The benefits of early intervention in obese diabetic patients with FBCx™ – a new dietary fibre

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Abstract

Backgrounds  Obesity and diabetes have become epidemic in the US. Dietary fibres have been reported to reduce the absorption of dietary fat, prevent weight gain, and reduce blood lipid levels. In the current double-blind study, obese patients with type 2 diabetes were recruited for a 3-month study to examine the health effects of a new dietary fibre, FBCx™.

Methods  Sixty-six participants were recruited and were randomized into FBCx™ or placebo groups. They were instructed to take two 1-g tablets per fat-containing meal and not to change their eating patterns or daily routine. Three-day dietary records and fasting blood samples were collected prior to enrollment in the study and at the end of months 1, 2 and 3.

Results  Dietary records showed that some participants changed their eating patterns; therefore body weight data were adjusted according to energy intake. As a group, in the 30 days leading into the study, all participants experienced an average weight gain of 1.0 ± 0.4 kg, while those in the placebo group continued to gain weight during the study, those in the FBCx™ group maintained their weight. Those in the FBCx™ group required more energy to maintain their body weight while those in the placebo group required less (p < 0.05). Participants with hypertriglyceridemia showed a reduction (−0.48 ± 0.24 mmol/L, −8.2%) in total cholesterol with FBCx™, while those with placebo had an increase (0.24 ± 0.21 mmol/L, 5.2%, p < 0.05). Adiponectin was increased in the FBCx™ but reduced in the placebo group (p < 0.05).

Conclusions  FBCx™ has thus shown promising benefits in weight maintenance, a reduction of blood lipids and an increase in adiponectin levels. It can be easily incorporated into a diabetic management regimen.

Introduction

Obesity, defined by body mass index (BMI) greater than 30 kg/m², has become a worldwide epidemic [1]. It is estimated that in the United States, more than 64.5% of the population is either overweight (BMI >25 kg/m²) or obese [2]. The numerous consequences of obesity include type 2 diabetes, cardiovascular disease, dislipidemia, hypertension, some forms of cancer, osteoarthritis and sleep apnea, to name but a few [3]. Paralleling the epidemic in obesity is an increase in the incidence of type 2 diabetes. In the year
2002, 6.9% of the US population, or more than 18 million Americans, were diagnosed with type 2 diabetes, an increase of 40% relative to the data from 1990 [4]. If this trend is not reversed, it is expected that individuals born in 2000 will have more than a 33% lifetime risk of developing type 2 diabetes [4]. Weight loss has been demonstrated to be effective in alleviating some of the symptoms of diabetes [5].

Obesity is the result of a positive energy balance; a sedentary lifestyle and/or over-consumption of food contribute to this positive energy balance. Theoretically, obesity can be reversed by increasing the levels of physical activity and/or by reducing energy intake. However, the successful rate of weight loss and maintenance of that weight loss is disappointingly low [6]. Currently, there are two pharmaceutical agents that are approved by the FDA for the treatment of obesity: Orlistat and Sibutramine. Clinical trials have shown that these two drugs can induce weight loss of 5–10% of the original weight over a 2-year period when combined with a hypo-caloric diet [7]. It should be noted that typically clinical trials of pharmacotherapies for obesity require all participants to be on an energy deficit diet [8]. The amount of weight loss induced by anti-obesity drugs is, on an average, about 2–4 kg greater than the amount produced by placebo (these studies usually run for 6–12 months). Orlistat causes gastrointestinal side effects while Sibutramine may induce palpitations [7]. The long-term beneficial effects of these drugs on health warrant further investigation.

Dietary fibres have been shown to be able to reduce the absorption of dietary fat and cholesterol, thus reducing the risk of cardiovascular disease [9]. A recent study indicates that, adjusted for lifestyle factors, each 10 g/day increase in dietary fibre intake lowers the risk of coronary events by 12% and coronary deaths by 19% [10]. Dietary fibre intake can also be used to predict body fat content [11]. Howarth et al [12] reviewed the literature and concluded that an increase in dietary fibre intake of 14% produces a significant reduction in energy intake (by 10%) and consequently body weight. At the present time, the average fibre intake of the US population is about 14 g, far short of the 25–35 g/day recommended by USDA.

α-Cyclodextrin is a soluble dietary fibre derived from corn. The World Health Organization has given it an acceptable daily intake of ‘not specified’. Furthermore, this material was recently granted ‘Generally Recognized As Safe’ status by the USFDA. FBCx™, the trade name used by ArtJen Complexus Holdings Corp. for α-cyclodextrin, has been shown to bind with free fatty acids in aqueous solution [13]. Animal research has shown that FBCx reduced weight gain in rats [14]. In addition, FBCx reduced blood triglyceride and leptin levels, as well as improved the calculated insulin sensitivity [14]. This animal study demonstrated that α-cyclodextrin has the very unique ability to complex with and prevent the absorption of 9 times its own weight in dietary fat. This phenomenon was previously unreported and unexpected. It appears that the α-cyclodextrin forms a very stable complex or emulsion with the dietary fat in the stomach and remains bound to the fat through the GI tract, first preventing the absorption of the bound fat in the small intestine and then fermentation by the intestinal flora. Based upon these properties of FBCx™, the current double-blind study was designed to investigate the beneficial effects of FBCx™ in obese patients with type 2 diabetes.

### Research design and methods

#### Subjects

Sixty-six obese (BMI ≥30) participants with type 2 diabetes were recruited initially. The main characteristics of these participants are presented in Table 1. The exclusion criteria included: <30 years of age, significant cardiac disease, hepatic disease, renal disease or terminal illness; currently taking other weight reduction medication or participation in another weight loss program; females who were pregnant, lactating or were of childbearing potential and planning to become pregnant.

#### Procedure

Written informed consent was obtained from those patients who met the inclusion criteria and agreed to participate in this study. There was an initial screening of all volunteers for renal and hepatic disease and, where applicable, pregnancy, prior to admission to the study. At this initial visit the volunteers were weighed and their hip and waist measurements were taken. The participants were instructed not to change their diet or exercise routine and to take two 1-gram tablets of FBCx™ or placebo per fat-containing meal (Defined as a meal that contained at least 20 g of fat.), a total of six tablets per day. At the beginning of this 3-month double-blind study, each participant was randomized to the active or placebo group and was given a 1-month supply of tablets; their 1-month supplies were replenished with each visit. A fasting blood sample was drawn at the beginning and at the end of months 1, 2, and 3 of the study. Blood serum measurements for glucose, creatinine, alanine aminotransferase, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, c-reactive protein and fructosamine were made on all samples.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the participants (mean ± SD)</th>
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<tbody>
<tr>
<td><strong>Active</strong> (n = 20)</td>
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<tr>
<td><strong>Placebo</strong> (n = 27)</td>
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<tr>
<td><strong>Gender distribution</strong></td>
</tr>
<tr>
<td>Male: 9 (45%)</td>
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<tr>
<td>Male: 13 (48%)</td>
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<tr>
<td>Female: 11 (55%)</td>
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<tr>
<td>Female: 14 (52%)</td>
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<tr>
<td><strong>Age (years)</strong></td>
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<tr>
<td>56.8 ± 8.6</td>
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<td>56.1 ± 9.8</td>
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<tr>
<td><strong>Body weight (kg)</strong></td>
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<tr>
<td>112.6 ± 18.2</td>
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<tr>
<td>114.4 ± 17.3</td>
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<tr>
<td><strong>Height (cm)</strong></td>
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<tr>
<td>171.5 ± 10.2</td>
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<tr>
<td>169 ± 10.1</td>
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<tr>
<td><strong>On insulin regimen</strong></td>
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<tr>
<td>12 (60%)</td>
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<td>14 (52%)</td>
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Serum 25-OH-vitamin D, leptin, insulin and adiponectin as well as blood HgbA1c were measured on the first and last samples. In addition, anthropometric data were collected, and dietary recalls (2 weekdays and 1 weekend day) were performed at each clinical visit. It should be noted that in this study no attempt was made to alter the participants’ diets, or to educate the participants about proper nutrition beyond the routine counseling that patients to this clinic normally receive. Our reason for adopting this approach was to examine the efficacy of FBCx in an all natural and habitual diet condition specific to each individual participant. This study protocol was approved by a human investigation IRB.

### Chemical analyses

Serum glucose, alanine aminotransferase, creatinine, triglyceride, cholesterol, HDL-cholesterol, high sensitivity C-reactive protein, fructosamine and blood HgbA1c levels were determined by Pointe Scientific Inc. (Canton, MI) on a Hitachi 917 Chemistry Analyzer with Pointe reagents. Serum insulin, leptin and adiponectin levels were determined by Linco Research (St. Charles, MO). Serum 25-OH-vitamin D was determined by radioimmunoassay performed by Beaumont Reference Laboratories (Royal Oak, MI). Dietary records were analysed by the Food Processor program (ESHA, Portland, OR).

### Statistics

Mean and standard errors were calculated. SPSS statistical package (Chicago, IL) was used to perform statistical analysis. Student’s t-tests were performed to compare the mean difference between active and placebo groups. Significance level was set at $p < 0.05$.

### Results

Thirteen of the 33 participants in the active group and 7 of the placebo group dropped out of this study. Chi-square test showed no statistical difference in drop-out rates between these 2 groups. Further analyses comparing the characteristics between those who dropped out with those who finished the study revealed no difference between these 2 groups. Ability to tolerate FBCx™ was not indicated as the reason for dropping out of this study. The most common reasons given were failure to adhere to their normal diet through the November/December holiday period and winter vacation travel. Of the remaining 20 participants in the active group 12 required insulin and of the 26 in the placebo group 14 required daily insulin injections. None of the volunteers reported experiencing any adverse side effects.

Initial review of the data revealed that there is no difference in body weight change between the active (0.27 ± 0.8 kg) and the placebo groups (1.54 ± 0.5 kg). However, these data indicated that participants in the active group did not gain any weight during the 3 month study period while those in the placebo group gained significant amount of weight ($p < 0.01$). There was no difference in body mass index (BMI) between the 2 groups at baseline (active: 38.3 ± 1.2 kg/m$^2$, placebo: 40.0 ± 1.5 kg/m$^2$). At the end of the study, BMI of the 2 groups were 38.3 ± 1.2 and 40.6 ± 1.5, respectively. The change in BMI of the active group was not significant. However, the change in BMI in the placebo group was statistically significant ($p = 0.007$), reflecting the increase in body weight in this group over the study period. Although the participants were asked not to change their eating habits, a statistically significant increase in energy intake between month 1 and month 3 was noticed in some participants. Therefore, body weight data were analysed in 2 ways: the first uses changes in energy intake as a co-variate for body weight change analyses, while the second is based upon the fact that it requires about 7700 kcal to gain or lose 1 kg of body weight; the total changes in body weight according to changes in energy intake were calculated. Figure 1 shows the changes in energy intake of the 2 groups of participants. Participants in the Active group consumed significantly more energy by month 3 relative to month 1 while participants in the placebo group reduced their energy intake. The difference between these 2 groups was statistically significant ($p < 0.05$). Figure 1 also illustrates that relative to the placebo group, the active group had a much lower food efficiency (amount of consumed energy required to maintain body weight), as demonstrated by an increase in energy needed to maintain body weight. The placebo group, on the other hand, required less energy to maintain body weight, as shown by a reduction in energy intake and food efficiency, although the difference failed to reach statistical significance. When analysis of co-variance was performed, it was apparent that participants in the placebo group gained body weight while participants in the active groups lost weight and the difference between these 2 groups was significant ($p < 0.05$, Figure 2). Since insulin injection may affect body weight gain, a posterior 2 x 2 factorial analysis was conducted using treatment and insulin usage as 2 independent factors. No difference between the insulin and non-insulin groups was observed.

The second approach to evaluate body weight change was to normalize the data based upon caloric intake as per the equation:

$$\text{Expected body weight} = \frac{\text{observed body weight}}{\text{baseline kcal}} \times \frac{7700}{\text{calories}}$$

Figure 3 illustrates the normalized weight change of the participants using treatment and insulin usage as factors. It is of note that at the end of the 3 month study, the normalized body weight decreased for the active group and increased in the placebo group. The difference in body weight change between these 2 groups was significant ($p < 0.005$). Although the main effect of insulin was not
Figure 1. Illustrated are the differences in the caloric intake and food efficiency between the active and placebo groups

Figure 2. Illustrated are the results of the analysis of co-variance for the active and placebo groups segregated by insulin usage. It is significant due to the large variability within each group, it is apparent from Figure 3 that those participants in the active group and not using insulin lost more weight compared to those in the placebo group and not using insulin (p < 0.05). In the non-insulin-using group, the difference was 4.9 kg.

Figure 3. Illustrated are the results of normalization of body weight change based upon 7700 Kcal/kg body weight for both the insulin users and non-users.

Blood lipid levels

Total cholesterol
The active group showed a reduction in the total cholesterol level (−0.22 ± 0.15 mmol/L) while the placebo group had an increase in the total cholesterol levels (+0.026 ± 0.13 mmol/L), although the difference failed to reach significance due to a large variability within each group. A 2 × 2 factorial analysis was performed using both treatment and blood triglyceride levels as factors. A significant interaction between treatment by triglyceride levels was observed (p < 0.01). For those in the active group, the participants who were hypertriglyceridemic (fasting blood triglyceride levels >1.70 mmol/L) prior to the commencement of the study, had a reduction in total cholesterol of 8.0 ± 5.4% (0.48 ± 0.24 mmol/L) from an initial level of 5.82 ± 0.30 mmol/L; for the placebo group it increased about 6.7 ± 4.7% from a baseline level of 4.55 ± 0.21 mmol/L. The difference in the change in total cholesterol levels was significant (p = 0.05). Normotriglyceridemic participants showed no significant change (Figure 4) from their baseline values of 4.51 ± 0.28 mmol/L (active) and 4.56 ± 0.18 mmol/L (placebo).

HDL-cholesterol
Mean HDL-cholesterol levels in the active group were increased (0.026 ± 0.03 mmol/L) while the placebo group showed no change (0.00 ± 0.03 mmol/L). However, the difference between the 2 groups failed to reach significance due to large variations within these groups. The changes in HDL-cholesterol levels between the 2 groups were not affected by insulin treatment.

LDL-cholesterol
No group difference (Figure 5) was found in the calculated LDL-cholesterol (calculated using the Friedewald
a reduction in LDL-cholesterol and the placebo showed a 0.22 ± 0.16 mmol/L increase (p < 0.01). No significant difference was observed in the normotriglyceremic patients. When LDL-cholesterol was measured similar but not significant results were obtained.

Triglyceride levels
Figure 6 illustrates that there was no statistically significant difference according to treatment or insulin usage. However, it would appear that there was a clinically significant decrease of 0.47 mmol/L (−6%), relative to the placebo (+12.3%), in the non-insulin active group. The lack of statistical significance is likely due to the wide variation in the changes and the small sample size.

Adiponectin levels
As a whole the participants in the active group had a significant increase in blood adiponectin levels as compared to those of the placebo group (Figure 7, p < 0.05). When segregated by insulin usage, the difference between the active and placebo groups approached significance in both groups: participants in the active insulin and non-insulin groups experienced increases of 31% and 19%, respectively (p < 0.06 for both).

Other laboratory tests
There was no significant difference in the levels of serum (Table 2) alanine aminotransferase, creatinine, fructosamine, high sensitivity C-reactive protein, vitamin D and leptin. Similarly, there was no difference in glycohaemoglobin levels (Table 2).

Discussion
In this study, the efficacy of the new dietary fibre FBCx™ on body weight regulation, fat storage/digestion
related hormones and reduction in blood lipid levels were examined. All of the participants were obese patients with type 2 diabetes. After 3 months on this study, body weight of the participants in the active group was the same as that of the baseline level, while participants in the placebo group gained significant amount of weight. All participants were instructed not to change their daily routine, including dietary pattern and activity levels. For reasons unknown, some of the participants increased their daily caloric intake while others reduced their intake. Consequently, the changes in body weight were normalized for energy intake. After these adjustments, participants in the active group lost weight while those on the placebo group gained weight. It should be noted that during the period of time between the prescreening and baseline visit, all participants were gaining an average of 1.0 ± 0.4 kg per month. It maybe speculated that if the participants in the active group had received nutritional counseling pertaining to increased over-consumption, body weight loss may have been achieved without adjustment for energy intake. As both groups were gaining weight prior to this study, the maintenance of body weight in the active group during the study may be seen as a positive result. Anecdotal comments from the participants indicated a general improvement in the sense of well-being by some of those individuals who were later identified as being in the active group, which may have resulted in the increased energy intake. It has been reported that obese patients with type 2 diabetes find it difficult to lose weight [16] even when anti-obesity drugs are prescribed [17]. Our observation that the active group was able to maintain their pre-study body weight, despite increased energy consumption, should be considered to be a significant finding.

It appears that the effects of FBCx™ were more pronounced in those patients who did not require insulin therapy. This may be due to more advanced stages of this disease or non-voluntary weight gain due to the effects of injected insulin. It is known that insulin, like some other medications used for the management of type 2 diabetes, may cause weight gain [7], thus reducing the efficacy of the FBCx™.

By normalizing the weight change for the difference in energy intake, based upon 7700 kcal/kg of body weight change, a clear pattern developed. The insulin users and non-users in the placebo group gained weight throughout the 3 month study. Conversely, both the insulin users and nonusers in the active group would have lost weight if they had maintained their energy intake. The cumulative difference for the insulin users was 2.5 kg and for the non-users, it was 4.9 kg. Again it would appear that noninsulin users respond better to FBCx™.

Based upon the food efficiency data it appears that the difference in energy intake between the active and placebo noninsulin groups was approximately 522 kcal/d which is consistent with the 540 kcal/d that we found in our animal study [14]. This difference was only 237 kcal/d with the two insulin using groups, suggesting a yet to be explained effect of the insulin injections.

Hypertriglyceridemia is a recognized risk factor for cardiovascular disease for patients with type 2 diabetes [18]. The significant reduction in blood cholesterol levels in the hypertriglyceridemic participants demonstrates a beneficial effect of FBCx™. The observation that FBCx™ had no effect on the blood cholesterol levels of normotriglyceridemic participants implies the possibility of a self-limiting mechanism whereby the cholesterol may not be forced to go too low. It would appear that the decrease in total cholesterol may be attributed to changes in the LDL-cholesterol, as no significant changes were observed in the HDL-cholesterol levels. The apparent but not significant decrease in triglyceride levels (0.47 mmol/L, 6%) of the active, noninsulin using group may prove to be very beneficial in the long term for patients with diabetes. Although the differences between the active and the placebo groups were not statistically significant, they may be considered to be clinically significant. The lack of significance is probably due to the large variation in the results and the small number of patients in each group. It is unclear at this point why there was no change in triglyceride levels amongst the insulin using patients.

Adiponectin levels have been demonstrated to be indicative of insulin sensitivity [19]. While the adiponectin levels of both the insulin using and non-using placebo groups remained unchanged throughout the study, the increase of 31.9% for the insulin using active group and 97.8% for the noninsulin using active group is very encouraging and warrants further investigation. These data may suggest that the initialization of insulin injections may be delayed and the dosage required may be decreased in patients with type 2 diabetes who take FBCx™ with their meals. As increased adiponectin levels have also been reported to have an antiatherogenic effect [20], these increased levels may reduce the risk or progression of cardiovascular disease (CVD) in these patients.

As FBCx™ is neither absorbed nor metabolized by humans; the lack of change to the creatinine and alanine aminotransferase levels was expected. These indicators of hepatic and renal function were monitored primarily to ensure that confounding issues did not arise during the study. Similarly, changes in the fructosamine and HgbA1c levels were not expected to be significantly different with this study group as all of the participants began the study with HgbA1c levels that were well within acceptable limits for patients with type 2 diabetes. It may be of interest to study the effects of FBCx™ on a less well-controlled population with higher HgbA1c levels. Although it has been reported that C-reactive protein (CRP) levels decrease with weight loss, such observations were not seen in this study. This may be due to the fact that the study population was too small and the variability too large for any statistical significance to be seen. HDL-cholesterol levels were not significantly higher amongst the active group although the data did suggest that it may be significant with a larger population; this is currently under investigation by us.
Although pre-clinical study in volunteers that do not have type 2 diabetes has indicated significant decreases in both insulin and leptin levels, such changes were not seen in this study population. This lack of change is likely due to the metabolic disturbances caused by both oral diabetes medications and insulin injections. It is of note that all of the participants in this study were either taking oral diabetes medications or insulin injections.

As FBCx™ functions by complexing with and removing dietary triglyceride from the digestive track, it was of concern that essential fat-soluble vitamins might also be removed. To monitor this possibility we measured 25-OH-vitamin D levels at the beginning and end of the study period. There was no significant difference between the active and placebo groups although both groups had lower levels by the end of the study. Despite these decreases all of the participants were still within the reference range. The decreases might best be explained as a result of the study being conducted during the winter months in Michigan.

In conclusion, from our data it would appear that the new soluble dietary fibre, FBCx™, is effective in reducing and/or maintaining body weight in obese patients with type 2 diabetes. Nutrition counseling and more rigid control of energy intake may enhance the benefits of FBCx™ in these participants. Cholesterol and triglyceride levels were both decreased in those participants who began the study with hypertriglyceridaemia. Significant increases in adiponectin levels may indicate delay in the onset of insulin usage and/or reduce the amount of insulin required by participants with type 2 diabetes. In those participants with very high energy intakes, the dosing levels of FBCx™ may have to be increased by one 1-g tablet for every 9 g of dietary fat beyond normal, in order that these participants receive the maximum benefit. Since taking these tablets with each meal is not a complicated practice, FBCx™ can be easily incorporated into the daily diabetic management regimen.

References


