The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes

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ABSTRACT

Objective: To study the effects of supplementation with organic and inorganic chromium on glucose tolerance, serum lipids, and drug dosage in type 2 diabetes patients, in the hope of finding a better and more economical method of control.

Method: Seventy eight type 2 diabetes patients were divided randomly into two groups and given Brewer's yeast (23.3ug Cr/day), and $CrCl_3$ (200ug Cr/day) sequentially with placebo in between, in a double blind cross-over design of four stages, each lasting 8 weeks. At the beginning and end of each stage, subjects were weighed, their dietary data and drug dosage recorded, and blood and urine samples were collected for analysis of glucose (fasting and 2 hour post 75g glucose load) fructosamine, triglycerides, total and HDL-cholesterol, and serum and urinary chromium.

Results: Both supplements caused a significant decrease in the means of glucose (fasting and 2 hour post glucose load), fructosamine and triglycerides. The means of HDL-cholesterol, and serum and urinary chromium were all increased. The mean drug dosage decreased slightly (and significantly in case of Glibenclamide) after both supplements and some patients no longer required insulin. No change was noted in dietary intakes or Body Mass Index. A higher percentage of subjects responded positively to Brewer's yeast chromium, which was retained more by the body, with effects on fructosamine, triglycerides, and HDL-cholesterol maintained in some subjects when placebo followed it, and mean urinary chromium remaining significantly higher than zero time mean.

Conclusion: Chromium supplementation gives better control of glucose and lipid variables while decreasing drug dosage in type 2 diabetes patients. A larger scale study is needed to help decide on the convenient chemical form, and dosage required to achieve optimal response.

Keywords: Chromium supplement, type 2 diabetes, glucose control, serum lipids, drug dosage.

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The role of trivalent chromium (Cr^{3+}) in improving glucose tolerance has been reported since the sixties.[1,2] This was confirmed later by supplementation studies in different countries,[3-6] followed by reports of beneficial effects of chromium supplements in reducing serum triglycerides level,[7] decreasing total and LDL-cholesterol,[8,9] and increasing HDL-cholesterol level.[10] Safe and recommended intake for Cr^{3+} was estimated at 50 - 200 mg/day for adults.[11,12] It has been suggested that marginal chromium deficiency may contribute to the progressive impairment of glucose tolerance with age, thus increasing the risk for diabetes, and possible coronary heart disease.[13] Response to

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Table 1 - Effect of different types of supplement on glucose and fructosamine levels (mean ± SD).

Groups	No of subjects	Fasting	(mg/dl) 2h + glu*	Fructosamine (mmol/L)
A+B at zero time	78	193.4±73.1	256.3±85.9	3.89±1.55
B after placebo in stage 1	37	187.4±72.4 p**=0.65	249.7± 83.5 p=0.6	3.95±1.62 p=0.61
A+B after Brewer's yeast in stages 1 & 2	74	153.3±64.1 p=5.4x10-4	222.7±77.7 p=9.2x10-4	3.0±1.27 p=5.2x10-3
A+B after placebo in stages 2 & 3	69	185.8±66.4 p=0.35	235.0±76.1 p=0.3	3.42±1.76 p=0.28
A+B after CrCl3 in stages 3 & 4	67	166.0±61.7 p=8.1x10-3	223.3±76.8 p=7.3x10-3	3.22±1.47 p=0.031
An after placebo in stage 4	31	186.2±75.9 p=.49	261.2±79.9 p=.38	3.78±1.67 p=0.42

*=2 hours after a 75g glucose load
P**= comparing values to zero time values

Table 2 - Serum lipids, serum and urinary chromium before and after different types of supplements (mean+SD).

Groups	Total cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	Triglycerides (mmol/L)	Chromium (ug/L)	
				Serum	Urine
A+B at zero time (n*=78)	5.16±1.37	0.99±0.28	1.97±1.11	0.104±0.032	0.378±0.093
B after placebo in stage 1 (n=37)	5.21±1.32 P**=0.85	0.97±0.29 P=0.93	1.89±1.07 P=0.63	0.097±0.034 P=0.87	0.364±0.097 P=0.75
A+B after Brewer's Yeast in stage 1 & 2 (n=74)	4.82±0.99 P=0.065	1.22±0.21 $P=5.2x10^{-3}$	1.5±0.68 $P=8.6x10^{-3}$	0.273±0.070 $P=5.4x10^{-4}$	0.709±0.242 $P=5.2x10^{-4}$
A+B after placebo in stage 3 & 4 (n=69)	4.92±0.83 P=0.34	1.0±0.27 P=0.75	1.94±0.63 P=0.48	0.154±0.056 $P=2.3x10^{-3}$	0.468±0.206 $P=8.6x10^{-3}$
A+B after CrCl3 in stages 3 & 4 (n=67)	4.99±1.29 P=0.31	1.19±0.25 $P=6.7x10^{-3}$	1.54±0.98 $P=9.2x10^{-3}$	0.281±0.080 $P=5.1x10^{-4}$	1.085±0.35 $P=3.9x10^{-4}$
A after placebo in stage 4 (n = 31)	5.26±1.26 P=0.69	0.95±0.21 P=0.51	1.98±1.12 P=0.65	0.146±0.039 $P=3.1x10^{-3}$	0.384±0.087 P=0.52

(n*=number of subjects)
P**= comparing values to zero time values

supplement is the only available indication of chromium status at present. As a result of two supplementation trials low chromium status was found to exist amongst some healthy residents of the Western region of Saudi Arabia,[14] and some patients with coronary artery disease.[15] Improved glucose control and lipid profile was noted in both trials, but the response was stronger when chromium was given in the organic form as Brewer's yeast than when inorganic Cr^{3+} was given in the second trial.[15] A decrease in drug dosage was also noted. Therefore, it was decided in this study to investigate the effect of the two types of chromium supplements on glucose tolerance, lipid profile and drug dosage in patients with type 2 diabetes, to see whether this inexpensive, safe supplement can help to decrease the economical burden of this disease, without sacrifying the control offered by the more conventional hypoglycemic drugs. Unlike previous studies on the effects of chromium supplementation on NIDDM patients, both types of chromium were given sequentially to all patients, with Cr-poor Torula yeast in between, taking into account dietary intakes and changes in weight during the study. Fasting serum and urinary chromium were also measured to monitor the absorption of the two types of Cr supplements.

Methods. Seventy-eight NIDDM patients (48 females and 30 males) ranging in age from 36 - 68 years old were recruited into the study from the out-patients clinics at King Abdulaziz University Hospital. All subjects gave informed consent, and the General Research Committee at King Abdulaziz University granted ethical approval. Subjects were either of Saudi origin or Arabs with at least 10 years residence in the country. Potential subjects were excluded if they had a history of pituitary, thyroid, kidney or liver disease, digestive problems, chronic infections, pancreatitis, hemochromatosis, were taking mineral or vitamin supplements or chronically ingested yeast. All subjects agreed to maintain their usual eating habits and health-related behaviors through out the study.

Experimental design. Selected subjects were medically examined, given code numbers and asked to present themselves on a specified date for sample collection. They were all requested to void their morning urine and to drink an 8 oz. glass of water before coming for testing. On arrival, total urine void samples were collected in Falcon polypropylene specimen containers from all subjects, and samples were treated as described earlier[16] before freezing at -20°C. Weights and heights were measured to

Table 3 - Types and dosage of various medications and number of subjects taking them at various stages of the study.

Groups	Glibenclamide (mg)	Metformin (mg)	Glipizide (mg)	Gliclazide (mg)	Insulin (IU)
A+B at zero time	2.5-10* 8.73±2.64** 50+	500 500±zero 33	5-10 7.81±1.83 22	40-120 80±20 4	32-74 57.7±16.1 6
B after placebo in stage 1	2.5-10 8.42±2.73 25 P++=0.72	500 500±zero 16	5-10 8.03±1.61 11 P=0.88	40-120 - 2	32-74 55.3±21.4 3 P=0.8
A+B after Brewer's yeast in stages 1 & 2	2.5-10 6.13±2.16 38 P=4x10-5	500-850 521±84.8 33 P=0.55	5-10 6.9±1.52 22	40-80 60±10 4 P=0.068	35-60 45±12.2 4 P=0.058
A+B after placebo in stages 2 & 3	2.5-10 7.96±2.91 42 P=0.31	500-850 521±84.8 33 P=0.55	5-10 7.45±1.73 22 P=0.34	40-120 80±20 4	30-65 47.5±12.1 6 P=0.09
A+B after CrCl3 in stages 3 & 4	2.5-10 6.52±2.23 42 P=8x10-4	500-850 521±84.8 33 P=0.55	5-10 7.2±1.67 22 P=0.19	40-80 60±10 4 P=0.068	37-60 45.4±9.5 5 P=0.067
A after placebo in stage 4	2.5-10 8.59±2.73 18 P=0.45	500 500±zero 17	5-10 7.95±1.17 10 P=0.82	80 - 1	37-70 55.7±16.9 3 P=0.68

*=Range
**=Mean±SD
+=No. of subjects
++=P comparing values to zero values

calculate body mass index (BMI). Blood samples were obtained while fasting and two hours after a 75g glucose load, using all plastic syringes, with minicath siliconized needles to avoid contamination with Cr, and transferred into appropriate tubes for analysis of the various parameters (fluoride oxalate for glucose analysis and plain tubes for others). The sample for Cr analysis was centrifuged immediately, the resulting plasma was allowed to clot and the serum transferred to a plastic tube. Magnesium nitrite was added as a matrix modifier/ashing aid,[17] and the samples were frozen at -20°C to the end of the study for analysis in one patch along with urinary chromium. While waiting, a 24-hour dietary recall and dietary history were obtained from each subject and reviewed by a personal interview. The subjects were divided randomly into two groups (A and B) in preparation for the supplementation study. The study design was double blind and cross-over with each stage lasting 8 weeks. The three types of supplements (Brewer's yeast, Torula yeast or placebo, and Cr chloride) were given consecutively in the form of capsules similar in shape, size and numbers. Neither the subjects nor the treating physicians knew which types were taken at any time, and there were four stages in all (Figure 1). Cr chloride, dose was 200 ug of Cr^{3+}/day, while Brewer's yeast supplement provided a total of 23.2 µg chromium/day, and Torula yeast provided a total of .54 µg/day, both verified by analysis in our lab. Group A subjects were given Brewer's yeast capsules in the first stage, followed by Torula yeast, chromium chloride, and finally Torula yeast in the fourth stage. Group B started with Torula yeast, followed by Brewer's yeast, then Torula yeast again, and finally chromium chloride. Patients were instructed to attend the outpatient clinics as usual and to contact a given number in case of any adverse effects. At the end of each stage, compliance was monitored by counting capsules, and subjects were reweighed, their dietary intakes and history recorded, and urine and blood samples were collected. Medications taken by the patients at various stages were obtained from these medical records at the end of the study.

Plasma glucose and serum triglycerides were estimated on the same day of sample collection. Fully automated methods were used for the analysis on Hitachi system 705, employing ‹gluco-quant› reagent pack for glucose estimations, and triglycerides fully enzymatic "TG" reagent pack for triglycerides estimations. Both are from Boehringer Mannheim. Quality control checks were carried out at the beginning and end of each run. Total cholesterol was estimated using "cholesterol enzymatiques PAP" kit from "Bio Merieux". HDL-cholesterol was determined using kits from "Bio Merieux" also.

Serum fructosamine was determined by nitroblue tetrazolium (NBT) method.[18] Chemicals were purchased from Sigma Chemical Company and measurement was carried out on Beckman spectrophotometer model 42. Serum Cr was measured using Perkin-Elmer 5000 atomic absorption spectrophotometer which was equipped with a tungsten-halogen lamp for enhanced background correction capabilities at 357.9nm Cr line, a graphite furnace (model HGA 500, Perkin-Elmer), and a strip-chart recorder (model 65, Perkin-Elmer). The method was based on work by Kayne et

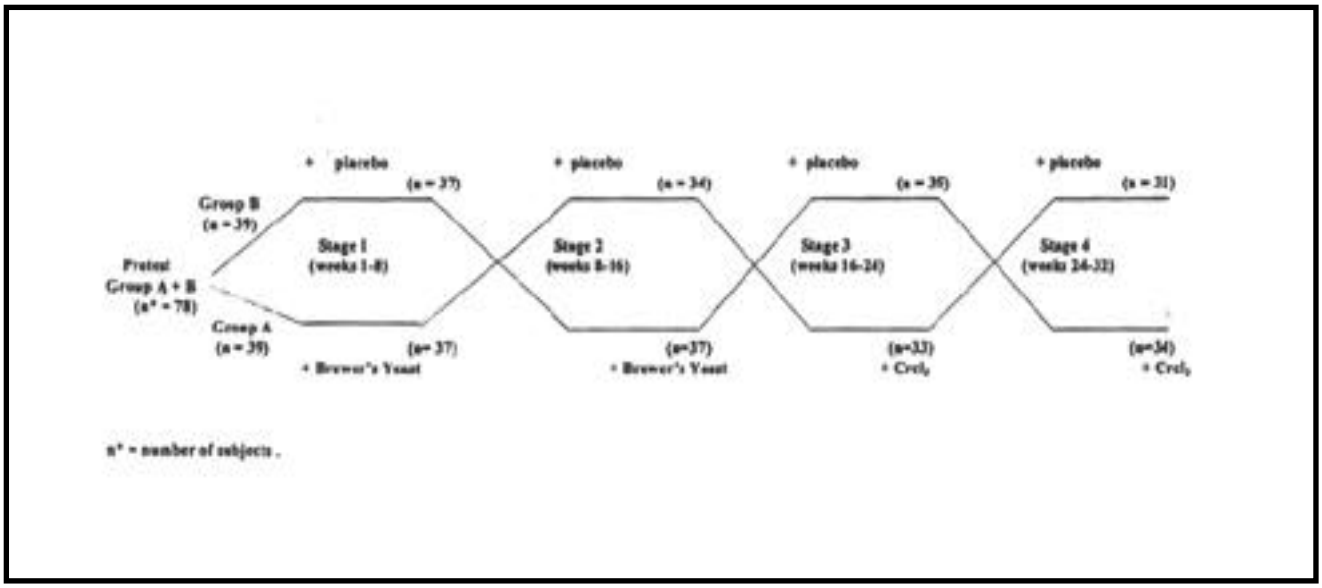

Figure 1 - Experimental design of supplementation study and numbers of subjects remaining after various stages.

al,[17] and Veillon et al[19] with some modification involving furnace programed reported earlier.[16]

Using the collected 24-hour food intake data, total calories consumed per day, carbohydrates, fats, proteins, calcium, iron, vitamins A and C intakes were calculated for each subject using the nutrient values given in various food composition tables,[20-22] as well as dietary information available with some of the packed foods consumed.

Statistical analysis. Results are expressed as mean $\pm$ SD and statistical analysis was by paired student's t-test. Significance was assigned at $P < .05$.

Results. Sixty seven subjects completed the study, with excellent compliance to therapy, and no reports of adverse effects. Others either dropped out or were excluded at various stages due to lack of compliance. The mean $\pm$ SD for BMI at the start of the study was 31.04 $\pm$ 8.41 indicating a high percentage of obesity amongst the selected sample. Dietary intakes of total calories and all calculated nutrients except iron were within or above RDA at the start of the study. Iron was < 77% of RDA in some female subjects. No significant change in BMI or calculated dietary intakes was found at any stage of the study.

The glucose and fructosamine levels at various stages of the study are presented in Table 1. Both types of Cr supplements, but not Torula yeast, caused significant decrease in the mean glucose levels in the fasting state and 2 h after the glucose load ($P = 5.4x10^{-4}$ and $9.2x10^{4}$ in case of Brewer's yeast, and $P = 8.1x10^{-3}$ and $7.3x10^{-3}$ in case of $CrCl_3$). The means after the two types of Cr supplements did not differ from each other significantly (P = 0.3 for fasting, and .42 for post glucose load level). When both supplements were stopped and followed by Torula yeast the fasting and 2 hour post glucose load means increased significantly ($P < .01$ in all cases), and became not significantly different to the zero time mean. Similarly, Brewer's yeast and $CrCl_3$ supplements, but not Torula yeast caused a significant decrease in the mean fructosamine level ($P = 5.2x10^{-3}$ and P = .031). The two means did not differ from each other significantly (P = .067), even though the mean after Brewer's yeast appeared lower. After stopping the two Cr supplements, the mean fructosamine level increased in both cases and became not significantly different to the zero time mean. However, some subjects continued to have lowered fructosamine values by > 15% less than zero time value when placebo followed Brewer's yeast but not when it followed $CrCl_3$ supplement.

The serum lipids before and after various supplements are presented in Table 2. No significant change in the total cholesterol level was found at any stage of the study. Mean HDL - cholesterol increased and mean triglycerides decreased significantly (exact p values are show in Table 2). following the two Cr supplements. The change was reversed and the mean levels became not significantly different to the zero time means in both cases after stopping the Cr supplement and giving Torula yeast instead, even though a few subjects maintained their lowered triglycerides or increased HDL - cholesterol level when placebo followed Brewer's yeast.

Serum and urinary Cr levels before and after supplements are presented in Table 2. Only Brewer's yeast and $CrCl_3$ supplements increased mean serum Cr significantly (exact p value show in Table 2). No significant difference was found between the two means. (P = .085) Stopping the Cr supplement and giving Torula yeast caused a significant decrease in the means ($P < .005$ in both cases), but both means remained significantly higher than the zero time mean ($P = 2.3x10^{-3}$ and $3.1x10^{3}$). Similarly, both types of Cr supplements increased the mean fasting urinary Cr significantly (see Table 2 for exact values). However, the mean following $CrCl_3$ supplement was significantly higher than the mean following Brewer's yeast ($P = 1.8x10^{-3}$). The mean after stopping Brewer's yeast and giving Torula yeast instead, decreased but remained significantly higher than the zero time mean ($P = 8.6x10^{-3}$). However, when Torula yeast followed $CrCl_3$ the mean decreased significantly ($P = 9.1x10^{-4}$) and became not significantly different to the zero time mean (P = .52)

The types and dosage of various medications taken by subjects at various stages of the study are presented in Table 3. No subjects needed increased dosage of medication at any stage of the study except for two subjects taking a combination of insulin and metformin. Those subjects stopped taking insulin shortly after starting the Brewer's yeast supplement and depended on an increased dosage of metformin only. Both of them went back to taking insulin after Brewer's yeast was stopped. When $CrCl_3$ was given, only one of them stopped taking insulin again. The other subjects taking insulin needed a lower dose following both supplements, with two of them limiting the frequency of injection to once instead of twice daily, as was the situation at zero time. Mean drug dose was calculated when the number of subjects were > 3. The means decreased slightly but insignificantly (in all cases except Glibenclamide) after Brewer's yeast and $CrCl_3$ supplements. The mean Glibenclamide dose decreased significantly after both Brewer's yeast (P = 4x10-5), and $CrCl_3$ ($P = 8x10^{-4}$). After stopping the Cr supplements, the means increased again in both cases and became not significantly different to the zero time mean.

Looking at individual cases, it was noted that not all patients showed similar response to the two types of Cr supplements. Some (9 subjects) showed a

definite positive response after both types of supplements (> 30 mg/dl decrease in fasting and 2 h post glucose load glucose level, and > 0.8 mmol/L decrease in fructosamine level). All of these subjects were obese (2nd and 3rd grade). Four more subjects showed this response after Brewer's yeast supplement only and maintained the improvement while taking placebo in the following stage. Twenty one subjects showed a less obvious response to both types of supplement (a decrease of 6 - 25 mg/dl in fasting and 2 h post glucose load glucose level or both, and a slight decrease in fructosamine level of < 0.5 mmol/L). Those subjects were all slightly to moderately overweight. Thirty one subjects maintained their zero time glucose level ± 5 mg/dl after both supplements, while an increase of 10 - 15 mg/dl was seen in 9 subjects following Brewer's yeast supplement, and in 6 subjects following $CrCl_3$.

Discussion. The aim of the study was to investigate the effect of two types of Cr supplements on glucose control, serum lipid, and drug dosage in patients with type 2 diabetes, in the hope of reducing the cost of management of this disorder while maintaining or improving its control. The use of double-blind cross over design has helped to minimizing most non-specific variations (assay variations, physiological differences, variations with time), while giving two types of Cr to the same subjects has helped to compare the response to different forms of Cr more accurately by eliminating variations caused by human physiological differences The lack of changes in BMI and dietary intakes throughout the study indicates that noted changes in biochemical parameters are due to the given Cr supplement, especially that placebo had no effect and there was no increase in drug dosage given to any of the subjects.

The noted improvement in glucose control (decreased mean glucose level while fasting and following glucose load, and decreased mean fructosamine level), and in lipid profile (decreased mean triglycerides and increased mean HDL-cholesterol) following both types of Cr supplements suggests that Cr deficiency exists in this group of patients and points to the benefit of supplementing patients with type 2 diabetes in our part of the world with Cr. In addition Cr supplement seems to lower the drug dosage needed by many of the studied subjects, which might help to reduce the management cost of this chronic disease. Of particular interest, the effect Cr had on insulin requirement, leading two subjects (33% of patients taking insulin injections) to replace insulin with an increased dose of metformin, and causing a decrease in the amount of insulin taken in others.

It is reported that Cr functions by potentiating the action of insulin, thus in the presence of adequate amounts of biologically active Cr, lower concentrations of insulin are required.[23] This will explain our findings, which indicate increased efficiency of circulating insulin (endogenous and exogenous). Hyperinsulinemia is a common finding in NIDDM patients due to decreased efficiency of insulin. This could lead to gradual exhaustion of the b-cells, and eventually to decreased secretion of insulin. Therefore, Cr supplementation of subjects suffering from glucose intolerance or patients with type 2 diabetes with high or normal insulin levels, might help to moderate insulin secretion from b-cells by potentiating insulin action, and thus preventing the process leading to exhaustion of these cells. This suggestion is supported by recent reports[24] of decreased fasting and 2h - insulin values following chromium supplementation.

However, the noted difference in response to the two types of supplements, with Brewer's yeast giving a positive response in more subjects; even though it provided a much lower amount of Cr; suggests that the chemical form of given supplemental Cr plays an important role in eliciting the response of studied subjects. The significant increase in urinary and serum Cr following both types of Cr supplements indicate proper absorption from both types, and that the lack of response of some subjects after $CrCl_3$ but not after Brewer's yeast is not due to defective absorption of $CrCl_3$. However, the higher mean urinary Cr after $CrCl_3$, followed by the decrease to zero time value when placebo was given in the following stage; compared with a persistent higher mean when placebo followed Brewer's yeast supplement; suggests that the higher intake of Cr from $CrCl_3$ (200 μg/day) is not equally well utilized or stored as the much lower amount provided by Brewer's yeast (23.2 μg/day). Brewer's yeast is said to contain biologically active Cr or "glucose tolerance factor GTF".[25] Thus, it can be suggested that Cr resulting from absorption of GTF, or the products of its digestion is more readily assimilated by the body, whereas the body pools of inorganic Cr are quickly saturated, and the excess after oral administration is excreted in urine. This will explain the maintained improvement in some subjects when placebo followed Brewer's yeast supplement, but not when it followed $CrCl_3$. Another possibility is that some individuals can not convert ingested inorganic Cr into a biologically active storable form and hence will not respond favorably to $CrCl_3$ supplement.

A larger scale supplement trial using different chemical forms and doses of Cr, and designed to include subjects suffering from glucose intolerance and having normal or increased insulin levels, as well as more patients with type 2 diabetes requiring insulin injections, would help to verify our findings, and choose the chemical form of Cr giving best response and the dose needed to achieve it. An increased dose might well be needed in some subjects as indicated by Anderson et al,[24] who

reported that individuals with type 2 diabetes needed 5 times the upper limit of the Estimated Safe and Adequate Dietary Intake to show significant beneficial effect on glucose variables. Encouraging results will definitely bring new hope to such patients by helping to reduce the requirement for insulin, thus limiting the frequency of injections to once daily, or eliminating the need for injection all together in some, and substituting insulin with the more convenient oral medication. Of equal importance the possibility of preventing the development of diabetes mellitus in glucose intolerant subjects responding favorably to Cr supplements.

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