

# The Beneficial Effects $\alpha$ -Cyclodextrin on Blood Lipids and Weight Loss in Healthy Humans

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$\alpha$ -Cyclodextrin ( $\alpha$ -CD) is a soluble fiber derived from corn. It has previously been reported that early intervention with Mirafit fbcx, a trademarked name for  $\alpha$ -CD, has beneficial effects on weight management in obese individuals with type 2 diabetes, and that it preferentially reduces blood levels of saturated and *trans* fats in the LDL receptor knockout mice. The current investigation involves overweight but not obese nondiabetic individuals and was intended to confirm the effects of  $\alpha$ -CD on both weight management and improving blood lipid levels. Forty-one healthy adults (age:  $41.4 \pm 13.6$  years) participated in this 2-month, double-blinded, crossover study. In 28 compliant participants (8 males and 20 females), when the active phase was compared to the control phase, there were significant decreases in body weight ( $-0.4 \pm 0.2$  kg,  $P < 0.05$ ), serum total cholesterol (mean  $\pm$  s.e.m.,  $-0.295 \pm 0.10$  mmol/l, 5.3%,  $P < 0.02$ ) and low-density lipoprotein (LDL) cholesterol ( $-0.23 \pm 0.11$  mmol/l,  $-6.7\%$ ,  $P < 0.05$ ). Apolipoprotein B (Apo B) ( $-0.0404 \pm 0.02$  g/l,  $-5.6\%$ ,  $P = 0.06$ ) and insulin levels also decreased by 9.5% ( $-0.16 \pm 0.08$  pmol/l,  $P = 0.06$ ) while blood glucose and leptin levels did not change. These results suggest that  $\alpha$ -CD exerts its beneficial health effects on body weight and blood lipid profile in healthy nonobese individuals, as previously reported in obese individuals with type 2 diabetes.

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## INTRODUCTION

Two out of every three adults in the United States are either overweight or obese (1). The number of obese individuals, at 33.8% of the US adult population, has more than doubled in the last 30 years (1). It is more likely for overweight (BMI  $>25$  kg/m<sup>2</sup>) individuals than normal weight individuals to transition into obesity (BMI  $>30$  kg/m<sup>2</sup>) (2); therefore, this is a very important demographic to study for weight loss and weight maintenance.

One of the major obstacles to weight loss is excess calorie consumption, especially from high-fat foods. Effective strategies to reduce energy intake are either to reduce energy consumption or block the absorption of consumed foods and energy. Some natural and pharmaceutical interventions have shown promise targeting these pathways, but many times with less than impressive results or unwanted side effects.

$\alpha$ -Cyclodextrin ( $\alpha$ -CD) is a cyclic oligosaccharide derived from corn (Trade name: Mirafit fbcx, ArtJen Complexus, Windsor, Ontario, Canada). It has been shown to form a stable complex with dietary fat. This complex is resistant to normal lipolytic hydrolysis by lipases and thereby reduces the absorption and bioavailability of dietary fat (3). In addition, the fiber-fat complex does not appear to be accessible to the human gut flora and therefore does not lead to the gastrointestinal side

effects associated with weight loss products that cause fat malabsorption (3,4). This fiber-fat complex is then excreted in the stool intact (3,5). Other weight loss products that inhibit lipase secretion allow free, uncomplexed, dietary fats to pass through the digestive system. This leads to steatorrhea (oily stool) and bowel incontinence (6).

In healthy human subjects  $\alpha$ -CD was able to reduce the glucose response (incremental area under the curve) to a test meal containing 50 g carbohydrate without affecting the insulin response (7). The lowered glycemic response along with the lipid binding properties of  $\alpha$ -CD suggest that this soluble fiber may be useful in individuals with dyslipidemia, type 2 diabetes and metabolic syndrome.

In a recent 3-month, double-blinded, placebo controlled study,  $\alpha$ -CD was shown to reduce blood lipids and increase adiponectin levels in obese type 2 diabetic subjects when compared to a placebo (4). Since plasma adiponectin levels correlate with insulin sensitivity,  $\alpha$ -CD potentially may be useful for treatment of type 2 diabetes (8).

The current double-blinded, controlled crossover study was undertaken to investigate the effects of  $\alpha$ -CD on glucose and lipid levels in overweight, yet otherwise healthy human subjects.

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**Table 1 Baseline anthropometric (mean ± s.d.) and selected blood characteristics (mean ± s.e.m.) of compliant and noncompliant participants**

	Compliant participants (n = 28)	Noncompliant participants (n = 13)
Age (years)	43.3 ± 14.1	37.3 ± 12.0
Gender m/f (%m/f)	8/20 (28.6/71.4)	6/7 (46.2/53.8)
Height (cm)	167.6 ± 10.2	171.5 ± 11.2
Weight (kg)	76.3 ± 8.8	83.1 ± 13.9
BMI (kg/m <sup>2</sup> )	26.9 ± 1.7	28.0 ± 2.1
Glucose (mmol/l)	5.10 ± 0.05	5.21 ± 0.14
Total cholesterol (mmol/l)	5.17 ± 0.19	5.05 ± 0.34
LDL-cholesterol (mmol/l)	3.40 ± 0.17	3.40 ± 0.29
HDL-cholesterol (mmol/l)	1.27 ± 0.07	1.33 ± 0.07
TC/HDL-cholesterol	4.30 ± 0.23	3.90 ± 0.24
Apolipoprotein B (g/l)	0.72 ± 0.04	0.77 ± 0.06
Triglycerides (mmol/l)	1.09 ± 0.13	1.07 ± 0.16
Insulin (pmol/l)	1.66 ± 0.11	1.64 ± 0.13
Leptin (nmol/l)	0.73 ± 0.08	0.72 ± 0.12
Adiponectin (µg/ml)	12.8 ± 1.25	10.0 ± 1.36
Total energy intake (kcal/day)	1,966 ± 432	2,053 ± 688
Total fat intake (g/day)	68.6 ± 23.8	78.6 ± 38.7
Total saturated fat (g/day)	20.5 ± 9.3	23.9 ± 13.2

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

## METHODS AND PROCEDURES

### Subjects

Forty-one participants (14 males and 27 females) between the ages 18–65 years with a BMI between 25 and 30 kg/m<sup>2</sup> were recruited from the greater Sacramento area and signed informed consents approved by the UC Davis institutional review board. Subjects with any chronic diseases (diabetes, hypertension, liver, or kidney disease, untreated thyroid disease, or taking lipid lowering medications) were excluded. Subjects with a history of eating disorders, malabsorption syndromes, or using medications or supplements affecting absorption were also excluded. Baseline characteristics are presented in [Table 1](#).

### Design

The protocol involved a 2-month, randomized, controlled, double-blinded, crossover study. After the baseline measurements, the participants were randomized to either the active ( $\alpha$ -CD) or control (cellulose) tablets for the first month. Subjects were given 180 tablets (2 tablets to be taken within an hour of each fat-containing meal, a total of 6 tablets per day) for 30 days. After the first month, subjects returned to the study site for testing. The leftover tablets were collected and counted; the alternate treatment tablets were distributed for the next 30 days. The participants were instructed not to change their eating and exercise habits. No further instructions were provided by the researchers, except to record any meals in which the tablets were not taken.

Noncompliance was defined as: (i) body weight variance of >5 pounds between screen and baseline data collection; (ii) daily energy intake variance of >60% (>2 standard deviation) among the baseline, month 1 and month 2 dietary records; (iii) >25% of the tablets were left untaken during either the active or control phase.

Three-day dietary records (2 weekdays and 1 weekend day) were obtained at baseline and at the end of the first and second months. The

**Table 2 Anthropometric (mean ± s.d.) and selected blood and diet parameters (mean ± s.e.m.) at the end of active and control phases for all the compliant participants (n = 28)**

	Active phase	Control phase	P <sup>a</sup>
Body weight (kg)	75.48 ± 1.58 <sup>b</sup>	75.93 ± 1.61	<0.05
Body fat %	33.96 ± 1.81	34.29 ± 1.78	ns
Glucose (mmol/l)	5.06 ± 0.05	5.00 ± 0.05	ns
Total cholesterol (mmol/l)	5.10 ± 0.15	5.38 ± 0.18 <sup>c</sup>	<0.05
LDL-cholesterol (mmol/l)	3.28 ± 0.13	3.51 ± 0.15	<0.05
HDL-cholesterol (mmol/l)	1.32 ± 0.07	1.34 ± 0.08 <sup>c</sup>	ns
TC/HDL-cholesterol	4.06 ± 0.18	4.24 ± 0.20	=0.065
Triglycerides (mmol/l)	1.11 ± 0.11	1.16 ± 0.15	ns
Apolipoprotein B (g/l)	0.73 ± 0.04	0.77 ± 0.04 <sup>c</sup>	=0.06
Insulin (pmol/l)	1.57 ± 0.12	1.73 ± 0.15	=0.06
Leptin (nmol/l)	0.75 ± 0.09	0.78 ± 0.09	ns
Adiponectin (µg/ml)	13.04 ± 1.31	13.67 ± 1.57	ns
Total energy intake (kcal/day)	1,875 ± 129	2,051 ± 110	ns

LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol. <sup>a</sup>Compare active vs. control phases. <sup>b</sup>Significantly lower than the baseline level. <sup>c</sup>Significantly higher than the baseline level.

records were later analyzed and averaged for food intake patterns using the Food Processor SQL program, version 9.8. (Esha Research, Salem, OR). At baseline and at the end of both months 1 and 2, anthropometrics, blood pressure and fasting blood samples were taken.

### Anthropometrics

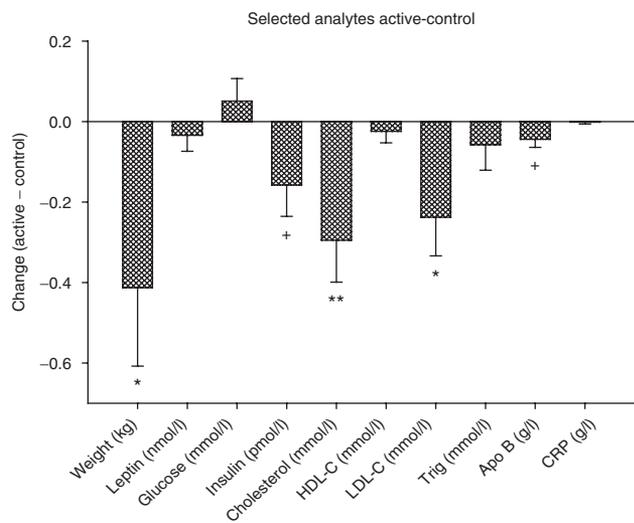
Each participant's weight was measured while wearing light clothing and no shoes using a Tanita BWB800-P Digital Medical Scale. Height was taken without shoes using an Ayrton Model S100 stadiometer. Body composition was determined using bioelectrical impedance (Biostat, Ashhurst, New Zealand).

### Assays and analyses

Plasma and serum samples were obtained after an overnight fast. The blood samples were assayed for lipids, glucose, insulin, adiponectin, and leptin. Glucose was measured using a YSI 2300 STAT Plus Glucose & Lactate Analyzer (YSI Life Sciences, Yellow Springs, OH). The coefficient of variation for glucose was 1%. Triglyceride, cholesterol, direct high-density lipoprotein (HDL) cholesterol, and apolipoprotein B (Apo B) were measured using a Poly-Chem System clinical chemistry analyzer (PolyMedCo, Cortlandt Manor, NY). The coefficient of variations for these assays were as follows: 4.0% for triglyceride, 3.5% for cholesterol, 3.6% for direct HDL, and 4.7% for Apo B. Low-density lipoprotein cholesterol (LDL) was calculated based on the equation LDL = total cholesterol – HDL – (triglyceride/5). Insulin, leptin, and adiponectin were measured using RIA kits (Linco Research, St Charles, MO) with coefficient of variations of 8.2%, 4.3%, and 6.5%, respectively. High-sensitivity C-reactive protein was measured with a highly sensitive latex-enhanced immunonephelometric assay. Both interassay and intra-assay coefficient of variations for this technique were <5%.

### Statistics

Means and s.e. of the means were calculated. The differences between active and control phases were compared using paired *t*-tests. The relationships between changes in blood concentrations and other parameters were evaluated by correlation analyses. All statistical analyses were performed using SPSS version 17 (SPSS, Chicago, IL). Significance level was set at *P* < 0.05.



**Figure 1** Changes (active phase – control phase) in selected analytes ( $n = 28$ ). The symbol “+” denotes  $P = 0.06$ . Apo B, apolipoprotein B; CRP, C-reactive protein; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

## RESULTS

Thirteen subjects out of 41 were deemed noncompliant based on the previously stated criteria and their data were excluded from analysis. Compliant and noncompliant subjects did not differ in their baseline values shown in [Table 1](#). The mean values of selected parameters at the end of active and control phases of all the compliant participants are presented in [Table 2](#).

### Anthropometric measures

Participants lost weight in both active and control phases. However, body weight was  $0.41 \pm 0.2$  kg lower (91% more weight loss) at the end of the active phase as compared to the control phase ( $P < 0.05$ , [Table 2](#), [Figure 1](#)). The BMI did not differ significantly. During the active phase, waist circumference and body fat percent were not different from those observed in the control phase.

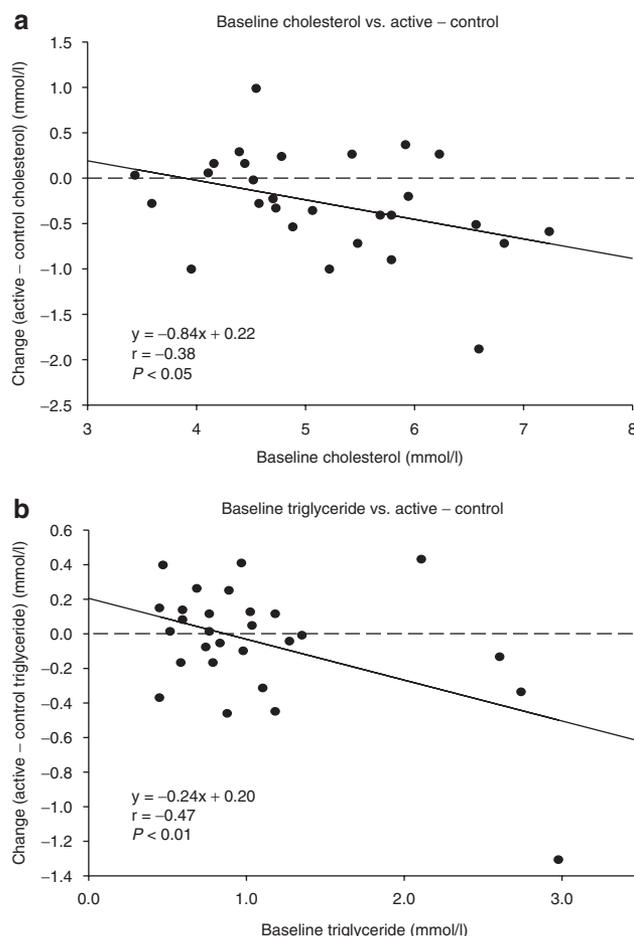
### Dietary records

No significant differences were observed between the active and control phases in total energy intake ( $-176 \pm 98$  kcal/day), total fat ( $-7.2 \pm 4.8$  g), and saturated fat ( $-1.8 \pm 2.0$  g) intakes.

### Blood parameters

During the control phase, participants had significantly higher total cholesterol, HDL-cholesterol and Apo B levels when compared to the baseline values. A nonsignificant increase ( $=0.08$ ) in HDL-cholesterol levels were observed during the active phase. No other difference between baseline and after 30 days of control or active phases was observed ([Table 2](#)).

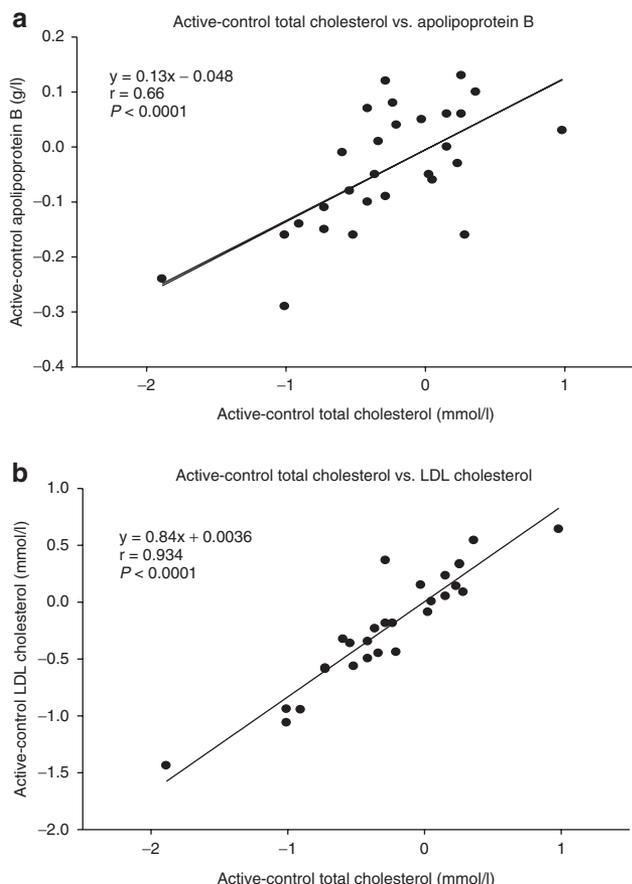
There were no differences in blood glucose, HDL-cholesterol, triglyceride, and C-reactive protein levels between the active and control phases ([Table 2](#) and [Figure 1](#)). During the active phase, significant reductions were observed in fasting total



**Figure 2** (a) The relationship between baseline cholesterol levels and the changes in cholesterol (active phase – control phase). (b) The relationship between baseline triglyceride levels and changes in triglyceride levels (active phase – control phase).  $N = 28$  for both figures.

cholesterol ( $-5.3\%$ ,  $P < 0.05$ ), and LDL-cholesterol ( $-6.7\%$ ,  $P < 0.05$ ). Reductions in insulin ( $-9.5\%$ ,  $P = 0.06$ ), Apo B ( $-5.6\%$ ,  $P = 0.06$ ), and total cholesterol/HDL-cholesterol ratio ( $P = 0.065$ ) were observed but failed to reach significance. The higher the baseline cholesterol levels, the greater the improvement in cholesterol in the active phase ( $r = -0.38$ ,  $P < 0.05$ , [Figure 2](#)). The reduction in total cholesterol was mainly due to the reduction in LDL and Apo B and not due to changes in HDL, as shown in [Figure 3](#) that the improvement during the active phase in cholesterol levels was correlated with the improvement in Apo B and LDL-cholesterol ([Figure 3](#)). The reduction in LDL-cholesterol during the active phase was significantly correlated with the reduction in Apo B levels ( $r = 0.759$ ,  $P < 0.0001$ ). The results also showed that the higher the baseline triglyceride levels, the greater the improvement that was observed during  $\alpha$ -CD supplementation ([Figure 2](#)).

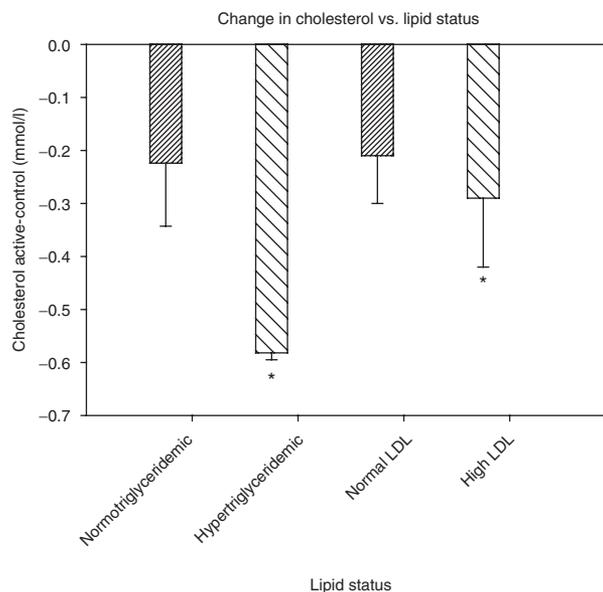
Blood cholesterol levels were reduced by  $0.349 \pm 0.105$  mmol/l ( $-6.7\%$ ) during the active phase in the hypercholesterolemic participants ( $>5.172$  mmol/l,  $n = 13$ ,  $P = 0.061$ ). For normocholesterolemic ( $n = 15$ ) participants, the reduction was  $0.212 \pm 0.105$  mmol/l ( $-4.0\%$ ,  $P = 0.062$ ). There were four



**Figure 3** (a) The relationship between changes (active phase – control phase) in total cholesterol levels and changes in apolipoprotein B levels (active phase – control phase). (b) The relationship between changes in total cholesterol and changes in low-density lipoprotein (LDL) cholesterol levels.  $N = 28$  for both figures.

participants whose baseline triglyceride levels were clearly above the normal triglyceride distribution as demonstrated by the Kolmogorov–Smirnov normality test (SPSS version 17). We have reported previously that obese patients with hypertriglyceridemia showed significant reductions in total cholesterol (4); we therefore divided the participants according to their baseline triglyceride levels. The participants with elevated baseline triglyceride levels ( $>2.26$  mmol/l,  $n = 4$ ) had a reduction of  $0.582 \pm 0.127$  mmol/l ( $-11.1\%$ ) in cholesterol levels in the active phase ( $P < 0.02$ ) while those with normal triglyceride levels ( $n = 24$ , all below 1.69 mmol/l) showed a nonsignificant reduction in cholesterol of  $0.224 \pm 0.116$  mmol/l ( $-4.3\%$ ,  $P = 0.074$ , Figure 4). A significant reduction in cholesterol levels was observed in the participants with high LDL-cholesterol levels ( $-0.292 \pm 0.116$  mmol/l,  $-5.4\%$ ,  $n = 22$ ,  $P = 0.04$ ). No such reduction was observed in participants with normal LDL-cholesterol levels.

No significant difference in fasting blood glucose levels was observed between the active and control phases. However, the reduction in fasting insulin levels approached significance ( $-0.159 \pm 0.081$  pmol/l,  $P = 0.06$ ) in the active phase. Serum leptin levels were reduced by 3.9% ( $-0.039 \pm 0.04$  nmol/l) in



**Figure 4** Changes in total cholesterol (active phase – control phase) based on the triglyceride and low-density lipoprotein (LDL) cholesterol status at baseline level.  $N = 28$  for both figures.

the active phase, but failed to reach statistical significance. C-reactive protein was also nonsignificantly reduced by 10.1% ( $-0.13 \pm 2.36$  mg/l) during  $\alpha$ -CD supplementation. No change in adiponectin levels was observed.

## DISCUSSION

This study differed from many other nutraceutical or pharmaceutical weight loss studies in two major aspects: First, overweight, but not obese subjects were included, which represent an important transitional group that can “transition” into obesity or back into a healthier weight class depending on modest dietary and lifestyle changes. Second, energy intake was not restricted and in fact, the participants were instructed not to change their diet and exercise habits during the study. We observed that 1 month of  $\alpha$ -CD supplementation led to significant weight loss in the compliant participants in the absence of any change in energy intake. Our findings are consistent with those of a previous clinical study in obese type 2 diabetic patients who were actually able to maintain body weight despite increasing their energy intake (4).

Other significant findings were the decreases in total cholesterol ( $-5.3\%$ ), LDL-cholesterol ( $-6.7\%$ ), and Apo B ( $-5.6\%$ ), in the absence of any other dietary modifications. Those subjects who had the highest baseline cholesterol and LDL-cholesterol tended to show the greatest reductions in those parameters when supplementing with  $\alpha$ -CD. Those participants with hypertriglyceridemia had more than twice the reduction in cholesterol levels as compared to normotriglyceridemic participants. These findings agree with previously reported findings that obese type 2 diabetic individuals with hypertriglyceridemia showed significant reduction in total cholesterol levels (4). It should be noted that in the current study, there were only four participants with hypertriglyceridemia. Even with this small

sample size, a significant reduction in cholesterol levels was still detected. These findings indicate that the reduction in cholesterol is robust and individuals with hyperlipidemia may benefit from taking  $\alpha$ -CD more than those with normolipidemia.

The effects of  $\alpha$ -CD have also been investigated in a hyperlipidemic experimental animal model: the LDL receptor knock-out mouse. These mice develop dyslipidemia at a young age and are susceptible to insulin resistance (9). In this animal model, the addition of  $\alpha$ -CD to a high fat/high cholesterol diet significantly reduced atherogenic Apo B levels (10). In addition, the fatty acid profile improved; both saturated and *trans* fatty acids were shown to be decreased in the plasma. This suggests preferential binding of  $\alpha$ -CD with saturated fats in the intestine, thus increasing their excretion as was demonstrated by Galaher *et al.* (5). Previous reports in both obese humans and animal models have shown reductions in total cholesterol ranging from 8 to 15% with  $\alpha$ -CD supplementation, yet reductions in triglyceride levels have differed greatly. Previous studies in male Wistar rats have shown impressive reductions (30%) in plasma triglycerides when  $\alpha$ -CD was administered along with a high fat diet (3). Similar to the previous study on obese type 2 diabetic individuals (4), we saw a trend but not a significant reduction in triglyceride levels during  $\alpha$ -CD supplementation. The subjects in both the current and previous studies (4) had baseline triglyceride levels in the normal range (<150 mg/dl, <1.7 mmol/l), hence no significant reduction in triglyceride levels should be expected as  $\alpha$ -CD appears to lower lipid levels most dramatically in hyperlipidemic individuals.

We also investigated the effects of  $\alpha$ -CD on glucose and insulin levels in our study participants. Although fasting glucose did not change significantly in either group, insulin decreased by 9.5%, suggesting an increase in insulin sensitivity. A dose-response study of  $\alpha$ -CD in healthy subjects demonstrated that when varying doses of  $\alpha$ -CD was provided in a 50 g white rice meal, 5 and 10 g doses of  $\alpha$ -CD reduced glucose levels 2 h postprandially compared to the control, while a 2 g dose did not show significant effects (7). In this particular study, there were no significant changes in insulin response. Although we did not observe any change in adiponectin levels in our study, Grunberger *et al.* demonstrated a significant increase in adiponectin levels in diabetic patients, while those on the placebo showed a decrease in adiponectin (4). Since adiponectin levels correlate with insulin sensitivity (ref. 11 for review) and increase with weight loss, lack of an increase in adiponectin was unexpected. This may be because baseline adiponectin levels are usually higher in individuals who do not have diabetes, making it more difficult to induce an increase (12).

When taken at a dose of 2 g  $\alpha$ -CD per fat-containing meal for a total of six tablets per day, participants in the current study did not report any adverse effects. However, a dose relationship in gastrointestinal complaints was detected by Buckley *et al.* (7) when  $\alpha$ -CD was consumed with a pure carbohydrate meal (50 g

white rice), starting at a dose of 2 g. It is speculated that 50 g of pure carbohydrate as the sole source of calories plus 2 or more grams of undigestible fiber may be too much of a carbohydrate load for some individuals' gastrointestinal tracts.

Based on the evidence from our study and other studies,  $\alpha$ -CD appears to be a safe (the Food and Drug Administration granted  $\alpha$ -CD GRAS status in 2004) and effective dietary supplement for use with normal to high fat and/or mixed meals in overweight, obese and type 2 diabetic subjects.

Our study demonstrated that supplementation of 6 g/day of  $\alpha$ -CD, without any diet or lifestyle changes, induced weight loss, reduced atherogenic lipoproteins, and increased insulin sensitivity in healthy overweight individuals. The potential benefits of  $\alpha$ -CD supplementation on reducing the risks for obesity and cardiovascular risk factor should be investigated further in long-term studies.

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#### DISCLOSURE

J.D.A. and K.-L.C.J. are principals of ArtJen Complexus Holdings Corp.

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