# EFFECTS OF STRAWBERRIES ON LIPID PROFILE IN SUBJECTS WITH DYSLIPIDEMIA AND ABDOMINAL ADIPOSITY

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Davis, CA

2009

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
MASTER OF SCIENCE
May, 2012

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# CHAPTER I

## INTRODUCTION

Cardiovascular disease (CVD) has been defined as hypertension, coronary heart disease (CHD), which includes myocardial infarction (MI) and angina pectoris, heart failure, stroke, and/or congenial cardiovascular defects (1). An estimated 82.6 million people, approximately one in three American adults, have at least one form of CVD: high blood pressure (76.4 million), CHD (16.3 million), myocardial infarction (7.9 million), angina pectoris (9 million), heart failure (5.7 million), stroke (7 million), and congenital cardiovascular defects (650,000-1.3 million) (2).

The incidence of cardiovascular events is affected by gender and age. Older men and women have higher incident rates than younger people of the same gender. In addition, women have a lower incidence rate than men of similar ages. The incidences of CVD in men are 3.3, 10.1, 21.4, and 34.6 per 1000 men for ages 35-44, 45-54, 55-64, and 65-74, respectively (3). The incidences of CVD in women are 1.2, 4.2, 8.9, and 20.0 per 1000 women for ages 35-44, 45-54, 55-64, and 65-74 respectively (3). This suggests that men at any given age are approximately 2 times more likely to have CVD than women of a similar age range.

In the United States, CVD as an underlying cause of death accounted for 33.6% of deaths in 2007 (2). In 2007, CVD claimed 813,804 lives (2). CVD death rates were 300.3 and 211.6 for men and women, respectively (2). Heart disease killed more Americans than cancer, chronic lower respiratory disease, and accidents combined, making it the leading cause of death for

elderly men and women in 2007 (2). Approximately 33% of deaths attributed to CVD occurred before the age of 75 years, which was below the average life expectancy of 77.9 years (2).

Epidemiological studies have found an association between increased consumption of fruits and vegetables and decreased risk of cardiovascular disease and all cause mortality (4, 5). Studies on specific fruits and vegetables attempt to isolate the bioactive component(s) that are responsible for the cardio-protective properties of fruits and vegetables. Fruits, such as berries, have been increasingly studied for their high concentration of fiber and antioxidant vitamins such as vitamins E and C, as well as their rich source of polyphenols (6, 7). The polyphenol, anthocyanins and anthocyanidins, rich in strawberries, have been associated with reduced risk of death all-cause CVD and certain CVD metabolic risk factors (8, 9).

The goal of the study is to investigate the effects of freeze-dried strawberries in metabolic risk factors for CVD in a randomized clinical trial. Parameters that were assessed are lipid profile, glucose metabolism, and markers of oxidative stress in subjects with dyslipidemia and abdominal adiposity versus age-gendered matched control at baseline, 6 and 12 weeks after strawberry supplementation.

The specific aims are to:

1. Investigate the effects of freeze-dried strawberries on anthropometric measures and blood pressure
2. Investigate the effects of freeze-dried strawberries on glucose, insulin, lipid profile, and markers of lipid oxidation (oxidized-LDL and malonaldehyde)

The null hypotheses are that:

- Freeze-dried strawberry supplementation will have no effects on anthropometric measures and blood pressure compared to control

- Freeze-dried strawberry supplementation will have no effects on glucose, insulin, lipid profile, and markers of lipid oxidation compared to control
- Freeze-dried strawberry supplementation will not affect safety parameters such as, liver and kidney function tests and blood cell count in subjects versus controls

# CHAPTER II

## CARDIOVASCULAR DISEASE & OBESITY IN THE UNITED STATES

Cardiovascular disease (CVD) has been a major cause of death in the United States for the last hundred years. Each year, cardiovascular disease kills more Americans than cancer, chronic respiratory disease, and accidents combined (10). In 2006, cardiovascular disease was the underlying cause of death for 831,272 lives, which accounts for 34.3% of deaths (1). An estimated 81.1 million people, approximately one in three American adults, have at least one form of cardiovascular disease (1). Forms of CVD are defined as hypertension, coronary heart disease (CHD), heart failure, stroke, or congenial cardiovascular defects (1). As a result of health care services, medications, and loss of productivity, heart disease will cost the United States $316.4 billion (1).

### OBESITY

Obesity has become an epidemic in the United States, where even children and adolescents are increasingly becoming overweight or obese. Nearly ten million children and adolescents ages six to nineteen are at or above the 95th percentile on the CDC growth charts for the United States for BMI-for-age (11). Adolescents who are overweight have been found to have a 70% chance of becoming overweight adults (1). If the United States continues with the current trend, by 2030, approximately 86% of adults will be overweight or obese (1). As a result, the estimated total health care costs for obesity could reach $861 to 957 billion, in 2030, which will account for 16-18% of US health expenditures (1).

Overweight and obesity is associated with increased risk of diseases and chronic conditions, such as CVD (12). Overweight individuals were 20% and 21% more likely to develop cardiovascular disease than normal-weight persons for women and men, respectively (12). Obesity increases the risk of developing cardiovascular disease by 64% and 46% in women and men, respectively (12). Being overweight was not found to be associated with increased mortality due to cardiovascular disease; however, being obese is associated with a significant increase in morality due to cardiovascular disease (12). In 2004, obesity was associated with 13% of cardiovascular disease deaths (13). Overweight and obesity are also associated with decreases in life expectancy (14).

In the 26 year cohort, the Framingham Heart Study studied the association of weight and cardiovascular disease. The 2252 men and 2818 women ages 28-62 were free of clinically recognizable cardiovascular disease upon entry and 18.9% and 20.5% were overweight in men and women, respectively. This study found obesity is an independent risk factor for cardiovascular disease (15). The association of weight and cardiovascular incidence was more pronounced in subjects younger than 50 years of age. When comparing the self reported weight of subjects at 25 years of age compared to entry, subjects who gained weight were associated with an increased risk of disease regardless of their obesity index. On the flip side, subjects who lost weight were associated with a decreased risk of disease. This implied that weight loss at any body mass index (BMI) may be beneficial to reducing risk for CVD. One of the most profound effects obesity has on cardiovascular health is that ≥75% of hypertension can be directly attributed to obesity (16). Other effects obesity has on cardiovascular health are the increased levels of triglycerides, elevated low density lipoprotein-cholesterol (LDL-C), and low high density lipoprotein-cholesterol (HDL-C) (16).

According to the Centers for Disease Control and Prevention (CDC), adults are categorized as obese when they have a body mass index (BMI) of 30 or higher. However, BMI often fails to differentiate between different body compositions; therefore, more effective ways in estimating body fat is by measuring skin-fold thickness and waist circumference. Differentiating persons with similar BMI but different body compositions is important because excess abdominal fat is associated with an increased risk of metabolic risk factors. Currently, waist circumference is considered the most effective diagnosis of obesity (17).

In obese individuals who are similar weight, more abdominal adipose tissue is related to increased metabolic abnormalities (18). Even in non-obese individuals, abdominal adiposity has been associated with increased risk of cardiovascular disease. In a case-control study of healthy subjects matched for BMI and age, subjects (n=350) with a waist-to-hip ratio $\geq$0.9 in males and $\geq$0.85 in females have significantly higher high sensitive C-reactive protein (hs-CRP) (1.96 $\pm$ 2.60 vs. 1.53 $\pm$ 1.74 mg/dl; P <0.01) levels compared to control (waist-to-hip ratio <0.9 in males and <0.85 in females, n=199) (19). Similarly, Lapice et al. (2009) found that subjects with visceral adiposity are approximately two times more likely to have CRP >3mg/dl and metabolic syndrome (P<0.01). High sensitive CRP and CRP are acute inflammatory proteins. Inflammation can lead to CVD through the progression and exacerbation of atherosclerosis, which is the fatty deposit build up in the artery walls (20). This suggested that abdominal adiposity may lead to an increased risk of CVD possibly through increasing systemic acute-phase inflammatory proteins. Hs-CRP plasma levels may be more indicative of cardiovascular disease risk in individuals who have low risk factors typical of cardiovascular disease (20). This is especially important since total cholesterol levels >200 mg/dL does not account for 35% of people with coronary heart disease (21). Therefore, this suggests that measuring abdominal adiposity may be a low cost tool with a strong correlation in identifying individuals at risk for cardiovascular disease, especially those who do not have elevated cholesterol levels.

## HYPERTENSION

Hypertension is defined as blood pressure ≥140 mmHg/ ≥90 mmHg, taking antihypertensive medication(s), or being told by a physician or health care professional at least twice that one has high blood pressure. An estimated 74.5 million adults over the age of 20 have high blood pressure (10). In 2006, the mortality of high blood pressure is 56,561 lives (22). In addition, high blood pressure was associated with shorter life expectancy and increased years a person lived with CVD (23). The total life expectancy of persons with high blood pressure is 5.1 and 4.9 years shorter than persons with normal blood pressure for men and women, respectively (23). At age 50, men with untreated high blood pressure lived 7.2 years shorter than men who lowered their blood pressure below 140/90 mmHg (23). In addition, those men who lowered their blood pressure also lived fewer years with CVD (23). Although hypertension have mostly been associated with men, the National Health and Nutrition Examination Survey (NHANES) found that gender differences between rates of hypertension are also age dependent (1). Men have higher rates of hypertension than women until the age of 45. From ages 45 to 64, men and women have the same rates of hypertension. And after age 64, women have a higher percentage of hypertension than men.

## DYSLIPIDEMIA AND ATHEROSCLEROSIS

Dyslipidemia is an increased level of circulating blood lipids: high levels of total cholesterol, low density lipoprotein (LDL), and triglycerides as well as low levels of high density lipoprotein (HDL). High blood cholesterol and lipids have been associated with the increase risk of heart disease, particularly CHD. In 2006, 16.2% of adults ≥20 years of age have total serum cholesterol levels ≥240 mg/dL (24). That is an estimated 35.7 million adults with high blood cholesterol levels. The Centers for Disease Control predicted that if there is a 10% population-wide decrease in total cholesterol levels, there will be an estimated 30% decrease in CHD

incidences (24). High levels of LDL cholesterol, also commonly referred as “bad” cholesterol, are usually associated with plaque buildup in arteries, which leads to an increased risk of developing heart disease. In 1999-2004, the age-adjusted prevalence of high LDL cholesterol in the US adults is 25.3% (25). HDL cholesterol, on the other hand, is known as “good” cholesterol and low levels levels (≤40 mg/dL) are considered a risk factor for heart disease and stroke. American adults ≥20 years of age have the mean level of HDL cholesterol of 54.3 mg/dL (NHANES 2003-2006, NCHS and NHLBI; unpublished analysis). The mean level of triglyceride level in American adults ≥20 years of age is 144.2 mg/dL (NHANES 2003-2006, NCHS and NHLBI; unpublished analysis). Triglyceride levels >150 mg/dL is considered a risk factor for heart disease and stroke. When the triglyceride levels are stratified by gender, the mean level for men is 156.5 mg/dL and for women it is 132.1 mg/dL.

High circulating levels of free fatty acids can lead to atherosclerosis (26). Free fatty acids increases ROS formation, which upregulates inflammatory cytokines, such as C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α). Inflammatory cytokines increases the translation or synthesis of endothelial adhesion molecules, such as intracellular adhesion molecules (ICAM) or vascular cell adhesion molecules (VCAM). Increased ICAM and VCAM on endothelial cells will induce monocyte adhesion, which initiates atherosclerosis. Macrophages, which are matured monocytes, engulf oxidized-low density lipoprotein (ox-LDL) to mature into foam cells. Ox-LDL also increases VCAM molecules, which further exacerbates the atherosclerotic process.

Lipids under increased oxidative stress and the concentration of metals (i.e. iron) can form lipid radicals (26, 27). Increased lipid radicals, such as ox-LDL can further mature macrophages and upregulate initiation of atherosclerosis. Lipid peroxidation products are also extremely toxic. Lipids can oxidize to form lipid alkoxyl radicals (LO•) or peroxyl radicals (LOO•) (27). Alkoxyl radicals and peroxyl radicals go through cyclisation to yield 4, hydroxynonenal (HNE) and malondialdehyde (MDA), respectively. HNE and MDA are both

extremely toxic products which cause DNA damage (27). HNE can affect signal transduction pathways, which can affect cell morphology and biochemical and physiological properties. MDA can disrupt DNA by reacting with DNA bases, forming adducts. HNE and MDA are frequently used to assess disease states such as cardiovascular disease, atherosclerosis, and cancer.

Hypercholesterolemia had been associated with vascular dysfunction, inflammation, and oxidative stress. Hypercholesterolemia has been associated with the inhibition of nitric oxide (NO) production, which is important in the regulation of vascular tone, prevention of platelet activation, inhibition of oxidative stress, cell growth, and inflammation (28). An inflammatory response catalyzed by increased circulating cholesterol or triglycerides leads to the progression of atherosclerosis through increased cell adhesion molecules, leukocyte recruitment, and rolling and adherence of the monocyte (28). Hypercholesterolemia has been associated with increased oxidative stress by the increased reactive oxygen species (ROS) through three major enzyme systems: NADPH oxidase (NOX), xanthine oxidase, and myeloperoxidase (28). Therefore, hypercholesterolemia is a major contributor to CVD by the dysfunction of the vascular endothelium, increase in inflammation and oxidative stress.

## INSULIN RESISTANCE AND IMPAIRED FASTING GLUCOSE

Insulin resistance results in impaired glucose metabolism which elevates glucose concentrations above levels classified as normal, but does not elevate glucose concentrations to levels classified as diabetes mellitus (DM). Insulin resistance is the body's inability to effectively use insulin that is produced. Since insulin is a hormone required for the uptake of glucose to the cell, insulin resistance frequently results in elevated plasma glucose concentrations. Elevated fasting glucose levels of 100-125 mg/dL are classified as impaired fasting glucose or pre-diabetes (29). Impaired fasting glucose is fasting glucose levels above normal, but does not qualify as

clinical DM. Prolonged hyperglycemia have been found to increase risk of atherosclerosis by increasing ROS formation through various pathways (26).

In a Danish prospective study, Jeppesen et al. (2007) studied whether or not insulin resistance was a risk factor for CVD independent of metabolic syndrome. This study followed 2493 men and women, who were free of major CVD at baseline, for an average of 9.4 years. CVD endpoints were defined as cardiovascular death, nonfatal ischemic heart disease, and nonfatal stroke. Insulin resistance was found to be an independent predictor of CVD (30). In addition, insulin resistance was found to increase the relative risk of CVD by 67%. This suggested that although impairment of glucose metabolism may not reach clinical levels, it may still have profound effects on the biological system, specifically to the cardiovascular system.

## OTHER CARDIOVASCULAR DISEASE RISK FACTORS

Several other factors associated with increased cardiovascular disease incidence include age, race, income, and occupational status. According to the 2003 Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System (CDC BRFSS) survey of adults ≥18 years of age, the prevalence of having ≥2 risk factors is highest amongst adults who reported being unable to work (69.3%). Second highest is amongst persons reporting household income of ≤ $10,000 (52.5%) (31). The next two indicators with the highest prevalence of cardiovascular disease risk factor is race. Blacks have a prevalence of 48.7% and American Indians/Alaska Natives have a prevalence of 46.7%. Other prominent indicators of risk factors include state/territory, the highest prevalence being persons living in Kentucky (46.2%). There are also twelve states and two territories that have multiple risk factor prevalence of ≥40%: Alabama, Arkansas, Georgia, Indiana, Kentucky, Louisiana, Mississippi, North Carolina, Ohio, Oklahoma, Tennessee, West Virginia, Guam, and Puerto Rico.

## FRUIT & VEGETABLE INTAKE IN THE UNITED STATES

The current dietary consumption of US adults ≥20 years old is limited to nutrient dense foods. The average fruit consumption is 1.1-1.8 servings/day across all race and gender groups with 5.8-11% meeting the guidelines of ≥4 servings/day. When 100% fruit juices are included, fruit consumption increases to 2-2.8 servings/day and 13.8-23.7% meeting the guidelines for fruit consumption. This may be of interest for intervention since most adult Americans are not eating enough whole fruits but almost double their intake if fruits are consumed in the form of a beverage. The average consumption of vegetables is 1.2-2.1 servings; 11-14% of whites, 5-10% of blacks, and 3-5% of Mexican Americans consume the recommended amount of ≥5 serving/day. Fruits and vegetables are a major source of dietary fiber and a large portion of the US adult population are not meeting recommended levels. Only 3-7% of whites, 2-3% of blacks, and 11-12% of Mexican Americans are consuming ≥28 g of dietary fiber/day. Diets high in fiber can help lower blood cholesterol which may lower risk of cardiovascular disease (32).

Diets high in fruits and vegetables have been found to be associated with lower risk of CVD morbidity and mortality (4, 5, 33). In prospective studies by Hung et al. (2004), fruit and vegetables were associated with a moderately significant decrease in chronic diseases ($p=0.07$) in healthy health professionals. However, further analyses indicated that the positive effects of fruits and vegetables were most significantly associated with a decrease risk in CVD, but were not found to be significantly associated with incidence of cancer. Similarly, Liu et al. (2000) found that increasing quintiles of fruit and vegetable intake were significantly associated with decreased incidence of CVD in healthy, female health professionals. Fruit and vegetable intake greater than 5 servings per day was significantly associated with a 12-32% decrease in CVD incidence (4, 33). Furthermore, increasing consumption of fruits and vegetables was associated with a greater and more significant reduction in relative risk of MI ranging from 43-61% (4). In addition, reduced risk of CVD and MI with increasing quintiles of fruit consumption was associated with a greater

and more significant reduction in CVD and MI compared to total fruits and vegetables and vegetables alone. Lastly, fruit and vegetable intake was found to be associated with reduced relative risks of CVD, specific CVD incidence, and total mortality (5). In the prospective cohort study by Bazzano et al. (2002), healthy subjects who consume fruits and vegetables greater than 3 times per day were found to have significantly lower risks of stroke, stroke mortality, ischemic heart disease, ischemic heart disease mortality, cardiovascular disease mortality, noncardiovascular disease mortality, and all-cause mortality ($p<0.02$). However, after multivariate adjustment, ischemic heart disease and noncardiovascular disease mortality were no longer found to be significant ($p>0.05$) and ischemic heart disease mortality was only moderately significant ($p=0.07$). There is suggestion that different fruits and vegetables may be involved with specific pathways that affect different cardiovascular disease endpoints. Dietary recommendations for the general public to consume at least 5 servings of fruits and vegetables in order to decrease risk of CVD were validated. More specifically, increased intake of fruits appeared to display greater cardio-protective properties. Thus, further studies on specific fruits and vegetables may help elucidate the bioactive ingredients that are responsible for the inverse association to chronic diseases.

## EPIDEMIOLOGICAL STUDIES

Several epidemiological studies have been conducted on the association of strawberry and CVD, markers of CVD, and CVD mortality. Strawberry and specific strawberry flavonoids have been associated with a lower risk of CVD and CVD markers (8, 9, 34). In the Women's Health Study, Sesso et al (2007) studied the following: 1) the prospective association of strawberry intake and CVD in 38,176 female health professionals and 2) the cross-sectional association of strawberry intake with lipids and CRP in 26,966 female health professionals for an average of 10.1 years. CVD was defined as confirmed myocardial infarction, stroke, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, and cardiovascular death. Strawberry intake was evaluated by a 131 item validated semi-quantitative food frequency questionnaire. Categories of strawberry consumption were divided into four groups: none, 1-3 servings/month, 1 serving/week, and ≥2 servings/week. In the prospective study, higher intake of strawberry was not associated with risk of CVD ($p=0.28$) nor was it associated with specific cardiovascular endpoints (all $p>0.05$). At strawberry intake ≥1 serving/week, there was a suggestion of lower risk of CVD mortality, but the findings are limited by the low amount of case counts. In the cross-sectional study, total- and LDL-cholesterol levels were both modestly lower with higher levels of strawberry intake. However, there were no associations between strawberry intake and the relative risk of higher plasma lipid levels ($p>0.05$).

In addition, after multivariate adjustment, women consuming ≥2 servings/week of strawberries had a 14% lower likelihood of having CRP levels ≥3 mg/L ($p=0.012$). Since CRP is negatively associated with strawberry consumption, this may indicate that strawberry intake was beneficial in decreasing inflammation. Sesso et al. (2007) may not have found more profound associations between strawberry intake and CVD endpoints and markers due to the small degree

of differentiation between the low to high strawberry groups. In addition, the high consumption group (≥2 servings of strawberries/week) was considerably lower than the United States Department of Agriculture (USDA) recommendation of 2 servings of fruits/day.

Further epidemiological studies examined the association of specific strawberry flavonoids on CVD mortality and incident hypertension (8, 9). In the Iowa Women's Health Study, Mink et al. (2007) examined the prospective cohort association between flavonoids intake and CVD mortality in 34,489 postmenopausal women over an average of 16 years. CVD mortality was defined as CVD, CHD, stroke, or total mortality. Flavonoid intake was evaluated by a 127 item food frequency questionnaire. After simple and multivariate adjustment, anthocyanidin intake (0.01-1040 mg/d or 0.03-3099.85 g of raw strawberries) was significantly associated with decreased rate of total, CHD, and CVD mortality ($p<0.05$) compared to no anthocyanidin intake.

In addition to anthocyanins, flavanones were also significantly associated with lower total mortality, CHD mortality, and CVD mortality ($p<0.05$) (8). However, after multivariate adjustment, the association of decreased total ($p=0.123$) and CVD mortality ($p=0.054$) with increased flavanones were less significant. Flavanone concentrations in frozen and raw strawberries were considerably less than anthocyanidin concentrations per 100 grams of strawberries (6). The median of flavanones in the lowest quintile was 7.6 mg/d, which was approximately 2923.08 g of raw strawberries (6). The low concentration of flavanone suggested that although there were positive health benefits associated with increased flavanone intake, strawberries were most likely not the source of consumption.

Mink et al. (2007) also found that individuals who consumed greater than 1 serving of strawberries per week had a lower rate ratio of CHD and CVD mortality ($p<0.05$). Total and specific flavonoids intake were not associated with risk of stroke mortality ($p>0.05$). In this study,

there were suggestions that minimal strawberry consumption may be beneficial in lowering risk of mortality due to CVD. Further studies on an appropriate dose of strawberries required to prevent CVD mortality may be warranted.

Cassidy et al. (2011) studied the prospective association of flavonoids subclasses and incident hypertension. Subjects were followed for an average of 14 years from the Nurses' Health Study I and II (n=87,242) and Health Professionals Follow-up study (n=23,043). Flavonoid intake was calculated from semi-quantitative food-frequency questionnaires. This study found that average anthocyanin intake was 12.5-15.2 mg anthocyanins per day and the main sources were blueberries and strawberries. The highest quintile of anthocyanin intake was associated with an 8% lowered risk of hypertension compared to the lowest quintile of anthocyanin intake ($p=0.03$). Additional analysis of participants under the age of 60 years in the highest quintile group compared to the lowest quintile group had a 12% reduction in incidence of hypertension ($p<0.001$). This increased protection against hypertension in the younger age group may possibly be due to the irreversible damage to endothelial function and blood pressure in older individuals. This also suggested the importance of early detection and implementation of dietary intervention to control blood pressure.

However, strawberry intake of >1 serving of strawberries per week was not significantly associated with a reduction in hypertension ($p=0.34$) (9). Although strawberry consumption was not associated with significant reduction in hypertension, blueberries displayed a significant reduction in hypertension. This suggested that berries may display anti-hypertensive properties. Since blueberries have approximately 4-5 times more anthocyanin content per 100 grams than strawberries (6), strawberry intake may be too low to exhibit a reduction in hypertension. Nevertheless, fruits rich in flavonoids such as anthocyanins may exhibit beneficial effects on controlling hypertension. Further clinical research on the appropriate dose of strawberry supplementation may help clarify the role of strawberries in reducing CVD risks.

## CLINICAL STUDIES

### Strawberries on antioxidant capacity and lipid peroxidation

Development of many chronic diseases had been attributed to the imbalance of oxidative stress products and antioxidants. Under normal physiological conditions, an estimated 1% of oxidation products form from mitochondrial electron flow to superoxide (35). The generation of this reactive oxygen species in normal cells is typically mediated by endogenous antioxidant systems such as glutathione, α-tocopherol, carotenoids, and ascorbic acid (35). However, oxidative stress occurs when oxidation products surpass antioxidant systems to attenuate stress. Exogenous sources of antioxidants have been evaluated as an intervention to decrease risk of chronic diseases. Strawberries have been studied due to their nutrient composition and popularity as a fruit. Strawberries contain significant amounts of vitamin C and polyphenols, which have been found to have significant antioxidant capacity. Several clinical trials have reported increased plasma antioxidant capacity and decreasing oxidative stress products after strawberry supplementation.

In a crossover intervention study by Henning et al. (2010), the impact of strawberry consumption on antioxidant capacity was investigated. Twenty one healthy females were recruited to consume 250 g of frozen strawberries with breakfast everyday for three weeks. Lipid peroxidation lag time increased from baseline in both fasting (25.4±21.0 to 31.5±22.9) and non-fasting (25.0±19.6 to 31.1±24.9) serum ($p<0.05$). LDL oxidation lag phase returned to baseline levels after washout of three weeks. This 20% increase in lipid peroxidation lag time suggested that strawberry intervention positively increased antioxidant capacity in the serum. Henning et al. also measured oxidative DNA damage by calculating the ratio of 8-oxo-dG to $10^6$ dG. There was a decreasing trend of approximately 1.3 and 0.5 in fasting and non-fasting levels, respectively ($p=0.12$). These findings suggested that supplementation of 250 g of strawberries everyday for 3

weeks decreased oxidative damage most likely from the increase in antioxidant capacity in the serum.

**Strawberries on blood pressure, inflammation, & lipids**

In a single-blind, randomized, placebo-controlled intervention, Erlund et al. (2008) investigated the effects of berry intervention on hemostatic function, serum lipids, and blood pressure (BP) in 72 subjects with CVD risk factors but are otherwise healthy and were not on medication. Subjects consumed 100g whole berries and 50 g crushed lingonberries every other day and 100 g black currant or strawberry puree and 0.7 mL of cold-pressed chokeberry and raspberry juice on the alternative days. The control group consumed 1 of 4 different calorie-control products each day. Erlund et al. found that blood pressure in the berry group was significantly different from control. Systolic blood pressure (SBP) significantly decreased by 1.5 mmHg in berry intervention and increased by 0.50 in control ($p=0.050$). Diastolic blood pressure (DBP), on the other hand, did not change in the berry intervention but increased by 0.9 mmHg in the control intervention ($p=0.044$). However, additional analysis of baseline BP showed that only the highest tertile of SBP was significantly different. In the highest tertile of SBP, there was a mean decrease of 7.3 and 0.2 mmHg in berry and control groups, respectively ($p=0.024$). This suggested that berry intervention more powerfully influenced blood pressure in higher ranges.

In addition, Erlund et al. found no changes in cholesterol and triacyglycerol levels. However, HDL cholesterol significantly increased in berry by 5.2% (0.08 mmol/L) compared to a 0.6% (0.01 mmol/L) increase in control ($p=0.006$). A positive increase in HDL cholesterol was considered positive for cardiovascular health.

Erlund and colleagues also measured platelet function through the measure of collagen and ADP (CADP-CT) time. Supplementation of berries was found to significantly increase collagen and ADP (CADP-CT) time by 11% (8.4 seconds) in berries versus a decrease of 1.4%

(1.2 seconds) in control (p=0.018). An increase in platelet aggregation time implied that berries were positive for cardiovascular health by reducing risk of clotting.

The results from this study suggested that berries were positive for cardiovascular health by exhibiting positive effects of blood pressure, cholesterol, and platelet function. However, the study included a mix of various berries; therefore, the individual effects of strawberries cannot be teased out. In addition, the dose of strawberry intervention was relatively modest (100g of strawberries every other day). Nevertheless, the profound effects on cardiovascular health despite the modest dose of berries per day were noteworthy. It also suggested that different types of berries, with complementary concentrations of different polyphenols, may have an increased benefit compared to consuming a single type of berry.

**Strawberries, lipid profile & lipid peroxidation**

Hyperlipidemia and obesity have been associated with increased risk of developing CVD (12, 26, 36). Targeting the decrease of adipocytes and circulating lipids may be beneficial in the management of CVD. Dietary management of CVD by increasing strawberry intake has been shown to attenuate lipid profile in several clinical studies (37-39). Strawberry intake was found to decrease lipid profile in participants at high metabolic risk (37).

Basu et al. (2009; 2010) conducted two intervention studies on the effects of freeze-dried strawberry powder (FSP) supplementation on atherosclerotic markers in subjects with metabolic syndrome. The study reported in 2009 was an intervention study without a control group (n=16), whereas the study reported in 2010 was a randomized controlled study (n=25). The intervention in both studies was 50 g FSP (approximately 500 g fresh strawberries) beverage. The control group in the study by Basu et al. (2010) received no intervention but consumed the equivalent amount in liquids.

Strawberry supplementation was found to significantly reduce total- and LDL-cholesterol. After 4 weeks of strawberry supplementation, Basu et al. (2009) found that subjects reduced total cholesterol levels from baseline by 5% (5.32 to 5.05 mmol/L) ($p<0.05$). LDL cholesterol also significantly decreased by 6% from baseline (3.2 to 3.0 mmol/L). Similarly, after 8 weeks of strawberry supplementation, Basu and colleagues (2010) found a significant decrease in total- and LDL-cholesterol compared to a non-intervention, liquid volume control. In the intervention group, subjects had a mean decrease of 10% in total cholesterol levels from 5.8±0.2 to 5.2±0.2 mmol/L compared to a non-significant decrease of 0.1 from 5.5 mmol/L in the control group. Additionally, subjects significantly lowered LDL cholesterol by 11% from 3.5±0.2 to 3.1±0.1 mmol/L compared to no change in the control group. Compared to the study from the previous year, total- and LDL-cholesterol decreased by approximately twice the percentage and also decreased by approximately twice the mmol/L. Since both intervention studies received a similar amount of FSP, this suggested that increased duration in strawberry intervention may provide additional reduction in total- and LDL-cholesterol.

After strawberry supplementation in the studies by Basu and colleagues (2009; 2010), total cholesterol levels decreased from levels considered “borderline high” to levels considered “best” (40). LDL-cholesterol levels stayed at levels categorized as “near ideal” in the study by Basu et al. (2009) but decreased from levels considered “borderline high” to levels considered “near ideal” in the study by Basu and colleagues (2010). However, since subjects in both studies are at risk for CVD, recommended LDL-cholesterol levels for people at risk for heart disease is lower. Therefore LDL-cholesterol levels should be reduced further in subjects in both studies in order to reduce the risk of heart disease. Although LDL-cholesterol levels did not lower to optimal levels for this population, the significant decrease may suggest possible therapeutic effects of strawberries at lowering LDL-cholesterol levels in subjects with metabolic syndrome.

In a randomized crossover study, Jenkins et al. (2008) found that strawberry supplementation maintained a lowered lipid profile in 28 hyperlipidemic subjects on a portfolio diet. Subjects in the intervention group were advised to buy and consume 1 lb per 200 kcal of fresh strawberries. Control participants received 65 g/d oat bran bread. Strawberry supplementation maintained a reduction in LDL cholesterol. However, there were no significant differences between strawberry supplementation and substudy baseline ($p>0.05$). This indicated that there were no significant strawberry-related effects on lipid profile. However, lipid peroxidation products, measured by thiobarbituric acid-reactive substances, were significantly lower in subjects who consumed strawberry supplementation compared to substudy baseline ($p < 0.05$). This suggested a protection against oxidative damage of lipids.

Participants in the studies by Basu et al. (2009;2010) and Jenkins et al. (2008) were hyperlipidemic subjects. Hyperlipidemia is a major CVD risk factor. Although participants in all three studies were hyperlipidemic, subjects in the study by Jenkins et al. were previously maintained on a low-saturated fat therapeutic diet for 2.5 years. Since there was already a marked decrease in lipid profile, the low-saturated fat therapeutic diet may have masked any additional decreases in lipid levels due to strawberry supplementation.

The strawberry dose for the study by Basu et al. (2009), Basu et al. (2010), and Jenkins et al. (2008) were comparable (454-500 g/day). However, Basu and colleagues prepared the strawberry beverage with FSP whereas Jenkins et al. used fresh strawberries. The intervention time was also the same in all three studies (4 weeks).

An inherent limitation of the intervention study by Basu et al. (2009) study was that there was no control. However, the study provided important preliminary information which warranted further investigation with similar dose, duration, and subject population. A strength in this study was that freeze-dried strawberries were more standardized than fresh strawberries purchased from

the store. Phytochemicals in strawberries are affected by agricultural systems, processing methods, and storage (41-43). FSP was more effective than commercial transfer and storage of strawberries in maintaining the integrity of nutrients thus ensured a more standardized product. On the other hand, commercially purchased strawberries in the study by Jenkins et al. reflected the practical application of including strawberries easily attainable by the general public. A criticism of the study by Jenkins et al. was that the compositions of the intervention and control diet were not well described. Strawberries and oat bran bread were only described to be similar in caloric content. Additionally, oat bran bread was described to contain 2 g of β-glucan, which has been shown to reduce total and LDL cholesterol (44). It is unclear whether 454 g/d of strawberries deliver similar fiber content to maintain lipid profile or whether the decrease was attributed to other factors in the composition of strawberries. Without a clear comparison of the relevant macro- and micronutrient of both diets, it is difficult to evaluate the characteristic responsible for the changes.

The high compliance rate for all three studies indicated that incorporating strawberries was feasible and largely acceptable by the participants. The palatability rating for strawberries were also significantly higher than that for oat bran bread ($p<0.001$). This again indicated the practicality of using strawberries as a dietary intervention. In addition, Basu and colleagues (2009;2010) and Burton-Freeman et al. (2010) incorporated strawberries in the form of FSP. This illustrated that FSP, which were 10% of the fresh weight of strawberries, can be easily incorporated as a beverage. Since fruit juice consumption was a major source of fruit intake in the American diet, strawberries introduced as a beverage may increase fruit consumption in the United States.

**Strawberries on postprandial metabolism**

***Strawberries on postprandial antioxidant capacity***

In a random sequence crossover control study by Cao et al. (1998), 8 healthy female subjects were recruited to study the effects of strawberries, spinach, red wine, or vitamin C on serum total antioxidant capacity. Cao et al. found that intake of 240 g of strawberries increased total antioxidant capacity. This increase in antioxidant capacity was demonstrated by increase in the area under the curve (AUC) in serum and urinary oxygen radical absorbance capacity (ORAC) and ferric reducing ability of plasma (FRAP). AUC of $ORAC_{PCA}$ and FRAP increased by 13% and 10%, respectively, compared to control. Urinary ORAC excretion after consumption of strawberries was significantly higher than control ($p<0.05$) (45). This increase in both serum and urinary antioxidant capacity indicated that there was absorption and/or increased production of antioxidants as a result of strawberry intake. Cao et al. also found that vitamin C and urate only accounted for 8.7% and 39.1% of total antioxidant capacity in plasma after strawberry supplementation, respectively. Thus, the remaining 50.5% antioxidant capacity may be contributed by other factors such as strawberry polyphenols and endogenous sources of antioxidants. This suggested that the composition of strawberries may contain compounds that increase antioxidant capacity or compounds that act to increase production of endogenous antioxidant sources.

In addition, further analysis by Paiva et al. (1998) investigated the postprandial plasma responses of carotenoids in 7 out of the 8 healthy women in the study by Cao et al. (1998). Five beverages were studied but only the spinach beverage had a significant source of carotenoid content. Strawberry intervention was expected to produce similar results as the control beverage, both which were practically devoid of carotenoids. The control intervention had no significant difference in carotenoid levels from baseline. However, strawberry beverage had lower postprandial carotenoid concentrations than baseline. At 11 and 15 hours postprandial, most of the carotenoids were significantly lower than baseline values ($p<0.05$). In addition, strawberry intervention had significantly lowered LDL cholesterol after 1 hr from baseline ($p<0.05$). The

peak decrease was at 15 hours and after 24 hours returned to levels closer to baseline. LDL cholesterol reduced by 14.1% from baseline. It was hypothesized by Paiva et al. that strawberries may have played a role in interfering with secretion of carotenoids. Since LDL cholesterol was a significant carrier of carotenoids (46), the decrease in LDL cholesterol suggested that alterations in carotenoid concentrations were not due to decreases in LDL concentrations. Since carotenoids have antioxidant activity, strawberry compounds may be protecting against postprandial oxidation by preventing the release of carotenoids from lipoprotein. It can be inferred that strawberries were a factor in affecting the metabolism of lipids. Further research on the effects of strawberry on carotenoid absorption and secretion may clarify this unexpected finding. Also, additional research on the decrease of LDL cholesterol may provide insight on the effects of strawberry on lipid metabolism.

***Strawberries on postprandial antioxidant capacity and lipid metabolism***

Clinical studies had found that intake of strawberries alone, with a meal, and with a high fat meal challenge increased postprandial antioxidant capacity or decreased oxidative damage products. Similar to Cao and colleagues (1998), Prior et al. (2007) found a significant increase in antioxidant capacity after strawberry supplementation. Prior et al. (2007) recruited seven healthy women to consume two servings of 300g Seascape' strawberries to determine the postprandial changes in antioxidant capacity. Prior et al. found that the AUC of whole plasma $ORAC_{FL}$ after strawberry supplementation is 4314±1153 μmol TE/L · h, which is a 7.0% increase over baseline ($p<0.05$).

Prior et al. (2007) found that consumption of strawberries peaked whole plasma ORAC 1.5 hours postprandial and declined thereafter. However, blood samples were not taken after 4.5 hours postprandial and whole plasma ORAC also did not return to zero, therefore it is difficult to determine the total change in antioxidant capacity after strawberry supplementation. At 4.5 hours,

changes in whole plasma ORAC declined to only approximately half of peak levels. Similarly, after concurrent intake of strawberries with a control coconut drink, Cao et al. (1998) found that the peak level for the percentage change in serum total antioxidant capacity ($ORAC_{PCA}$) is 2 hours postprandial. In contrast to the findings by Prior et al (2007), antioxidant capacity returned to baseline after 4 hours postprandial. The rise in antioxidant capacity by strawberries was affected by foods eaten concurrently. Since intake of foods without antioxidants has been found to decrease antioxidant capacity (47), serum antioxidant capacity may have returned to baseline more rapidly in the study by Cao et al. (1998) because of the addition of the control meal. This suggested the importance of incorporating foods high in antioxidants, such as strawberries, during each meal in order to attenuate the postprandial decrease in antioxidant capacity.

In addition, in a randomized, placebo-controlled, 12-week crossover study by Burton-Freeman et al. (2010), strawberry supplementation significantly reduced triglyceride and oxidized-LDL (ox-LDL) levels compared to control. This study investigated the postprandial effects of strawberry supplementation in response to a high fat meal (HFM) challenge (approximately 28% fat) in 24 participants with dyslipidemia. Participants 1) at baseline, ingested a 10 g freeze-dried strawberries or a macronutrient matched controlled beverage and a HFM and 2) after 6 weeks of consuming strawberry or control beverage daily, both groups ingested a HFM with the control beverage only, without a strawberry beverage. Burton-Freeman et al. (2010) found that acute and chronic supplementation of strawberry beverage protects postprandial rise after a high fat meal challenge in plasma levels. However, chronic supplementation did not change fasting clinical endpoints.

After consuming a strawberry beverage with a HFM, there was a significant reduction in postprandial rise in plasma TG ($P=0.005$), HDL ($P=0.003$), and ox-LDL ($P=0.0008$) compared to control. Mean plasma TG were at normal levels (135.7±1.8 mg/dL) in the control group and strawberry intervention group (130.8±1.8 mg/dL) (48). According to the American Heart

Association (AHA), intensive lifestyle and dietary changes can possibly reduce TG levels up to 50% (48). Therefore, incorporation of strawberries that were a significant decrease in TG concentrations may be beneficial in decreasing CVD risk. Mean plasma HDL levels were considered at risk for the control group (44.4±0.2 mg/dL) and the strawberry intervention group (43.8±0.2 mg/dL). Although reductions in HDL cholesterol are considered negative to cardiovascular health, the mean difference between intervention groups may be statistically significant; however, the 0.6 mg/dL difference may be of less biological significance.

Furthermore, Burton-Freeman et al. (2010) found that after adjustment for the subject's fasting ox-LDL concentrations, mean change in plasma ox-LDL concentration was significantly lower in the strawberry intervention group than in the control group. In the strawberry intervention group, there was an average decrease of 1.0±1.5 U/L in ox-LDL in the plasma. On the other hand, the control group had an average increase of 6.3±1.5 U/L in ox-LDL in the plasma. A decrease in ox-LDL may be due to an increase in antioxidant which protected against oxidation or a decrease in LDL cholesterol concentrations. On the contrary, Burton-Freeman et al. (2010) found a significant increase in LDL cholesterol in the strawberry intervention ($p=0.04$). This small but significant increase of 1.5 mg/dL from 118.4 mg/dL in the control group demonstrated that strawberries protected against LDL oxidation without a decrease in LDL cholesterol.

In addition, after 6 weeks of strawberry intervention, postprandial rise in mean cholesterol ($p=0.0001$), LDL ($p=0.0002$), and TG ($p<0.0001$) were significantly reduced compared to the control intervention. This displayed that chronic consumption of strawberries, even if not consumed concurrently with the HFM challenge, will reduce the postprandial rise of mean cholesterol, LDL, and TG. This protection against postprandial lipemia was found to be independent of changes in fasting lipid levels.

The implications of these studies were that the types of foods eaten concurrently with strawberries may affect the duration and AUC of postprandial rise and fall of lipids. Further studies on the changes of postprandial response to different micro- and macronutrient compositions of meals eaten with strawberries may be warranted. Another implication was that strawberries incorporated into the daily diet as well as a one-time incorporation with a meal will protect against postprandial lipemia and oxidation of LDL without changing fasting plasma levels. This suggested that including strawberries into the diet may be one way of protecting against CVD by minimizing the postprandial rise of lipids and oxidation of LDL. These data agree with other studies that suggest the positive role of strawberries in cardiovascular health.

***Strawberries on postprandial inflammatory and thrombotic responses***

In a crossover study by Ellis et al. (2011), strawberry supplementation was found to significantly protect against postprandial increases in fibrinolytic and inflammatory factors after high carbohydrate/fat (HCF) meal. In this study, 24 overweight subjects consumed strawberry or control beverage for 6 weeks to investigate the effects of strawberry consumption on plasma glucose and insulin secretions as well as inflammatory and fibrinolytic factors in 1) fasting plasma levels and 2) postprandial, after a HCF meal challenge and placebo beverage. The strawberry beverage contained 10 g freeze-dried strawberry powder (approximately 100 g fresh strawberries) and the control beverage was matched for calories, fat, protein, and carbohydrates. The HCF meal with the placebo beverage consisted of 134.3 g of carbohydrate (55.9% of kcals) and 30.6 g fat (28.6% of kcals).

After 6 weeks of intervention, there were no significant differences in fasting values for glucose, insulin, inflammatory and hemostatic factors between strawberry and control beverages ($p>0.05$). However, high sensitive (hs)CRP ($p=0.09$), interleukin (IL)-1β ($p=0.08$), and tumor necrosis factor (TNF)-α ($p=0.07$) in the strawberry intervention showed marginal decrease

compared to the control group. The marginal decrease found in this study was most likely due to the low dose of strawberries. Other studies have observed a difference in oxidative or inflammatory stress products after chronic supplementation in doses 2 to 5 times greater than in this study (37-39, 49).

However, strawberry supplementation with a HCF meal displayed anti-thrombotic and anti-inflammatory postprandial response by decreasing plasminogen activatory inhibitor (PAI)-1 and interleukin (IL) activity. After 6 weeks of strawberry intervention, strawberries significantly decreased PAI-1 ($p=0.002$) and IL-1β ($p=0.05$) compared to control. Also, IL-6 concentrations was found to decrease marginally when controlling for fasting IL-6 concentrations ($p=0.07$). PAI-1 is an inhibitor of fibrinolysis (50). An increase in PAI-1 suggested an increase risk for thrombosis by inhibiting break down of blood clots (51). IL-1β is a cytokine and a marker for inflammation. There were no treatment related differences in postprandial glucose, insulin, hsCRP, or TNF-α response ($p>0.05$).

Ellis et al. (2011) added to the continual evidence that strawberries modify response to oxidative and inflammatory stress. In this study, strawberries were found to attenuate postprandial rise in inflammatory cytokines and pro-thrombotic responses in overweight men and women after 6 week of daily supplementation. Similar to Burton-Freeman et al. (2010), chronic supplementation of strawberries attenuated postprandial responses even in the absence of strawberries during that particular meal. In addition, there was only a marginal change in fasting levels of inflammatory and oxidative stress markers after chronic supplementation. This displayed the protective properties of strawberries in the absence of alterations in plasma concentrations.

### *Strawberries on postprandial glucose metabolism*

Postprandial metabolism of glucose has become increasingly important. Impairment in postprandial control of serum glucose concentrations appeared to be related to increase risk of

CVD (52). Postprandial hyperglycemia has been identified as an independent risk factor for CVD (52). Hyperglycemia alters endothelial function, increases thrombosis, and increases adhesion molecules (52). Endothelial function is affected by the decrease in nitric oxide (NO), which regulates vascular tone. A dysfunction in the vasodilation of the endothelium in combination with the increased platelet aggregation may lead to cardiovascular dysfunction (52). Hyperglycemia also induces the increase in adhesion molecules, intercellular adhesion molecule (ICAM)-1. Increased expression of ICAM molecules have been attributed to the activation of atherosclerosis. In addition, excessive postprandial glucose concentrations are toxic and generate oxidative stress (53). These cell toxicity and oxidative stress products may increase glycation end-products and free radicals that promote atherosclerosis.

Strawberries in the form of a mixed berry purée had been found to affect the postprandial glucose response (54). Törrönen et al. (2009) conducted a randomized, controlled, cross-over study on the postprandial effects of a mixed berry purée on plasma glucose in twelve healthy subjects. The test meal consisted of 37.5 g of each of the following berries: black currants, bilberries, European cranberries, and strawberries (a total of 150 g of berries). The control meal had a similar carbohydrate profile as the berry meal with 35 g sucrose, 4.5 g glucoses, and 5.1 g fructose. Participants ingested the test meal or control meal after a 12 hour overnight fast and blood samples were taken at baseline and at different time points postprandial. Törrönen et al. (2009) found that after consuming the berry meal, plasma glucose concentrations peaked at approximately 7.4 mmol/l after 45 minutes. The plasma glucose concentration in the participants that ingested the control meal peaked at approximately 8.5 mmol/l after 30 minutes postprandial. Recommended glucose concentrations are less than 10.0 mmol/L 1-2 hours after a meal (55), therefore glucose concentrations in the participants are within normal range. Although the control and berry meal had similar carbohydrate profiles, the control meal elicited a more rapid and higher peak in plasma glucose concentration than the berry meal.

Polyphenols from berries have been found to inhibit α-glucosidase and α-amylase activity, enzymes important in digestion of carbohydrates (56). Specifically, α-glucosidase digests sucrose into glucose and α-amylase digests polysaccharides into glucose and maltose (57). Since the control meal was comprised of simple sugars, inhibition of α-glucosidase is more likely the cause of the decrease in glycemic index in the berry meal. In a study by Kurotobi et al. (2009), strawberry jams composed of different ratios of saccharides and fiber were shown to affect postprandial glucose response differently. The glycemic index of strawberry jams made from differing free sugar concentrations ranged from 17 to 76 (58). Additional studies measuring *in vivo* α-glucosidase activity after berry consumption may confirm the role of polyphenols in carbohydrate metabolism.

Furthermore, Törrönen et al. (2009) found that at 15 and 30 minutes postprandial, the berry meal had significantly lowered plasma glucose concentrations than control ($p<0.05$ and $p<0.001$, respectively). According to the graph, at 15 minutes postprandial, plasma glucose was approximately 5.5 mmol/l in the berry purée meal and 6.5 mmol/l in the control meal. And at 30 minutes postprandial, plasma glucose was an estimated 7.2 mmol/l in the berry purée meal and 8.5 mmol/l in the control meal. In addition, at 150 minutes postprandial, the berry meal had a significantly higher plasma glucose concentration than control (approximately 4.9 mmol/l vs 4.5 mmol/l, respectively). The differences in glucose concentration at those three time points were not due to changes in AUC. Although the AUC tended to be lower after the berry meal than after the control meal, this was not found to be significant ($p=0.29$). This indicated that berry purée attenuated postprandial glucose concentrations without decreasing the AUC concentrations of glucose.

An attenuation of glucose concentrations after a meal may be beneficial in cardiovascular health since excessive postprandial glucose can be cytotoxic (59). Excessive and prolonged increase in glucose levels can lead to increased protein glycation and increased free radical

production (59). This in turn may increase risk of CVD by affecting endothelial function (59). The subjects in the study by Törrönen et al. (2009) were healthy and maintained glucose concentrations within normal limits; however, foods that attenuate glucose concentrations may be more pertinent in participants who have impaired glucose tolerance or diabetes. Therefore, further studies on the effects of berries on postprandial glucose may be beneficial in subject populations who are at risk for glucose intolerance or diabetes. In addition, further studies on strawberries alone may help elucidate the role of strawberries on glucose metabolism.

# CHAPTER III

## MATERIALS AND METHODS

### Participants

Following approval from the Institutional Review Board (IRB), men and women with abdominal adiposity and dyslipidemia were recruited from the Clinical Research Center (CRC) at Oklahoma University and at the Department of Nutritional Sciences (NSCI) at Oklahoma State University through flyers and campus e-mail advertisements. Participants had an initial telephone screen and then were scheduled for a screening visit. Subjects were qualified through inclusion and exclusion criteria. After qualification, 17 subjects were randomized to match for age and gender. Eight subjects were enrolled in the strawberry intervention and 9 subjects were enrolled in the control group.

### Inclusion criteria

Subjects were included based on inclusion criteria:

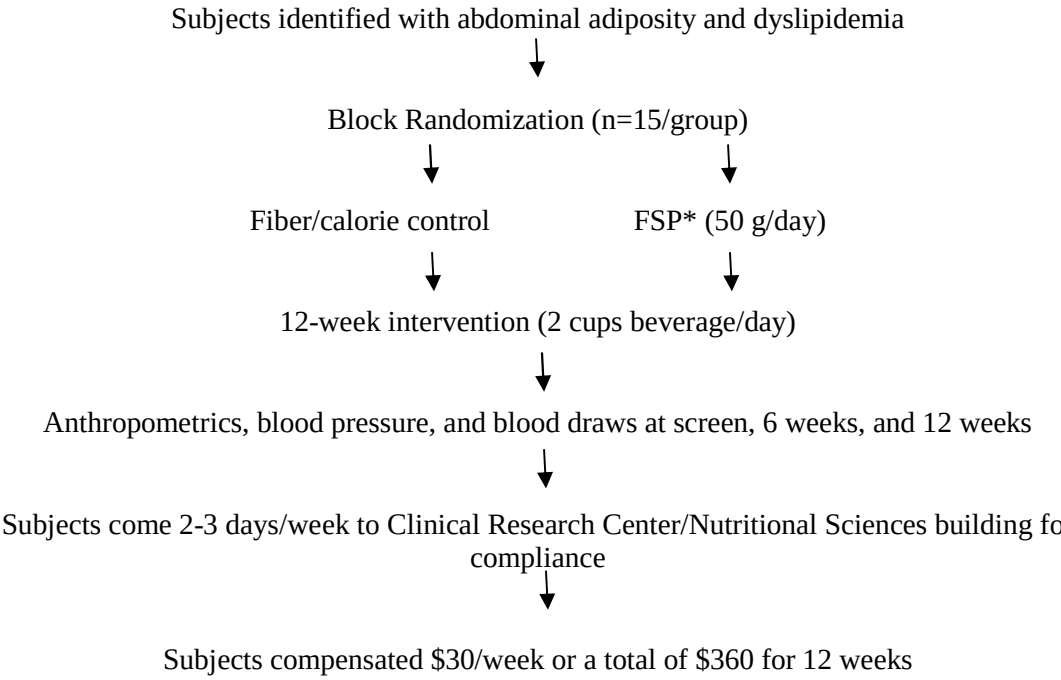
1. Abdominal adiposity (men >40 inches, women >35 inches) (60)
2. Dyslipidemia (two of four criteria: fasting total cholesterol >200 mg/dL, triglycerides >150 mg/dL, low density lipoprotein (LDL) –cholesterol >100 mg/dL, or high density lipoprotein (HDL)-cholesterol (men <40 mg/dL, women <50 mg/dL) (60)
3. Normal liver, kidney, and thyroid function tests
4. Stable multivitamin/mineral supplements or prescription medications (except hypolipidemic, hypoglycemic, and steroid agents) will also be included
5. Males and females
6. Any ethnic group

**Exclusion criteria**

Subjects were excluded based on exclusion criteria:

1. Pre-existing disease (e.g. anemia, cancer, heart disease, diabetes [fasting glucose ≥126 mg/dL], liver, or renal disorders)
2. Pregnancy and lactation
3. Consumption of mega doses of antioxidants/fish oil supplements (>1 g/day)
4. Consumption of hypolipidemia, hypoglycemic, and steroid medications
5. Abnormal hemoglobin (Hb) (normal range: 12.0-18.0 g/dL), white blood cell (WBC) (normal range: 4.0-11.0 K/mm3), or platelets (140-440 K/mm3)
6. Hypo/hyperthyroidism (normal range for thyroid stimulating hormone: 0.35-4.940 uiu/mL)
7. Abnormal liver enzymes (normal range for aspartate transaminase (AST): 7-40 units/L; alanine transaminase (ALT): 10-45 units/L)
8. Abnormal kidney function (normal creatinine: females: 0.7-1.2 mg/dL; males: 0.8-1.2 mg/dL; normal blood urea nitrogen (BUN): 1-59 years: 7-18 mg/dL; >59 years: 8-21 mg/dL)
9. Smoking and drinking alcohol (>1 oz/day)

**Methods: Research design**




*FSP = Freeze-dried strawberry powder

**Intervention and compliance**

Subjects consumed 2 cups of the intervention beverage or control beverage daily for 12 weeks. The intervention beverage consisted of 50g freeze dried strawberry blended into 2 cups of water with splenda (optional) per day. The control beverage consisted of 8 g fiber (dietary cellulose + Metamucil), 8 tsp sugar, 2 tsp of strawberry Koolaid©, and 4 drops of red food coloring blended into 2 cups of water per day. Nutrition composition of the strawberry and control intervention is listed on Table 1.

All subjects made mandatory visits to the research facilities 2-3 days/week to ensure compliance. The remaining quantities of beverages were provided in containers for later consumption. Height, weight, blood pressure, and waist circumference were measured by trained personnel at the Clinical Research Center (CRC) at Oklahoma University (OU) and at Nutritional Sciences building at Oklahoma State University (OSU) at screen, 6 weeks, and at 12 weeks of the

study. Blood draws were performed by trained nurses at CRC and by trained phlebotomists at Stillwater Medical Center at OSU.

**Dietary analyses**

All subjects were asked to follow their usual diet and lifestyle but refrain from other sources of berries and related products while on the study. Subjects also maintained 3-day food (2 weekday and 1 weekend) records at screen, 6 and 12 weeks of the study. Three day averages of micro- and macronutrient intakes were calculated using Food Processor (ESHA Research, Salem, OR). If a participant ate a food that was not in the database, an online search of the nutrient composition was made or a food with very similar nutrient composition was chosen.

**Clinical variables**

Fasting blood samples, after each draw were immediately sent to OU Medical Center laboratory or the Stillwater Medical Center laboratory for comprehensive metabolic panel (CMP) including glucose, insulin, glycated hemoglobin, lipid panel, electrolytes, liver, kidney, thyroid tests, and complete blood count at each visit. Remaining plasma and serum samples were stored at -80ºC for future analyses.

**Biomarkers of oxidative stress**

Plasma concentrations of oxidized-LDL were measured using enzyme-linked immunosorbent assay (ELISA) kits (Mercodia, Uppsala, Sweden)) according to the manufacturer's instructions. Lipid peroxidation were measured in serum as malondialdehyde (MDA) using a colorimetric assay according to the manufacturer's protocol (LPO-586TM, Oxis Health Products, Inc., Portland, OR). All samples were assayed in triplicates within our established inter assay variations of 10% for each variable.

**Statistical analyses**

Descriptive statistics were used to calculate the frequency, mean, and standard error of each parameter. Baseline differences between strawberry intervention and control were assessed by independent sample *t* test.

Changes in anthropometric measures, blood pressure, serum glucose, insulin, and lipid profile between strawberry and control groups were assessed by the differences in measurements of each group at baseline, 6 weeks, and 12 weeks. One-way ANOVA test was used to assess statistical difference between different time points between strawberry and control intervention. Additional analysis of within group changes at different time points were assessed by repeated measures ANOVA. Statistical significance was set at $P < 0.05$. Data are represented as mean ± standard error. All statistical analyses were run by SPSS for Windows (version 17.0, SPSS, 2008).

# CHAPTER IV

## RESULTS

A total of 25 participants were screened for the study. Of those subjects, 17 participants met the satisfactory inclusion and exclusion criteria and agreed to be enrolled in the study. Eight subjects were randomized into the strawberry intervention and 9 subjects were randomized into the control intervention. All the subjects who were enrolled completed the 12 week study. In addition, 100% of the subjects in both groups adhered to the diet, which was assessed by returning bottles empty of research contents to researchers 2-3 times per week. There were no complaints from the participants about adverse effects from supplementation.

No significant differences were found in baseline characteristics between strawberry intervention and control (Table 2).

### Anthropometric measures and blood pressure

At baseline, anthropometric measures and blood pressure of the strawberry and control intervention groups were not statistically different.

Anthropometric measures did not significantly change in the strawberry intervention group from 0 to 12 weeks (Table 3). Waist circumference significantly decreased by 0.694 inches ($p=0.015$) from 0 to 6 weeks, but increased by 0.712 inches from 6 weeks to 12 weeks ($p<0.05$). However, the net change from 0 to 12 weeks was not significantly different. Similarly, anthropometric measures did not significantly change in the control intervention after 12 weeks

of supplementation (Table 3).

Blood pressure did not significantly change in the strawberry or control group after 12 weeks supplementation. Between group differences in blood pressure were not statistically significant.

**Glucose and insulin**

At baseline, glucose, hemoglobin A1c, and insulin were not significantly different between strawberry and control group ($p>0.05$).

Fasting glucose, hemoglobin A1c, and insulin did not significantly change in the strawberry and control group after 12 weeks supplementation (Table 3). Between group differences in glucose, hemoglobin A1c, and insulin were not statistically significant.

**Lipid profile**

Baseline lipid panel between strawberry and control intervention were not statistically different.

Lipid profile did not significantly change in the strawberry and control group after 12 weeks supplementation (Table 3). Between group differences in lipid panel were not statistically significant.

**Biomarkers of lipid oxidation**

In the strawberry group, mean ox-LDL was 133.5 ± 5.1 U/L at baseline (Table 3). After 6 weeks intervention, ox-LDL decreased significantly from baseline by a mean of 10.4 U/L ($p=0.011$) (Table 5). From 6 weeks to 12 weeks, ox-LDL decreased further by a mean of 3.9 U/L. Ox-LDL significantly decreased from baseline to 12 weeks by 10.6% ($p=0.004$) (Table 5).

At baseline, mean ox-LDL was 127.0 ± 5.8 U/L in the control group (Table 3). From baseline to 6 weeks of the study intervention, mean ox-LDL significantly decreased by a mean of 7.1 U/L (p=0.001) (Table 5). From 6 weeks to 12 weeks, ox-LDL decreased further by a mean of 1.0 U/L. After 12 weeks, ox-LDL significantly decreased by 6.4% compared to baseline (p=0.001).

The between group changes from baseline to 6 weeks, 6 weeks to 12 weeks, and baseline to 12 weeks were not statistically different for ox-LDL (p>0.05) (Table 4). However, from baseline to 12 weeks, participants who consumed the strawberry supplementation had a decreasing trend of ox-LDL concentrations compared to control (p=0.054).

In the strawberry group, mean MDA was 3.0 ± 0.22 μM at the beginning of the study (Table 3). After 6 weeks of supplementation, MDA significantly decreased by a mean of 0.45 μM (p=0.021) (Table 5). After 12 weeks, MDA decreased further by a mean of 0.17 μM from 6 weeks. At the end of the study, MDA significantly decreased by a total of 23.3% from baseline (p=0.007).

At baseline, mean MDA was 0.17 ± 0.09 μM in the control group. From 0 weeks to 6 weeks of the study, MDA significantly decreased by a mean of 0.48 μM (p=0.010) (Table 5). However, from 6 weeks to 12 weeks, MDA increased by a mean of 0.07 μM. After 12 weeks, MDA significantly decreased by a total of 14.8% (p=0.048).

The between group changes from baseline to 6 weeks, 6 weeks to 12 weeks, and baseline to 12 weeks were not statistically different for MDA (p>0.05) (Table 4). From baseline to 6 weeks, MDA decreased in both groups. However, from 6 weeks to 12 weeks, the strawberry intervention had a decreasing trend in MDA concentrations compared to control (p=0.093). Nevertheless, the summed change in MDA concentrations was not significantly different between groups from baseline to 12 weeks.

**Dietary intake**

Dietary intake of the strawberry and control group for baseline and 12 weeks were presented on Table 6. Nutrient analyses were not statistically different on any of the nutrients at baseline and week 12 for the strawberry and control intervention ($p>0.05$). The baseline dietary intake for one participant in the strawberry group was not indicative of usual intake because the subject was suffering from gastrointestinal problems unrelated to the study.

At week 6, fiber intake in the control group was significantly higher than the strawberry group ($19.4 \pm 5.9$ g vs $13.3 \pm 1.7$ g, respectively) ($p=0.036$). At week 12, selenium intake was significantly higher in the strawberry group than the control group ($56.1 \pm 9.0$ vs $33.7 \pm 5.0$, respectively) ($p=0.04$).

**TABLE 1**: Composition of strawberries and control beverage

| Nutritive value | Freeze-dried strawberries (50g) [1] | Control [2] |
|---|---|---|
| **Calories (kcal)** | 150 | 150 |
| **Protein (g)** | 3.5 | - |
| **Fat (g)** | 0.5 | - |
| **Carbohydrates (g)** | 50 | - |
| **Dietary fiber (g)** | 8 | 8 |
| **Ash (g)** | 3.17 | - |
| **Vitamin C (mg)** | 109 | 3 |
| **Total Phenolics (mg)** [3] | 2006 | - |
| **Total Anthocyanins (mg)** [4] | 154 | - |
| **Ellagic acid (mg)** | 41 | - |
| **Phytosterols (mg)** | 50 | - |

[1] Ten percent fresh weight; California Strawberry Commission (Watsonville, CA, USA).
[2] Fiberstir LLC (Plymouth, MN, USA)
[3] Expressed as milligram gallic acid equivalents
[4] Expressed as milligram cyaniding-3-glucoside equivalents

**TABLE 2**: Baseline characteristics of participants[1]

| | Strawberry Intervention | Control |
|---|---|---|
| ***n*** | 8 | 9 |
| **Age (years)** | 46.5 ± 4.1 | 51.8 ± 2.8 |
| **Male/Female (n/n)** | 2/6 | 1/8 |
| **Waist circumference (inches)** | 45.3 ± 2.0 | 41.5 ± 1.0 |
| **BMI (kg/m$^2$)** | 39.0 ± 2.9 | 35.6 ± 1.9 |
| **TC(mg/dL)** | 212.9 ± 11.5 | 211.7 ± 12.9 |
| **LDL (mg/dL)** | 140.0 ± 11.9 | 128.0 ± 10.9 |
| **HDL (mg/dL)** | 45.1 ± 7.2 | 46.3 ± 3.2 |
| **TG (mg/dL)** | 179.9 ± 24.2 | 185.2 ± 25.5 |
| **Multivitamin users (%)** | 2.0 | 1.0 |
| **ALT (IU/L)** | 24.5 ± 2.6 | 28.1 ± 2.4 |
| **AST (IU/L)** | 24.1 ± 1.2 | 24.0 ± 1.8 |
| **BUN (mg/dL)** | 13.5 ± 0.6 | 15.3 ± 1.0 |

[1]Data are means ± standard error.

Abbreviations: BMI, body mass index; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen.

**TABLE 3**. Anthropometric measures, blood pressure, glucose control, and lipid panel of participants after 12-wk supplementation with freeze-dried strawberries or control treatment[1]

| | **Desirable Range**[2] | **Strawberry Intervention** (n=8) | | | **Control Intervention** (n=9) | | |
|---|---|---|---|---|---|---|---|
| | | 0 week | 6 week | 12 week | 0 week | 6 week | 12 week |
| **BMI (kg/m$^2$)** | 18.5-24.9 | 39.0 ± 2.9 | 38.8 ± 2.9 | 38.9 ± 3.2 | 35.6 ± 1.9 | 35.7 ± 2.0 | 35.6 ± 1.9 |
| **Waist (inches)** | Men <40<br>Women <35 | 45.3 ± 2.0 | 44.6 ± 1.8 | 45.3 ± 2.0 | 41.5 ± 1.0 | 41.6 ± 1.0 | 42.1 ± 1.2 |
| **SBP (mmHg)** | <120 | 136.5 ± 4.2 | 134.6 ± 3.7 | 134.5 ± 5.2 | 130.8 ± 4.5 | 131.1 ± 3.9 | 131.1 ± 3.0 |
| **DBP (mmHg)** | <80 | 86.4 ± 3.7 | 84.9 ± 3.3 | 84.1 ± 3.5 | 82.1 ± 1.2 | 80.8 ± 1.6 | 93.4 ± 1.6 |
| **Glucose (mg/dL)** | 90-130 | 89.5 ± 5.6 | 95.8 ± 6.5 | 89.0 ± 5.9 | 91.0 ± 6.1 | 98.8 ± 4.6 | 93.4 ± 6.6 |
| **HbA1c (%)** | 4.5-6 | 5.9 ± 0.19 | - | 5.8 ± 0.31 | 6.0 ± 0.18 | - | 5.7 ± 0.14 |
| **Insulin (µU/mL)** | 5-20[3] | 17.7 ± 3.1 | 18.6 ± 2.6 | 15.5 ± 3.0 | 26.4 ± 5.8 | 20.0 ± 1.4 | 18.2 ± 2.4 |
| **TC (mg/dL)** | <200 | 212.9 ± 11.5 | 202.0 ± 8.4 | 201.8 ± 7.3 | 211.7 ± 12.9 | 209.4 ± 13.8 | 213.1 ± 13.9 |
| **LDL (mg/dL)** | <100 | 140.0 ± 11.9 | 128.5 ± 5.8 | 123.6 ± 8.7 | 128.0 ± 10.9 | 128.2 ± 11.7 | 127.2 ± 11.3 |
| **HDL (mg/dL)** | Men >40<br>Women >50 | 45.1 ± 7.2 | 43.0 ± 6.3 | 44.5 ± 4.7 | 46.3 ± 3.2 | 44.9 ± 3.4 | 49.4 ± 3.6 |
| **VLDL (mg/dL)** | 5-40[3] | 35.8 ± 4.8 | 39.3 ± 3.8 | 37.4 ± 4.0 | 37.0 ± 5.1 | 36.2 ± 6.1 | 35.7 ± 5.1 |
| **TG (mg/dL)** | <150 | 179.9 ± 24.2 | 195.0 ± 17.4 | 185.1 ± 19.6 | 185.2 ± 25.5 | 180.9 ± 30.6 | 168.6 ± 20.8 |

[1]Data are means ± standard error.

[2]Ranges from MayoClinic.com.

[3]Ranges from Drugs.com.

Abbreviations: BMI, body mass index; Waist, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; TG, triglycerides.

**TABLE 4**. Change in lipid profile and oxidative stress markers at different time points after 12-wk supplementation of freeze-dried strawberries or control treatment[1]

| | Δ (0-6 wk) | | Δ (6-12 wk) | | Δ (0-12 wk) | |
|---|---|---|---|---|---|---|
| | **Strawberry Intervention** | **Control** | **Strawberry Intervention** | **Control** | **Strawberry Intervention** | **Control** |
| **TC (mg/dL)** | 10.9 ± 8.3 | 2.2 ± 6.7 | 0.25 ± 5.9 | -3.7 ± 8.4 | 11.1 ± 8.9 | -1.4 ± 12.1 |
| **LDL (mg/dL)** | 11.5 ± 8.8 | -0.22 ± 8.0 | 4.9 ± 7.9 | 1.0 ± 5.1 | 16.4 ± 11.1 | 0.78 ± 9.2 |
| **HDL (mg/dL)** | 2.1 ± 2.6 | 1.4 ± 1.6 | -1.5 ± 2.1 | -4.6 ± 2.7 | 0.63 ± 3.2 | -3.1 ± 3.7 |
| **VLDL (mg/dL)** | -3.5 ± 3.3 | 0.78 ± 4.0 | 1.9 ± 2.9 | 0.56 ± 3.3 | -1.6 ± 3.2 | 1.3 ± 2.8 |
| **Ratio LDL:HDL** | 0.14 ± 0.20 | -0.13 ± 0.12 | 0.36 ± 0.14[†] | 0.11 ± 0.19 | 0.5 ± 0.26 | -0.02 ± 0.19 |
| **TG (mg/dL)** | -15.1 ± 16.7 | 4.3 ± 20.9 | 9.9 ± 15.1 | 12.3 ± 17.6 | -5.3 ± 16.5 | 16.7 ± 11.3 |
| **OX-LDL (ng/mL)** | 10.4 ± 2.4 | 7.1 ± 1.1 | 3.9 ± 1.7 | 1.0 ± 1.6 | 14.3 ± 2.7[†] | 8.1 ± 1.3 |
| **MDA (uM)** | 0.45 ± 0.12 | 0.48 ± 0.12 | 0.17 ± 0.09 | -0.07 ± 0.15 | 0.63 ± 0.13 | 0.41 ± 0.13 |

[1]Data are means ± standard error.

[†] Trend, $0.05 < P < 0.1$ difference compared to control.

Abbreviations: TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; TG, triglycerides; OX-LDL, oxidized low density lipoprotein; MDA, malondialdehyde.

**TABLE 5**: Repeated measures ANOVA comparison of within groups at 0 week, 6 weeks, and 12 weeks[1]

| | Strawberry Intervention | Control |
|---|---|---|
| **OX-LDL (ng/mL)** | | |
| 0 Week | 133.5 ± 5.1[a] | 127.0 ± 5.8[a] |
| 6 Weeks | 123.1 ± 4.2[b] | 119.9 ± 5.9[b] |
| 12 Weeks | 119.3 ± 3.4[b] | 118.9 ± 6.1[b] |
| **MDA (uM)** | | |
| 0 Week | 3.0 ± 0.22[a] | 2.7 ± 0.18[a] |
| 6 Weeks | 2.5 ± 0.14[b] | 2.2 ± 0.16[b] |
| 12 Weeks | 2.3 ± 0.13[b] | 2.3 ± 0.17[b] |

[1] Data are means ± standard error.

*Values in the same column with different superscripts are significantly different for each set of observations ($p<0.05$).

Abbreviations: OX-LDL, oxidized lipoprotein; MDA, malondialdehyde.

No differences between times within groups on cholesterol, triglycerides, LDL, HDL, and LDL:HDL.

**TABLE 6.** Nutrient analysis of dietary intake at 0 week and 12 weeks

| | 0 week | | 12 weeks | |
|---|---|---|---|---|
| | **Strawberry Intervention** | **Control** | **Strawberry Intervention** | **Control** |
| **Calories (kcal)** | 1716.6 ± 345.8 | 1949.0 ± 146.2 | 1786.3 ± 151.1 | 1809.2 ± 100.8 |
| **Protein (g)** | 72.6 ± 13.0 | 66.5 ± 5.6 | 83.3 ± 14.4 | 67.7 ± 7.7 |
| **Carbohydrates (g)** | 196.7 ± 43.6 | 238.5 ± 20.7 | 202.4 ± 23.4 | 202.2 ± 8.2 |
| **Fiber (g)** | 14.3 ± 1.8 | 16.7 ± 2.3 | 16.6 ± 2.1 | 16.6 ± 2.1 |
| **Fat (g)** | 70.4 ± 16.7 | 84.5 ± 6.5 | 73.5 ± 6.4 | 79.5 ± 6.4 |
| **Saturated Fat (g)** | 21.4 ± 4.9 | 24.7 ± 2.5 | 21.5 ± 2.7 | 27.6 ± 3.2 |
| **Monounsaturated Fat (g)** | 14.5 ± 4.2 | 17.4 ± 3.5 | 13.8 ± 2.9 | 16.5 ± 2.1 |
| **Polyunsaturated Fat (g)** | 7.6 ± 2.5 | 10.7 ± 1.1 | 7.7 ± 1.7 | 8.6 ± 1.0 |
| **Total Cholesterol (mg)** | 208.2 ± 41.2 | 209.3 ± 19.9 | 175.2 ± 36.3 | 238.0 ± 45.3 |
| **A-RAE (µg)** | 566.2 ± 175.3 | 323.2 ± 109.9 | 384.7 ± 174.5 | 359.3 ± 68.1 |
| **Vitamin C (mg)** | 101.8 ± 38.8 | 50.6 ± 10.9 | 73.6 ± 15.2 | 59.2 ± 15.9 |
| **EToco (mg)** | 2.6 ± 0.52 | 7.0 ± 2.0 | 4.1 ± 1.4 | 4.4 ± 1.1 |
| **Folate (µg)** | 231.4 ± 55.5 | 349.3 ± 138.0 | 213.3 ± 35.1 | 245.0 ± 61.7 |
| **Calcium (mg)** | 758.1 ± 243.0 | 575.3 ± 90.4 | 613.7 ± 152.4 | 646.0 ± 46.0 |
| **Copper (mg)** | 0.61 ± 0.19 | 0.63 ± 0.11 | 0.67 ± 0.09 | 0.57 ± 0.09 |
| **Iron (mg)** | 10.8 ± 1.5 | 12.8 ± 2.6 | 10.5 ± 0.85 | 15.6 ± 2.5 |
| **Selenium (µg)** | 55.2 ± 16.1 | 36.9 ± 6.4 | 56.1 ± 9.0* | 33.7 ± 5.0 |
| **Zinc (mg)** | 5.9 ± 1.5 | 6.8 ± 1.9 | 6.8 ± 1.2 | 5.7 ± 0.9 |

[1] Data are means ± standard error.

Abbreviations: RAE, retinol activity equivalents; EToco, tocopherols.

* Significantly different than control at p=0.04

# CHAPTER V

## CONCLUSION

Our study showed a significant decrease in baseline ox-LDL and MDA from 6 weeks and 12 weeks after strawberry and control intervention. Ox-LDL also showed a decreasing trend after 12 weeks of strawberry supplementation compared to control. In this 12 week study in subjects with dyslipidemia and abdominal adiposity, strawberry beverage did not significantly change anthropometric measures, blood pressure, glucose, insulin, lipid panel, and biomarkers of lipid oxidation compared to a fiber-control beverage.

Different forms of strawberries that have been used in different clinical trials are freeze-dried, frozen, fresh, jam, and puréed. Of the 12 clinical trials that were reviewed, 4 studies similarly used freeze-dried strawberry powder (37, 38, 50, 61), 1 study used frozen strawberries (49), 4 studies used fresh strawberries (39, 45, 47, 62), 1 study used strawberry jams (58), and 2 studies used a mix of different berries (63, 64). The fresh strawberry equivalent for the doses used in the studies using FSP, frozen strawberries, and fresh strawberries were 100-500 g, 250 g, 250-454 g, respectively. The dose in the study using strawberry jams was 20 g jam. In the two previous studies that used mixed berries, 150-160 g of berries were consumed, where 100 g of strawberry purée was consumed every other day in one study and the second study used 37.5 g of strawberries per day. Therefore, the dose of strawberries in our study is greater or equal to that used in previous studies.

Since freeze-dried powder (FSP) strawberries are approximately 10% of the fresh

strawberry weight, FSP allows for larger doses of strawberries to be consumed per day and is also a concentrated source of strawberry polyphenols and fiber. In previous clinical trials, the fresh weight equivalent of various forms of strawberries used ranged from 100 g to 500 g. According to the USDA MyPlate.gov, men and women 19-50 years of age require 1.5-2 cups of fruits per day. 50 grams of FSP strawberries or 500 g of fresh strawberries used in our study equate to approximately 3.5 cups of strawberries per day. This is well within the appropriate recommendation for fruit consumption per day.

In our study, the intervention was longer than previous long term studies involving strawberry supplementation (12 weeks vs 3-8 weeks, respectively). There were also multiple time points at baseline, 6 weeks, and 12 weeks in order to better assess the changes in each participant.

**Strawberries on anthropometrics and blood pressure**

Anthropometric measures did not significantly change from baseline to 12 weeks. Similar to other studies, body weight, waist circumference, and BMI did not change after long term strawberry intervention (37-39, 64).

However, in contrast to the null finding on blood pressure in this study, in a study by Erlund et al. (2008) berry supplementation has been shown to significantly decrease systolic blood pressure (SBP) in healthy subjects with cardiovascular disease (CVD) risk factors compared to calorie control (64). There may be multiple explanations for this difference in finding. First of all, Erlund and colleagues used a blend of berries rather than an isolated species of berry. The varying concentrations of different polyphenols may be working synergistically in the biological system to decrease blood pressure. Secondly, the control in the study by Erlund et al. was a calorie control whereas the control in our study was a fiber and calorie matched control. According to a meta-analysis of the relationship between dietary fiber and blood pressure, increasing dietary fiber, where levels are below recommendations, decreases both systolic and

diastolic blood pressure (65). Therefore, there may not have been any differences between groups due to the blood pressure lowering effects of fiber. In addition, the sample size in the study by Erlund and colleagues were approximately four times the size of the sample size in our study. Lastly, although subjects in both studies were pre-hypertensive, subjects in our study have higher BMIs and abdominal adiposity compared to the subjects in the study by Erlund and colleagues. Subjects in our study were obese whereas subjects in the study by Erlund et al. were at the cusp between normal and overweight. Since obesity and abdominal adiposity are independent risk factors for developing hypertension (66), the increased metabolic stress may require interventions closer to pharmacological doses in order to elicit a change in blood pressure.

**Strawberries on glucose and insulin**

In our study, strawberry supplementation did not significantly affect glucose, hemoglobin A1c, and insulin concentrations. In a study by Torronen et al. (2009), berry supplementation did not change the postprandial area under the curve response of serum glucose. However, berry supplementation was found to attenuate the spiked glucose response after a meal. This may suggest that strawberries may attenuate postprandial rise in serum glucose without changing overall glucose concentrations. A decrease in hemoglobin A1c may suggest a decrease in mean serum glucose levels over the course of the study. However, the non-significant small decrease and large variation limits the interpretation of these numbers. More importantly, glucose and hemoglobin A1c levels were within desirable ranges (67), a significant decrease in glucose control would not be beneficial to subjects.

**Strawberries on lipid profile**

In our study, we found that within group and between groups changes in lipid profile were not significantly different after strawberry supplementation. Although total cholesterol (TC) did not significantly decrease from baseline nor were there significant between group changes, it

decreased by a mean of 11.1 mg/dL in the strawberry group, which may have possible biological significance. Although not significant, mean TC reduced to levels close to ideal (mean T=201.8 mg/dL vs ideal <200 mg/dL) . Similarly, although there were no significant decrease from baseline nor significant between group changes, LDL cholesterol reduced by 16.4 mg/dL in the strawberry intervention group after 12 weeks supplementation. The baseline LDL levels were "borderline high" but after 12 weeks supplementation are "near ideal" (67). Although not statistically significant, the reduction in LDL in the strawberry group compared to little change in the control group may have been significant if given a larger sample size. In addition, the positive change in categorization of LDL cholesterol concentrations may suggest positive biological effects after chronic consumption of strawberries.

In other clinical studies, the effects of chronic strawberry supplementation on lipid profile have been conflicting. In one study, berry supplementation did not significantly affect total cholesterol and triglycerides, but HDL concentrations significantly increased compared to control (64). The strawberry dose in that study was relatively small compared to the dose used in our study (160 g berries vs ~500 g fresh equivalent, respectively). However, the study participants were given a mixture of four types of berries rather than a single dose of strawberries. The positive effects on HDL from the modest intake of berries may be due to the interaction from the different sources of berries. In another study, supplementation of 454 g of fresh strawberries did not significantly change total cholesterol, LDL, HDL, triacylglycerols, and ratio of LDL/HDL compared to a fiber control (39). Although the form of strawberries was different, the dose was comparable to our study. Subjects in that study were also hyperlipidemic, which is similar to subjects in our study. In addition, the control was also an intervention that consisted of fiber.

In contrast, in two clinical studies, total cholesterol and LDL cholesterol were found to significantly decrease from baseline (37, 38). In addition, total cholesterol and LDL cholesterol were significantly different from a non-intervention control (38). In our study, there were

preliminary data that suggested a mean decrease from baseline in total and LDL cholesterol after 12 weeks of strawberry supplementation; however, changes did not reach statistical significance. The baseline characteristics of the study participants in all three studies are comparable. In the two clinical trials, subjects had metabolic syndrome. Similarly, participants in our study have two or more (out of the three criteria) that defines metabolic syndrome. The dose and form of the strawberry intervention in all three studies is also the same (50 g FSP). The duration is three times longer in our study than in the two clinical trials. Since the subject baseline characteristics, dose and form of intervention are comparable or the same, the conflicting results in our study from the study by Basu et al. (2009; 2010) is most likely due to the small sample size and large variation between participants in our study. Nevertheless, the effects of strawberries on lipid panel appear to be conflicting between clinical trials. Larger clinical trials on different subject populations and comparable control groups may help elucidate the effects of strawberry supplementation on serum lipids.

**Strawberries on biomarkers of lipid oxidation**

In this study, ox-LDL and MDA significantly decreased from baseline but there were no significant differences between intervention groups. In addition, the reduction in ox-LDL after 12 weeks supplementation had a decreasing trend in the strawberry compared to control ($p=0.054$). Oxidized-LDL is pertinent in the progression and exacerbation of atherosclerosis, therefore, a decreasing trend in ox-LDL may be protective in the prevention of atherosclerosis. Since ox-LDL had a decreasing trend in the strawberry group, an increase in sample size may provide for better statistical analysis to find the possible differences between groups.

In previous studies, strawberry anthocyanins have been found to increase antioxidant capacity and decrease lipid oxidation (37, 39, 49). However, a previous epidemiological study has also found that an increase in dietary fiber has been associated with a reduction in C-reactive

protein (CRP), a stable marker of inflammation (68). Inflammation and oxidative stress can mutually trigger the other so a decrease in inflammation may lead to a decrease in oxidative stress. This may explain why the fiber-calorie control also found a significant decrease in lipid oxidation products from baseline. However, epidemiological studies cannot eliminate the possibility that foods high in dietary fiber contain confounding components such as phytochemicals that may have antioxidant and anti-inflammatory properties. Fiber has also been shown to decrease lipid profile {Anderson, 1987 #308}, which may indirectly reduce lipid oxidative products. However, our study does not indicate a significant change in lipid panel in either strawberry or control group.

In one study, oxidative damage to LDL, as measured by thiobarituric acid-reactive substances, decreased significantly compared to fiber and calorie control (39). Therefore, there is suggestion that strawberry supplementation may have additional antioxidant benefits in addition to its fiber content.

**Dietary intake**

Although there may have been a statistical significance in fiber and selenium intake between groups at different time points, the biological significance of this difference is in question. Since the macro- and micronutrient intake of the participants ranged widely and the accuracy and amount of detail each participant chose to record their 3 day recall varied, the statistical significance in the differences in dietary intake may have minor biological significance. In addition, the nutrient analysis of certain items had to be manually inputted through internet searches of the item, and therefore may contain an insufficient database on the content of selenium. Since the accuracy of dietary analyses increases with larger sample size, the number of subjects in this study may not be sufficient in finding statistical and biological significance in the differences in dietary intake.

## Limitations

One major limitation in this current study is the small sample size. Based on two pilot studies by Basu and colleagues (37, 38) the sample size of at least 15 subjects per group is required to detect 21.8% difference in total cholesterol and 30.6% difference in LDL-cholesterol at a significance level of 5% with an 80% power. However, in the current analyses, there are only 8 and 9 subjects for the strawberry and control group, respectively.

Another limitation, which is linked to the small sample size, is the large variation between participants. The increased deviation between subjects in conjunction with the small sample size increases the variability and therefore decreases the likelihood of finding significant results. In one instance, the body mass index of subjects in the study ranges from 29 to 52 $kg/m^2$. Subjects who are at the cusp of overweight and obese compared to subjects who are well above the BMI for extreme obesity may have different metabolic stresses and therefore increased dietary intake of fruits, such as strawberries, may see less effect. Larger clinical trials on strawberry supplementation will help clarify the degree to which dietary interventions may attenuate metabolic stress.

Although freeze-dried strawberries are a more standardized product compared to fresh strawberries, it raises a caveat in our study in its ability to generalize the results. Since freeze-dried strawberry powder (FSP) is used and purchased for research purposes only, whether FSP and commercial strawberry products are similar on its effects on lipid profile and products of lipid oxidation are in question. Further studies on the effects of fresh or frozen strawberries on metabolic stress may be warranted.

## Conclusion

In our study, freeze-dried strawberry and fiber-calorie control supplementation significantly decreased markers of lipid oxidation compared to baseline. We found no differences

between intervention groups for anthropometric measures, blood pressure, glucose, insulin, lipid profile, and markers of lipid oxidation. However, strawberry supplementation had a decreasing trend of ox-LDL compared to control. Based on our study, supplementation of strawberries as a therapeutic intervention to decrease lipid profile is not warranted. However, there has been a recent emergence of the antioxidant capacity of strawberries in other studies. If our study had a larger sample size, the reduction in ox-LDL may have provided more significant evidence in the ability of strawberries to reduce lipid oxidation. Nevertheless, fruit consumption, particularly those rich in antioxidants, such as berries, have been found to have cardio-protective properties in other clinical and epidemiological studies. Therefore, increasing berry consumption should be encouraged, especially in populations with low fruit and vegetable intake and high risk of cardiovascular disease.

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VITA

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Master of Science

Thesis: EFFECTS OF STRAWBERRIES ON LIPID PROFILE IN SUBJECTS WITH DYSLIPIDEMIA AND ABDOMINAL ADIPOSITY

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Title of Study: EFFECTS OF STRAWBERRIES ON LIPID PROFILE IN SUBJECTS WITH DYSLIPIDEMIA AND ABDOMINAL ADIPOSITY

Pages in Study: 58 Candidate for the Degree of Master of Science

Major Field: Nutritional Sciences

Scope and Method of Study: Clinical Research/Human Intervention Study

Findings and Conclusions:

Strawberries have been shown to exert cardio-protective benefits in several studies. However, clinical investigation is lacking on its effects in subjects with dyslipidemia. We examined the hypothesis that strawberry supplementation will lower lipid profiles and improve lipid peroxidation in subjects with abdominal obesity and dyslipidemia. Subjects (n=17) with abdominal adiposity (abdominal adiposity men>40 inches, women >35 inches) and dyslipidemia (two of four criteria: fasting total cholesterol >200 mg/dL, triglycerides >150 mg/dL, LDL-cholesterol >100 mg/dL, or HDL-cholesterol (men<40 mg/dL, women <50 mg/dL) were randomly assigned to strawberry (50g/day freeze-dried strawberries) or control (8 g fiber/day) daily for 12 weeks. Blood draws, anthropometrics, blood pressure, and dietary data were collected at screen, 6 and 12 weeks of the study. Strawberry and control beverage revealed a significant decrease in oxidized-LDL (ox-LDL) and malondialdehyde (MDA) versus baseline ($p<0.05$). The between group changes in ox-LDL showed a decreasing trend in the strawberry intervention compared to control after 12 weeks supplementation ($p=0.054$). No effects were noted in anthropometric measures, blood pressure, glucose control, and lipid profile. Although strawberries did not significantly reduce lipid oxidation compared to control, the decreasing trend in ox-LDL suggests strawberries may produce selected cardio-protective effects.
Funded by California Strawberry Commission, CA, USA

ADVISER'S APPROVAL: Dr. Arpita Basu