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THE EFFECT OF ALPHA-CYCLODEXTRIN ON ACUTE BLOOD LIPID AND GLYCEMIC RESPONSES TO A FAT CONTAINING MEAL

by

EVAN FLETCHER

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Introduction

Obesity is an ever growing problem in the United States. In the past thirty years the number of obese individuals has more than doubled, with nearly two out of every three adults being overweight or obese (1). Obesity is defined as a body mass index (BMI) over 30 kg/m² and overweight is defined by a BMI of 25-29.9 kg/m² (2). Obesity is a result of a positive energy balance, due to a sedentary lifestyle, and/or over consumption of food. Occasionally it is a result of genetic or metabolic defects but these instances are rare. Many chronic diseases have their roots from obesity. Cardiovascular disease (CVD) is the number one cause of death in the United States. Obesity is one of the major modifiable risk factors for CVD, along with smoking, diabetes, low levels of high density lipoprotein cholesterol (HDL-C), high levels of low density lipoprotein cholesterol (LDL-C), inactivity, diets low in soluble fiber and high in saturated and trans fats and cholesterol (3,4). It is recommended that individuals should reduce intake of saturated and trans fat, increase intakes of soluble fiber and omega-3 fats or fatty fish in order to reduce the risk of CVD (3). However, studies have shown that the general public in the United States does not have an adequate intake of dietary fiber, with an average intake of 12-18 g/day which is significantly below the recommended average of 25-35 g/day (2, 5) set forth by the academy of Nutrition and Dietetics.

Dietary fiber (DF) is a heterogeneous group of natural food components in unprocessed grains that includes all parts of plants that human body cannot digest. It is an important part of a healthy diet. The simple classification breaks DF into two subcategories, soluble and insoluble, based on water solubility. Soluble fibers, which are composed of pectin, gums, mucilages and storage polysaccharides, have been shown to have favorable effects on glucose and lipid metabolism (6). This is believed to be in part due to the increase in the viscosity of the luminal contents by dietary fibers (6). Insoluble fibers, which are made up of cellulose, hemicelluloses, and lignin to name a few, provide bulk to the feces as well as soften the stool. DF comes from fruit, vegetables, grains, and legumes in the diet.

DF has been proven to have many beneficial health effects. It has been shown to help promote satiety during a meal. There are several factors that come into effect to induce such benefits. The intrinsic physical properties of fiber such as gel formation, bulking, and the change in the viscosity of the gastric contents may help to play a role in delayed gastric emptying and in the increase in satiety of the consumed meal (7). This alteration may also help to lower the glycemic response of the meal by slowing the gastric absorption rate and lowering insulin response to the foods that are being consumed. This is of high importance to individuals who are diabetic. DF may also influence satiety by increasing the meal duration by increasing the mastication of the foods that are being consumed (8). In addition to increasing satiety, DF has been shown to reduce the absorption of dietary fat and cholesterol by binding bile acids, cholesterol, and free fatty acids thereby increasing bile excretion and synthesis, thus making it beneficial for the reduction of the risk of cardiovascular disease (9, 10). In particular, soluble fibers are also able to reduce blood cholesterol levels by the production of short-chain fatty acids (SCFAs) through a fermentation process of the undigested fiber by colonic microflora and can reduce liver lipid levels (11). A previous study has shown that each additional 10 g/day increase in DF intake lowers the risk of coronary events by 12% and coronary deaths by 19% (12).

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The use of supplements has become a growing practice in the public with the hope of improving health. DF is one of the supplements that have been used widely by the general public. DF supplements are taken for a range of reasons, from weight loss to general health to ease of constipation. However the efficacy of the supplements that are being consumed may often be of question. The general public's perception is often that if a product is natural then it is also both safe and highly efficacious. Unfortunately there is often little research behind a typical mass produced supplements.

Alpha-Cyclodextrin (α -CD) is a cyclic oligosaccharide derived from corn (Trade name: FBCx, ArtJen Complexus USA, LLC, Detroit MI, USA) and is currently sold as a food supplement. It is a polymer of 6 glucose units in a cyclic ring structure with the polar hydroxyl groups facing outward. The core of the ring is hydrophobic and readily binds to various hydrophobic compounds, including free fatty acids (13). It has been granted generally regarded as safe (GRAS) status from the USDA. It has been shown in both in vivo and in vitro studies that one gram of α -CD will form a stable complex with 9 grams of fat. This complex, which is resistant to normal lipolytic activities by lipases, reduces the amount of dietary fat that is absorbed and the bioavailability of the fat (14). Initial animal research had shown that α -CD reduced weight gain in rats fed a high fat diet (14). In addition these studies showed evidence that the α -CD had beneficial effects on blood lipid parameters and improved insulin sensitivity in rat models (14). When fed a high fat diet in conjunction with α -CD, serum leptin level in rats were significantly lowered and comparable to levels seen in rats feed a low fat diet (14). The addition of α -CD also resulted in 30% lower triglyceride levels than that seen in the control group (14). The insulin-glucose ratio was significantly reduced, indicating the improvement in insulin sensitivity

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(14). Rats fed a high fat diet in conjunction with α -CD showed increased fecal lipid as a percentage of total dry weight of fecal matter (14). In a separate study, specific alterations in cholesterol levels were observed in a mouse model (15). The mice that were a part of the α -CD group showed a reduction in proatherogenic apolipoprotein (apo) B-containing VLDL and LDL/IDL fractions, thus lowering the LDL/IDL to HDL ratio compared to the control group (15). In addition the ratio of Trans- plus saturated fatty acids to unsaturated fatty acids in blood showed a significant reduction (15). This is promising as research has shown Trans-fatty acids to have a positive correlation with coronary heart disease and obesity (15). In human clinical trials, studies have reported that α -CD has beneficial effects for the maintenance of body weight in obese diabetic individuals (16). If the absorption and bioavailability of the fat are altered, then the effect on the blood lipid profile may also be altered. In healthy human subjects α -CD has been shown to reduce glucose response to test meals consisting of 50 g of carbohydrate (white rice) yet it did not affect the insulin response (17). This lowered glycemic response suggests that this soluble fiber may increase insulin sensitivity and may benefit individuals that have dyslipidemia, type-2 diabetes and metabolic syndrome. In a three month, double-blinded, placebo controlled study, α -CD was shown to reduce blood lipids and increase adiponectin levels in type 2 diabetic subjects when compared to the placebo (16). Increased adiponectin levels have shown to be correlated to increased insulin sensitivity and have an antiatherogenic effect (18, 19), thus α -CD may reduce the progression of type-2 diabetes and cardiovascular disease (CVD). In addition, the α -CD group maintained their weight during the 3month study period while the individuals in the placebo group continued gaining weight at the same rate as observed before the study began (16). It appears that α -CD may be effective in

reducing and/or maintaining body weight in obese individuals with type-2 diabetes (16). It is of note that the effects of the α -CD were more pronounced in the diabetic individuals who did not require insulin therapy (16). The individuals who had hypertriglyceridemia at the start of the study experienced significant reductions in their total cholesterol levels. This study demonstrated that α -CD not only prevented weight gain but also improved insulin sensitivity in obese individuals with type-2 diabetes (16).

The fiber-fat complex appears to be unaccessible by the human digestive enzymes, thus it does not promote the gastrointestinal side effects such as bloating and steatorrhea that are associated with other weight loss products (14, 16). The fiber-fat complex is then excreted from the body in the stool while still intact (14, 20). Unlike α -CD, other weight loss products inhibit the lipase secretion thus allowing free, uncomplexed, dietary fats to pass through the digestive system. This can lead to steatorrhea and bowl incontinence (21). In this case the undesirable side effects make the product impractical for everyday use. A concern however is the effect that the α -CD may have on the fat-soluble vitamins. If the α -CD removes the fat, then the essential fat-soluble vitamins may be removed as well. However, a study showed that there was no significant difference between active and placebo groups in 25-OH- vitamin D levels after 3-month supplementation (16). It is of note that both groups did have lower levels by the end of the study, but this may be explained by the fact that this study was performed during the winter months in the state of Michigan (16). In this study, hepatic and renal function was also monitored by measuring the levels of creatinine and alanine aminotransferase levels (16). There was no change in these indicators due to the fact that the α -CD is not absorbed or metabolized.

The lipid lowering effect of α -CD is well documented, but the short term acute effect of α -CD on blood lipid levels after a fat-containing meal is not yet known. The current study was designed to investigate the effect of α -CD on acute blood lipid and glycemic responses after consuming a fat containing breakfast. This was a double blind study where the participants were given a placebo one time and the α -CD another while consuming the same meal each time. The effect that the α -CD on triglycerides post meal was an area of great interest, both for heart health and for its ability to assist in weight management as shown from a previous study (16). To obtain a baseline for the participants, a fasting blood sample was collected. The blood samples that were collected were all capillary samples from the fingers. The meals that were consumed were of a high fat and high caloric breakfast as typical of the western diet that is consumed by general population of the United States.

Research design and methods

Subjects

Thirty four healthy male (n=6) and female (n=28) adults between the ages of 18 and 65 were recruited from a university campus in the Midwest. Those who were vegetarian, pregnant, nursing, did not consume pork, or had a chronic health condition such as CVD or diabetes were excluded from this study. The mean BMI was 25.04 ±4.08kg/m², range 19.3-35.9. Participants signed a University Institutional Review Board approved consent form. This study was approved by the university Institutional Review Board.

Procedure

Written informed consent was obtained from the individuals who met the inclusion criteria and agreed to participate in the study. All participants were screened prior to initiation of the study to verify that they met all criteria. The participants were informed to arrive at the lab (Science Hall, Wayne State University, Detroit, Michigan) in the morning in a fasting state, at least 12 hours without food and only water to drink for two non consecutive days, but within three days of each other. Self-reported height and weight measurements were recorded on the first visit only. Prior to obtaining a blood sample, the fingertip was cleaned by swabbing with alcohol and then air dried. The blood sample was obtained using a pressure activated safety lancet with a depth of 2.8mm for a capillary blood sample. The blood sample, about 50ul, was collected into a capillary tube and transferred into the LDX cartridge. This LDX cartridge was inserted into a Cholestech machine (Alere, Hayward, CA). Blood measurements

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of total cholesterol, LDL, HDL, triglycerides, and glucose were obtained. Once the baseline was recorded the participants were asked to consume a breakfast that was provided to them. The breakfast was high in calories with a majority of calories coming from fat. All participants received the exact same breakfast to ensure similar caloric and fat consumption on both testing days. On one of the two days the participants received two 1000 mg tablets of α -CD, and on the other day they received two identical-looking placebo tablets. The two tablets were consumed within 10 minutes of the consumption of the breakfast and taken with water. The tablets were randomly picked by the participant on the first testing day. Finger pricks were also performed at 1, 2, and 3 hours after finishing breakfast and the two tablets to obtain capillary blood samples. Five minutes after the LDX cartridge was inserted into the machine, the results were automatically printed out via the Cholestech printer. The participants were instructed to not consume any food or drinks during the entire study period (about 4 hours), aside from water which was advised as to allow for adequate blood draw efficiency. All the participants were instructed not to participate in any strenuous exercise before the final finger prick was completed. The same procedure was used for both days. This approach was used to determine the effect and efficacy, if any, the α -CD would have on the participants' acute blood lipid and glycemic responses after consuming a fat containing meal. The placebo and α -CD tablets were unmarked and had identical appearance except that that α -CD was made with alpha-Cyclodextrin and the placebo was made with cellulose. The research protocol was approved by the Institutional Review Board of Wayne State University.

Breakfast

The breakfast consumed was a sandwich that consisted of pork based sausage, egg, pasteurized process American cheese, and an English muffin with liquid margarine. The macronutrient profile of the sandwich was 21g of protein, 30g carbohydrate, and 26g fat for a total caloric value of 440 calories with 234 calories coming from fat. There were 10g of saturated fat in the sandwich as well as 2g of sugar and 2g of fiber. This is a prime example of a typical western style breakfast. The participants were given bottled water to drink and were instructed to stay well hydrated during the process for adequate blood flow and sampling.

Chemical analyses

Blood glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride levels were determined by using a Cholestech LDX Analyzer (Hayward, CA). The devices were calibrated every day for accuracy prior to use. The safety lancets used were VitalCare 216 lancets (VitalCare Group Inc, Miami Gardens, Florida). All samples and lancets were disposed of according to University Standards with hazardous materials.

Statistics

Mean and standard deviations were calculated. SPSS statistical analysis package (IBM Corp, Armonk, New York) was used to perform the statistical analysis for this study. Paired *t*-tests were performed to compare the mean difference between the α -CD tablet and the

placebo results for all serum blood lipids and glucose levels of all the participants. The level for significance was set at p < 0.05.

Results

Blood parameters at baseline and at one, two, and three hour postprandial are presented in Tables 1 and 2 for the active and placebo phases. Blood triglyceride levels were significantly different between the active and placebo phases (p<0.01 or 0.05). The differences for glucose, cholesterol, HDL-C, and LDL-C were not statistically significant. Due to large differences between participants at the baseline, all the responses to the test meal were standardized to the baseline values (percent relative to baseline). No difference was observed between the two phases for glucose, total cholesterol, LDL, and HDL cholesterol. When post prandial triglyceride levels were expressed as percent of fasting values, there were significantly lower triglyceride levels after the α -CD supplement as compared with the placebo (Figures 1 -4). The total three hour triglyceride response to the test meal (area under the curve) was also compared. The total area under the curve after α -CD supplement was significantly lower than that observed after placebo. No other total response difference was identified (Table 2).

three hour's postprandial (mean±SD) during α -CD trial.				
	Baseline	1 Hour	2 Hours	3 Hours
Triglyceride	105 ± 57	112.2 ± 49	127.7 ± 45	116.1 ± 43
Total Cholesterol	178.8 ± 39	173.5 ± 40	173.5 ± 40	175 ± 43
HDL-C	52.9 ± 17	51.5 ± 16	55.3 ± 16	52.5 ± 17

101.3 ± 32

98.8 ± 23

96.1 ± 34

90.3 ± 11

99.6 ± 34

87.1 ± 6

LDL-C

Glucose

104.5 ± 36

89.3 ± 9

Table 1: Blood levels of TG, TC, HDL-C, LDL-C and glucose (mg/dL) at baseline, one, two and three hour's postprandial (mean \pm SD) during α -CD trial.

	Baseline	1 hour	2 hours	3 hours
Triglyceride	95.3 ± 40	124 ± 63	135 ± 51	134 ± 58
Total Cholesterol	179 ± 41	176 ± 40	175 ± 38	178 ± 40
HDL-C	56 ± 17	51.7 ± 17	55.2 ± 15	52.7 ± 15
LDL-C	104.9 ± 31	97.5 ± 33	91 ± 29	98.7 ± 32
Glucose	91.7 ± 10	99.5 ± 25	90.5 ± 13	90.5 ± 12

Table 2: Blood levels of TG, TC, HDL-C, LDL-C and glucose (mg/dL) at baseline, one, two and three hours postprandial (mean±SD) for placebo trial.

	Placebo	α-CD	P Value
LDL	285 ± 35	271 ± 28	.15
Glucose	309± 18	305 ± 29	.59
HDL	300± 48	292 ± 42	.48
Cholesterol	291 ± 17	295 ± 12	.36
Triglyceride	419 ± 97	359 ± 107	.025

Table 3: Area under the curve (mg/dl/ 3 hr) for the placebo and the α -CD phases.

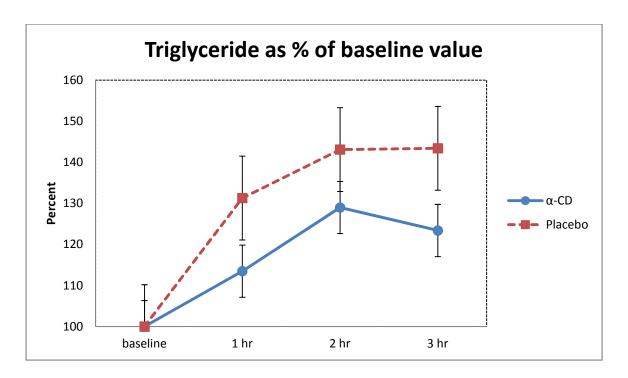


Figure 1. Triglyceride responses after the test meals as percent of the baseline. The percent response was significantly less in the α -CD phase than the placebo phase.

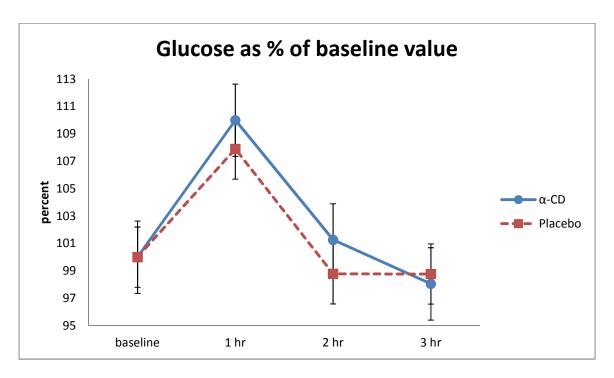


Figure 2. Glucose responses after the test meals as percent of the baseline value. There was no statistically significant difference between the placebo and the α -CD.

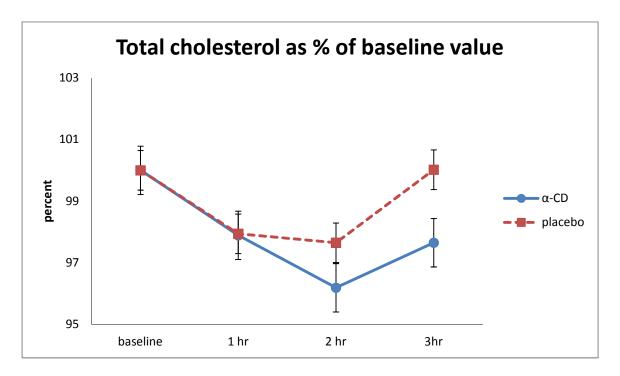


Figure 3. Total cholesterol responses after the test meals as percent of baseline. There was no statistically significant difference between the two phases.

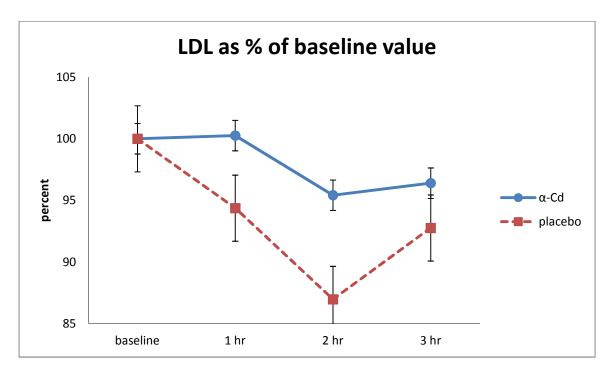


Figure 4. LDL responses after test meals as percent of baseline. There was no statistically significant difference between the two phases.

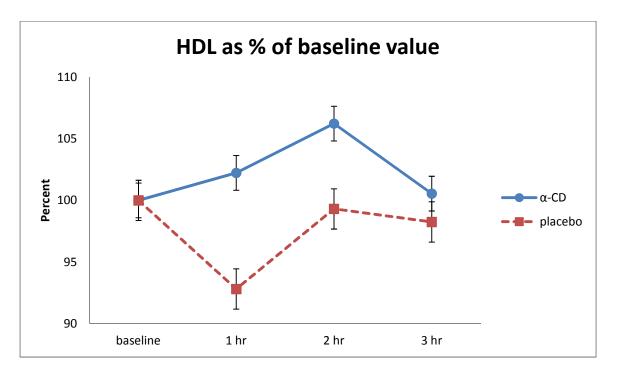


Figure 5. HDL responses after test meals as percent of baseline value. There was no statistically significant difference between the two phases.

Discussion

In this study we investigated the effects of α -CD on acute blood lipid and glycemic responses to a fat containing meal. The results showed that blood triglyceride levels were significantly lower after a fat containing meal supplemented with α -CD in comparison to the ingestion of a placebo. This is due to the ability of α -CD to form a stable complex with dietary fat while in the gut (14). Due to this ability to form a stable complex, α -CD may be beneficial to individuals who are at an elevated risk for cardiovascular disease because of hyperlipidemia. Hypertriglyceridemia (hTG) is a condition in which triglyceride levels in the blood are constantly at an elevated level. This condition is very prevalent in the United States and is of increasing concern in many industrialized countries (22). It is often exacerbated by diabetes mellitus, obesity, and sedentary lifestyle (23). Studies have shown that hTG and hyperlipidemia are risk factors for coronary artery disease (23, 22). Postprandial increases in TG may have health consequences as well, as oxidative stress and increased markers of inflammation have been reported as a consequence of hyperlipidemia following consumption of a high fat meal (24). Bansal et al. (2007) have reported that elevated triglyceride levels 2-4 hours postprandial have an independent and strong association with adverse cardiovascular events in women (25). Nordestgaard et al. (2007) have reported similar findings in a large Danish study of both men and women (26). The significant acute reduction of blood triglyceride levels in this study, in conjunction with the previous studies that showed reduction in triglycerides, leads to the conclusion that α -CD is beneficial to individuals suffering from hTG and is beneficial for heart health.

Previous studies have shown that α -CD has the ability to regulate and/or prevent weight gain (16). While our study did not measure weight gain or loss and was a short term study, the ability of the α -CD to reduce the triglyceride level may have a direct link to the prevention of weight gain. If the α -CD is bound to the triglyceride in the gut and forming a stable complex that is easily excreted from the body, then the body is not absorbing the calories that come from the dietary fat source. This may explain why previous studies have shown that supplementing with up to 6g/day of α -CD can prevent weight gain and perhaps may assist in the induction of weight loss (27).

While we hypothesized that the α -CD would lower the glucose response based on a previous study (17), our results did not show any significant reduction. However this may be in part due to the high percentage of calories from fat in the breakfast used in the current study that the postprandial glucose response may be blunted. Dietary fat has shown to also inhibit the release of insulin after a meal (28) and hence blunted the effects of α -CD on blood glucose levels. In a previous dose response study it has been shown that the addition of 5g or 10g of α -CD, in conjunction with a meal of 50g white rice, resulted in a statistically significant reduction in the incremental area under the curve for plasma glucose levels post prandial (17). The dose of α -CD in the current study was 2g. Due to the dosage of α -CD being significantly smaller, this may have led to the result not being what we had expected. In a previous study, it was shown that the addition of 2g of α -CD did not show significant effects on glucose levels but adiponectin levels were increased (16). A separate study showed that insulin decreased by 9.5%, although there was no significant change in fasting blood glucose (27). These data demonstrated that there was increased insulin sensitivity after α -CD.

There was no significant reduction in the total cholesterol levels. Significant alteration of total cholesterol would take a longer period of time to achieve. Due to the short term acute nature of our study, we did not predict significant changes in total cholesterol or its component levels. A previous long term study has shown a significant reduction in total cholesterol levels, approximately a 5.3% reduction (27). The largest decrease was shown to be in individuals with higher baseline cholesterol or triglyceride levels (27). In conjunction with the significant reduction in triglycerides in this study, it appears that α -CD can be beneficial to individuals with hypertriglyceridemia or hypercholesterolemia.

Similar to the result of the total cholesterol, there was nosignificant change in LDL levels. This again was as expected due to the short term nature of this study. To achieve significant change in LDL, a longer study period would be necessary. Comerford et al have reported that long term supplementation with α -CD can reduce LDL levels up to 6.7% and Apolipoprotien B(pro-atherogenic) up to 5.6% (27). This was achieved without any dietary modifications. In animal models, α -CD has been shown to significantly lower atherogenic Apo B and improve overall fatty acid profile in LDL receptor knockout mice (15). Reduction in LDL is beneficial to cardiovascular health. The effects of α -CD should be further studied for a longer period of time and on a large population with hyperlipidemia to determine its long term health beneficial effects.

There was no significant reduction of HDL after consumption of α -CD. In a previous study, α -CD had shown an increase in mean HDL but the change was not significantly significant (16). Due to the ability of HDL to act as part of reverse cholesterol transport, the lack of

reduction of this lipoprotein is beneficial. An increase in this lipoprotein is viewed as having a positive health effect. If the α -CD is only affecting the total and LDL cholesterol levels but not impacting the HDL cholesterol, this would be beneficial in obtaining a healthier lipoprotein TC/HDL ratio. The effect of α -CD on HDL should be studied further in order to ascertain if it has long-lasting heart healthy benefits in regards to this lipoprotein particle.

There were no adverse side effects reported by the study participants. Previous studies have shown minimal side effects, mostly limited to gastrointestinal complaints of discomfort when the dose was too high (17). The exact cause of the gastrointestinal upset is not known but is suggested that it may be due to the high carbohydrate load and that some individuals may not be able to process the amount of carbohydrate ingested. For individuals with habitual low fiber intake, sudden increase in fiber intake may also contribute to some of the GI discomfort. However, no such adverse side effect was reported by the participants in the current study.

In summary, this short-term study showed that the supplementation of 2g α -CD with a fat containing meal significantly lowers blood triglyceride levels. The improvement shown in this study, as well as previous studies (14, 15, 17, 20, 27) demonstrates that there is a beneficial effect in supplementation with α -CD for improvement in blood lipid levels. Further long-term clinical studies should be performed for more indications on the health benefits of α -CD had CVD, type-2 diabetes, inflammation, and obesity in humans.

Limitations

There were some limitations to this study. The main limitation was that although participants were instructed to not eat anything for 12 hours prior to the study, they were not monitored and it was impossible to guarantee that nothing was consumed. However, this uncertainty was taken care of by calculating the blood parameters as percent of the baseline levels. Although most participants were in the lab during the rest periods between the blood samplings, some had to attend classes or other activities and it was taken as participants' words that they did not consume anything but water or do any vigorous activities. If something had been consumed that may result in a lesser effect of the α -CD on the target levels. Throughout the study there were also some results that the Cholestech LDX Analyzer was not able to report. Although the exact reasons for this are not known, it is speculated that the cold temperature of the lab was responsible for this. This was rectified by placing a space heater in the lab in a close proximity to the area where the cartridges were stored. There were also cases that not enough blood was collected into the capillary tubes. Dehydration was suspected to cause this. All participants were encouraged to drink more water during the three hour study period. The study also was of limited size and length. Some participants were not able to return for a second day of testing. These individuals were omitted from the study. Future studies should recruit a larger sample in order to overcome these problems of losing participants.

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ABSTRACT

THE EFFECT OF ALPHA-CYCLODEXTRIN ON ACUTE BLOOD LIPID AND GLYCEMIC RESPONSES TO A FAT CONTAINING MEAL

by

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Degree: Master of Science

Obesity and hyperlipidemia have become major concerns in the United States over the past 30 years. Alpha-Cyclodextrin (α -CD), a naturally occurring soluble dietary fiber, has been shown to reduce dietary fat absorption and improve blood lipid levels in an animal model (mouse and rat) and in human studies. In the current double blind study, 34 healthy male and female participants were recruited to test if α -CD had any acute effect on blood lipid and glycemic responses to a fat containing meal. The participants received the α -CD on one occasion and a placebo the other to determine if there was any difference in the resulting acute blood lipid and glycemic responses. When the α -CD was consumed with the meal, the blood triglyceride levels showed a significant reduction post meal (placebo=419 ± 97 vs. α -CD= 359 ± 107) when compared to the placebo phase. The results for blood glucose, total cholesterol, low-density lipoprotein, and high-density lipoprotein did not show any significant difference between the two phases. These results suggest that α -CD may be beneficial for individuals who suffer from hypertriglyceridemia.

AUTOBIOGRAPHICAL STATEMENT

On my journey through my college career, as the first male in my family to do so, like most students I was lost. But after taking an introductory nutrition class at Wayne State University I had found something to be passionate about. I had found something that made sense to me and that I enjoyed learning about. After earning my Bachelor's degree I went on to work on obtaining a Master's degree under the advisement of Dr. Cathy Jen. Dr. Jen opened my eyes to the endless possibilities that nutrition has on health and wellbeing. In doing my research with her, and through my advanced course work, and have found what I want to do with my future. I want to obtain a PhD in a medical field so that I may help to bridge the gap between Nutrition and Medicine. Through my own research I hope to continue to build on this field and someday teach the next generation to lead us.