known to indicate increased chromium intake is urinary chromium excretion (Vincent, 2003). However, budgetary restraints prohibited such a recording from being taken.

4) Information on other moderating factors – Physical activity level was not quantifiably recorded. Instead, verbal reports were used as they were for body weight changes and pill-taking compliance. Alterations in eating habits may also influence HbA1c, so three-day food records may have been helpful in explaining the data. In any case, these limitations, as well as body weight monitoring are partly off-set by the cross-over design used in the study. With such a design, each subject serves as their own control, and it is assumed that their lifestyle would not drastically change over the duration of the study.

1.6: DELIMITATIONS

This study was delimited to adults (youngest subject was 41) with type 2 diabetes. The study was further delimited to the effects on HbA1c of a dosage of 400 μg of glucose tolerance factor (GTF) chromium administered for eight weeks.

CHAPTER 2: REVIEW OF LITERATURE

2.1: INTRODUCTION

Background Information

Chromium's role in nutrition was first elucidated in 1959 with the demonstration of the existence of a chromium-dependent dietary factor which was absent in the diets of rats fed Torula yeast as their sole protein source. Rats consuming the diet developed an inability to remove glucose efficiently from the bloodstream, which was reversed by adding foods rich in chromium or by adding synthetic inorganic trivalent chromium. This chromium-dependent dietary factor was named "glucose tolerance factor" (GTF) (Schwartz & Mertz, 1959).

Conclusive evidence of the role of trivalent chromium in human nutrition was first reported in 1977 when symptoms including hyperglycemia, weight loss, ataxia, and peripheral neuropathy in a female patient on long-term total parenteral nutrition (TPN) were alleviated by supplemental chromium (Jeejeebhoy, Chu, Marliss & Greenberg, 1977). Similar cases have been documented in the scientific literature several times since then (Anderson, R.A. et al., 1997b; Mertz, 1993). Medical studies would appear to indicate that chromium is required for normal carbohydrate and lipid metabolism. However, beneficial effects from the administration of chromium have not been observed in all cases (Vincent, 1999).

The reported beneficial effects of chromium have included potentiation of insulin, weight loss, increased burning of fat, muscle gain (Lukaski, 1999), decreased cholesterol levels and diabetes control (Hellerstein, 1998). There has even been a study reporting that chromium picolinate increases longevity (albeit in a population of rats) (Evans & Meyer,

1992). Reports such as these have contributed to chromium becoming the second largest selling mineral supplement in the United States, behind only calcium (Hellerstein, 1998). Chromium supplements (specifically chromium picolinate) generated nearly half a billion dollars in sales in 2000 (Mirasol, 2000).

Basic Chromium Biochemistry

Chromium is an essential trace element that can occur in several oxidative states, but the two most commonly occurring forms are hexavalent (VI) and trivalent (III) (Cerulli, Grabe, Gauthier, Malone & McGoldrick 1998; Jeejeebhoy, 1999). Trivalent chromium is the form associated with nutrition, while hexavalent chromium is used industrially for dyes, leather tanning and chrome plating (Katz & Salem, 1993). Therefore, unless otherwise specified, the use of the word "chromium" will refer to trivalent chromium for the remainder of this report.

The understanding of chromium's role in nutrition has been hindered by the failure to determine the structure, function and mode of action of biologically active chromium (which has recently led some to question the need for chromium) (Vincent, 1999), and by the lack of universally accepted measures of clinical chromium status (Hellerstein, 1998; Mertz, 1993) and chromium deficiency (Jeejeebhoy, 1999). These limitations will be discussed in detail now.

Progress in the mechanistic understanding of chromium biochemistry has proven to be exceedingly difficult (Hellerstein, 1998). Most of today's evidence suggests that the GTF is, in fact, not the intrinsic biologically active form of chromium as Schwartz and Mertz suggested in 1959. Neither is chromium picolinate the intrinsic biologically active

form. These chromium complexes are most likely only readily absorbable sources (Vincent, 1999).

A breakthrough in establishing the mechanism of chromium action at a molecular level occurred in the 1980`s when a unique chromium binding oligopeptide was identified. This molecule was called low-molecular-weight chromium binding substance or chromodulin (Vincent, 2000a). At present, this seems to be the most likely candidate for the biologically active form of chromium (Vincent, 1999, 2000b). Several studies on rat adipocytes have demonstrated the ability of chromodulin to potentiate the effects of insulin on the conversion of glucose into carbon dioxide or lipid (Vincent, 1999, 2000a). The stimulation occurs without changing the concentration of insulin and is directly dependent on the chromium content of chromodulin (Vincent, 2000a). A study by Vincent in 1999 showed that approximately four chromic ions per oligopeptide are required for maximal activity, which is consistent with the results of other studies. Chromodulin is thought to exist inside insulin-sensitve cells in a chromium-free form, called apo-chromodulin. Increases in plasma insulin concentrations have been found to result in movement of chromium from the blood into insulin dependent cells. This transfer is likely mediated by the transport protein transferrin. Once inside the cell, chromium binds to apo-chromodulin, which can then bind to the insulin receptor, helping to maintain its active conformation and amplifying insulin signalling (Vincent, 1999, 2000a). In summary, chromodulin`s role in glucose metabolism appears to occur after insulin binds to its receptor and at or before carbohydrate is transported into the cell (Vincent, 1999, 2000b).

If this mechanism involving chromodulin is correct then several points can be rationalized. For one, it can be seen why chromium serves only as a nutrient and not as a therapeutic. Benefits of extra chromium would only occur in those people who have less than adequate amounts to stimulate all the insulin receptors. Also, if this mechanism is correct, then chromium must be removed from cells to stop the activation activity. Studies show that urinary chromium losses increase after ingestion of high-carbohydrate loads. Presumably, chromodulin may be removed from insulin responsive cells to relieve its effects and then excreted in urine (Vincent, 1999, 2000b).

The combination of no measurable physiological or biochemical parameter affected by chromium deficiency or repletion and no reliable biochemical index of chromium status helps explain both the slow scientific progress and the emergence of potentially unfounded health claims regarding this nutrient. Because no intermediate physiological markers of chromium adequacy are available, claims about chromium deficiency or replacement cannot easily be tested. And because subjects cannot be stratified on the basis of baseline chromium status, proper selection or stratification of subjects for clinical intervention trials has not been possible (Hellerstein, 1998; Lukaski, 1999).

At present, there is no solid method to diagnose chromium deficiency. Most diagnoses have been made retrospectively in patients on TPN that unexpectedly developed hyperglycemia and neuropathy and responded to chromium infusion (Jeejeebhoy, 1999; Vincent, 2000a). Elevated levels of plasma chromium while on TPN cannot be interpreted as adequate intake, as those patients who have experienced these symptoms have had elevated plasma chromium levels (Jeejeebhoy, 1999). Studies have

shown that circulating chromium does not reflect chromium concentrations in biologically important tissues (Lukaski, 1999; Mertz, 1993). In general, the symptoms reportedly associated with chromium deficiency include impaired glucose tolerance, elevated circulating insulin concentration, glycosuria, fasting hyperglycemia, hypoglycemia, neuropathy, encephalopathy, increased intraocular pressure, decreased insulin binding and decreased insulin receptor number (Jeejeebhoy et al., 1977; Luskaski, 1999).

Chromium and Food

The 1989 edition of the Recommended Dietary Allowances (RDA`s) listed an estimated safe and adequate daily dietary intake for chromium to be 50-200 μg/day (Food and Nutrition Board, 1989). Since that time, a new system known as the Dietary Reference Intakes (DRI`s) has replaced the RDA`s as the main reference for nutrient requirements. Under the new DRI system, an adequate intake (AI) for chromium has been established at 35 μg/day and 25 μg/day for young men and women, respectively. The AI for a nutrient is the amount believed to cover the needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of persons covered by this intake. For this reason, the AI for chromium was set based on estimated mean intakes (National Academic Press, 2002); a study by Anderson, R.A. and Kozlovsky (1985) reported mean daily intakes of 33 ± 3 μg for men and 25 ± 1 μg for women consuming normal diets.

Even diets designed by nutritionists may be deficient in chromium; in 1992 Anderson, R.A., Bryden and Polansky analyzed the chromium content of 22 daily diets

designed by nutritionists to be well-balanced. The average amount of chromium per diet was only 13.4 ug/1000 Calories.

Chromium naturally occurs in food sources such as Brewer's yeast, animal meats and whole grains (Cerulli et al., 1998). In 1992 Anderson, R.A. et al. measured the chromium content of various foods and found beef cubes and turkey ham (a luncheon meat) to have the highest amount of chromium per serving among the meat products measured. Waffles, English muffins and bagels were the highest among grain products, while the content of fruits and vegetables varied widely, with juices, green beans and broccoli having the most chromium per serving. However, determining the exact amount of chromium in a food can prove arduous for a number of reasons. For one, chromium is only present in foods in very small amounts (Lukaski, 1999). Also, the content of individual lots of the same food can vary widely, and seems to be dependent on chromium introduced in the growing, transport, processing and fortification of the food (Anderson, R.A. et al., 1992). These factors were only realized in the last twenty years, so reports of the chromium content of foods made before this time are often mistakenly high (Lukaski, 1999).

In its inorganic state, very little trivalent chromium is absorbed, perhaps less than 2 percent of the dose (Jeejeebhoy, 1999). Several dietary factors seem to influence chromium uptake, although the exact mechanism of absorption is unclear. Oxalate intake, iron and zinc deficiency, ascorbic acid, nicotinic acid and diets with less than 40 μg of chromium per day have been shown to increase absorption (Anderson & Kozlovsky, 1985). Phytate intake has been shown to decrease absorption (Jeejeebhoy, 1999). Also, consuming a high-sugar diet may contribute to an inadequate chromium intake in two

ways: 1) high-sugar diets are usually low in chromium and 2) high-sugar diets have been shown to increase chromium excretion (Anderson, R.A., 1997a). Some non-dietary factors causing chromium depletion include certain physiological stressors such as physical trauma, acute (but not chronic exercise), lactation (Lukaski, 1999) and aging (Jeejeebhoy, 1999).

In contrast, organic forms found in supplements such as chromium nicotinate, chromium picolinate and chromium in yeast are better absorbed (Jeejeebhoy, 1999), perhaps as much as 4-5% (Vincent, 2003). Some interesting information about the fate of absorbed chromium picolinate was discovered in the 2002 in-vivo study by Hepburn and Vincent. The researchers injected rats with chromium and H-labeled chromium picolinate for 14 days. Injection was used to avoid the low absorption rates that accompany oral ingestion. The amount injected daily corresponded to 5 μg of chromium, which after accounting for differences in body size, would be equivalent to a slightly greater than average amount of chromium ingested normally for humans. They concluded that chromium picolinate is degraded rather rapidly in cells (within 24 hours of injection). Although the liver and kidney accumulated appreciable amounts of chromium from the supplement, the vast majority, if not all of the chromium was not in the picolinate form after 24 hours. While this decomposition minimizes the risk of deleterious effects from chromium picolinate itself, it does not eliminate the need for long-term studies.

Toxicity

Chronic exposure to hexavalent chromium has been linked to a variety of health problems, including lung cancer, and is 100 times more toxic than trivalent chromium (Katz & Salem, 1993). From a dietary perspective, trivalent chromium is considered safe

when consumed in normal amounts (Cerulli et al., 1998; Lukaski, 1999); it is also considered to have a safety factor that is much higher than many other trace elements (Jeejeebhoy, 1999). So few serious adverse effects have been associated with excess intake of chromium from food, a tolerable upper intake level (UL) has not been established (National Academic Press, 2002).

From the perspective of chromium supplementation, 19 randomized clinical trials in which individuals received between 175 μg and 1000 μg/day of chromium supplements orally for durations ranging from 6-64 weeks, produced no evidence of any toxic effects (Jeejeebhoy, 1999). In 1997, Anderson, R.A. pointed out that there had been no controlled studies documenting any negative effects of chromium supplements taken orally in the last 30 years. Despite the lack of toxicity reported in these controlled trials, the potential for chromium toxicity would seem to be greater when ingesting supplemental, rather than dietary chromium, as the supplemental form is better absorbed (Vincent, 2003). There have been at least three cases of chromium toxicity from supplementation reported in the literature, all of which involved chromium picolinate. These cases are described below:

1) Female, 33 years old who presented to hospital with weight loss (4.5 kg in the previous two weeks and 11.4 kg over three months), anemia, thrombocytopenia, hemolysis, liver dysfunction and renal failure. She had ingested 1200-2400 μg of chromium per day (in the form of 200 μg tablets of chromium picolinate) over 4-5 months to enhance weight loss. She was subsequently diagnosed with an eating disorder. After 26 days of hospitalization, the patient was discharged with a final

diagnosis of hemolysis, as well as acute liver and renal failure secondary to chromium toxicity (Cerulli et al., 1998).

2) Female, 49 years old who ingested 600 μg/day of chromium picolinate for six weeks to lose weight. Five months after the ingestion of chromium, the patient presented with severe chronic active interstitial nephritis consistent with heavy metal exposure. However, the likelihood of this patient's nephritis being attributable to chromium toxicity was heavily questioned in a series of letters to the editor subsequent to the original article (Wasser, McCarty, Hathcock, Michenfelder & Mennen, 1997).

3) Female, 67 kilogram body builder, 24 years old with no significant medical history presented with dehydration and a four day history of diffuse muscle weakness, pain and bilateral leg cramping. Two days before the onset of the cramping, she added chromium picolinate to her complex dietary supplement regime. She consumed 1200 μg of chromium over 48 hours. The diagnosis was rhabdomyolysis. Although the patient was a well-conditioned athlete who had maintained a stable diet and exercise program for eight weeks before taking chromium picolinate and developing the syndrome, the authors do admit that considering the multitude of supplements she was consuming and the fact that she was involved in strenuous exercise, it was impossible to exclude other etiologies (Martin & Fuller, 1998).

Other potentially worrisome results have been found in in-vitro studies. As with the case studies, all in-vitro studies reporting deleterious effects used the chromium picolinate form. Perhaps the most famous of these was the study by Stearns, Wise, Patierno and Wetterhahn in 1995, which tested several trivalent chromium complexes for their ability to produce chromosomal aberrations (clastogenicity) in Chinese hamster

ovary cells. This study concluded that chromium picolinate was clastogenic, but the clastogenicity was more likely attributable to the picolinate, rather than the chromium. Neither chromium chloride nor chromium nicotinate produced such clastogenic damage. However, Lukaski (1999) noted that the concentration of chromium picolinate added to the cell culture system exceeded by more than 1000 times the concentration of chromium reported in human circulation. Therefore, the results of this experiment may not be applicable to human models.

Another study in 1999 by Speetjens, Collins, Vincent and Woski using concentrations of chromium picolinate believed to correspond to those in the cells of individuals taking the supplement for prolonged periods of time found that significant DNA cleavage resulted from the generated hydroxyl radicals. The damage was likely attributable to the combination of chromic ions and picolinate, which yields an alteration in the redox potential of chromium making it susceptible to biologically relevant reducing agents. Neither chromium nor picolinate caused such damage separately.

With such evidence, the potentially harmful effects from supplementation with chromium picolinate outweigh the potential benefits, especially when alternative forms of chromium supplements are available (Vincent, 2003).

Chromium and Diabetes

Individuals with diabetes have altered chromium metabolism, compared with nondiabetic control subjects, with higher chromium absorption but also greater chromium excretion. For this reason, it is postulated that the chromium requirement increases with increased glucose intolerance in diabetics (Anderson et al., 1997b).

A study with results supporting this postulation was done in 1999 by Morris, et al. who assessed chromium handling in 93 type 2 diabetics compared to 33 healthy volunteers. Diabetic patients had mean levels of plasma chromium significantly lower and urinary chromium values significantly higher than those found in healthy controls. Also, the healthy control group showed a significant negative correlation between fasting levels of plasma chromium and insulin. This was not evident in diabetic patients. Morris et al. concluded that large chromium losses over many years may exacerbate an already compromised chromium status in diabetic patients and might contribute to the developing of insulin resistance seen in patients with type 2 diabetes.

On a similar note, it has also been postulated that marginal chromium deficiency may increase an individual's risk for developing diabetes (Mertz, 1993).

2.2: METHODS FOR REVIEWING LITERATURE

A PubMed search was performed in October of 2001 using the words "chromium" and "diabetes". The search was limited to articles dealing only with human models, written in English and dating back to 1966. This search yielded 201 references of which the abstracts were scanned. All available articles deemed relevant were reviewed. Any articles dealing with chromium as it pertains to diabetes in children or pregnant women were not reviewed. Also, articles must have had some measure of blood glucose control as a dependent variable to qualify for review. Further references were obtained by accessing other databases, namely: Cumulative Index to Nursing and Allied Health Literature, Sport Discus. Finally, other relevant articles cited in the reference lists of the articles found using these database searches were reviewed. A second PubMed search was conducted in June of 2003.

Of the articles reviewed, 22 were original experiments; a summary of their results is presented in Appendix A. Each of these studies underwent a quality critique using a scoring system that was designed for this purpose. A summary of the scoring system can be seen in Table 1:

Table 1: Scoring System Used To Critique Articles

Criteria	**Point Allocation**
Compliance testing	Compliance tested = 1, no compliance testing = 0
Control	Use of a control group = 3, no control = 0
Cross-over design	Cross-over + washout = 3, cross-over no washout = 1.5, not a cross-over design = 0
Dependent variable	HbA1c = 3, other measure of blood glucose = 1.5
Duration	12 or more weeks = 3, 8-11 weeks = 2, 4-7 weeks = 1, <4 weeks = 0
Statistical analysis	Appropriate = 3, partially appropriate = 1.5, inappropriate or incomplete = 0
Researcher blinded	Proof of blinding = 3, statement of blinding = 1.5, not blind = 0
Subjects blinded	Proof of blinding = 3, statement of blinding = 1.5, not blind = 0
Subject number	>30 subjects = 3, 20-29 subjects = 2, 10-19 subjects = 1, <10 subjects = 0
Miscellaneous Factors	Any other notable characteristics considered for a score out of 1

2.3: RESULTS OF LITERATURE REVIEW

The validity of pooling the results of all the studies done on the effects of chromium supplementation on blood glucose control is compromised by the differences in the individual studies. For example, the dosage of chromium supplementation in the studies ranged from 10.8 μg to 1000 μg per day. The duration of the test periods ranged from 3 weeks to 16 months. Ten studies used chromium in the form of chromium chloride, four used chromium picolinate, five used trivalent chromium, six used chromium-rich yeast and one study used chromium nicotinate (four studies used more than one type). However, by subjecting the studies to the same scoring system, some objectivity in evaluating the quality of each study is obtained. Scores of the studies ranged from 3 to 21.5, with a mean score of 15.43.

Of all the different variables, none seemed to be more significant than the diabetic status of the subjects. No other variable influenced the effect of chromium supplementation on blood glucose control more than this one. For this reason, it was most practical to group studies according to this variable and discuss the results of each group.

Studies on Individuals with Diabetes

Nine of the studies tested diabetic subjects exclusively. Six of these nine reported some improvement in blood glucose control after supplementation, while three studies reported no improvement. According to the scoring system, the six studies showing improved blood glucose control had a total score of 78.5 points. The three studies showing no improvement had a total score of 46.5. These scores seem to indicate the strength of evidence lies with the studies reporting positive effects of chromium supplementation on blood glucose control in diabetics.

Studies on Individuals without Diabetes

The studies on individuals without diabetes provided the most confusing results when pooled. There were nine such studies in total and their results differed widely. Only four of the nine studies presented results that could easily be classified into either an effect or no effect category.

The double-blind, cross-over study by Anderson, R.A., Polansky, Bryden, Bhathena and Canary in 1987 could be said to have found a positive effect. This study reported that all measured parameters of blood glucose improved after three months of supplementing with 200 μg of chromium chloride. It is interesting to note that all eight subjects used in this study had symptoms of hypoglycaemia prior to the initiation of the

study, suggesting that although not diabetic, their management of blood glucose was somewhat impaired.

The study by Wang, Fox, Stoecker, Menendez and Chan (1989) could be immediately classified as not showing any significant effect of chromium supplementation on blood glucose control. The subjects (who had high serum cholesterol at the outset of the study) did however, experience improvements in their cholesterol levels. The study by Uusitupa et al. (1992) could be grouped in this same category. This study found no differences in any measure of blood glucose between a group receiving 160 μg of chromium per day and another group receiving a placebo. It is noteworthy that the subjects in this study had persistent impaired glucose intolerance. Finally, the study by Hermann, Arquitt and Stoecker (1994) reported that fasting blood glucose was unaffected by supplementation, but beneficial effects could be seen in blood lipids when subjects were sub-divided according to baseline levels.

The five remaining studies have results that cannot be conveniently summarized as having an effect or no effect. Three of these five found differing results for different groups within the study. A double-blind, cross-over study by Anderson, R.A. et al. (1983) reported no significant effects on fasting blood glucose when all subjects were combined, but when subjects were stratified based on the results of a 90 minute glucose tolerance test, improvements were seen in blood glucose control in the group with the least amount of glucose tolerance. Martinez, MacDonald, Gibson and Bourn (1985) found no effect of supplementation in a group of women who took medications that may affect glucose tolerance. However, non-medicated subjects who were judged to be at high risk for glucose intolerance had a significant decrease in blood glucose two hours post-load. The

study by Anderson, R.A., Polansky, Bryden and Canary (1991) found that glucose tolerance, circulating insulin and glucagon improved only in those subjects who had elevated blood glucose levels after a tolerance test performed at baseline.

The last two studies on non-diabetic subjects cannot be easily categorized because they found different effects on different measures of blood glucose. Riales and Albrink (1981) measured a variety of blood glucose related parameters, but found only fasting blood glucose was lowered by chromium supplementation. The study by Urberg and Zemel (1987) reported fasting glucose and glucose tolerance after a test were improved only by chromium nicotinate, and not by either chromium or nicotinic acid alone. Fasting and 1-hour insulin levels or HbA1c were not affected by any treatment.

In summary, although these nine studies did not use diabetic subjects, five of them reported at least some of their subjects as having some degree of impaired glucose tolerance. Of these five studies, four reported a beneficial effect of chromium supplementation while only one reported no effect.

Studies Involving Both Groups of People

Four studies reviewed used a mixture of diabetic and non-diabetic subjects.

Sherman, Glennon, Brech, Klomberg and Gordon (1968) found chromium supplementation to have no effect on fasting or 2-hour post-prandial blood glucose in four healthy and 10 diabetic males. Likewise, Abraham, Brooks and Eylath (1992) found no effect on blood glucose when comparing groups receiving either 250 μg of chromium chloride per day or a placebo; however, beneficial changes were seen in some blood lipids.

Contrary to these findings, Offenbacher and Pi-Sunyer (1980) reported that after a glucose load, glucose tolerance improved significantly and insulin output decreased in 16 healthy and eight mildly diabetic subjects with only 10.8 μg of chromium per day compared to a placebo. Glinsmann and Mertz (1966) also concluded that their diabetic subjects did improve their blood glucose control over what they described as "long-term" supplementation with chromium. No improvements were found with "short-term" supplementation in diabetics or with any of their healthy subjects.

2.4: DISCUSSION OF LITERATURE

Upon examining each of these 22 studies at face value, it is difficult to notice any trends. Indeed, it is easy to see why such great polarity of opinions exists regarding the benefits of chromium supplementation. However, when the evidence is viewed considering the diabetic state of the subjects studied, some degree of clarity is provided. Of the 22 studies, 18 used at least some subjects with some degree of impaired blood glucose control. Twelve of these 18 studies reported that such individuals improved their blood glucose control with chromium supplementation. These studies accumulated 174.5 points. The six studies reporting no effect of supplementation on such individuals garnered only 96 points. None of the 22 studies reported negative effects on glucose control or any toxic effects in general.

The conclusion of this review is consistent with the conclusions of other reviews. Notably, Lukaski (1999), who found that most recent studies on the effects of chromium picolinate, or other chromium supplements, on healthy human subjects produced no observed beneficial effects from supplementation. Lukaski offered the explanation that this was because the subjects in the studies were not chromium deficient. This review

also supports the argument put forth by Mertz (1993), that an impaired glucose tolerance can be improved or normalized by chromium supplementation or can be maintained in spite of a reduced insulin output, but a normal glucose tolerance is not further improved. The meta-analysis done by Althuis, Jordan, Ludington and Wittes (2002), using data from 15 trials and including 618 participants (193 of which had type 2 diabetes), found no effect of chromium supplementation on glucose or insulin response in non-diabetic subjects. The effects of chromium supplementation on individuals with diabetes were deemed inconclusive, as a result of too few trials with diabetic subjects having been conducted.

2.5: CONCLUSIONS FROM LITERATURE REVIEW

1) Individuals with impaired glucose metabolism may experience improvements in their blood glucose control with supplemental chromium. This finding is especially important for individuals with diabetes mellitus.

2) Individuals with probable low chromium status may experience decreased blood glucose control, which may be alleviated by supplemental chromium. Again, this conclusion is particularly important for individuals with diabetes as they tend to excrete more chromium, which may exacerbate already compromised blood glucose control

3) A reliable measure of chromium status is sorely needed to stratify patients, compare populations, determine deficiency, evaluate compliance, and differentiate between replacement and pharmacological effects

4) More understanding is needed with regards to the mechanistic metabolic actions of chromium to lower blood glucose concentrations.

5) More studies are needed on the effects of chromium supplementation on blood glucose control, particularly in individuals with diabetes

CHAPTER 3: METHODS

3.1: SUBJECTS

The sample used in this study was comprised of 12 individuals with type 2 diabetes. Two additional individuals started the study but were unable to finish after missed blood tests. The sample consisted of nine men and three women. Nine individuals resided in Thunder Bay and three lived in Dryden. The ages of the subjects ranged from 41 to 74, with a mean age of 59.7. The mean HbA1c level at the onset of the study was 0.07645.

Power analysis revealed that 15 subjects would be needed for the study. This is considering that this study used a cross-over design (see Section 3.2) and each subject would represent both the placebo and chromium test periods. This was the number of subjects calculated to achieve statistical significance with $p = 0.05$, statistical power equal to 90%, an estimated standard deviation of 1.0 and an ability to detect a difference between treatment groups in HbA1c of 0.5 (Kraemer et al., 1987).

All subjects were recruited via an article in the October 11th, 2002 edition of the Chronicle Journal newspaper (see Appendix B). In light of the relative difficulty in recruiting subjects, a somewhat liberal inclusion criteria was implemented in this study:

1. Subjects must have been diagnosed with type 2 diabetes mellitus. (This criteria was chosen in lieu of a more stringent HbA1c cut-off point in an effort to maximize the number of subjects able to participate in the study).
2. Subjects must have been adults
3. Subjects must not have taken chromium supplements two months or less prior to the study
4. Subjects must have taken their pill daily (either chromium or placebo)
5. Subjects must have reported to all four testing sessions

All subjects were informed of the purpose, details and risks of the study and were aware that they could withdraw from the study at any time. Approval for the study was granted by the Lakehead University Ethics Board.

3.2: PROCEDURES

The study utilized a repeated measures, double-blind, cross-over design, consisting of two study periods separated by a washout period. Both study periods, as well as the wash-out period, were eight weeks in duration. In each study period, half the subjects took a 400 μg glucose tolerance factor (GTF) chromium supplement per day while the other half ingested a placebo. Both chromium supplements and placebos were supplied by Jamieson's Laboratories and were identical in appearance and taste. Subjects were assigned to either group 1 or 2 prior to the beginning of the study in a random draw done by an independent party. Testing occurred at the beginning and end of each study period, for a total of four separate testing sessions. A table outlining the study design is presented below:

Table 2: Study Design

	Test 1	Test 2	Test 3	Test 4
Group 1 (n=6)	Chromium	Wash-out	Placebo	
Group 2 (n=6)	Placebo		Chromium	
	Week 0	Week 8	Week 16	Week 24

The dependent variable, or primary outcome measure of blood glucose control, was haemoglobin A1c (HbA1c). Each subject reported to their most conveniently located MDS Laboratory for the blood drawing. MDS Labs also handled the HbA1c analysis from the blood samples. Regular telephone interviews were conducted with subjects to monitor pill-taking compliance, and body weight and physical activity changes.

3.3: RATIONALE FOR PROCEDURES

Why Use HbA1c as the Measure of Blood Glucose Control?

The Diabetes Control and Complications Trial (DCCT) showed conclusively that glycemic control as assessed by HbA1c can predict the risk of developing microvascular diabetic complications in type 1 patients (DCCT Research Group, 1993). This finding was later expanded to include type 2 diabetics with The United Kingdom Prospective Diabetes Study (the largest clinical study of diabetes ever attempted, conducted over 20 years and involving 5,102 type 2 diabetics) (U.K. Prospective Diabetes Study Group, 1998). As a consequence, the usefulness of the HbA1c assay has been validated and its use recommended (Kilpatrick, 1997). It is currently the pre-eminent measure of long-term blood glucose control reported in biomedical literature (Austin, 2001; Hom, Ettinger & Lin, 1998).

Why a Cross-Over Design?

The advantages of a cross-over design are well known. Comparisons of treatments are made within-subjects, predisposing them to within-subject, rather than between-subject error (Armitage & Hills, 1982). This design affords the use of statistical tests with greater power; that is, a difference of a given size between two sample means is more likely to be found significant using a within-subjects test than a between-subjects test (Diekhoff, 1992). Another advantage is that since more precision is obtained with this method, the number of subjects needed for the experiment is economized (Armitage & Hills, 1982).

Another reason for implementing a cross-over design is that previous studies on chromium and blood glucose control have either not done so, or failed to do so

effectively. Of the 22 prior studies on this topic, eight employed the cross-over technique; however, four of these studies had no wash-out period between trials and two other studies had wash-out periods of less than two weeks. Failure to include a wash-out period, or wash-out periods of such a short duration compromise the findings of these studies. Only one study to date has had a wash-out period of a similar length to the one used in this investigation (eight weeks). The eighth study gave no indication if a wash-out period was used or not.

Why Eight Weeks Duration for Each Study Period and Wash-Out?

Choosing the duration of the study periods was dependent largely on the physiology of the main dependent variable, HbA1c. Two months seems to be a reasonable estimate as to the time period over which HbA1c reflects blood glucose control. Although there does not seem to be a consensus as to exactly how long a period of blood glucose control HbA1c reflects, several sources have indicated that two months is a reasonable estimation. References citing time frames over which HbA1c reflects blood glucose control are presented in the following table:

Table 3: References Suggesting a Time Frame for HbA1c

Author and Year	**Suggested Range**
Austin, 2001	2-3 months
Mahan & Escott-Stump, 2000	2-3 months
Hom et al., 1998	2-3 months
Meltzer et al., 1998	2-4 months
Kilpatrick, 1997	6-8 weeks
Tahara & Shima, 1995	1-3 months
Goldstein et al., 1994	2-3 months
Koch, 1990	2-3 months

One of the previous cross-over studies used two-month test periods, three used shorter test periods and four used longer test periods. Selecting a longer test period would

increase subject burden, and is not necessarily justified considering the physiology of HbA1c.

Why Give 400 µg of Chromium?

Firstly, evidence that 400 µg is an acceptable dose can be found in the previous 22 studies on chromium supplements and blood glucose control. The most common dosage used in these studies has been 200 µg per day, which was used in nine studies. Two studies have used the same dose as that used in this study, 400 µg. Three studies have used doses higher than this; two have used 600 µg and one study used as much as 1000 µg. None of these studies documented any negative effects of their chromium supplements. Essentially, and most importantly, negative side effects resulting from ingestion of this amount of chromium was highly unlikely.

Secondly, chromium has an established safety factor that is much higher than many other trace elements (Jeejeebhoy, 1999). For dietary chromium, the intake at which harmful or toxic effects result is so high that it currently can only be estimated (Vincent, 2003).

Thirdly, higher doses may be particularly well tolerated by people with diabetes, as were used in this study. There is evidence to suggest that diabetics have greater than normal chromium excretion, therefore, a greater than normal chromium requirement (Anderson, R.A. et al., 1997b; Morris et al., 1999). Admittedly, the established adequate intake (AI) for chromium cannot specify with confidence the percentage of persons covered by this intake (National Academic Press, 2002). It is likely that the persons with diabetes require a chromium intake greater than the AI.

Finally, 400 μg was selected over a lower dose to try and avoid a "no effect" result simply because subjects did not receive enough chromium.

What Type of Chromium Supplement Will Be Used?

This study used tablets containing GTF chromium. There were two main advantages of using this type of chromium:

1) No study to date has used a GTF chromium supplement. Perhaps the most similar chromium supplement is chromium nicotinate. Nicotinic acid has been identified as possibly, but not conclusively, being part of the GTF complex (Mahan & Escott-Stump, 2000). Only one previous study has used chromium nicotinate in examining effects on blood glucose control (Urberg & Zemel, 1987). In summary, more research is needed on this form of chromium supplement.

2) In-vitro studies suggest that forms of chromium other than picolinate are unlikely to be susceptible to generating the same type of oxidative damage; therefore, the use of compounds other than chromium picolinate would appear warranted (Vincent, 2003).

3.4: DATA ANALYSIS

The intent when using a cross-over design is to ultimately pool the data obtained from both test periods. However, this step is not always justifiable. It must first be determined if there is a treatment X period interaction, otherwise known as a carry-over effect. Only after such an effect is disclaimed can the data be pooled (Armitage & Hills, 1982).

Two methods outlined by Hills and Armitage (1979) were used to test for this treatment X period interaction:

1) An independent t-test between the HbA1c change scores of groups 1 and 2 after each of their respective chromium supplementation periods (for group 1, the change scores for weeks 0-8; and the change scores from weeks 16-24 for group 2). Another independent t-test was run comparing the HbA1c change scores for both groups' placebo periods.
2) A dependent sample t-test between each subject's HbA1c level before each test period i.e. test 1 and test 3. This was to ensure that each subject's HbA1c level was relatively similar before the start of both test periods.

Upon discovery that these procedures both produced no significant differences ($p>.05$), it could safely be assumed that the washout-period was effective and data from the two test periods could be pooled into change scores for the main analysis; basically, leaving each subject with two pieces of data for comparison: 1) the difference between their HbA1c level pre and post chromium supplementation period and 2) the difference between their HBA1c level pre and post placebo. Data such as this lends itself to statistical analysis using a repeated measure, within-subjects t-test. With this procedure, it was possible to determine the significance of the effect of chromium supplementation on HbA1c in comparison to the placebo.

CHAPTER FOUR: RESULTS

4.1: TEST FOR CARRY-OVER EFFECT

The independent t-tests produced values of $t_{(10)} = -1.337$ and 0.541 for the tests in HbA1c difference pre and post chromium and placebo, respectively. Neither value exceeded the $t_{(crit)} = 2.228$ at a significance level of $p = .05$ and were therefore not significant. The dependent t-test on the HbA1c levels of all individuals at test 1 and test 3 produced a result of $t_{(11)} = 0.217 < t_{(crit)} = 2.201$, again indicating a non-significant difference. Since no procedure used to test for a treatment X period effect produced a significant result, a carry-over effect was not present. Therefore, data from the two test periods could be pooled for the main analysis.

4.2: MAIN ANALYSIS

No subject reported a notable change in their weight throughout the duration of the study. One subject reported an increase in exercise during the washout period.

Individual Raw Data

Table 4: HbA1c of Each Subject at Each Test Period

Subject	Test 1 (Week 0)	Test 2 (Week 8)	Test 3 (Week 16)	Test 4 (Week 24)
A [1]	0.079	0.080	0.071	0.080
B [1]	0.055	0.054	0.055	0.058
C [1]	0.056	0.055	0.054	0.055
D [1]	0.117	0.124	0.096	0.095
E [1]	0.080	0.086	0.087	0.083
F [1]	0.067	0.079	0.057	0.064
G [2]	0.100	0.102	0.082	0.077
H [2]	0.073	0.089	0.095	0.093
I [2]	0:064	0.065	0.067	0.073
J [2]	0.075	0.081	0.080	0.081
K [2]	0.061	0.066	0.066	0.067
L [2]	0.090	0.086	0.098	0.100

[1] = subject took Cr during 1st test period (weeks 0-8)
[2] = subject took Cr during 2nd test period (weeks 16-24)

Descriptive Statistics

The following table displays the mean HbA1c levels for each group at each individual test, as well as the change scores after both the chromium and placebo test periods:

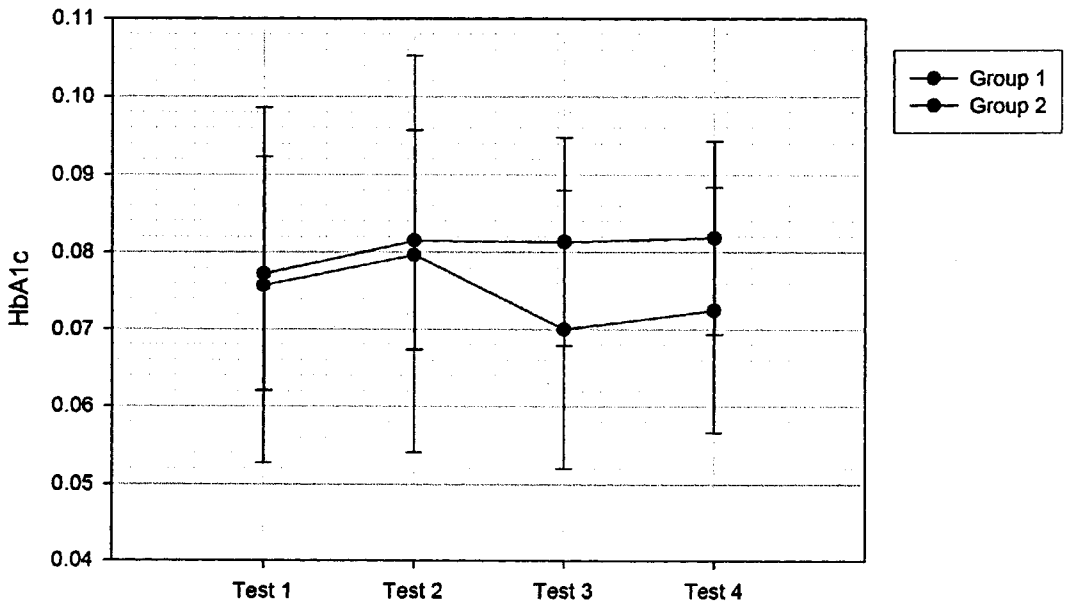
Table 5: Important Mean HbA1c Levels with Standard Deviations

Group	Test 1	Test 2	Change Score Weeks 0-8	Test 3	Test 4	Change Score Weeks 16-24
1 (n=6) Cr: weeks 0-8 Pl: weeks 16-24	0.0757 ±0.0229	0.0797 ±0.0256	-0.0040 ±0.0052	0.0700 ±0.0180	0.0725 ±0.0159	-0.0025 ±0.0049
2 (n=6) Cr:weeks 16-24 Pl: weeks 0-8	0.0772 ±0.0151	0.0815 ±0.0142	-0.0043 ±0.0067	0.0813 ±0.0135	0.0818 ±0.0125	-0.0005 ±0.0037

Cr = chromium test period; Pl = placebo test period

The average HbA1c values along with the standard deviations for both groups at each test are illustrated by the following graph:

Figure 1: Mean HbA1c Levels with Standard Deviations



In both test periods, mean HbA1c levels increased from pre to post. An improvement in blood glucose control would be indicated by a decrease in HbA1c. Therefore, before doing any further statistical tests, it is already known that the hypothesis of chromium supplements improving blood glucose control will be rejected.

Dependent t-Test

The mean change score for the 12 subjects during their chromium treatment period was -0.0023 (standard deviation 0.0047) compared to a mean change score of -0.0034 (standard deviation 0.0057) during the placebo period. The result of the repeated measure, within-subjects t-test was $t(11) = 0.496 < t(crit) = 2.201$. Therefore, the difference between these two means was not significant. In other words, chromium and the placebo did not affect HbA1c differently.

CHAPTER FIVE: DISCUSSION

The main result of this study is that chromium supplementation does not improve the blood glucose control of individuals with type 2 diabetes. This finding supports those of six previous studies that have explored this topic on individuals with impaired glucose metabolism (see Appendix A).

The results of a study such as this have particular interest to the millions of people suffering from diabetes around the world, as well as to the various manufacturers in the multi-million dollar nutritional supplement industry. However, it is important not to extend the findings of this study beyond its previously mentioned delimitations (see Section 1.6). This study was delimited to the effects of an eight week daily dose of 400 μg of GTF chromium on the HbA1c levels of type 2 diabetics who entered the study with a mean HbA1c level of 0.07645. Some of these delimitations will now be discussed in further detail, with specific comparisons made to the previous literature when appropriate.

5.1: EIGHT WEEK STUDY PERIODS

After conducting the main analysis of the data, it is clear that the results of this study suggest chromium does not improve blood glucose control. However, upon giving the data some closer inspection, an interesting pattern is uncovered. Consider the mean HbA1c for group 1 at test 1 and test 3 (see Figure 1). At test 1 they had an average HbA1c of 0.0757, and by test 3 (after taking chromium for eight weeks, then stopping for eight weeks) their average HbA1c had lowered to 0.0700. Although this decrease was not deemed statistically significant using a repeated measure, within-subject t-test, such improvement in blood glucose control may have some clinical importance. From The

United Kingdom Prospective Diabetes Study, epidemiological analysis showed that for every percentage point decrease in HbA1c (e.g. 9% to 8%) there was a 35% reduction in microvascular complications, 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality and 18% reduction in combined fatal and non-fatal myocardial infractions. There was also no evidence of any glycemic threshold for any of the microvascular or cardiovascular complications above HbA1c levels of 6.2% (U.K. Prospective Diabetes Study Group, 1998). Four of the six individuals in group 1 experienced improvements in their blood glucose control from test 1 to test 3. Subject A improved by 0.8%, subject C by 0.2%, subject D by 2.1% and subject F by 1%. The HbA1c of subject B remained the same at 0.055 at test 1 and test 3.

Further evidence for the importance of an HbA1c improvement from 0.0757 to 0.0700 can be found in the 1998 clinical practice guidelines for the management of diabetes in Canada. This reference lists values less than 0.070 as an "optimal" level of blood glucose control for adults with diabetes. They define "optimal" control as being likely related to minimal long-term complications. Contrarily, the subjects' mean HbA1c level of 0.757 at test 1 would be classified as "sub-optimal" control under these guidelines, or likely not adequate to prevent complications (Meltzer, et al., 1998).

From the group 1 decrease in HbA1c from test 1 to test 3, two theories emerge: 1) It is possible that the chromium took the entire 16 weeks to start working. Since many aspects of chromium metabolism remain unknown (Vincent, 1999), the exact time frame required for chromium to be assimilated into the bodies' biologically active stores cannot be predicted with any certainty.

2) HbA1c may take longer than eight weeks to reflect changes in blood glucose control. Although this time frame does fall into the range suggested by several sources (see Table 3), it is at the lower end of most. Choosing a time frame at the higher end of these suggested ranges may have been more appropriate for use in this study. Also, it would have been interesting to measure other parameters of blood glucose control at various times throughout the study, while still relying on HbA1c as the primary measure of long-term control.

In the previous literature, there is a precedent for a "no-effect" result in studies that have used test periods with durations similar to that of the present study. Uusitupa et al. (1983) reported that chromium supplementation had no effect on HbA1c after a slightly shorter test period (six weeks) than the one used in this study. Another similarity between this and the present study was that both implemented a cross-over design (although Uusitupa et al. failed to include a wash-out period). Trow et al. (2000) also concluded that chromium failed to improve blood glucose control or insulin levels after an eight week supplementation period.

In summary, this study as well as those mentioned above showed no significant improvement in HbA1c after eight weeks of supplementation with chromium; therefore, we must conclude that individuals with impaired glucose metabolism should not expect to find benefits in taking chromium for this length of time. However, after closer scrutiny of the data obtained in this study, we may be justified in speculating that benefits may occur with longer supplementation.

5.2: GTF CHROMIUM

This was the first documented study to use GTF chromium. The one study that used a similar chromium supplement (chromium nicotinate) also reported a failure of the supplement to significantly affect HbA1c (Urberg & Zemel, 1987). It could simply be that this type of chromium supplement is not as effective as others.

5.3: HAEMOGLOBIN A1c

Great improvements in HbA1c should not be expected if levels are already fairly well controlled. It could be argued that this was the case for the subjects in this study. At test 1 the 12 subjects had an average HbA1c of 0.07645. The 1998 clinical practice guidelines for the management of diabetes in Canada would classify this level of blood glucose control as "sub-optimal", but not "inadequate". "Inadequate" control is defined by HbA1c levels above 0.084. Such high levels are related to a markedly increased risk of long term complications, requiring a reassessment and readjustment of therapy (Meltzer et al., 1998). Only three subjects had levels in this range at the onset of the study. Only one of these was assigned to receive chromium in the first test period. When we use this individual to revisit the postulation that longer study periods may have produced more benefits, we see that this subject's HbA1c dropped from 0.117 at test 1 to 0.096 at test 3, which was the biggest fluctuation of any subject in the study. Four subjects fell into the "sub-optimal" category (0.07-0.084), three into the "optimal" category (less than 0.07) and two subjects began the study with HbA1c levels that would be defined as "ideal" or normal for a non-diabetic individual (0.04-0.06). Both these individuals were assigned to group 1. One experienced a 0.2% improvement in HbA1c from test 1 to test 3 (subject C), while the other maintained exactly the same HbA1c level

at these tests (subject B). Only small improvements in HbA1c levels as low as these could be expected, regardless of duration of supplementation. Significant improvements as a result of chromium supplementation, or any other treatment, would be more likely to be seen in subjects with "inadequate" blood glucose control.

Two examples of similar phenomenon can be pulled from the literature: Anderson, R.A. et al. (1997b) found chromium to significantly improve HbA1c after two months in subjects with initial HbA1c levels ranging from 0.080-0.120. Meanwhile, the study by Uusitupa et al. (1992) reported HbA1c remained unchanged by chromium supplementation in a sample of individuals who began the study with a mean HbA1c level of 0.0535.

5.4: SUMMARY

The main result of this study is that supplementation with GTF chromium was unable to significantly improve the HbA1c of type 2 diabetics with a mean initial HbA1c level of 0.07645 after an eight week treatment period. Support for this finding can be found in the previous literature. The findings of this study should not be generalized beyond the specified delimitations. There is room for further study in this area.

CHAPTER SIX: RECOMMENDATIONS

Future research in the field should heed the following recommendations:

- Studies should continue to use HbA1c as the measure of long-term blood glucose control, however, the duration of the test periods should exceed eight weeks. Test periods of 12 weeks or even 16 weeks may be appropriate. For a 16 week test period, it may be desirable to do two HbA1c tests, one after eight weeks and another at the end of the 16 weeks. If test periods of this length are not possible, post-study follow-up tests could be implemented. To conclusively determine the time frame over which HbA1c reflects blood glucose control, more research could be done on this topic as well.
- GTF chromium is an under-studied form of this supplement; more research is needed.
- All studies should report the initial HbA1c levels of the subjects. This will enable researchers to test the theory that chromium's ability to improve blood glucose control is greater when baseline levels of blood glucose control are inadequate.
- Obtaining data on other factors that could possibly affect blood glucose control (such as body weight, exercise level and diet) can help to better explain the main findings of the study.
- A reliable measure of chromium status is sorely needed to stratify patients, compare populations, determine deficiency, evaluate compliance, and differentiate between replacement and pharmacological effects.

REFERENCES

Abraham, A.S., Brooks, B.A. & Eylath, U. (1992). The effects of chromium supplementation on serum glucose and lipids in patients with and without NIDDM. *Metabolism,* 41, 768-71

Althuis, M.D., Jordan, N.E., Ludington, E.A. & Wittes, J.T. (2002). Glucose and insulin response to dietary chromium supplements: a meta-analysis. *American Journal of Clinical Nutrition,* 76(1), 148-155

Anderson, K.N. & Anderson, L.E. (1998). Mosby's Pocket Dictionary of Medicine, Nursing and Allied Health 3rd Ed. U.S.A.; Mosby Inc.

Anderson, R.A. (1997a). Chromium as an essential nutrient for humans. *Regulatory Toxicology and Pharmacology,* 26, S35-S41

Anderson, R.A., Bryden, N.A., & Polansky, M.M. (1992). Dietary chromium intake. *Biological Trace Element Research,* 32, 117-121

Anderson, R.A. Cheng, N., Bryden, N.A., Polansky, M.M., Cheng, N., Chi, J., et al. (1997b). Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes,* 46, 1786-1791

Anderson, R.A & Kozlovsky, A.S. (1985). Chromium intake, absorption and excretion of subjects consuming self-selected diets. *American Journal of Clinical Nutrition,* 41, 1177-1183

Anderson, R.A., Polansky, M.M., Bryden, N.A., Bhathena, S.J., & Canary, J.J. (1987). Effects of supplemental chromium on patients with symptoms of reactive hypoglycaemia. *Metabolism,* 36(4), 351-355

Anderson, R.A., Polansky, M.M., Bryden, N.A., & Canary, J.J. (1991). Supplemental chromium effects on glucose, insulin, glucagon, and urinary chromium losses in subjects consuming controlled low-chromium diets. *American Journal of Clinical Nutrition,* 54, 909-16

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Mertz, W. & Glinsmann, W. (1983). Chromium supplementation of human subjects: effects on glucose, insulin and lipid variables. *Metabolism,* 32, 894-899

Andreoli, T.E. (2001) Cecil Essentials of Medicine 5th Ed. Philadelphia PA; W.B. Saunders Company

Armitage, P. & Hills, M. (1982). The two-period crossover trial. *The Statistician,* 31(2): 119-131

Austin, G.E. (2001). Home fructosamine testing: will it improve diabetic control. *Diabetes Technology and Therapeutics,* 3(3), 405-408

Bahijiri, S.M., Mira, S.A., Mufti, A.M., & Ajabnoor, M.A. (2000). The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes. *Saudi Medical Journal,* 21(9), 831-837

Barlow-Pugh, M. et al. (2000) Stedman's Medical Dictionary 27th Ed. Baltimore MA.; Lippincott Williams and Wilkins

Cerulli, J., Grabe, D.W., Gauthier, I., Malone, M., & McGoldrick, M.D. (1998). Chromium picolinate toxicity. *Annals of Pharmacotherapy,* 32, 428-31

Diekhoff, G. (1992). Statistics for The Social and Behavioural Sciences: Univariate, Bivariate and Multivariate. U.S.A.; Wm. C. Brown Publishers

The Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine,* 329, 977-986

Evans, G.W. (1989). The effect of chromium picolinate on insulin controlled parameters in humans. *Int J Biosocial Med Res,* 11, 163-180

Evans, G.W. & Meyer, L. (1992). Chromium picolinate increases longevity. *Age,* 15, 134

Food and Nutrition Board (1989). Recommended Dietary Allowances 10th Ed. Washington, D.C.; National Academy Press

Glinsmann, W.H. & Mertz, W. (1966). Effect of trivalent chromium on glucose tolerance. *Metabolism,* 15(6), 510-520

Goldstein, D.E., Little, R.R., Wiedmeyer, H.M., England, J.D., Rohlfing, C.L., Wilke, A.L. (1994). Is glycohemoglobin testing useful in diabetes mellitus? Lessons from the diabetes control and complications trial. *Clinical Chemistry,* 40, 1637-1640

Hellerstein, M.K. (1998). Is chromium supplementation effective in managing type II diabetes? *Nutrition Reviews,* 56(10), 302-306

Hepburn, D.D. & Vincent, J.B. (2002). In vivo distribution of chromium from chromium picolinate in rats and implications for the safety of the dietary supplement. *Chemical Research in Toxicology,* 15(2), 93-100

Hermann J., Arquitt, A., & Stoecker, B. (1994). Effect of chromium supplementation on plasma lipids, apolipoproteins and glucose in elderly subjects. *Nutrition Research,* 14, 671-674

Hills, M. & Armitage, P. (1979). The two-period crossover clinical trial. *British Journal of Clinical Pharmacology,* 8, 7-20

Hom, F.G., Ettinger, B. & Lin, M.J. (1998). Comparison of serum fructosamine vs. glycohemoglobin as measures of glycemic control in a large diabetic population. *Acta Diabetologica,* 35, 48-51

Jeejeebhoy, K.N., Chu, R.C., Marliss, E.B. & Greenberg, G.R. (1977) Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation in a patient receiving long-term parental nutrition. *American Journal of Clinical Nutrition,* 30, 531-538

Jeejeebhoy, K.N. (1999). The role of chromium in nutrition and therapeutics and as a potential toxin. *Nutrition Reviews,* 57(11), 329-35

Katz, S.A. & Salem, H. (1993). The toxicology of chromium with respect to its chemical speciation: a review. *Journal of Applied Toxicology,* 13, 217-24

Kilpatrick, E.S. (1997). Problems in the assessment of glycemic control in diabetes mellitus. *Diabetic Medicine,* 14, 819-831

Koch D. (1990). Fructosamine: how useful is it? *Laboratory Medicine,* 21, 497-503

Kraemer, H.C. et at. (1987). How Many Subjects?: Statistical Power Analysis in Research. U.S.A.: Sage Publications, Inc.

Lukaski, H.C. (1999). Chromium as a supplement. *Annual Review of Nutrition,* 19, 279-302

Mahan, L.K. & Escott-Stump, S. (2000). Krause's Food, Nutrition and Diet Therapy 10th Ed. Philadelphia PA; W.B. Saunders Company

Martin, W.R & Fuller, R.E. (1998). Suspected chromium picolinate induced rhabdomyolysis. *Pharmacotherapy,* 18, 860-862

Martinez, O.B., MacDonald, A.C., Gibson, R.S., & Bourn, D. (1985). Dietary chromium and effect of chromium supplementation on glucose tolerance of elderly Canadian women. *Nutrition Research,* 5, 609-620

Meltzer S et al. (1998). 1998 clinical practice guidelines for the management of diabetes in Canada. *Canadian Medical Association Journal,* 159(8 Suppl), S1-S29

Mertz, W. (1993). Chromium in human nutrition: a review. *Journal of Nutrition,* 123(4), 626-633

Mirasol, F. (2000). Chromium picolinate market sees robust growth and high demand *Chem Market Rep,* Feb. 14, 2000, 257

Morris, B.W., MacNeil, S., Hardisty, C.A., Heller, S., Burgin, C., & Gray, T.A. (1999). Chromium homeostasis in patients with type II diabetes. *Journal of Trace Elements in Medicine and Biology,* 13, 57-61

Mossop, R.T. (1983). Effects of chromium III on fasting blood glucose, cholesterol and cholesterol HDL levels in diabetics. *The Central African Journal of Medicine,* 29(4), 80-82

National Academic Press (2002). Dietary reference intakes. June 6, 2002, http://book.nap.edu/books

Offenbacher, E.G. & Pi-Sunyer, F.X. (1980). Beneficial effect of chromium rich yeast on glucose tolerance and blood lipids in elderly subjects. *Diabetes,* 29, 919-924

Rabinovitz, H., Leibovitz, A., Madar, Z, Gabai, G., & Habot, B. (2000). Blood glucose and lipid levels following chromium supplementation in diabetic elderly patients on a rehabilitation program. *Gerontologist,* 40, Spec Issue 1: 8

Rabinovitz, M.B., Gonick, H.C., Levin, S.R., & Davidson, M.B. (1983). Effects of chromium and yeast supplements on carbohydrate and lipid metabolism in diabetic men. *Diabetes Care,* 6(4), 319-327

Ravina, A., Slezak, L., Mirsky, N., Bryden, N.A. & Anderson, R.A. (1999). Reversal of corticosteroid induced diabetes mellitus with supplemental chromium. *Diabetic Medicine,* 16, 164-7

Riales, R & Albrink, M.J. (1981). Effect of chromium chloride supplementation on glucose tolerance and serum lipids, including HDL, of adult men. *The American Journal of Clinical Nutrition,* 34, 2670-2678

Rubin R.J., Altman, W.M. & Mendelson, D.N. (1992). Health care expenditures for people with diabetes. *Journal of Clinical Endocrinology and Metabolism,* 78, 809A-F

Schwartz, K. and Mertz, W. (1959). Chromium (III) and glucose tolerance factor. *Archives of Biochemistry and Biophysics,* 85, 292-295

Sherman, L., Glennon, J.A., Brech, W.J., Klomberg, G.H. & Gordon, E.S. (1968). Failure of trivalent chromium to improve hyperglycemia in diabetes mellitus. *Metabolism,* 17(5), 439-442

Speetjens, J.K., Collins, R.A., Vincent, J.B. & Woski, S.A. (1999). The nutritional supplement chromium (III) tris(picolinate) cleaves DNA. *Chemical Research in Toxicology,* 12, 483-87

Stearns, D.M., Wise, J.P., Patierno, S.R., & Wetterhahn, K.E. (1995). Chromium (III) picolinate produces chromosome damage in Chinese hamster ovary cells. *FASEB (Federation of American Societies for Experimental Biology) Journal,* 9, 1643-1648

Tahara, Y. & Shima, K. (1995). Kinetics of HbA1c, glycated albumin and fructosamine and analysis of their weight functions against preceding plasma glucose level. *Diabetes Care,* 18(4), 440-447

Tan H. & MacLean D.R. (1995) Epidemiology of diabetes mellitus in Canada. *Clinical and Investigative Medicine*, 18, 240-6

Trow, L.G., Lewis, J., Greenwood, R.H., Sampson, M.J., Self, K.A., Crews, H.M., et al. (2000). Lack of effect of dietary chromium supplementation on glucose tolerance, plasma insulin and lipoprotein levels in patients with type 2 diabetes. *International Journal for Vitamin and Nutrition Research,* 70(1), 14-18

United Kingdom Prospective Diabetes Study Group (1998). Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet,* 352, 837-853

Urberg, M. & Zemel, M.B. (1987). Evidence for synergism between chromium and nicotinic acid in the control of glucose tolerance in elderly humans. *Metabolism* 1987, 36(9), 896-899

Uusitupa, M.I.J., Kumpulainen, J.T., Voutilainen, E., Hersio, K., Sarlund, H., Pyorala, K.P., et al. (1983). Effect of inorganic chromium supplementation on glucose tolerance, insulin response and serum lipids in noninsulin-dependent diabetics. *The American Journal of Clinical Nutrition,* 38, 404-410

Uusitupa, M.I.J., Mykkanen, L., Siitonen, O., Laakso, M., Sarlund, H., Kolehmainen, P., et al. (1992). Chromium supplementation in impaired glucose tolerance of elderly: Effects on blood glucose, plasma insulin, c-peptide and lipid levels. *British Journal of Nutrition,* 68, 209-216

Vincent, J.B. (1999). Mechanims of chromium action: low molecular weight chromium-binding substance. *Journal of the American College of Nutrition,* 18(1), 6-12

Vincent, J.B. (2000a). The biochemistry of chromium. *Journal of Nutrition,* 130, 715-718

Vincent, J.B. (2000b). Quest for the molecular mechanism of chromium action and its relationship to diabetes. *Nutrition Reviews,* 58(3 part 1), 67-72

Vincent, J.B. (2003). The potential value and toxicity of chromium picolinate as a nutritional supplement, weight loss agent and muscle development agent. *Sports Medicine*, 33(3), 213-230

Wang, M.M., Fox, E.A., Stoecker, B.J., Menendez, C.E. & Chan, S.B. (1989). Serum cholesterol of adults supplemented with brewer's yeast or chromium chloride. *Nutrition Research*, 9, 989-998

Wasser, W.G, McCarty, M.F., Hathcock, J.N., Michenfelder, H.J., & Mennen B. (1997). Over-the-counter chromium and renal failure (letters). *Annals of Internal Medicine*, 127, 654-656

Appendix A:
Characteristics of Studies Reviewed

Table 6: Studies Using at Least Some Subjects with Some Measure of Impaired Glucose Tolerance

Studies Showing Positive Effects on Subjects with Impaired Glucose Tolerance							
Reference	Subjects	Cr Supplement & Daily Dose	Design	Dependent Variables	Results	Comments	Score
Glinsmann and Mertz, 1966	10 healthy and 14 diabetic subjects (men); 23-54 yrs	150-1000 µg CrCl	15-120 d. treatment period; subjects were all subjected to a control period followed by the treatment period	Blood glucose post load	Longer supplement periods showed improvement in 3 of 6 diabetics. Short term supplement had no effect	Inconsistent dosage and length of treatment; Not double-blind; Wash-out period needed?	9
Offenbacher and Pi-Sunyer, 1980	16 healthy and 8 mildly diabetic subjects, mean age 78	Cr rich brewer's yeast (~10.8 µg per dose) or Cr poor torula yeast (~ no Cr)	Single-blind, 8 wks, both test and control groups had 8 healthy and 4 diabetic individuals	Blood glucose post load, insulin	Glucose tolerance improved significantly, insulin output ↓	Genders? Placebo and Cr groups had equal numbers of diabetics	15
Anderson et al., 1983	76 normal, free-living (48 men and 28 women), 21-69 yrs	200 µg CrCl or placebo	Double blind, crossover, 3 mos.	Blood glucose 90 min post test, fasting blood glucose	No significant effects on fasting blood glucose when all subjects combined; blood glucose control ↑ in individuals with the least amount of glucose tolerance	Wash out period? Why and when were groups established based on baseline GTT?	19
Mossop, 1983	26 diabetics in Zimbabwe	600 µg CrCl or placebo	Groups randomly assigned, 3 mos.	Fasting blood glucose	Improvement with Cr supplements	No mention of statistical analysis; Zimbabwe applicable to North America? No mention if subjects were blinded; Ages? Genders?	11.5
Martinez et al., 1985	85 free-living Canadian women; yrs 59-82	200 µg CrCl or placebo	Double blind, 10 wks	Glucose tolerance, serum insulin	Non-medicated subjects at ↑ risk for glucose intolerance had significant ↓ in blood glucose 2 hrs post-load; No effects in other subjects	Why and when were groups established based on risk for glucose intolerance? Duplicate diets collected	17.5
Anderson et al., 1987	8 women with symptoms of hypoglycaemia; yrs 33-69	200 µg CrCl or placebo	Double-blind, cross-over, two 3 mo. periods	Over 40 parameters i.e. hypoglycaemic symptoms, hypoglycaemic glucose values, insulin receptor number	All glucose related parameters improved	Blood sugar not used to define hypoglycaemia; No washout	17
Evans, 1989	6 men and 5 women with type 2 diabetes; 40-70 yrs	200 µg chromium picolinate or placebo	Double-blind, cross-over (two 42 d. periods, 14 d. washout); subjects divided randomly into 2 groups	Fasting blood glucose, HbA1c	Significant ↓ with supplementation	2 wk wash-out not long enough as there were residual effects	15.5

Table 6 continued

Anderson et al., 1991	17 healthy subjects (11 women and 6 men); 22-65 yrs	200 µg CrCl or placebo	Double-blind, cross-over, 2 groups: 1) Those subjects with blood glucose from 5.56 – 11.1 mmol/L post load 2) all remaining subjects as controls; 14 wk test period	Glucose tolerance, circulating insulin, glucagons	Values improved with supplementation in group 1, unchanged in group 2	Subjects put on low Cr diets; Number of subjects per group? Washout period?	18.5
Anderson et al., 1997	180 type 2 diabetics in Beijing (men and women); 35-65 yrs	1) 100 µg chromium picolinate twice/day 2) 500 µg Cr twice/day 3) placebo	Double-blind; Groups assigned randomly (n=60)	HbA1c Fasting glucose Two-hour glucose Fasting and 2-hour insulin	Improved significantly after 2 mos. in 1000 µg group and was ↓ in both Cr groups after 4 mos. vs. placebo ↓ in 1000 µg group after 2 and 4 mos. vs. placebo ↓ for 1000 µg group after 2 and 4 mos. vs. placebo Significant ↓ in both Cr groups after 2 and 4 mos. vs. placebo	Beijing applicable to North America?	21.5
Ravina et al., 1999	3 patients with steroid induced diabetes (2 women, 1 man); 62, 54 44 yrs	600 µg chromium picolinate	Pilot study (case reports)	Fasting blood glucose, hypoglycaemic drug use	Diabetes control improved	No control group; No statistical analysis; Small subject number	3
Bahijiri et al., 2000	78 type 2 diabetics (48 women, 30 men); 36-68 yrs	Brewer's yeast (23.3 µg of Cr/ day) or 200 µg CrCl	Random division into 2 groups and given supplements sequentially with placebo in between in a double-blind, cross-over design of 4 stages, each lasting 8 wks	Fasting blood glucose and blood glucose 2 hour post glucose load	Significant ↓ with both supplements	Higher % of subjects responded positively to Brewer's yeast; No washout; Cr supplement ↑ urinary Cr	19
Rabinovitz H et al., 2000	39 diabetic elderly patients within an active rehabilitation program (18 men, 21 women); mean age 73	200 µg of chromium picolinate twice/day	Measures taken pre and post – treatment; 3 wk test period	Fasting blood glucose, HbA1c	Fasting blood glucose significantly ↓; HbA1c also ↓	No control group; Patients fed low sugar diet throughout study	8

Table 6 continued

Studies Showing No Effect on Subjects with Impaired Glucose Tolerance							
Sherman et al., 1968	10 diabetic and 4 healthy men; 28-47 yrs	50 µg trivalent Cr and placebo thrice daily	Double blind, cross-over, 16 wk periods	Fasting and 2 hr post-prandial blood glucose	No improvement	No wash-out period	17
Rabinovitz MB et al., 1983	31 outpatient diabetic men	1) 150µg CrCl 2) brewer's yeast with GTF 3) brewer's yeast without GTF 4) placebo	Clinical double-blind, random cross-over trial with each man getting 3 of the 4 supplements for 4 mos. each	Fasting plasma glucose, blood glucose post-test and lipids	Not significantly altered by Cr supplements	Washout period = 2 mos.; Ages of those completing study? Supplement ↑ Cr content of hair and RBC's	21.5
Uusitupa et al., 1983	10 diabetics (6 men and 4 women) in Finland; yrs 37-68	200 µg CrCl or placebo	Double-blind, cross-over, 6 wk periods	Fasting blood glucose, blood glucose and serum insulin 2-hr post-load, HbA1c	No significant changes	Finland applicable to North America? No wash-out period	16.5
Abraham et al., 1992	76 patients with atherosclerotic disease (63 men, 13 women, 25 diabetics); 42-83 yrs	250 µg CrCl or placebo	Random assignment to either group; Mean of 11.1 mo. test period (range 7-16 mos.)	Fasting blood glucose	No significant change	Equal number of diabetics in both groups; Serum Cr and HDL did ↑	14.5
Uusitupa et al., 1992	24 elderly subjects with impaired glucose tolerance (12 men, 12 women); 65-74 yrs	Cr-rich yeast (160 µg/day) or placebo	Double-blind, groups randomly assigned; 6 mos.	GTT, HbA1c, plasma insulin, C-peptide	No differences in Cr group and placebo group	24 hr urinary Cr ↑ in Cr group than placebo group	18
Trow et al., 2000	12 free-living adults with type 2 diabetes (7 men, 5 women) 45-67 yrs	100 µg from Cr rich yeast	Pilot study, subjects underwent GTT at baseline, 4 wks, 12 wks (8 wk supplement period between wks 4 and 12)	Fasting blood glucose, insulin	No significant differences pre and post supplement	Uncontrolled	8.5

yrs = age in years; mos. = months; wks = weeks; d = day; hr = hour; Cr = chromium; CrCl = chromium chloride; GTT = glucose tolerance test

Table 7: Studies Using Healthy Subjects with Normal Blood Glucose Control

Reference	Subjects	Cr Supplement & Daily Dose	Design	Dependent Variables	Results	Comments	Score
Riales and Albrink, 1981	23 men; 31-60 yrs	200 µg trivalent Cr or placebo daily 5 days each week	Double blind; 12 wks	Fasting glucose, glucose tolerance (blood glucose and insulin)	Only significant result was ↓ fasting blood sugar in Cr group after 6 wks	Concluded that Cr ↑ insulin sensitivity in those with evidence of insulin resistance but results not significant	16
Urberg and Zemel, 1987	16 elderly subjects; > 65 yrs	200 µg CrCl, 100 mg nicotinic acid, and both supplements together	Random assignment to one of three groups: 1) Cr supplement 2) nicotinic acid supplement 3) both supplements; 28 day test periods	Fasting glucose, glucose tolerance after test Fasting and 1-hr insulin, HbA1c	Unaffected by either supplement alone, improved by both supplements together No effect of any treatment	Numbers of subjects in each group? Genders? Control group?	13
Wang et al., 1989	30 healthy subjects with ↑ cholesterol (18 men,12 women); 31-66 yrs	50 µg CrCl or 15 µg Cr in brewer's yeast five d per wk	3 groups (n=10 in each): 1) CrCl 2) brewer's yeast 3) placebo; 12 wks	Fasting serum glucose, insulin	No significant change in any group	Subjects had normal glucose levels initially; Cholesterol levels ↓ in Cr groups	17.5
Hermann et al., 1994	42 subjects (34 women, 8 men); 60-87 yrs	150 µg CrCl in lactose daily or lactose placebo	Groups randomly assigned; 12 wks	Fasting glucose	No significant effect	Improvement seen in lipid profiles of subjects with ↑ baseline levels	19

yrs = age in years; mos. = months; wks = weeks; d = day; hr = hour; Cr = chromium; CrCl = chromium chloride; GTT = glucose tolerance test

Appendix B:
Article from The Chronicle Journal

SANDI KRASOWSKI/THE CHRONICLE-JOURNAL

Lakehead University student Denis Collier is working on a study into chromium supplements.

Chromium seen as key to curbing type II diabetes

BY KRIS KETONEN
THE CHRONICLE-JOURNAL

A Lakehead University student is embarking on a research project that could have positive effects for most diabetes sufferers.

Kinesiology master's student Denis Collier is studying the effects of chromium supplements on type II diabetes, citing previous studies that hint the mineral helps the body's ability to make use of the insulin it produces.

"It's not all of them (the studies), so this is why more research is needed," Collier said yesterday at Lakehead University.

Type II diabetes sufferers, he said, produce insulin — a hormone that helps blood sugar control — but their bodies can't use it. In type I diabetes, the body doesn't produce insulin.

Both are serious health risks and can cause problems like heart disease or eye problems, Collier said.

Type II diabetes is far more common, said Collier, who's also a registered dietitian. The Canadian Diabetes Association says 6,000 people in Thunder Bay suffer from diabetes, and about 90 per cent are type II. About 1.5 million people in Canada have a form of diabetes.

If Collier's research proves chromium helps, it will have positive effects on those with type II, he said.

"If we can find a way to help them control their blood sugar, obviously big implications for the health of these people," he said.

Collier said it's believed chromium helps by attaching to insulin receptors in the body's cells, and putting out a "stronger signal to get insulin to attach."

The second positive effect would be financial.

"If we can keep them healthy for a longer period of time, it cuts down on the cost of health care," Collier said, adding over-the-counter chromium supplements are far cheaper than the drugs and insulin diabetes patients currently need.

Collier is looking for volunteers with type II diabetes to help with the study. It will be placebo-controlled: half the participants will take chromium supplement pills; the others will take a placebo.

The first stage will last two months, followed by a two-month break.

Then the groups will switch, taking the opposite pill, for another two months.

Results will likely be known by summer, he said.

For more information or to volunteer, e-mail djcollie@mail.lakeheadu.ca or call 807-766-5775.

Appendix C:
Cover Letter

Dear Potential Participant,

My name is Denis Collier. I am a candidate for a Master's of Science degree from Lakehead University, and a registered dietitian. I am the primary researcher in a study entitled "The Effect of Chromium Supplementation on Blood Glucose Control in Individuals with Type 2 Diabetes". Your participation in this study would be greatly appreciated.

There have been several reports in the scientific literature of chromium's ability to improve blood glucose control. This finding would be particularly important to individuals with diabetes. However, not all studies have found this result. For this reason, more research is needed to determine if taking chromium supplements can truly improve your blood glucose control.

Should you decide to participate, you will report for a routine blood sample sometime in early November. This would be to determine your level of haemoglobin A1c (HbA1c) before the study starts. Immediately after this test you will begin taking a daily pill which will be either 400 μg of GTF chromium or a placebo (neither of us will know which it really is). This will continue until early January at which time your HbA1c level will be tested again. The following two months will serve as a "washout" period – essentially for these two months you will have a break from this study. The exact same process used in the November-January test period will be repeated from early March to early May, with the only difference being that this time you will receive the opposite pill. Should you desire, the results of the study can be made available to you after it is completed.

By participating in this study, benefits may come to you personally and to other individuals with diabetes. You may find that chromium improves your blood glucose control. As well, the results of this study may ultimately go on to help many other people with the disease.

Participation in this study is unlikely to have any negative side effects. Toxic effects from chromium are exceptionally rare; only two cases have ever been reported and even these cases are considered to be questionable. Also, in these cases, a different form of chromium than the one that will be used in this study was ingested. Chromium has an established safety factor that is much higher than many other similar minerals. No controlled study using an orally administered chromium supplement has documented negative side effects of any kind in the last 30 years.

Participation in the study is totally voluntary and you may withdraw at any time. Any information obtained about you will be kept confidential. A code number will be used instead of your name to record and analyze the data which you supply. The data records will be stored under lock at Lakehead University for a period of seven years.

Again, I hope you give strong consideration to participating in this worthwhile study.

Sincerely,

Denis Collier, RD, M.Sc. candidate

Ian Newhouse, Ph.D.

Appendix D:
Participant Consent Form

I, _____ have read and understood the cover letter of the study entitled "The Effect of Chromium Supplementation on Blood Glucose Control in Individuals with Type 2 Diabetes". Please consider this letter my formal consent to participate in the study.

I am aware that being involved in this study means participating in the following:
1) Taking a pill every day from early November to early January; and then again from early March to early May. In one of these two-month periods the pill will be a 400 μg GTF chromium supplement, the other time it will be a placebo; but I will not know which pill I am taking during either period.
2) Reporting for a routine blood sample four times (those times being early November, early January, early March and early May). The purpose of these blood tests will be to determine my level of HbA1c.

I have been assured that the chances of developing any negative side effects from taking GTF chromium are very small. No controlled study using an orally administered chromium supplement has documented any negative side effects in the last 30 years.

I am aware that I may withdraw from this study at anytime.

Should I desire, I have been informed that I may have access to the results of the study once it is completed.

I have been informed that any information obtained about me will be kept confidential. A code number instead of my actual name will be used to record and analyze the data which I will provide.

I realize that by participating in this study, my own blood glucose control may improve. Also, the findings of this study may go on to help other people with diabetes.

If at any time during this study I should find that questions arise, Denis Collier, the primary researcher has urged me not to hesitate to contact him using the contact information provided.

Signature of Participant: _____ Date: _____

Witness: _____ Date: _____

Primary Researcher: _____ Date: _____

Research Advisor: _____ Date: _____