

THE EFFECT OF BREWERS YEAST CONTAINING GLUCOSE TOLERANCE FACTOR ON THE RESPONSE TO TREATMENT IN TYPE 2 DIABETICS. A SHORT CONTROLLED STUDY

by

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TRIVALENT chromium has been identified as an essential trace element in the maintenance of normal carbohydrate metabolism, both in man and in animals. Its deficiency leads to an impairment of glucose tolerance which is reversed when the diet is supplemented by chromium salts, and more rapidly by foods with a high organic content.¹

The absorption of chromium depends upon the chemical form in which it is present. The active principle 'glucose tolerance factor' (GTF) is present in a variety of foods including liver, meat, cheese and whole grain. GTF fulfils the criteria of an essential micronutrient more closely than simple chromium salts. Its gross composition appears to be a complex with niacin and amino acids. The richest known source is brewers yeast but the synthesis of pure GTF has not yet been completely successful. GTF is rapidly absorbed and biologically active chromium potentiates the action of insulin on the peripheral receptor sites.²

Inorganic chromium salts have been used in the treatment of human diabetics and good results have been reported in some, but not all, instances. More recently administration of GTF in the form of brewers yeast has been tried with some success. The subject still remains in the exploratory stage, with a lack of controlled studies and of a pure active complex for chemical testing. The present hypothesis is that impaired glucose tolerance in good responders may be related to insulin resistance associated with nutritional chromium deficiency.³

In view of the increasing interest in this subject and the apparent importance of geographical location, we felt a short preliminary double blind cross over study with brewers yeast and a placebo might be helpful before setting up a more extensive trial. We limited the sample to Type 2 diabetics who might reasonably be expected to have insulin resistance rather than an absolute deficiency. In addition to standard parameters of diabetic control which have been the subject of previous reports, (fasting blood glucose, the glucose tolerance test and the serum cholesterol and triglyceride levels), we were particularly interested to see if any beneficial effect might occur in the levels of glycosylated haemoglobin (Hb A_{1c}) and high density lipoprotein (HDL).

METHODS

Thirty seven non insulin-dependent diabetics (18 male/19 female) were studied as outpatients. The mean age of the group was 64 ± 1.6 years (mean \pm S.E.M.), duration of diabetes 7.0 ± 1.0 years and the percentage of ideal body weight ranged from 105 to 120 per cent. All the subjects were treated with diet and a sulphonylurea derivative. Treatment was kept constant for three months prior to the trial and throughout the trial itself.

After informed consent had been obtained, patients entered the random-order double blind cross over study. The trial consisted of two successive 7-week treatment periods during which existing treatment was supplemented with either brewers yeast (as a source of GTF) or placebo. Two opaque capsules containing either 200 mg of brewers yeast or a cellulose placebo were taken four times daily before meals. The chromium content of the yeast was 0.8 ug/g so that during active treatment subjects ingested an additional 1.28 ug of organic chromium daily.

Fasting blood was withdrawn from an antecubital vein prior to treatment and at the end of each treatment period. Plasma glucose concentration was measured by a glucose oxidase method on a Techicon Autoanalyser II.⁴ Percentage haemoglobin A_{1c} (Hb A_{1c}) was determined by column chromatography.⁵ Serum cholesterol and triglyceride were estimated using an automated enzymatic system.⁶ HDL concentration was estimated after precipitation of LDL and VLDL with manganese chloride,⁷ and the supernatant measured for cholesterol by the standard technique. In addition, subjects underwent an oral glucose tolerance test 50 g load (OGTT), before the trial and at the end of each treatment period. The area under the curve of the OGTT was calculated by manual counting of squares.

The initial values and the values observed after the placebo and active treatment periods are shown in Table I. The values observed after treatment were compared with the initial values using analysis of variance, which was performed at the Queen's University of Belfast Computing Centre.

TABLE I
Effect of 1.6g brewers yeast (GTF) daily compared with placebo on blood glucose Hb A_{1c} and serum lipids after 7 weeks treatment.

	<i>N</i>	<i>Initial</i>	<i>Placebo</i>	<i>GTF</i>
HbA _{1c} %	37	8.0 (± 0.3)	7.5 ^a (± 0.3)	6.6 ^b (± 0.2)
Fasting blood glucose (mmol/l)	37	9.2 (± 0.5)	9.0 (± 0.7)	9.1 (± 0.7)
Area under GTT	37	29.3 (± 1.4)	29.3 (± 1.4)	29.1 (± 1.3)
Triglyceride (mmol/l)	24	1.4 (± 0.2)	1.6 (± 0.2)	1.5 (± 0.2)
Cholesterol (mmol/l)	26	5.7 (± 0.2)	5.8 (± 0.2)	5.7 (± 0.2)
HDL (mmol/l)	13	1.1 (± 0.1)	1.2 (± 0.1)	1.5 ^c (± 0.1)

Results are given as mean and (± SEM)

^ap < 0.001 placebo v initial

^bp < 0.001 GTF v placebo

^cp < 0.05 GTF v placebo

Statistical significance by analysis of variance

RESULTS

Hb A_{1c} levels reduced from 8.0 ± 0.3 per cent to 7.5 ± 0.3 per cent during placebo treatment ($p < 0.001$). Active treatment with GTF was associated with a fall in Hb A_{1c} to 6.6 ± 0.2 per cent which was significantly greater than that observed after placebo treatment ($p < 0.001$).

All subjects improved in the first treatment period irrespective of whether this was yeast or placebo. This could have been due to improved dietary compliance. In the 15 subjects who had placebo before yeast GTF Hb A_{1c} levels fell from 7.91 ± 0.42 per cent to 7.53 ± 0.30 per cent during placebo treatment, and fell further to 6.28 ± 0.31 per cent during active treatment. In the 22 subjects who received active treatment before placebo Hb A_{1c} levels fell from 8.14 ± 0.46 per cent to 6.91 ± 0.35 per cent during active treatment but rose to 7.56 ± 0.38 per cent during placebo treatment. These results confirm an order-of-treatment effect but suggest that active treatment can reduce Hb A_{1c} levels.

In GTF v placebo comparison, active treatment with GTF was also associated with an increase in HDL levels ($p < 0.05$).

Fasting plasma glucose levels, serum cholesterol, triglyceride levels and the area under the curve of an OGTT were unchanged after placebo and active treatment when compared with initial values.

DISCUSSION

The average daily intake of chromium has been estimated as approximately 60 ug with a range of 5-150 ug, but only 1 per cent of the inorganic form is absorbed as against 10-25 per cent of biologically active organic GTF. The minimal requirements of the latter are estimated 10-30 ug.³ The body pool of chromium depends upon an adequate background level. Where the water supply (the main source of inorganic chromium) shows no detectable levels of chromium, tissue chromium levels are low and carbohydrate tolerance impaired.⁸ The water supply source for Belfast contains 20 ug/1 chromium; the European Economic Community standard is 50 ug/1. It is possible that our subjects were relatively chromium depleted and would therefore be expected to respond favourably to dietary chromium supplementation. Even though poorly absorbed, inorganic chromium has produced beneficial effects after several weeks to months in diabetics where there is reason to consider the body stores were low.^{9, 10, 11, 12} However, a double blind cross over study of inorganic chromium and placebo in younger diabetics (ages 28-47) failed to show improvement in glucose tolerance.¹³

Organic chromium complex in the form of brewers yeast has been shown to improve glucose tolerance,^{14, 15} but these studies included no placebo treatment period for comparison. Large quantities of brewers yeast must be ingested daily to ensure adequate amounts of GTF. Previous studies have used 5-10 g daily.^{14, 15} This creates a problem of patient compliance, which is difficult to check as plasma chromium levels are only slightly increased during chromium supplementation.¹¹ In an attempt to overcome these difficulties a single blind study in elderly subjects, both normal and diabetic, compared the effect of 9 g of brewers yeast against chromium poor torula yeast given in orange juice over an eight week period.¹⁶ Glucose tolerance improved, insulin output decreased and cholesterol fell with brewers yeast; unfortunately difficulties in assay precluded reliable data for chromium studies.

Our own investigation has also been limited by an inability to assess the chromium status with accuracy. As yet chromium is a difficult element to determine reliably^{17, 18} and the spread of mean value reported for chromium in the serum is very large 0.14 to 782 ng Cr ml. We were unable to obtain a brewers yeast with a high chromium content and were advised a torula yeast might be toxic. A double blind trial is limited by patients conforming and a dosage of eight capsules daily was considered as acceptable. Our study with small amounts of organic chromium over a seven week period nevertheless suggested a beneficial effect on two important parameters of diabetic control not previously reported on, namely the HDL and Hb A_{1c} levels. The discrepancy between the fall in Hb A_{1c} values and the lack of change in fasting blood glucose value requires comment. The correlation between these two parameters of glucose control is accepted as approximately $r=0.75$ in Type 2 diabetics.¹⁹ Single fasting blood glucose estimates are subject to fluctuation and depend on patient co-operation in the immediate period before the test, and close supervision in this period as with inpatients might have given a more reliable correlation. The Hb A_{1c} results may therefore have been a better index of glucose control under the outpatient conditions of our trial. The correlation between Hb A_{1c} values and the oral glucose tolerance is accepted as poor and does not negate our findings. The latter estimates the response to an artificial glucose load and the former the average daily blood glucose level over a 4-6 week period.²⁰

In spite of its limitations the present study is confirmatory that organic chromium may be of value in Type 2 diabetes. Hb A_{1c} levels of 12.6 per cent and above may be related to the microvascular complications of diabetes,²¹ and so a reduction in this may improve the individual prognosis. It has also been suggested that chromium deficiency may have a role in insulin resistance and sepsis.²² Chromium is still worthy of attention and research. Many of the present difficulties will be resolved when reliable and reproducible methods of chemical estimation become generally available, and the effects of more concentrated forms of organic chromium or GTF are subjected to clinical trials.

SUMMARY

Fasting blood glucose, the integrated area under a two hour 50 g glucose tolerance test, and Hb A_{1c} were measured in 37 Type 2 (non insulin-dependent) diabetics with maturity onset. Subjects were out-patients on diet and sulphonylurea therapy which remained unchanged. Estimations of serum cholesterol, triglyceride and HDL were completed in a proportion of patients. A double blind cross over study compared a placebo with glucose tolerance factor in the form of brewers yeast supplementation containing 1.28 ug chromium daily over a 7 week trial period. Treatment with brewers yeast (GTF) improved diabetic control as demonstrated by a fall in Hb A_{1c} per cent ($P < 0.001$) and a rise in HDL ($P < 0.05$). The local water supply is low in chromium at 20 ug per litre.

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