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ORIGINAL RESEARCH

On the binding ratio of α-cyclodextrin to dietary fat in humans

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Abstract: α-Cyclodextrin (α-CD), a soluble dietary fiber, has been shown to bind and eliminate nine times of its own weight in dietary fat. Studies with different animal models have reported that α-CD preferentially binds saturated fatty acids, reducing saturated and trans fatty acid levels in blood. A clinical trial demonstrated that α-CD prevented weight gain in obese diabetic patients. The present study was designed to examine whether α-CD also shows a preference in binding saturated fatty acids in humans and to confirm the 1:9 binding ratio in humans. Sixty-six obese diabetic patients were recruited at the beginning of this 3-month, double-blind, and placebo-controlled study. Patients were randomly assigned to the Active or Placebo group. Blood samples and 3-day dietary records were collected at baseline and at the end of months 1, 2, and 3. A bottle of 180 tablets of active or placebo tablets was dispensed to each participant at the beginning of each month. Dietary records were analyzed using The Food Processor software. It was observed that α-CD has a higher affinity towards saturated fats than to unsaturated fats. Participants with higher intakes of total and saturated fat lost more weight than those with lower intakes ($P < 0.05$ and < 0.01, respectively). These data support the earlier observation in both in vitro and animal studies that α-CD binds with dietary fat in a 1:9 ratio and further demonstrate the efficacy of α-CD in binding to and eliminating dietary fat, especially saturated fats. α-CD may play a significant role in reducing blood cholesterol and triglyceride levels as well as stopping chronic weight gain.

Keywords: FBCx®, fat binding capacity, 1:9 binding ratio, reducing blood cholesterol levels, saturated, dietary analysis

Introduction

Dietary fibers are known to bind to dietary cholesterol and triglyceride, consequently reducing the risk of developing cardiovascular disease.[1] It has been reported that a 10 g increase in dietary fiber intake resulted in a 12% reduction in cardiovascular disease and a 19% decrease in coronary death.[2] It has also been reported that a 14% increase in fiber intake reduced energy intake and body weight significantly.[3] Considering that the US Department of Agriculture recommends the daily consumption of 25–35 g of fiber per day and that the average fiber intake of the general population of the US is about 15 g/day, there appears to be an urgent need to increase fiber consumption.

Naturally occurring cyclodextrins (CD) are cyclic oligosaccharides of 6, 7, or 8 D-glucose units; named α-, β- and γ-CD respectively. In water they take on a toroidal shape, with a hydrophilic exterior surface and hydrophobic interior cavity. These unique properties allow CDs to form inclusion complexes with small hydrophobic molecules, rendering them water soluble in the process. Artiss et al[4] have shown, both in vitro

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and in vivo, that α-CD is capable of forming 1:9 complexes with triglycerides.

Shimada et al[5] have demonstrated that the formation of inclusion complexes with fatty acids occurs at oil–water interfaces and that 2–3 molecules of α-CD can thread themselves onto a single fatty acid, like beads onto a string, depending on the length of the fatty acid. Bochot et al[6] have shown that under certain stringent conditions, α-CD–oil "beads" can be formed, in a ratio of about 1:4. They also report that complexes, but not beads, can be formed by varying their conditions. The same group of investigators[7] have in fact, demonstrated that these beads can be used as a delivery system for hydrophobic drugs. Bochot et al[6] have suggested that partial-inclusion complexes form between one fatty acid of a triglyceride molecule and α-CD, which imparts amphiphilic properties to the complex, allowing additional triglyceride molecules to complex with the hydrophobic end of the complex. It has been suggested that in behaving as a surfactant, the α-CD inclusion complex is able to interact with other molecules of triglyceride at an oil–water interface,[5] which would explain the large binding ratios with triglyceride. It is of note that the conventions for expressing binding ratios are based upon mass interactions. However, as the molecular weight of triglyceride and α-CD are similar, the mass:mass and mole:mole ratios are likewise similar.

α-CD is a soluble dietary fiber derived from corn. It has been given "generally recognized as safe" status by the US Food and Drug Administration, and the World Health Organization has set the daily allowable intake as "not specified." An earlier study by us, using animal models, has demonstrated that rats fed a high fat diet with added α-CD had, unlike the control group, a weight gain that was not different from that of the rats fed a low fat diet. This study also showed that the extra dietary fat that was bound by α-CD was excreted in the feces. Based on weight not gained and the amount of dietary fat and α-CD that these animals consumed, it was determined that 1 g of α-CD bound nine times its own weight in dietary fat.[8] Furthermore, it has been shown that α-CD preferentially binds with saturated and trans-fatty acids, resulting in significantly lower blood levels of saturated and trans-fatty acids relative to unsaturated fatty acid levels.[9] This preferential binding of saturated fatty acids was reflected in the increased excretion of saturated fat in the feces of rats, as reported by Gallaher et al.[10]

Animal studies have demonstrated that α-CD preferentially binds with saturated and trans-fatty acids in triglyceride molecules. We have reanalyzed data from a previously reported clinical trial conducted by Grunberger et al,[11] to look at the macronutrient binding preferences of α-CD in obese humans.

Methods

The detailed procedure for this study was published previously.[11] In brief, 66 obese (body mass index [BMI] $\geq$ 30 kg/m^2) individuals with type 2 diabetes were initially recruited to this double-blind, placebo-controlled, 3-month study. Individuals less than 30 years of age; having significant cardiac disease, hepatic disease, renal disease, or terminal illness; participating in other weight loss programs; or females who were pregnant or lactating were excluded from this study. The α-CD used in this study was commercially available as FBCx® (Soho Flordis International, New South Wales, Australia).

Procedure

Written informed consent was obtained from those participants who met the inclusion criteria and agreed to participate in this study. The participants were randomly assigned to one of two groups, either the Active group, receiving FBCx, or the Placebo group, and were instructed not to change their diet or exercise routine and to take two 1 g tablets per fat-containing meal, a total of six tablets per day. At the beginning of the first, second, and third months of this 3-month, double-blind study, each participant was given a 1-month supply of either FBCx or placebo tablets while they were in the clinic for their routine checkups. The active and placebo (cellulose) tablets were identical in appearance. Each tablet of FBCx contained 1000 mg of α-CD. A fasting blood sample was drawn at the beginning and at the end of months 1, 2, and 3 of the study, for measurement of glucose, creatinine, alanine aminotransferase, cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, C-reactive protein, and fructosamine; the data were published previously.[11] In addition, data from dietary recalls (2 weekdays and 1 weekend day) were obtained at each clinical visit and analyzed using The Food Processor software (Esha Research Inc, Salem, OR, USA). This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures were approved by the Quorum Institution Review Board (Quorum Review IRB, Seattle, WA, USA).

Statistics

Mean and standard errors were calculated. The IBM SPSS Statistics package version 20 (Armonk, NY, USA) was used to perform the statistical analysis. Student's *t*-tests were performed to compare the mean difference between the Active

and Placebo groups. Analyses of variance with repeated measures were used to compare within group differences at different time points. Pearson's correlation coefficients were calculated between dietary factors and body weight changes. The significance level was set a $P < 0.05$.

Results

All participants exhibited at least one characteristic of metabolic syndrome. At each office visit, a routine physical exam was conducted. There were no significant changes (eg, blood pressure, gastrointestinal symptoms, etc) observed between the two groups. A total of 47 participants completed the 3-month study (20 in the Active group and 27 in the Placebo group). The characteristics of the participants in the Active group were: nine males and eleven females; 56.8 ± 8.6 years of age; 112.6 ± 18.2 kg; 171.5 ± 10.2 cm in height; and 12 (60%) were on an insulin regimen. In the placebo group, there were 13 males and 14 females; 58.1 ± 9.8 years of age; 114.4 ± 17.3 kg; 169 ± 10.1 cm in height; and 14 (52%) were on an insulin regimen. The inability to tolerate FBCx was not indicated as a reason for dropping out of the study (13 in the Active group and six in the Placebo group). Due to an unforeseen manufacturing issue, tablet production was delayed, thus there was a lapse of 47 ± 35.7 days (from 11 to 127 days) between the initial screening and the collection of baseline data. During this lapse period, participants from both groups gained weight at a rate of 1 kg/month. There was no difference in body weight change between the Active and Placebo groups, nor was there a significant difference in total energy intake between the Active and Placebo groups during the 3-month study period. The Active group gained 0.27 ± 0.8 kg, while the Placebo group gained 1.54 ± 0.5 kg during the 3-month period. However, there was a statistically significant change in energy intake within each group between month 1 and month 3, despite the fact that participants were instructed not to change their eating habits. 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 during the same period (Table 1). Consequently, the body weight data were analyzed based upon the fact that it requires about 7700 kcal to gain or lose 1 kg of body weight[12] the total changes in body weight according to changes in energy intake were calculated as adjusted body weight. Energy intake was also used as a covariate to analyze weight changes. With both approaches to the analyses, the difference between these two groups was statistically significant ($P < 0.05$).[11] 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 two groups was significant.

Dietary analysis

In addition to total energy intake, other macronutrient intakes were collected and analyzed, and these data are presented in Table 1. No difference was observed between the Active and Placebo groups with respect to macronutrient intakes.

Calculation of fat:FBCx binding ratio

Based upon the reported increased energy intake over the 3-month period, the Active group should have gained 2.7 kg but in fact, gained only 0.8 kg, a difference of

Table 1 Energy and nutrient intakes

	Baseline		Month 1		Month 2		Month 3	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Total energy (kcal/d)	1931 ± 97 (1291–2729)	2149 ± 11 (920–3844)	2147 ± 139 (1333–3462)	1924 ± 114 (664–3082)	2145 ± 182 (957–4226)	2054 ± 128 (1085–4146)	2126 ± 164 (1228–3499)	2031 ± 135 (774–3509)
Total fat (g/d)	91 ± 11 (45–270)	98 ± 8 (46–185)	90 ± 9 (41–193)	82 ± 7 (35–158)	97 ± 12 (33–259)	88 ± 6 (46–193)	90 ± 8 (40–173)	93 ± 8 (30–172)
Saturated fat (g/d)	32.3 ± 4.7 (11–109)	33.5 ± 3.1 (10–64)	31.2 ± 3.9 (11–77)	30.0 ± 3.2 (12–76)	34.4 ± 5.6 (10–114)	32.9 ± 2.8 (12–74)	29.7 ± 3.7 (8–70)	31.3 ± 2.6 (10–54)
Unsaturated fat (g/d)	58.8 ± 7.8 (26–143)	46.5 ± 6.4 (18–121)	58.9 ± 5.4 (25–116)	51.8 ± 4.5 (21–97)	62.6 ± 7.3 (23–145)	55.5 ± 4.2 (13–119)	60.5 ± 5.1 (31–111)	61.4 ± 5.4 (20–119)
Carbohydrates (g/d)	212 ± 15 (101–365)	233 ± 14 (71–398)	244 ± 14 (174–393)	219 ± 14 (50–325)	210 ± 14 (104–317)	230 ± 19 (82–500)	217 ± 18 (116–359)	211 ± 15 (82–364)
Protein (g/d)	97.5 ± 6.6 (67–180)	93.0 ± 5.4 (51–166)	102.2 ± 8.5 (55–185)	83.4 ± 4.5 (40–135)	109.6 ± 9.2 (56–189)	88.4 ± 4.9 (20–132)	103.7 ± 6.5 (58–166)	90.5 ± 6.5 (20–178)
Body weight (kg)	112.6 ± 4.0	114.9 ± 3.4	112.8 ± 4.3	115.6 ± 3.5	113.7 ± 4.5	116.4 ± 3.6	112.9 ± 4.2	116.4 ± 3.6

Notes: Values are expressed as mean ± SEM (range). No difference was observed between the Active and Placebo groups at each data collection point.
Abbreviations: SEM, standard error of the mean; kcal/day, kilocalories per day; g/d, grams per day.

1.9 kg (not gained). Similarly, due to a decrease in energy intake, the Placebo group should have lost 2.4 kg but in fact, gained 1.7 kg, a difference of 4.1 kg (gained). Based on the difference in weight change of 6.0 kg (4.1 to −1.9), the calculated energy elimination in this 6.0 kg difference is about 46,200 kcal or the equivalent of about 5133 g of dietary fat. This 5133 g of fat was eliminated by 540 g of α-CD taken during the 3-month period. Thus, each gram of α-CD eliminated 9.5 g of dietary fat.

When analyzing data by dividing all participants into the highest quartile vs the lowest quartile, according to macronutrient intake (Table 2), it appears that participants in the highest quartile in total fat, saturated fat, carbohydrate, and protein intakes had a lower adjusted weight, relative to those at the lowest quartile for these nutrients, in the Active group. No such difference was observed in the Placebo group.

Table 2 Comparison of adjusted weight changes (kg) based on the lowest quartile and highest quartile of macronutrient intakes

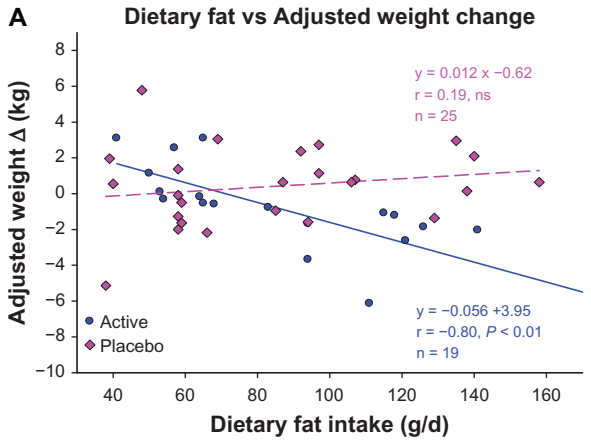
	Lowest quartile	Highest quartile	*P*
Active group			
Total fat intake			
Month 1	1.3 ± 0.7	−3.0 ± 1.1	<0.01
Month 2	1.1 ± 1.4	−2.0 ± 1.0	=0.11
Month 3	0.5 ± 0.7	−2.9 ± 1.3	<0.05
Saturated fat intake			
Month 1	0.6 ± 0.6	−4.0 ± 1.1	<0.01
Month 2	0.1 ± 1.3	−0.6 ± 0.7	=0.81
Month 3	0.3 ± 0.8	−2.9 ± 1.3	=0.07
Carbohydrates intake			
Month 1	0.4 ± 1.3	−1.9 ± 1.6	= 0.12
Month 2	1.1 ± 0.7	−1.5 ± 0.4	<0.01
Month 3	0.4 ± 0.9	−3.1 ± 1.1	<0.05
Protein intake			
Month 1	1.0 ± 0.6	−2.6 ± 1.3	<0.05
Month 2	1.3 ± 1.0	−2.0 ± 1.0	<0.05
Month 3	−0.7 ± 1.5	−2.6 ± 1.6	=0.37
Placebo group			
Total fat intake			
Month 1	0.8 ± 2.3	0.8 ± 0.5	=0.98
Month 2	1.3 ± 0.5	0.7 ± 0.6	=0.47
Month 3	1.2 ± 1.0	−0.1 ± 0.8	=0.44
Saturated fat intake			
Month 1	0.1 ± 1.5	1.6 ± 0.5	=0.36
Month 2	1.2 ± 1.0	1.1 ± 0.4	=0.82
Month 3	0.6 ± 0.8	0.9 ± 1.0	=0.82
Carbohydrates intake			
Month 1	2.4 ± 1.0	0.5 ± 0.8	=0.16
Month 2	4 ± 0.7	0.9 ± 0.6	=0.58
Month 3	1.9 ± 0.8	−2.3 ± 0.7	=0.07
Protein intake			
Month 1	−1.1 ± 1.2	1.2 ± 0.7	=0.12
Month 2	0.7 ± 0.7	0.4 ± 0.4	=0.64
Month 3	1.2 ± 0.7	0.4 ± 1.0	=0.51

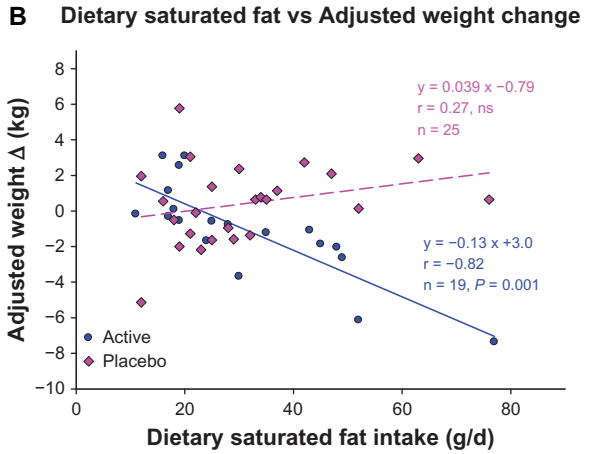
Further analysis of the relationships between adjusted weight change and different types of fats revealed that total fat, saturated, and unsaturated fat intakes are all significantly negatively correlated with the changes to adjusted weight (Figure 1) at month 1, in the Active group but not in the Placebo group. The adjusted weight loss was not correlated with total carbohydrate intake in either group. For protein intake, a significant positive relationship was observed in the Placebo group (r = 0.48) ($P < 0.05$) and a negative correlation in the Active group (r = −0.53) ($P < 0.05$). At month 3, the adjusted weight loss was related to the total fat, saturated fat, total unsaturated fat (Figure 2), and carbohydrate intakes (r = −0.60) ($P < 0.01$) but not with protein (r = −0.41) ($P = 0.09$), in the Active group. In the Placebo group, the adjusted weight loss was not correlated with the consumption of any of these macronutrients.

Discussion

Using an animal model, Artiss et al[4] have demonstrated that α-CD has the unique ability to bind and eliminate nine times its own weight in dietary fat, a binding ratio of 1:9. Wagner et al[9] using a low density lipoprotein (LDL) receptor knock-out mouse model, has reported that α-CD consumption disproportionately lowers saturated and trans-fatty acid blood levels relative to unsaturated fats. Another animal study has demonstrated that α-CD increases the amount of saturated fat eliminated in the feces of rats.[10]

These animal studies indicate that in various animal models, α-CD binds with dietary fat and eliminates it in the feces, furthermore, that α-CD preferentially binds and eliminates saturated and trans-fats. The current study has demonstrated similar results in humans to those obtained in animals, that is, that α-CD binds with dietary fat in a ratio of 1:9. These in vivo studies appear to be consistent with the in vitro work performed by other investigators.[6,7] By doing so, the continued weight gain observed in the study group of obese diabetic patients was prevented, while those patients receiving placebo tablets continued their pretrial weight gain. The relationship between adjusted weight change and saturated fat intake was stronger than that with total unsaturated fats, suggesting that as in the animal data, α-CD has a higher affinity for saturated than unsaturated fats (although all fats appear to be bound by α-CD). This apparent preferential binding might be explained by the fact that saturated and trans-fatty acids are straight chains whereas unsaturated fatty acids have one or more bends (depending on





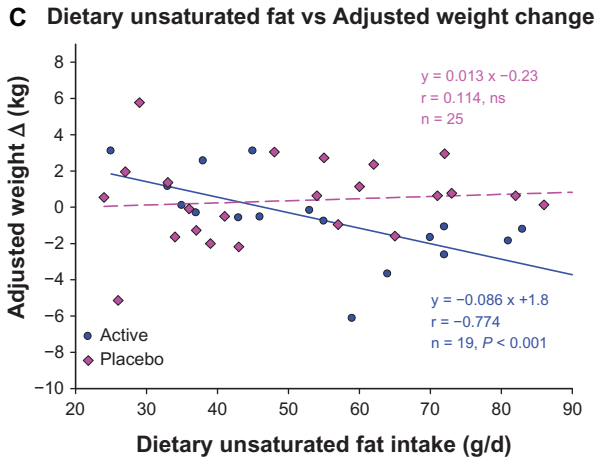
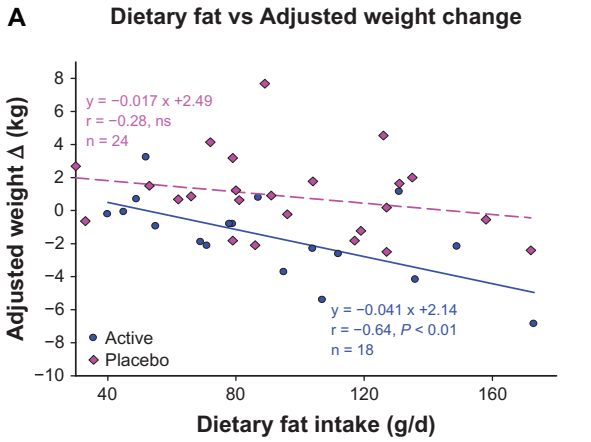
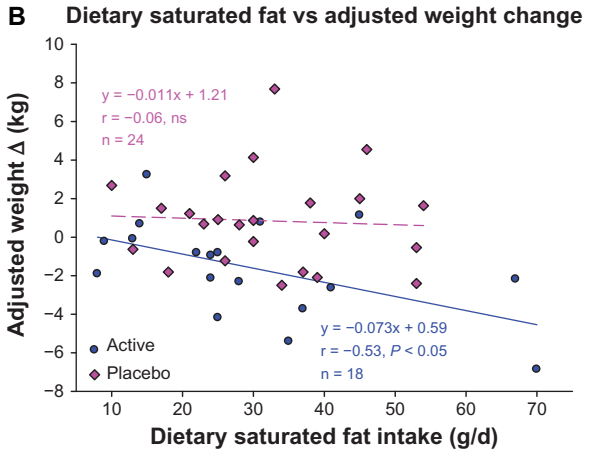


Figure 1 The relationships between adjusted weight change and intakes of total fat (**A**), saturated fat (**B**), and unsaturated fat (**C**) after 1 month of supplement.
Notes: The blue regression line represents the Active group and the pink regression line represents the Placebo group. Lines of regression are expressed as y = mx+b; y = adjusted weight change, m = slope, x = dietary fat intake, b = y intercept.
Abbreviations: vs, versus; ns, not significant; g/d, grams per day.





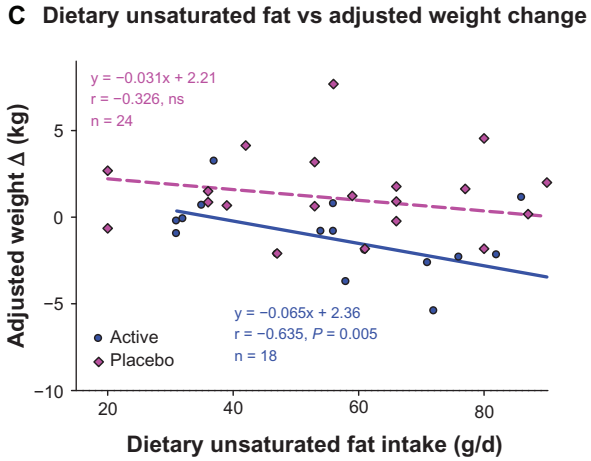


Figure 2 The relationships between adjusted weight change and intakes of total fat (**A**), saturated fat (**B**), and unsaturated fat (**C**) during month 3 of supplement.
Notes: The blue regression line represents the Active group and the pink regression line represents the Placebo group. Lines of regression are expressed as y = mx+b; y = adjusted weight change, m = slope, x = dietary fat intake, b = y intercept.
Abbreviations: vs, versus; ns, not significant; g/d, grams per day.

the degree of unsaturation, in the chain), which may restrict the ability of α-CD to form an inclusion complex.

We have also reported in vitro studies that demonstrate the α-CD:fat binding ratio of 1:9.[4]

Saturated fats are the most important dietary factor in increased blood cholesterol levels, elevating the synthesis of cholesterol in the liver and impairing its clearance.[13] By reducing the intake of saturated fats, blood choles-

terol levels are lowered.[14] With α-CD consumption, more dietary saturated fats will be bound and eliminated, thus reducing blood cholesterol levels. This reduction in blood cholesterol levels was especially apparent in participants who had hypertriglyceridemia at the start of the study.[11] Our previously reported crossover study with overweight but not obese individuals also demonstrated that α-CD induced a decrease in total cholesterol (5.3%), LDL cholesterol (6.7%), and the proatherogenic apolipoprotein B (5.6%),[15] within the 30 days of the study. Since high dietary fat leads to high blood cholesterol levels, which in turn are associated with an elevated risk of developing cardiovascular disease, lowering blood cholesterol by consuming α-CD may have significant health benefits.

α-CD is a dietary fiber with "generally recognized as safe" status. Furthermore, its consumption is well tolerated, with no adverse effects reported by participants taking the recommended daily dose. Because fat is bound to α-CD as it passes through the large bowel, there is no free fat available as a carbon source for the micro flora, thus eliminating unwanted gastrointestinal effects such as "leakage," flatulence, and diarrhea. This contrasts with the antiobesity lipase inhibitors, which do not physically bind the fat and therefore allow free fat to pass into the colon, which in turn, may cause steatorrhea and/or bloating.[16] Due to these adverse effects, lipase inhibitors have not been well received by consumers who are forced onto a low-energy, low-fat diet.

It should be noted that in this study, the participants did not go through a restricted dieting stage before the intervention nor any dietary restrictions during the study period. They were instructed only to not change their regular eating and exercise routines. This paradigm was designed to mimic the everyday lifestyle of the participants and is very different from all other studies investigating the effects of weight loss agents where the participants were all placed on an energy-deficit diet.[16,17] This study design may have limited the effects of FBCx even though significant differences in body weight (adjusted) and blood lipid levels were still observed. Future studies offering participants nutrition counseling or restricted energy intake is warranted to further elucidate the health benefit of FBCx.

Even though FBCx is known to bind and eliminate dietary fat, this 3-month study did not identify any fat-soluble vitamin deficiency when vitamin D levels were used as a marker.[11] Whether or not long-term use of FBCx may affect fat-soluble vitamin status deserves further investigation.

Participants in the Active group increased their energy intake, a finding that was not expected. At the end of this study, after the code was broken, anecdotal statements by the participants revealed that their general feeling of well-being was improved and that their food tasted much better. This may explain the increased energy intake in the Active group. These statements further enhanced the notion that energy intake has to be controlled in order to ensure equal energy intake between Active and Placebo groups.

Conclusion

Data from the current study demonstrate that α-CD binds nine times its own weight in dietary fat. The bound dietary fat is eliminated, thus preventing weight gain or promoting weight loss if taken as directed. These findings are in agreement with previously reported animal studies. Furthermore, α-CD appears to have a higher affinity towards saturated than to unsaturated fats. In participants with higher intakes of total or saturated fat, a higher amount of adjusted weight loss was observed as compared with those with lower intakes. Since α-CD preferentially binds with saturated fat and lowers blood cholesterol levels, it may become part of an efficacious regimen to prevent/treat hypercholesterolemia in humans.

Disclosure

K-L C Jen and JD Artiss are officers of ArtJen Complexus Inc. The authors report no other conflicts of interest in this work.

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