Effects of Corn Flour Consumption on Cardiovascular Disease in Adults with High Cholesterol

by

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ABSTRACT

The prevalence of cardiovascular diseases, closely associated with elevated cholesterol levels, remains a significant public health concern worldwide. Dietary interventions, particularly the consumption of whole grains, have been advocated for their potential in reducing cholesterol levels and mitigating cardiovascular risk. However, the specific impact of corn flour, a staple in many diets, on cholesterol modulation remains underexplored. This thesis aims to address this gap by exploring how three varieties of corn flour (refined, whole grain, and excellent fiber mixture) provided by the North American Millers Association Corn Division (NAMA) affect both LDL cholesterol levels and triglycerides. This study was conducted using a randomized-single blinded crossover design. There were three treatment periods that were each 4-weeks long, each treatment period consisting of a different flour treatment. There was a 2-week washout period in between each treatment making the study a total of 16 weeks. During each treatment period, blood samples were collected from each participant to analyze LDL and triglyceride levels. At the beginning and end of each treatment period, two blood samples were taken to account for day-to-day variability. Pre-intervention LDL cholesterol levels were compared to post-intervention LDL cholesterol levels using a general linear model. This study found that LDL cholesterol levels were significantly reduced by the excellent fiber mixture by ~10 mg/dL. Whole grains and refined grains, however, had no significant effect on LDL cholesterol levels. None of the corn flour treatments had a significant effect on triglyceride levels. The overall results of the study indicated that implementing the excellent fiber mixture into the diet could be effective in reducing risk for cardiovascular disease.

DEDICATION

I would like to dedicate this thesis to my mom, dad, and sister, Hilary, Brent, and Abby Probst. Thank you for being so supportive throughout my entire graduate school career. It has been some of the highest highs and lowest lows of my life and I truly could not have gotten through it without you three.

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CHAPTER 1

INTRODUCTION

One person dies from cardiovascular disease every 34 seconds in the United States.[1] Globally, it is the leading cause of death, and the number of cases is still rapidly increasing.[1] There is an urgency to reduce both cardiovascular disease risk and its prevalence because of the strong association it has with morbidity and mortality. In fact, one in every five deaths in the United States is caused by cardiovascular disease.[1] The magnitude of cardiovascular disease burden is polarizing and is continuing to rise at an alarming rate. Further research needs to be done to manage the incidence of cardiovascular disease and reduce its risk factors.

Purpose of Study

There are many different risk factors for cardiovascular disease. While some are modifiable and others are not, some risk factors include high blood-pressure, diabetes, obesity, smoking, unhealthy diet, and physical inactivity. A strong association has been reported between reduced risk for cardiovascular disease and consumption of whole grains.[2] Whole grains are a great source of dietary fiber and resistant starch and are thought to produce a positive effect on cholesterol levels.[2] Cereal and staple grains (wheat and oats) have the ability to influence cholesterol levels, potentially because of nutritional components such as fiber.[2]

There are two main types of fiber in the diet: soluble and insoluble. Soluble fibers can be found in foods like fruits and vegetables while insoluble fibers are more generally found in cereal and whole grain products.[3] Fermentation of most dietary fiber occurs in the gastrointestinal tract, but soluble fiber tends to ferment more readily than insoluble cereal fibers.[3] The laxative effects of coarse wheat was first described by Hippocrates, and interest in the health benefits of dietary fiber emerged in the 1920's through publications like that by Kellog.[3,4] Kellog explored the health benefits of bran such as laxation and disease prevention. In the 1970's, publications from Burkitt emphasized the protective effects of fiber for diabetes mellitus, colon cancer, and obesity.[5] Current fiber intake recommendations in the United States are between 30 and 35 grams per day for men and 25 and 32 grams per day for women.[5]

One of the main biomarkers of cardiovascular disease is the measurement of circulating blood cholesterol levels. People with high LDL cholesterol and low HDL cholesterol are at an especially high risk. Cholesterol can be detected and measured in fasting plasma, and this method was used to measure participants' LDL, HDL, and triglyceride levels throughout the study.

There has been extensive research on how modifiable risk factors and pharmaceutical interventions can reduce cardiovascular disease symptoms. While dietary interventions such as whole grains have been investigated, the research on corn flour is scarce. Corn, or maize, is an important crop globally as it contains phytochemical compounds and is a source of nutrition.[6] These phytochemicals play an important role in disease prevention. The decoction of maize silk, roots, leaves, and cob are used for nausea, vomiting, and other stomach problems, while the resistant starch from maize reduces risk of cecal cancer, atherosclerosis, and obesity-related complications.[6] These benefits from corn engender the belief that corn flour could potentially lower cholesterol levels and reduce cardiovascular disease risk. The goal of this study is to lower cholesterol levels through dietary changes, specifically by implementing three different types of corn flour into the diet and looking at their effects on cholesterol levels.

Research Aim and Hypotheses

The overarching aim of this study is to explore corn flours containing different levels of fiber and determine the effects that each one has on cardiovascular health in adults with high LDL cholesterol levels. The three types of flour are: (1) whole grain corn flour, (2) refined corn flour, and (3) a novel mixture of corn bran derived from whole corn meal mixed with refined corn flour, which will be referred to in the present article as the excellent fiber mixture. The first aim of this study is to investigate the effects of these three corn flours on LDL cholesterol levels after four weeks of consumption in adult males and females who are not on statin drug therapy and who have elevated LDL (>110 mg/dL) cholesterol levels. The authors hypothesize that the whole grain and excellent fiber mixture will be effective in lowering LDL cholesterol in these adults compared to the refined corn flour mixture. The second aim of this study is to measure and evaluate how the different corn flours affect triglyceride levels in the adult participants with high cholesterol levels. The authors hypothesize that the whole grain and excellent fiber mixture will be more effective in lowering triglyceride levels compared to the refined flour mixture.

Significance of Study

Research has found cereal fiber to be most effective at lowering cholesterol and lowering risk for cardiovascular disease.[3] Corn flour and its effect on cholesterol levels, however, is less explored. The research aims proposed above will add to the literature by investigating the effects of corn flour and fiber in lowering both cholesterol and triglyceride levels.

Definition of Terms

- Cereal fiber: fiber derived from grains
- Excellent Fiber Mixture: a novel mixture of corn bran derived from whole corn meal mixed with refined corn flour
- Cardiovascular Disease: a group of disorders of the heart and blood vessels
- LDL cholesterol: low-density lipoproteins
- HDL cholesterol: high-density lipoproteins
- Triglycerides: main constituent of natural fats and oils; high concentration in the blood indicate elevated risk of stroke

CHAPTER 2

REVIEW OF LITERATURE

Cardiovascular Disease Background

Cardiovascular disease is a group of diseases affecting the blood circulatory system. It is the leading cause of death globally.[7] The rate of deaths from cardiovascular disease is consistently increasing; the number of deaths had nearly doubled from 1990 to 2019.[7] Not only is it the leading cause of death, but it is also the number one cause of disease burden in the world.[7] The term 'cardiovascular disease' encompasses all types of afflictions that affect the blood circulatory system, including the heart and vasculature, which displace and convey the blood, respectively.[8] Types of cardiovascular diseases include coronary artery disease, widely known as heart disease, cerebrovascular disease (stroke), peripheral artery disease, and aortic atherosclerosis, which will be discussed throughout the present article. [9] Being a multicausal disease, many studies focus on extracting environmental, individual, and societal risk factors that aim to reduce the risk factors.[8] While there are multiple causes for this ever-prevalent disease, there are also many lifestyle changes that can prevent or lessen symptoms.

To better understand cardiovascular disease, it is important to understand the pathophysiology of the disease. A precursor of cardiovascular disease is atherosclerosis. Atherosclerosis is the primary cause of both heart disease and stroke and is the underlying cause of about 50% of all deaths.[10] It is a progressive disease and chronic inflammatory condition characterized by the accumulation of lipids and fibrous elements in the large arteries.[10] In this process, monocytes and lymphocytes are recruited to the artery wall, causing calcification and accumulation of lipids. This triggers the blood vessels to narrow and activates inflammatory pathways.[11] The narrowing of the vessels and inflammatory pathway activation cause atheroma plaque formation, leading to cardiovascular complications.[11] Epidemiological studies have found a plethora of risk factors for atherosclerosis, including both genetic and environmental risk factors.[10] These risk factors are directly linked with those of cardiovascular disease and ultimately lead to myocardial infarction, heart failure, or stroke.[12] Cardiovascular diseases can manifest in a few different ways. Some of them are asymptomatic such as silent ischemia, while others present with symptoms like the chest pain that is associated with myocardial infarction.[9] Physical examination and clinical history are imperative in diagnosing cardiovascular disease. The treatment of cardiovascular disease including medications and lifestyle changes which will be further discussed. However, focus of the disease has shifted to prevention methods rather than treatment given the steady increase in cases.[9]

Risk Factors for Cardiovascular Disease

The leading risk factors of cardiovascular disease are high blood pressure, diabetes, obesity, physical inactivity, hyperlipidemia, unhealthy diet, and smoking, which are considered modifiable risk factors, as well as age, gender, and genetics, which are non-modifiable risk factors. Although these risk factors are not considered causal for cardiovascular disease, research suggests that they may play a role in disease development. Finally, hypertension can be combated via drug therapy, commonly by statin drugs.

As previously stated, the risk factors for cardiovascular disease are not considered causal; however, hypertension displays the strongest association of causality and highest prevalence of exposure.[13] This is the strongest risk factor for cardiovascular disease.

Hypertension is defined as systolic blood pressure greater than or equal to 130 mmHg or diastolic blood pressure greater than or equal to 80 mmHg, or currently taking medication to lower blood pressure.[14] Large cohort studies have proven that high blood pressure is a key risk factor for heart failure, coronary heart disease, and stroke.[15] Data from the National Health and Nutrition Examination Survey done in 2017-2018 found that hypertension was present in about 45% of the population, and is higher in men than women. They also found that the prevalence of hypertension increases with age.[14]

Type 2 diabetes is another chronic disease that is common across the world and is continuing to rise. In individuals with type 2 diabetes, cardiovascular disease is the most common cause of mortality as there is a close link between diabetes and CVD.[16] Both diseases have overlapping risk factors such as hypertension, dyslipidemia, and obesity, creating a close link between the two conditions. In patients with type 2 diabetes, the biological mechanisms associated with diabetes mellitus independently increase the risk of cardiovascular disease.[16] Therefore, it is essential to target cardiovascular risk factors in these patients to minimize long-term complications of the disease.[16]

Obesity directly contributes to many of the leading risk factors of cardiovascular disease and can lead to the development of cardiovascular disease alone. Recent studies have found that waist circumference, independent of body mass index, is a risk marker for cardiovascular disease.[17] Obesity is closely related to the process of atherosclerosis and can accelerate the early stages of it via insulin resistance and inflammation.[17] Insulin resistance alone is related to dyslipidemia and metabolic syndrome, and is positively associated with atherosclerosis and therefore CVD. The likelihood of low-density lipoprotein oxidation increases with obesity due to increased inflammation, further increasing risk for cardiovascular disease.[17] A high population meta-analysis of adults found that BMI in the overweight and obese range was associated with elevated risk of coronary artery disease.[18] With each increasing level of BMI, a higher risk for coronary artery disease and cardiovascular mortality was found.[18] As evident in current research, obesity is a major driving force for cardiovascular disease risk as it has been associated with increased blood pressure, cholesterol, inflammation, LDL, and glucose levels.

Physical activity is essential in maintaining a healthy lifestyle and decreasing risk for cardiovascular disease. The World Health Organization recommends that adults between 18 and 64 years old should get 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity per week.[19] Independent of age, sex, and pre-existing CVD, increased physical activity levels have been found to be negatively correlated with cardiovascular mortality.[19] Limited physical activity or lack of physical activity completely is not just associated with cardiovascular disease risk but can also lead to a cascade of negative metabolic processes. This includes increased risk of disorders like diabetes, osteoporosis, or cancer.[19] A recent meta-analysis followed over three million participants over a median period of 12 years. It was found that people who met the World Health Organization's physical activity guidelines had a 17% lower risk of cardiovascular events and a 23% lower risk of cardiovascular mortality.[20]

While diet is closely related to cardiovascular disease, the findings are not as significant as other risk factors and there are many confounding variables when it comes to measuring dietary intake. Consuming an unhealthy diet, however, is a significant risk factor for cardiovascular disease, specifically high consumption of saturated fats, sugar, and sodium intake.[21] A diet high in alcohol consumption is also associated with higher risk of coronary heart disease and myocardial infarction.[22] Excessive alcohol consumption contributes to a greater burden of cardiovascular disease and overall mortality risk.[22] People who abstain from drinking completely or only imbibe moderately have been observed to have a much lower risk of cardiovascular disease in epidemiological studies.[22]

Smoking is a modifiable risk factor for cardiovascular disease and plays a big part in atherosclerotic cardiovascular disease.[23] Smoking and effects from secondhand smoke account for more than 30% of mortality from coronary heart disease, and causes many proatherogenic effects including inflammation, vasomotor function, and negative impacts on platelet function.[23] These effects double a person’s risk of mortality compared to a non-smoker. Data from the World Health Organization determined that 10% of all cardiovascular diseases are attributed to smoking.[23] Likely due to genes involved in thrombin signaling, female smokers seem to have a greater risk of developing cardiovascular disease than males who smoke the same amount. They present with a 25% higher risk of cardiovascular disease development than a man with the same smoke exposure.[23]

Family history is another risk factor related to cardiovascular disease. Studies have found positive relationships between reported family history of CVD and perceived risk of CVD development.[24] Family history presents as an independent risk factor; there is a linear increase with premature coronary heart disease and number of affected family members.[25]

The final risk factor of cardiovascular disease are cholesterol levels, which are the focus of the present article. High cholesterol levels are associated with high cardiovascular disease risk in young adults, while lower cholesterol levels are associated with a significantly lower risk for the disease.[26] Cholesterol is a modifiable risk factor, and just a 10% decrease in total blood cholesterol levels can reduce risk for cardiovascular disease by about 30 percent.[27] Cholesterol levels can be lowered through many lifestyle changes such as exercise, dietary changes, weight loss, or pharmaceutical interventions.

Cholesterol

The role of cholesterol in the human body is to enable normal cell function, which is essential for human life. It acts as a precursor in the synthesis of steroid hormones like cortisol and aldosterone, vitamin D, and sex hormones like testosterone and estrogen.[28] Cholesterol also aids in digestion and facilitates the absorption of the fat-soluble vitamins A, D, E, and K.[28] Cholesterol is a lipophilic molecule, meaning it needs to be carried by lipoprotein particles to transport through the bloodstream.[28] It can be carried by high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and chylomicrons.[28] These lipoproteins can be detected and measured in fasting plasma to find the amount of cholesterol in the bloodstream, which is beneficial in clinical settings.[28]

While cholesterol is an essential molecule for the human body, it is also something that can be harmful when it reaches high levels in the bloodstream. When LDL levels are too high, risk for atherosclerosis, and therefore, cardiovascular disease, increases.[29] Approximately two-thirds of circulating cholesterol is transported by LDL particles to peripheral tissues and therefore LDL acts as a major cholesterol transporter.[28] LDL cholesterol is the most atherogenic lipoprotein; a decrease in LDL cholesterol significantly decreases the risk for cardiovascular disease mortality.[28] Lifestyle changes that were previously discussed such as smoking cessation, increasing physical activity levels, and reducing saturated fat intake while increasing fiber consumption can be implemented to reduce LDL cholesterol levels.[28]

HDL collects excess cholesterol in the bloodstream and return it to the liver for excretion, making it beneficial for cardiovascular health. This cholesterol is often referred to as the ‘good’ or ‘beneficial’ cholesterol. Unlike LDL, it has been found to have anti-atherogenic properties and provides a positive effect on the body. A person who is at the greatest risk of cardiovascular disease is someone with high LDL and low HDL levels.[28] Lipoproteins exist in other forms such as chylomicrons, intermediate-density lipoproteins (IDL), and VLDL. Hyperlipidemia, the term for increased blood lipids, is another highly prevalent chronic condition that is often treated in the United States.

Measuring cholesterol levels and obtaining lipid profiles can help in both diagnosing and managing diseases. Cholesterol levels can be measured from serum through a blood draw.[30] A non-fasting lipid test can be done anytime but a fasting lipid test requires twelve hours of fasting except for water. Non-fasting lipids are beneficial as it is simple for the patient and does not rely on their compliance. Fasting lipid panels are recommended for patients with type 2 diabetes, obesity, or patients taking medications that may affect lipid levels like beta blockers. Triglyceride levels can also be affected by the patients last intake, and this acts as a limitation in studies. A fasting lipid panel is more accurate overall and presents less limitations.

Interventions and Treatments for Cardiovascular Disease

Pharmaceutical Interventions (Statins)

Drugs known as statins are often used as both primary and secondary prevention methods for cardiovascular disease. A total of 19 randomized clinical trials compared statins to a placebo in adults who were at increased risk for cardiovascular disease but had not experienced prior CVD events.[31] The participants who had statin therapy had a decreased risk of both all-cause and cardiovascular mortality, stroke, and myocardial infarction.[31] These benefits were consistent in both clinical and demographic subgroups, but the overall benefits appeared higher in groups of people at a higher baseline risk.[31]

Another review examined 15 studies in which statin therapy was used as primary and secondary prevention. For statin use as primary prevention, they found that statins reduced the risk of cardiovascular mortality and the risk of a coronary event occurring.[32] As far as secondary prevention, statin therapy reduced the risk of a coronary event, cardiovascular mortality, and all- cause mortality.[32] There was also a reduced risk for fatal and nonfatal strokes in secondary prevention statin therapy.[32]

Physical Activity and Weight Loss

There are many possibilities for lifestyle interventions that decrease risk of cardiovascular disease. One of these interventions is increasing physical activity levels. Increased physical activity levels can positively affect insulin sensitivity, blood glucose levels, improve cholesterol levels, and provide an anti-inflammatory defense.[33] In an animal study looking at diabetic rats, glucose levels were found to be much lower in the rats who had exercise training compared to those that were sedentary.[34] The rats with exercise training also had decreased body weight and lower triglyceride levels.[34] Exercise in both humans and rats promotes improved insulin resistance and increases glucose uptake, improving insulin sensitivity. HDL is more sensitive to physical activity than LDL.[33] In animal studies, it has been found that increased physical activity is associated with reduced LDL levels, but this has not been reported in human trials.[35] HDL levels, however, tend to increase in both rats and humans after engagement in physical activity.[35] Exercise, even in small amounts, fights against cardiovascular disease by attenuating sympathetic activity, heart rate, arterial pressure, decreasing inflammation, and increasing blood flow.[33] Therefore, it can be recognized as a defense mechanism against onset and progression of cardiovascular disease.

Physical inactivity alone is the fourth risk factor of death worldwide and a lack of exercise causes up to 6% of coronary heart disease cases across the world.[36] Multiple studies have found a clear dose-response relationship between increased physical activity levels and decreased risk for cardiovascular disease.[36] As a general guideline, the American Heart Association recommends 150 minutes of exercise per week to prevent cardiovascular disease. It is the duration of physical activity, not necessarily the intensity, that is beneficial and preventative towards cardiovascular disease.[36] People who have cardiovascular disease and are classified as overweight or obese are encouraged to lose 5-10% of their body fat to decrease their CVD risk.[37] Weight loss between 5-10% were found to be associated with significant improvements in cardiovascular disease risk factors at one year, but greater amounts of weight loss were associated with greater benefits.[37]

Decreased Alcohol Consumption

Observational studies suggest that light to moderate daily alcohol consumption (one to two standard drinks) is associated with a decreased risk of cardiovascular disease.[38] Heavier alcohol consumption, however, is positively associated with an increased risk of cardiovascular disease.[39] There is an exponentially greater risk of developing cardiovascular disease with higher levels of alcohol consumption.[39] When compared to nondrinkers, people who consume alcohol have a 14% increased risk of CVD risk factors like stroke.[38]

Dietary Changes

Diet has an indisputable effect on many aspects of the human body, and disease is no exception. The current dietary recommendations suggest consuming a diet high in fruits, vegetables, whole grains, nuts, and legumes.[40] The current recommendations include moderate consumption of low-fat dairy and seafood, and low consumption of sodium, refined grains, sugar-sweetened beverages, and processed meats.[40] Improving dietary composition (via these guidelines) and reducing consumption of excess calories may prevent both primary and secondary cardiovascular events.[40] Intake of fruits and vegetables, for example, was found to be inversely associated with cardiovascular disease risk.[41] Whole grain intake is associated with a much lower risk of CVD while refined grain consumption has an increased, but nonsignificant, association with CVD.[42] Considering meat consumption, intake of processed meat like hot dogs or deli meat shows an increased risk of cardiovascular disease in a strong, linear fashion.[43] Increased consumption of red meat has also been found to increase risk of mortality from cardiovascular disease.[43]

Fiber specifically has been consistent in reducing risk of CVD and improving risk factors in dietary intervention and observational studies.[44,45] A seven-gram increase in fiber per day was found to decrease incidence of coronary heart disease in a meta-analysis of 22 cohorts.[44] Cereal fiber alone has been found to reduce all-cause mortality among myocardial infarction survivors, revealing a 27% reduction risk of death in people who had the highest consumption of cereal fiber.[46] Fiber reduces LDL cholesterol levels, decreases serum triglycerides, and helps regulate glucose response, all leading to reduced cardiovascular disease risk.[40]

Dietary patterns and quality can also be used to measure and assess eating habits.[40] Both the Mediterranean and DASH diet are associated with a 20% decreased risk of CVD mortality.[47] The DASH diet, dietary approaches to stop hypertension, is highly recommended by the American Diabetes Association and American Heart Association guidelines.[48] This dietary pattern consists of fruits, vegetables, low-fat dairy, whole grains, nuts, and legumes and limits sweets, saturated fat, red and processed meats, added sugars, salt, and sugar-sweetened beverages.[48] Adoption of the DASH diet is associated with decreased incidence of cardiovascular disease, coronary heart disease, stroke, and diabetes in prospective cohort studies.[48] In controlled trials, the DASH diet was associated with decreases in blood pressure, total cholesterol, LDL cholesterol, fasting blood insulin, and body weight.[48] That being said, current evidence suggests adaptation of the DASH diet can decrease incidence of cardiovascular disease and improve blood pressure.

The DASH diet provides the two main types of dietary fiber: soluble and insoluble. Since this diet is mostly plant-based, the fiber provided is primarily derived from plant contributors of fiber such as leafy greens and fruits.[49] Soluble fiber is typically found in fruits and vegetables while insoluble fiber is provided from products like cereals and whole grains.[50] Soluble fiber is resistant to digestion but is partially fermented in the large intestine. When in the large intestine, soluble fiber is fermented by bacteria to short-chain fatty acids.[51] The production of these short-chain fatty acids produces a hypocholesterolemic effect of soluble fiber.[52] Insoluble fiber, however, moves through the entirety of the digestive tract intact.[51] Soluble fiber tends to be fermented more readily than insoluble cereal fibers; however, cereal fibers have been found to be more effective in lowering cholesterol than fruits and vegetables.[50] The current recommendation for dietary intake of fiber is 30-35 grams per day for men and 25-32 grams per day for women. In the United States, fiber consumption is at about 50% of what it should be. Fiber can sequester cholesterol when consumed in the diet as it adds bulk to the diet, decreases hepatic absorption, and increases excretion through both bile and fecal lipids.[51] Randomized controlled trials and observational studies have found that dietary fiber can be used to complement statin therapy in lowering LDL cholesterol levels.[51] Soluble and insoluble fiber in whole grains, specifically, have health benefits that improve lipoprotein profiles helping reduce cardiovascular disease risk.

Whole grains refer to grain-based foods that utilize the entire grain in their production as opposed to removing components of it, which results in what are considered refined grains. Whole grains provide many health benefits including the provision of different types of fiber. The type of fiber in a whole grain depends on the plant it is derived from. Cellulose and lignin are types of insoluble fiber found in whole grains such as wheat bran. Whole grain sources of soluble fiber include beta-glucan, found in oats, and resistant maltodextrin, which is produced from corn. Soluble corn fiber may be effective in managing cardiovascular disease risk, but there is currently not sufficient evidence in this area.

Whole grains have been overwhelmingly found to reduce risk of cardiovascular disease and coronary heart disease. Whole grains contain the endosperm, germ, and bran while refined grains have the germ and bran removed during the milling process.[55] The outermost layer of the grain, the bran, contains nutrients such as B vitamins and trace minerals like iron, magnesium, and zinc. The germ contains vitamin E and antioxidants while the endosperm provides protein, carbohydrates, and energy.[56]

A meta-analysis found that consumption of whole grains lowers LDL and total cholesterol levels compared to non-whole grain control consumption in healthy adults. Whole grain oats were the most effective type of whole grain for lowering cholesterol levels.[2] A double-blind randomized controlled trial from 2016 compared whole grains to refined grains and looked at their effects on hypertension, body composition, and other related mediators of cardiovascular disease in obese and overweight adults. Either a whole grain diet or refined grain diet was provided to participants for two 8-week periods with a 10-week washout period in between diets. There was a significant improvement found in diastolic blood pressure levels when adults were consuming the whole grain diet. This indicates that whole grain consumption might be helpful in treating hypertension, reducing risk for cardiovascular disease.[54]

In ten different cohort studies, there was a strong cardiovascular reduction risk with higher whole grain intake. The findings of these studies suggest increased consumption of whole grains reduces the risk of chronic diseases, specifically cardiovascular and coronary heart disease.

Cereal grains are often referred to in studies about whole grains. Wheat, barley, oat, and rye all fall under the category of cereal grains. The different types and products vary in the amount of fiber they contain but have all been found to improve cardiovascular health.[57] Whole grains, or cereal grains, have been found to be the most effective dietary method of reducing cardiovascular disease risk- even more than fruits and vegetables. A randomized controlled trial fed one group of overweight and obese women a diet rich in whole grains and the other group a diet rich in fruits and vegetables to see which was more effective at lowering cholesterol levels. The results of the study suggested that a diet high in whole grains might have a more beneficial effect on lowering cardiovascular disease risk than a diet rich in fruits and vegetables.[58]

Corn and Corn Flour

While whole grains have been extensively studied, corn and corn flours have not been explored as much. To date, only a few studies have explored corn flour and its effect on lipid-lowering or lipid metabolism, however, these studies were done on rats. One of the studies done on rats found a significant decrease in serum and liver cholesterol levels after both the wheat flour and corn flour feedings.[59] While animal studies suggest a lipid-lowering effect of corn consumption, there is currently not sufficient evidence of this effect in humans.

Corn is the most highly produced grain worldwide. There are multiple ways to break down and process corn. A typical corn kernel contains mostly starch, 10% protein, and about 5% oil.[60] From a processing perspective, the corn kernel consists of the endosperm, germ, pericarp, and tip cap. The endosperm makes up 83% of the kernel and is mostly starch surrounded by protein. The germ has a high fat content with vitamin E, B vitamins, enzymes, and nutrients for corn development and growth. The pericarp is essential for its high fiber content, and the tip cap is where nutrients travel to get to the kernel.[60] There are multiple processes used in producing corn grain products.

The wet milling process of corn divides corn into starch, germ, fiber, and protein. After the corn is cleaned, it is soaked for 30 to 40 hours to initiate the breakdown of the starch and protein bonds.[61] Then, to separate the germ from the rest of the kernel, a coarse grind removes the starch, fiber, and protein surrounding it. These are all finely ground and screened to remove the fiber from the protein and starch. Finally, the starch is separated from the protein and can then be converted into other products like corn syrups via fermentation processes.[61] In addition to wet milling, there is also a dry milling process. This consists of reducing the size of the whole corn, with or without separation, so that it retains most of the original fiber and germ. Whole products are produced after the dry milling process separating the bran, germ, and endosperm. Wet maize processing, however, separates starch and protein. The different materials and equipment used to process and break down corn are readily available; however, the nutrients left after the processing can vary greatly. The nutritional components can also vary due to factors like the structure of the kernel, genetics, or environmental conditions. Nutrient loss can also occur during processing, harvesting, and transportation processes. Studies have shown that corn products provide a good source of both polyphenols and carotenoids. These nutrients are associated with decreased risk of diseases of diseases such as cardiovascular disease as they are antioxidants and act as regulators of the human body immune system.[62]

With high food demand from a growing population, corn farmers want to yield the most economic yet sustainable benefits from their crop. The average yield from corn in a traditional farming method is about 72 percent.[63] There is room to improve the yield. Since corn is the most highly produced crop, studying the benefits of corn flour consumption would be beneficial not only to people at risk for cardiovascular disease, but to farmers as well. Studies suggest that corn may be beneficial in reducing cardiovascular disease risk factors, but the research done has only scratched the surface of the potential benefits of corn and corn-based products.

CHAPTER 3

METHODS

Participants and Recruitment

Participants were recruited for this study by posted flyers, word of mouth, digital marketing through Arizona State University Tempe and Downtown Phoenix campuses. Clinics, libraries, and community centers were some of the places that flyers were posted for recruitment (see Appendix A). This study targets adult males and females (n=45) who have high LDL blood cholesterol levels but who are not taking lipid-lowering medication such as statins. Inclusion criteria for this study include healthy English and Spanish speaking males and females ages 18-70 years old with elevated circulating cholesterol levels. Elevated circulating cholesterol levels are defined as LDL-c levels greater than or equal to 110 mg/dL. If a person has LDL levels over 190 mg/dL, they can participate but they must have a letter from their doctor saying they are comfortable with them taking part in this study. Exclusion criteria consists of people who have experienced weight fluctuations of more than five pounds in the last three months. People following restrictive or specialized diets such as veganism or carbohydrate restrictive diets were excluded. Use of supplements such as fiber, antioxidants, or botanicals, people with allergies to dairy, corn, gluten, or eggs, use of antibiotics in the past two to three months, and people who use lipid lowering medication like statins were all excluded. People who took part in regular physical activity of more than 30 minutes per day for greater than or equal to five days per week or people with gastrointestinal diseases/disorders that may impair gut metabolism and function were also excluded from this study.

Study Design

This study was a randomized, single-blind, 3x3 crossover study where each individual participant served as their own control. Each participant spent a total of 16 weeks in this study. After completing the laboratory screenings and filling out consent forms, participants were fully consented. There were three intervention phases, each lasting four weeks with two-week washout periods in between the three different grain interventions (see Appendix B). In a random order, participants consumed 48 grams per day of each of the three types of corn flour mixtures. These consisted of a whole-grain corn flour (1), refined corn flour (2), and a novel mixture which is 50% refined corn flour plus 50% of corn bran derived from whole grain cornmeal and is referred to as the excellent fiber mixture (3). Participants consumed the 48 grams in two servings of 24 grams and ate them with meals or a snack at least three hours apart from each other. The grain products were provided as food items such as muffins and pita bread. They were added to participants' normal diets as a replacement for wheat, oat, and other grain products.

Blood Draw Timelines

The first visit was an eligibility verification visit where participants came to the facility in a fasted state for a blood draw screening. The nurse drew approximately 7 mL of blood to verify the presence of mild-moderately high blood cholesterol levels (LDL above 110 mg/dL). Once eligibility was verified and consent was obtained, a fasting blood draw of 40 mL was taken to complete a biomarker panel. The blood samples were sent to Sonora Quest labs where a standard lipid panel was run providing total cholesterol, HDL, LDL, VLDL, and triglyceride levels. At the second visit, another blood draw was conducted along with anthropometric data. Height, weight, waist circumference, and blood pressure were all measured three times and averaged to ensure accuracy. At visit three (test day B), a confirmatory fasting blood draw of about 7 mL was taken to measure blood lipids. This accounts for day-to-day variability and is averaged with values from the previous visit to get the most accurate measure. At this visit, participants were provided with the corn-based muffins and pita bread to be consumed during the first 4-week intervention period.

Participants were given one week of food supplies of each item to be consumed twice a day in the fourth, fifth, and sixth visits. Visit seven began at the end of the first treatment, test day A. At this visit, post-intervention testing was completed by taking a fasting blood draw of 40 mL to complete a biomarker panel. The next day, at visit eight, a confirmatory fasting blood draw of 7 mL was averaged with the previous visit's blood draw to account for day-to-day variation. Visits two through eight were repeated twice for the other two interventions, making a total of about 22 visits throughout the study. Visits 9-15 was the intervention period for the second corn flour treatment. After completing a two-week washout period, participants began the second treatment and repeated the blood draw and fecal sample timeline for the next intervention period. Once the second intervention was completed, visits 16-22 were the third and final treatment. After a two-week washout, participants began the third corn flour treatment and repeated the blood draw timelines.

<u>Muffins and Pita Bread</u>

The corn-based food given to participants was provided as either a muffin or pita bread. A standardized recipe was used when making the food and each ingredient was weighed to ensure each batch was the same. The only ingredient that differed in each recipe was the type of flour used (refined, whole grain, or excellent fiber mixture) to create a food product with a different type of flour for each intervention period. The North America Millers Association-Corn Division provided the refined and whole grain flours, while the excellent fiber mixture is a mixture of refined flour and bran. The bran and refined flour were received separately and then mixed to make a 75-gram to 165-gram ratio.

The recipe for the muffins included the corn flour variation needed for the participant, shortening, granulated sugar, salt, instant starch, native starch, maltodextrin, non-fat dry milk, whole eggs, honey, vanilla extract, baking powder, wheat gluten, enzyme softase 4040, and water. The muffins made with excellent fiber mixture provide 286 calories with 9.92 grams of dietary fiber. The whole grain muffins contain 301 calories with 1.95 grams of dietary fiber. Finally, the refined grain muffins contain 304 calories and 0.65 grams of dietary fiber.

The pita bread recipe included the variation of corn flour needed for the participant, wheat gluten, water, dry yeast, granulated sugar, salt, ICS 56, softase 4040, baking powder, shortening, and lecithin/topsithin UB. The pita containing the excellent fiber mixture provides 146 calories and 10 grams of dietary fiber. The whole grain pita provides 164 calories with 1.99 grams of dietary fiber, while the refined grain pita contains 167 calories with 0.68 grams of dietary fiber.

Clinical Measures

Questionnaires are used as a measure throughout the study starting with a general health and demographic questionnaire filled out at the eligibility verification appointment. A software program known as REDcap was used for data management and survey completion throughout the study. Dietary analysis was collected from the participant's report and recorded using the nutrition data system for research (NDSR). This software accounts for the day, time, and location the food was consumed, as well as the contents of the meal.

Laboratory Analyses and Statistical Modeling

The first laboratory visit consists of taking a fasting blood draw, completing baseline questionnaires, blood pressure, and collecting anthropometric data. The 3-day diet records were carefully reviewed for completeness and the data were analyzed using Nutrition Data System for Research (NDSR) software (University of Minnesota, Minneapolis, MN). A trained phlebotomist takes a fasting blood draw of about seven mL of blood from the patient's arm which gets examined for blood lipids via clinical chemistry analyzer, Beckman-Coulter AU480. Blood was centrifuged at 1,100 x g at 4°C for 20 minutes, plasma was separated from serum, aliquoted, and stored at -80°C for future analysis. A complete lipid panel (total cholesterol, HDL, LDL, and triglycerides) were measured in plasma using colorimetric enzyme reagents.

Anthropometrics, height (m), and weight (kg) were measured via calibrated SECA scale and wall-mounted stadiometer. Waist circumference was also measured in centimeters using a spring-loaded measuring tape taken at the umbilicus. Participants pointed their finger at the belly button for waist circumference measurement and it was taken three times to get the most accurate measurements. The average of the three measurements was recorded. Blood pressure was taken three times while the participant was seated in a comfortable, still position using an Omron IntelliSense HEM-907XL automated blood pressure monitor.

All data were evaluated for normality using the Shapiro-Wilk test. Normally distributed variables were reported as means and standard deviations while non-normally distributed variables were reported as median (interquartile range). Blood lipid data were assessed using a general linear model that included sequence (random order of treatments), period (chronological order of intervention phases), time (pre and post intervention), treatment and a nested variable [id(sequence)] to account for the repeated measures and cross-over design. This nested variable allowed every participant to statistically serve as their own control. Model residuals were inspected to ensure normality and that models met all required assumptions. Interactions including, time*treatment, were assessed and reported if statistically significant. Covariates such as body weight/BMI were included if relevant and models permitted. Only participants who completed the study from start to finish were included in the results. This allows each participant to act as their own control.

CHAPTER 4

RESULTS

Participant Characteristics

A total of 58 participants were enrolled in the study with 54 participants beginning the intervention sequence. Of these participants, 36 finished all three intervention phases to complete the entire study (Table 1). Participants were predominantly female, of Caucasian descent, and the majority of people were overweight (BMI between 25 and 29.9 kg/m^2).

Table 1. Participant Baseline Characteristics Table (N=36)

Variable	Subcategories	Mean ± SD or n (%)
Age, y		40.19 ± 13.41
Biological Sex		
	Male	15 (42%)
	Female	21 (58%)
Race		
	American Indian/Alaskan Native	0 (0%)
	Asian	5 (13.9%)
	Native Hawaiian or other Pacific Islander	0 (0%)
	African American	0 (0%)
	Caucasian	26 (72.2%)
	Individuals identifying with multiple races	2 (5.5%)
	Unknown / Not reported	5 (13.9%)
Body Mass Index (BMI), kg/m^2		28.3 ± 5.27
	Normal	10 (27.8%)

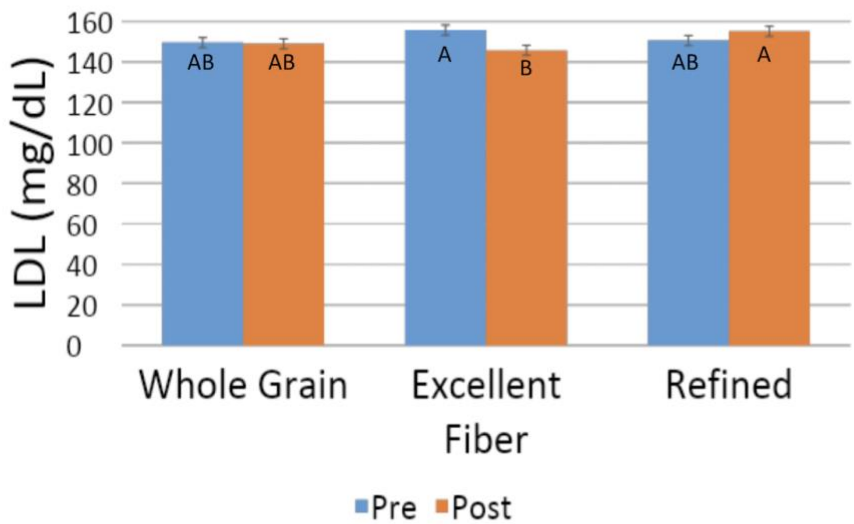
	Overweight	16 (44.4%)
	Obese	10 (27.8%)
Blood Lipids, mg/dL		
	Plasma Total Cholesterol	231.99 ± 33.92
	Plasma Triglycerides	134.90 ± 51.72
	Plasma Low Density Lipoprotein (LDL)	178.98 ± 39.74

Table 2. Daily Habitual Dietary Intakes Prior to the Three Treatment Aims for Participants with Adequate Dietary Data.[1]

Variables	**WCM (*n* = 28)**	**RCM+B (*n* = 28)**	**RCM (*n* = 28)**
Energy, kcal	1,646 ± 484	1,664 ± 577	1,763 ± 594
Carbohydrate, g	175.6 ± 93.1	170.6 ± 81.0	192.2 ± 91.3
Dietary fiber, g	15.3 ± 5.7	16.5 ± 6.6	17.5 ± 6.3
Soluble, g	4.8 ± 2.1	5.1 ± 2.3	5.5 ± 2.3
Insoluble, g	10.4 ± 4.3	11.2 ± 5.1	11.8 ± 4.8
Fat, g	70.3 ± 19.9	74.8 ± 25.5	75.1 ± 21.9
Saturated, g	20.7 ± 6.8	22.4 ± 8.8	22.4 ± 7.3
Protein, g	78.1 ± 31.4	78.8 ± 33.3	82.4 ± 30.1
Cholesterol, mg	268.5 ± 194.4	253.5 ± 180.7	265.1 ± 168.6
Minerals			
Phosphorus, mg	1,035.9 ± 295.9	1,055.3 ± 386.7	1,114.3 ± 366.0
Potassium, mg	1,935.1 ± 584.5	2,051.2 ± 808.5	2,075.7 ± 670.1
Sodium, mg	2,842.1 ± 1,479.3	2,888.0 ± 1,430.7	3,038.7 ± 1,463.1
Vitamins			
B1 (Thiamin), mg	1.6 ± 1.1	1.6 ± 1.1	2.0 ± 1.6
B2 (Riboflavin), mg	1.9 ± 1.2	1.9 ± 1.2	1.9 ± 1.2
B3 (Niacin), mg	22.3 ± 9.7	22.4 ± 11.2	25.0 ± 10.5
B5 (Pantothenic acid), mg	5.2 ± 2.2	5.1 ± 2.1	5.1 ± 1.8
Folate, mcg	333.6 ± 149.3	322.7 ± 147.6	381.1 ± 194.5

[1]Values are displayed as means ± SDs, unless stated otherwise.
[2]Data from 8 participants was not complete and thus, not included.

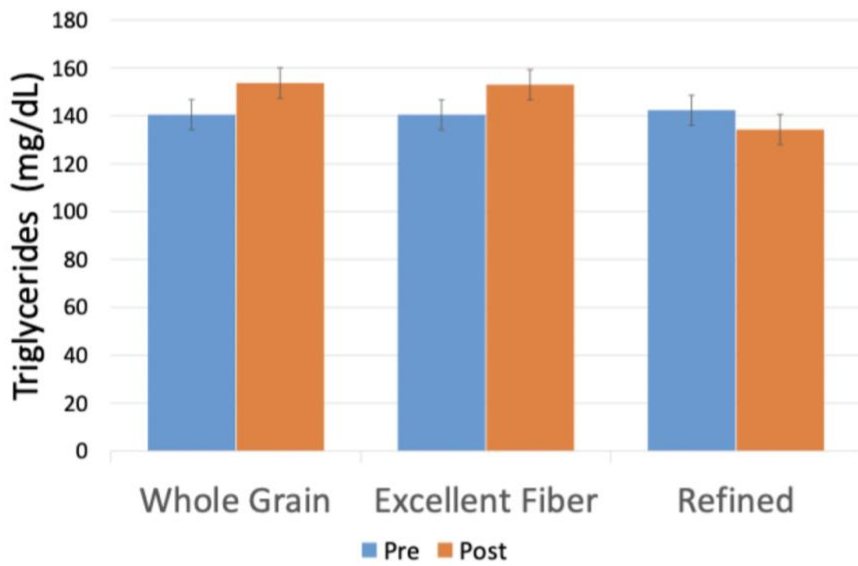
Outcomes of H_1 are presented in Figure 1. For the whole grain corn flour treatment, there was no significant decrease in LDL cholesterol after the intervention. For the excellent fiber mixture treatment, there was a significant decrease in LDL cholesterol after intervention (0.719; p<0.0001). For the refined corn flour treatment, there was no significant change in LDL cholesterol after the intervention.



Mean +/- SE, different letters denote statistical differences at p<0.05

Figure 1: Bar Graph of LDL Cholesterol Levels Before and After Treatment of Bran-Enriched Corn Flour

Outcomes of H_2 are presented in Figure 2. For the whole grain corn flour treatment, there was no significant decrease in triglycerides after the intervention. For the excellent fiber mixture treatment, there was no significant decrease in triglycerides after intervention. For the refined corn flour treatment, there was no significant change in triglycerides after the intervention. It is important to note that there was some variability before and after intervention, but it was not significant between treatments or over time.



Mean +/- SE, different letters denote statistical differences at p<0.05

Figure 2: Bar Graph of Corn Flour and its Effect on Triglycerides Pre and Post Treatment

CHAPTER 5

DISCUSSION

It is evident that methods for the prevention of cardiovascular disease are urgently needed. To the author's knowledge, the current literature has not explored the efficacy of the consumption of a novel corn flour blend containing corn bran and refined corn flour as a method for reducing LDL and triglyceride levels. This study functions as the first to pursue this methodology. The findings of this research suggest that incorporating about six grams of fiber from corn bran into refined corn meal yielded positive outcomes for heart health. The refined corn flour with added bran led to a notable average reduction in LDL cholesterol levels of around 10 mg/dL. Conversely, consuming whole grain corn flour did not lead to significant enhancements in LDL cholesterol levels during the same timeframe. There was no significant effect found for any of the corn flour treatments related to triglycerides.

The present study discovered that incorporating corn flour enriched with corn bran into the habitual diet resulted in decreased LDL cholesterol levels among individuals with mild-to-moderately high LDL cholesterol who were not using statins or other medications to lower blood lipids. While prior studies have linked the addition of bran from cereal grains with cholesterol levels, corn bran had not been extensively investigated in human subjects for several decades.[65,66,67] Nonetheless, there are existing studies examining the impact of corn bran across different populations. For instance, Shane and Walker investigated the inclusion of corn bran, at 20 g/d, in a low-fat controlled diet among men with hypercholesterolemia. Their findings showed a significant decrease in VLDL cholesterol, triglycerides, and total cholesterol levels while changes in LDL and HDL were only trending.[64] Interestingly, this study compared the effectiveness of corn bran to an identical dose of wheat bran with the wheat having no effect on any of the blood lipids measured. This is an interesting finding given that both wheat and corn bran contain similar ratios of insoluble and soluble dietary fiber. Further, both grains contain arabinoxylans which have been shown to lower cholesterol levels.[68] This makes wheat a feasible comparator to our study findings given the lack of data on corn bran. A study by Osfor et al. explored the impact of wheat bran consumption over a similar period to the present study (one month) and observed a significant decrease in LDL cholesterol levels (149.67±39.62 to 121.89±44.38) and a non-significant increase in HDL cholesterol.[66] This study did not report the amount of fiber being consumed by participants which makes it difficult compare the dose and magnitude of change to the present study. Other cereal brans have also been effective at lowering LDL cholesterol. In the study done by Berg et al., a dose of 35-50 g/drams of oat bran reduced LDL cholesterol levels by 56.3±35.1 mg/dL.[65] In comparison to our study, the oat flour appeared to have a more significant decrease in cholesterol levels but it is important to note that the oat bran treatment was combined with caloric restriction and changes in fat consumption which may have enhanced the lipid-lowering effects observed. Studies on rice bran indicate that while the fibrous component of rice bran does not significantly alter LDL cholesterol levels, rice bran oil does, indicating a distinct mechanism of action.[67] Participants in the rice bran portion of this study were given 13-22 grams of dietary fiber per day for three weeks but cholesterol levels were not affected. [67] In the rice oil part of this study, participants consumed rice bran oil as ⅓ of their total dietary fat intake for 10 weeks and LDL levels decreased by about 7 percent.[67] A notable difference from the present study is the time period of ten weeks of dietary supplement consumption versus four weeks, however both produced reduction in LDL cholesterol levels. These findings collectively suggest that the effects of bran fiber from grain products, vary across different grains but that each seem to have lipid lowering effects making corn a potential option for those who may not like other cereal bran products.

The fibrous component of corn bran flour was the speculated physiological mechanism responsible for impacting cholesterol levels in this study. Looking at research conducted by Anderson and Clydesdale, corn bran has been estimated to contain 50.12% dietary fiber.[69] The corn bran in the present study, however, was about 80% dietary fiber by weight which is more than the study by Anderson and Clydesdale. Fiber consumption in the present study likely led to decreased cholesterol levels through multiple pathways. One mechanism entails a reduction in cholesterol absorption within the intestinal lumen, while another mechanism may result from enhanced absorption of short-chain fatty acids in the gut, subsequently reducing cholesterol synthesis by the liver.[51] Another pathway suggests that fiber could lower cholesterol levels by promoting increased synthesis of bile acids, a process also occurring in the liver. Additionally, fiber was found to shorten gastric transit time, leading to a decreased duration for nutrient absorption in the intestines.[51]

The lack of substantial reductions in LDL cholesterol levels following the consumption of whole grain corn flour contradicts findings from studies on other whole grains. Numerous studies have investigated the impact of whole grains on cholesterol levels, consistently demonstrating a cholesterol-lowering effect. A meta-analysis conducted by Holloender et al. examined 24 studies evaluating the effects of whole grain intake on LDL cholesterol.[2] This analysis encompassed studies on oats, wheat, rice, rye, barley, and mixed whole grains. The collective findings from these studies indicated that consuming whole grains led to reductions in LDL cholesterol and triglyceride levels, albeit without a significant effect on HDL cholesterol.[2] Surprisingly, whole grain corn flour in the present study did not produce a significant change in cholesterol levels on average. In a study done by Cooper et. al, healthy adults were given 13.7 grams of fiber per day through a unique whole grain product, and LDL levels were significantly reduced.[70] The product was composed of mostly whole wheat (75%) and lower amounts of whole corn (15%) and whole grain rice (10%). There are plausible explanations why this study demonstrated decreased LDL levels compared to the present study. The whole grain product was primarily wheat-based as opposed to the present study's corn-based product; corn flour contains less soluble fiber than most of the other whole grain flours, including wheat.[57] As such, the participants consumed 13.7 g of fiber compared to the present study's 4 g of fiber, indicating that this higher amount of fiber may be necessary to see an LDL-lowering effect. Additionally, this study was 6 weeks in length compared to the present study's 4-week intervention period; this extended intervention period may have had an effect on the results, suggesting that a longer intervention time may be necessary to produce reduced LDL levels. There are further differences in nutrient composition, particularly in terms of dietary fiber content and types, between corn and other grains, potentially resulting in variations compared to other sources of whole grains.

In regard to the second study aim (H2), which focused on the efficacy of three different corn flours in lowering triglyceride blood levels, there were no significant effects found. It was hypothesized that the excellent fiber mixture and the whole grain flour would be effective in lowering triglyceride levels compared to the refined flour. Overall, the R^2 adjusted value for the triglyceride model was 0.638. However, with a p-value = 0.161, there was no significant time*treatment difference for triglycerides following consumption of any of the flour mixtures. In a study done by Shane and Walker, participants consumed a low fat diet and were assigned a supplement of either 20 grams of corn bran or 20 grams of wheat bran.[64] The study found that the addition of corn bran to a controlled diet resulted in a significant reduction in triglyceride levels (2.24±1.12 to 1.94±0.87).[64] It is important to note that the addition of a low-fat diet significantly lowered triglycerides, and the corn bran supplement lowered triglyceride levels further. The study by Shane and Walker had a higher daily amount of fiber (20 grams) given to participants compared to the present study (12 grams) which could affect the ability to reduce triglycerides if fiber was the mechanism. When exploring plausible reasons why the excellent fiber mixture did not lower triglycerides, the effect of carbohydrate intake on triglyceride levels was considered. Excess carbohydrates can lead to increased triglyceride levels in the blood.[71] When looking at Table 2, which displays a comprehensive analysis of the participants' dietary intake throughout the study, it can be seen that the carbohydrate intake during the excellent fiber mixture intervention was not excessive (mean carbohydrate intake in grams = 170.6 ± 81.0, compared to mean energy intake in kcals = 1,664 ± 577 during the excellent fiber intervention). The mean percent of kcals from carbohydrates was less than 60%. The Dietary Guidelines for Americans recommend that carbohydrates make up between 45% and 65% of total daily calories, making 60% within the recommended range.[72] Although 60% of carbohydrate intake is in the recommended range, when dietary carbohydrates are consumed over 55% of total energy intake per day, blood concentrations of triglycerides rise.[73] This could have negatively impacted triglyceride levels in the present study.

Triglyceride formation is influenced by the types of carbohydrates consumed, with simple and complex carbohydrates having distinct effects on lipid metabolism. In the present study, 27.9 grams of simple carbohydrates, 13.9 grams of complex carbohydrates, and 11.1 grams of fiber were consumed per day. Comparing the amount of simple carbohydrates (27.9 grams) to complex carbohydrates plus dietary fiber (25 grams) we might expect a negative effect on triglycerides as the amount of simple carbohydrates is higher. The increased amount of simple carbohydrates in the diet may help explain why there was no reduction in triglycerides for any treatment in this study. Simple carbohydrates, such as those found in sugary beverages, candies, and processed foods, are rapidly absorbed into the bloodstream, causing an increase in blood glucose levels.[71] This spike in blood sugar triggers insulin release, which promotes the conversion of excess glucose into triglycerides through de novo lipogenesis (DNL) in the liver.[74] Consequently, high intake of simple carbohydrates can lead to elevated triglyceride levels, contributing to dyslipidemia and cardiovascular risk. In contrast, complex carbohydrates, found in whole grains, fruits, vegetables, and legumes, are rich in fiber, which slows down digestion and the absorption of glucose. This gradual release of glucose into the bloodstream helps maintain stable blood sugar levels and reduces the demand for insulin. Additionally, the fiber content of complex carbohydrates promotes satiety, leading to better appetite control and potentially lower calorie intake.[75] Overall, choosing complex carbohydrates over simple ones can help regulate triglyceride levels and support overall metabolic health.

Further exploring possible explanations for the excellent fiber mixture's lack of impact on triglycerides, dietary fat intake could present a possible explanation for the lack of triglyceride reduction. Previous literature has found that the type of fat intake affects triglyceride levels.[76,77] Increased intake of monounsaturated and polyunsaturated fats compared to saturated fats have been shown to decrease triglyceride levels, while excess saturated fat can lead to elevated triglyceride levels.[76] Table 2 shows participants' saturated fat intake averaged about 20 g of saturated fat per day. The participants were found to be consuming over 10% of calories from saturated fat in their diet (mean saturated fat intake was 22.4 ± 8.8 g contributing to a mean energy intake of 1,664 ± 577 kcal). The American Heart Association recommends aiming for a diet with 5-6% of calories coming from saturated fat as many years of scientific research has supported that increased saturated fat intake can lead to increased LDL cholesterol levels.[77] Because the participants' mean saturated fat intake was greater than this parameter, it can be suggested that excess saturated fat intake could be a reason why the excellent fiber mixture was not successful in lowering triglyceride levels. Limiting intake of saturated fat while increasing consumption of monounsaturated and polyunsaturated fats may help maintain triglyceride levels and reduce the risk of cardiovascular disease.

This study demonstrated various strengths that enhanced the solidity of the data. The duration of each treatment period was noteworthy as it facilitated a more comprehensive evaluation of the intervention's effects over an extended period of time. Additionally, the randomized nature of the study was a strength, limiting potential unintended biases. However, there were limitations that may have influenced the results as well. The restricted sample size could have impacted the outcomes, as the data analyzed in this thesis were derived from a limited pool of participants due to the ongoing nature of the overall study and sample analysis. Another potential limitation was that the intervention involved the addition of only one item to each participant's daily diet, lacking control over their habitual dietary patterns during treatment and washout periods. However, three-day diet records were gathered from participants during these periods to offer insights into their daily dietary habits.

It is crucial to cultivate innovative methods in which individuals can consume foods that meet these guidelines and help to mitigate the risk of cardiovascular disease and other chronic diseases. The outcomes of this study carry implications for both public health and clinical practice. They align with prior research indicating that including the bran component of grains in one's diet can effectively lower LDL cholesterol levels. This supports the notion that nutrition experts could advocate for the incorporation of bran-enriched corn flour into dietary recommendations to mitigate LDL cholesterol levels, especially among individuals at low risk for cardiovascular disease. Further investigation is warranted to delve into the underlying mechanisms affecting cholesterol. This is crucial as different grains exert varying effects on cholesterol and triglyceride levels. Broadening the scope of this research to include a larger and more varied demographic would strengthen the validity of the results.

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APPENDIX A

RECRUITMENT FLIER

ASU College of Health Solutions
Arizona State University

Corn + Heart Study

CORN + HEART STUDY

RESEARCH PARTICIPANTS NEEDED

We are looking for healthy males and females (18-70 years old) with high cholesterol
We are studying the ability of corn fiber to reduce blood cholesterol.

We need you to visit the ABC building, in Downtown Phoenix 13 times for data collection, and 9 check-ins to replenish your study food items (food can be picked up or delivered).
We need you to consume pita breads and/or muffins made from 3 unique corn flours. Each flour will be consumed for 4 weeks with 2-week breaks in-between.

Receive 2 blood draws (at the beginning and at the end) of each of the 4-week intervention periods.

$300 COMPENSATION

Participation is Voluntary

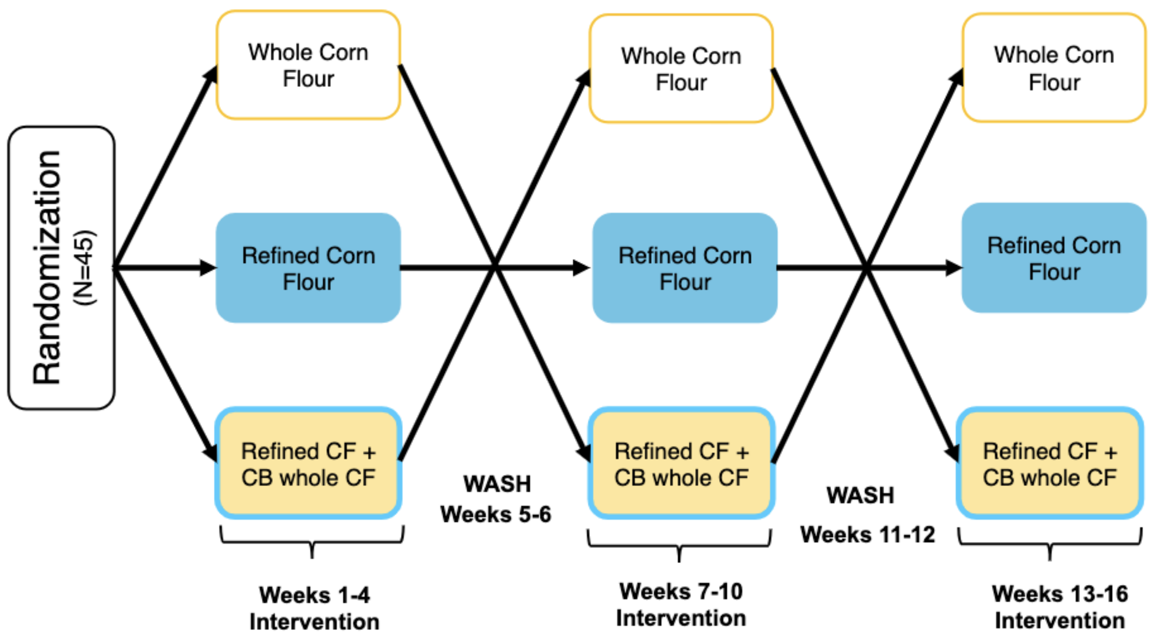
Interested?

Email: tzgross@asu.edu

or call **(480)-440-5183** for more information

APPENDIX B

SCHEMATIC OF STUDY DESIGN


Randomization
(N=45)
Whole Corn Flour
Refined Corn Flour
Refined CF + CB whole CF
Weeks 1-4 Intervention
WASH
Weeks 5-6
Whole Corn Flour
Refined Corn Flour
Refined CF + CB whole CF
Weeks 7-10 Intervention
WASH
Weeks 11-12
Whole Corn Flour
Refined Corn Flour
Refined CF + CB whole CF
Weeks 13-16 Intervention

49

APPENDIX C

IRB APPOVAL

APPROVAL: EXPEDITED REVIEW

On 1/6/2018 the ASU IRB reviewed the following protocol:

Type of Review:	Initial Study
Title:	Evaluating the effects of corn flour consumption on cardio-metabolic outcomes and the gut microbiome in adults with high cholesterol.
Investigator:	Corrie Whisner
IRB ID:	STUDY00007518
Category of review:	(2)(a) Blood samples from healthy, non-pregnant adults, (4) Noninvasive procedures, (7)(a) Behavioral research
	Name: North American Millers' Association (NAMA)
Grant Title:	
Grant ID:	
Documents Reviewed:	• Full Study Consent Form_Track Changes, Category: Consent Form; • FoodAcceptablityAndSatisfaction_NAMA.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • IRB Protocol Track Changes, Category: IRB Protocol; • Demographics_NAMACornStudy.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • 3-day food record form_NAMAcorn.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • NAMA corn Study Recrutment Flyer_1.8.18.pdf, Category: Recruitment Materials;

	• Screening Verification Consent Form, Category: Consent Form; • PhysicalActivityQuestionnaire_NAMAcorn.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Email and Social Media Recruitment_12.27.17.pdf, Category: Recruitment Materials; • Visit2DataStart_NAMACornStudy.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Corn Proposal 3.5.2017 Final Revised Submission.docx, Category: Sponsor Attachment; • HealthHistoryScreener_NAMACorn.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Visit1BaselineDataLDLScreening.pdf, Category: Screening forms; • NAMA_Corn_Study_Online_Screener.1.8.18.v3.pdf, Category: Screening forms; • Full Study Consent Form, Category: Consent Form; • IRB Protocol, Category: IRB Protocol; • Gastrointestinal_Symptoms_NAMACornS.pdf, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions);

The IRB approved the protocol from 1/6/2018 to 1/5/2019 inclusive. Three weeks before 1/5/2019 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 1/5/2019 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).