The Effects Of Almond Consumption In Subjects With Type 2 Diabetes: Differences Between Men And Women

by

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ABSTRACT

Type 2 diabetes affects approximately 7.3% of Americans, leading to debilitating and life-threatening comorbidities. Estrogen and testosterone levels have been linked to inflammatory and oxidative stress markers, as well as glucose and insulin concentrations. The present study was designed to determine the link between sex differences, glucose control, and inflammation and oxidative stress related to daily almond ingestion among subjects with type 2 diabetes. Subjects were randomized to an intervention group, which received 1.5 oz. almonds daily for 12 weeks, or to the matched control group, which maintained their current diet. No significant differences were found in changes in glucose control in response to ingestion of almonds. However, CRP was significantly reduced by an average of 36.2% in those that received almonds daily ($p = 0.017$). Although not significant, women randomized to the intervention group appeared to have improvements in insulin resistance compared to women with no dietary change. Results suggest that the addition of almonds to the diet may be an effective intervention for managing inflammation associated with type 2 diabetes. The addition of almonds to the diet is a low cost intervention that is easily implemented into daily lifestyle. Due to the small sample size, additional studies are needed to determine the impact and mechanisms of almond ingestion in subjects with type 2 diabetes.

ACKNOWLEDGEMENTS

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DEFINITION OF TERMS

Glycemia: the presence of glucose in whole blood

Postprandial: the 2-hour period following ingestion of food

Typical diet: adhering to similar dietary patterns to which one is accustomed with minimal variation in macro- and micronutrient content.

Oxidative stress: imbalance between oxidative radicals and antioxidant species within the human body leading to an increased risk for disease and pathology

Inflammation: immunological reactions resulting from physiological stressors

Estrogenic activity: having effects of, similar to, or antagonistic to estrogen

Framingham risk score: a cardiovascular risk scoring system based on the Framingham Heart Study used to estimate cardiovascular risk over 10 years

Hyperglycemia: fasting blood sugar ranges over 126mg/dL or 2-hour post ingestion glucose ranges over 145 mg/dL

MET hours: estimated physical activity intensity multiplied by the duration of physical activity to estimate total physical activity performed weekly

CHAPTER 1

INTRODUCTION

It is estimated that 7.8% of people in the United States, and approximately 135 million people worldwide, have diagnosed or undiagnosed type 2 diabetes[1,2]. It is conservatively estimated to be the seventh leading cause of death in the U.S[1]. These patients have an increased risk for neuropathy, cardiovascular disease (CVD), poor wound healing, periodontal disease, retinopathy, kidney disease, certain cancers, gallstone disease and death[1,3]. The American Diabetes Association cites the total cost of diabetes nationwide at $245 billion as of 2012[3].

Because of these startling figures, there is an increased need for safe, effective and affordable interventions that will help to decrease these risks. Almonds may be an excellent functional food for those exposed to the increased risk factors associated with type 2 diabetes by lowering risks and improving outcomes[1,3]. Many current diabetic treatments involve uncomfortable or even dangerous side effects, including hypoglycemia, weight gain, gastrointestinal disturbances, peripheral edema and potential cardiovascular effects[4].

Although mechanisms are not clearly defined, almond intake has been associated with decreased total cholesterol, lower concentrations of low-density lipoprotein (LDL) cholesterol, a favorable ratio of LDL cholesterol to high-density lipoprotein (HDL) cholesterol, plasma apolipoprotein B concentrations, and nonesterified fatty acids – all of which are important indicators of cardiovascular risk. Almond intake has also been linked to lower concentrations of fasting insulin, fasting glucose and homeostatic model assessment of insulin resistance (HOMA-IR) [2].

Almonds are a good source of many nutrients, including vitamin E, riboflavin, niacin, manganese, calcium, magnesium and zinc. A single serving contains approximately 3 grams dietary fiber, 6 grams protein, and an average of 25.01 mg flavonoids. Arginine, fiber, monounsaturated and polyunsaturated fatty acids, vitamin E, and phenolic acids, have all been suggested as bioactive agents underlying the ability of almonds to produce cardioprotective effects, however the amounts of these substances vary by almond variety[5].

Historically, men and women have starkly different degrees of risk for diabetes and its associated complications throughout their individual life cycles. For example, when compared to men, women typically have some protection from heart disease prior to menopause in spite of other known risk factors including obesity and smoking. However, in women with diabetes and women with decreased estrogen status, this protection is removed. Lundberg et al. described the relative risk for CVD in men with diabetes to be 2.9, while the relative risk for women with diabetes was 5.0 and women were approximately 1.75 times more likely to die from a myocardial infarction than men[6]. Moreover, Homko et al. found that total cholesterol, LDL cholesterol and blood pressure were significantly higher among women with diabetes than men with diabetes, even though Framingham risk scores and treatments were not statistically different between the groups. Additionally, women tend to have higher prevalence and more pronounced impaired glucose tolerance than men, whereas men have higher rates of impaired fasting glucose. Post-challenge hyperglycemia is present in 72% of diabetic women, but only in 48% of diabetic men and post glucose challenge hyperglycemia is a better predictor of cardiovascular disease in women than in men[7].

Additionally, Inflammation and triglyceride concentrations predict increased cardiovascular risk and metabolic syndrome better in women than in men. Premenopausal women have lower rates of hypertension than men matched by age, yet postmenopausal women have higher rates of hypertension than men their same age.

In addition to having different degrees of disease risk, studies have shown that men and women may respond differentially to various interventions and treatments. Women display low salt sensitivity before menopause, but increased sensitivity after menopause[7]. In an intervention trial, hypertensive women with diabetes exhibited a significant dose-dependent response to a walking intervention whereas the men did not[8]. These differential responses to treatment are important because identical treatments are typically prescribed by doctors and other healthcare professionals when a treatment that is effective for one sex is not necessarily effective or may even exacerbate a condition for the other sex. In fact, studies have found that women with cardiac risk factors are less aggressively evaluated and treated than men[9]. This may in part be due to the mistaken acceptance that women have a higher protection from disease, the lack of research describing the different responses between men and women to various treatments, and a historical preference for male subjects in intervention trials.

A potential reason for these sex-related differences may be varying concentrations of the sex hormones estrogen and testosterone between the sexes and within different age groups. Low estrogen states such as menopause have been linked to disease states including cardiovascular disease and type 2 diabetes. Inflammatory and oxidative stress markers as well as glucose and insulin are also elevated in postmenopausal women and men with genetic estrogen receptor deficiencies or loss of aromatase function (an enzyme

necessary for endogenous estrogen synthesis). Studies show that treatment with estrogen in women often improves insulin sensitivity and lowers glycemia. This effect appears to be most potent in individuals predisposed to oxidative stress[10,11]. Other studies, however, suggest that estrogens may be pro-inflammatory among older populations of women or among those who have been hormone-free for longer periods of time[12,13].

These discrepancies may be explained by estrogen's complicated role in the body. Exogenous estrogens differ pharmacokinetically and are more potent, while endogenous estrogens exist in several subtypes, which may have altered or collaborative actions[14]. It may also be related to irreversible changes that may occur in the body with extended periods of estrogen deficiency. Estrogens function via two estrogen receptor (ER) subtypes – alpha and beta. ER-alpha is most commonly expressed in bone, reproductive tissues, white adipose tissue and liver, while ER-beta is expressed in ovaries, prostate, lungs, gastrointestinal tract, bladder, hematopoietic cells and the central nervous system. Polymorphisms in the gene that codes for ER-alpha correlate with cardiovascular disease, type 2 diabetes, myocardial infarction, hypertension, and other metabolic disorders[11].

Testosterone deficiency has been linked to renal disease, obesity, cardiovascular disease, metabolic syndrome and type 2 diabetes, among others. Additionally, hypogonadal subjects with diabetes treated with testosterone replacement therapy have exhibited improvements in insulin resistance, fasting glycemia and hemoglobin A_{1C} (HbA_{1C}), improved inflammatory cytokine profile, and decreased visceral fat. Testosterone has been effectively increased through lifestyle modifications such as weight loss and exercise[15-17].

A handful of studies have examined the effects of almond intakes ranging from 28 to 113 grams on blood glucose control. The majority of these studies demonstrated improvements in blood glucose control in healthy individuals, those with prediabetes and those with stable diabetes[2,18-21]. Cohen and Johnston studied the effects of low-dose almonds on HbA_{1C} in subjects with well-controlled diabetes. They demonstrated significant decreases in HBA_{1C} over a 12-week period[22]. Li et al. found that the addition of 60 g almonds per day decreased fasting insulin, HOMA-IR and fasting glucose in dyslipidemic patients with type 2 diabetes with stable blood glucose prior to study initiation[2]. Wien et al. also reported decreases in fasting insulin, HOMA-IR and HOMA-B in subjects with prediabetes provided with a standard dietary intervention or the same intervention with 20% energy from almonds (about 57 g). However, decreases in HbA_{1C} did not reach statistical significance ($p = 0.070$) [20].

In a 3-arm crossover trial involving 13 healthy subjects, Cassady et al. found that 55 g of almonds increased GLP-1 and decreased insulin concentrations postprandially in a dose-response manner related to the amount of mastication the almonds received[23]. Conversely, a free-living study done by Lovejoy et al. did not find a significant correlation between almond intake and insulin sensitivity in healthy individuals after 4 weeks of 100 g almonds per day. However, insulin sensitivity improved modestly for women in the study and neared significance ($P = 0.09$). Moreover, the addition of almonds to the diet of 30 subjects with type 2 diabetes in a controlled feeding study did not significantly alter glycemia relative to control diets. While subjects from Lovejoy et al. were excluded if fasting blood glucose was less than 140 mg/dL or greater than 200 mg/dL [21], it is difficult to use fasting blood sugar to estimate overall blood glucose

control. Josse et al. found that various doses of almonds (30-90 g) added to a high-carbohydrate meal decreased postprandial glycemia in a dose-response manner for nine healthy subjects with normal fasting blood glucose levels[19].

Of these studies, none considered the differential responses to almond ingestion between men and women[2,18-20]. All of these studies except Cohen and Johnston[22]included high almond doses – at least twice the size of a single serving, and only 2 studies had greater than 20 participants[2,20]. All studies appeared to have included only healthy subjects or those with well-controlled blood glucose[2,18-20,22,23]However, this is difficult to extrapolate as only Cohen and Johnston, and Wien et al. reported baseline HbA_{1C} for subjects with diabetes. Nonetheless, Li et al. reported that their subjects had stable blood glucose for the 3 months prior to study enrollment[2]and subjects from Lovejoy et al. were excluded if fasting blood glucose was less than 140 mg/dL or greater than 200 mg/dL[21].

Functional foods like almonds that have significant health benefits such as improving blood lipid profiles, lowering blood sugar concentrations and decreasing oxidative stress and inflammation, would be invaluable to the diabetic community as a safe, effective and inexpensive intervention for improving risk profiles and preventing negative outcomes in this population. Additionally, the dose of almonds used in this intervention is realistic for implementation in the diabetic population, lending high external validity to the study.

Purpose of Study

The purpose of this study was to examine the effect of almond ingestion versus control diets (unchanged dietary patterns) on glycemic, inflammatory, and oxidative

stress biomarkers and the differential responses to almond ingestion between men and women.

Aims and Hypotheses

- Primary Aim:

To determine the relationship between sex and markers of glucose control, oxidative stress and inflammation following 12 weeks of daily almond consumption in individuals with type 2 diabetes.

- Primary Hypothesis:

The effect of almond ingestion on blood markers of glucose control, oxidative stress and inflammation in subjects with type 2 diabetes will not differ by gender.

Delimitations and Limitations

Because the population for this study was self-selected there was a potential for selection bias. Individuals who volunteered for this study may represent a subset of the population and results may not be generalizable to all members of the population in question (those with type 2 diabetes). Additionally, the sample size obtained was likely too small to detect significant differences between the control and intervention groups. Because of the high HbA1c requirement, results are not generalizable to those with an HbA1c lower than 6.5.

Because this study did not include a placebo, I could not control for the placebo effect. Participants could not be blinded to their study condition and therefore results may reflect participant bias. In addition, this study was not able to identify all components of

almonds that may exert positive antiglycemic, anti-inflammatory and antioxidant effects. It is assumed that subjects adhered to the study protocol.

However, because of strict controls and exclusion criteria, the data obtained from this trial may have high internal validity. The intervention allows for high external validity because it was implemented on an outpatient basis, using real life scenarios and is therefore very generalizable to subjects similar to those used in this study.

CHAPTER 2

REVIEW OF LITERATURE

Type 2 Diabetes

Carbohydrate Metabolism

Carbohydrates include simple sugars such as the disaccharides lactose and sucrose and monosaccharides such as glucose and galactose, as well as complex carbohydrates such as fiber, amylose and glycogen. They are necessary for energy in certain cells including red blood cells and testicular cells, and are the preferred fuel source for virtually all cells in the body[24]. Carbohydrates are broken down primarily in the small intestine, though some breakdown of alpha-1,4 bonds occurs in the mouth as well. In the stomach, S cells from the duodenum release secretin, a hormone that stimulates the pancreas to release bicarbonate and create a pH in which sugar enzymes can work effectively. K cells in the duodenum and jejunum release glucose-dependent insulinotropic peptide, which stimulates insulin secretion into the blood in preparation for the glucose that will soon be entering circulation. The pancreas releases pancreatic alpha-amylase, which breaks down a majority of carbohydrates into small pieces, after which brush border enzymes are released to break down disaccharides. These enzymes include lactase, maltase and the sucrase-isomaltase complex[24].

Mono- and disaccharides then enter enterocytes using sodium-glucose cotransporter 1 or carrier-mediated glucose transporter (GLUT)5. They then enter blood circulation via GLUT2 or passive diffusion across the basolateral membrane. Glucose is then transported to the liver or to various cells for energy using GLUT 1, 2, or 4 transporters. At this point, sugars undergo glycolysis to produce ATP for energy, or

glycogen synthesis (primarily in myocytes) to store sugars as glycogen for later use. GLUT4 is activated by insulin and muscle contractions, and mediates glucose uptake into adipose and muscle cells[24-26].

Pathophysiology of Type 2 Diabetes and Glucoregulation

The exact etiology of type 2 diabetes is not entirely clear. Type 2 diabetes appears to be the result of a complex interaction between key inherited and environmental factors including hormone imbalance, neurotransmitter dysfunction, genes, body weight, increased glucose reabsorption in the kidneys, diet, exercise and lifestyle. Overweight and obesity are heavily correlated with the development of insulin resistance and impaired glucose tolerance. Overweight and obesity increase leptin, reduce adiponectin and increase glucagon concentrations, leading to an imbalance of these hormones. They also lead to increased inflammatory cytokine concentrations of tumor necrosis factor(TNF)-alpha and interleukin(IL)-6, suppress cytokine signaling and reduce other inflammatory signals. Overweight and obesity cause a consequent increase in non-esterified fatty acid release increasing cellular concentrations of diacylglycerol and fatty acyl-CoA, which in turn decrease insulin postreceptor signaling. Abnormalities in glucagon-like peptide-1 (GLP-1), hyperglucagonemia and increases in other counter-regulatory hormones may also contribute to insulin resistance, reduced insulin secretion and hyperglycemia[4].

Type 2 diabetes develops when GLUT4 transporters become unresponsive to insulin signaling. When beta cells are unable to compensate for the reduced GLUT4 sensitivity to insulin by secreting more insulin, type 2 diabetes develops. This decline in

beta cell function appears to be related to glucotoxicity, lipotoxicity, oxidative stress, inflammation and amyloid formation created from a chronic state of hyperglycemia and hyperinsulinemia. Additionally, pancreatic alpha cell function declines in many cases of type 2 diabetes resulting in increased glucagon secretion that not only promotes further hyperglycemia, but may also reduce prandial GLP-1 secretion[4].

Studies suggest that glucose excursion determines the degree of oxidative damage measured by isoprostane production better than HbA_{1C}. Greater postprandial hyperglycemia is linked to greater oxidative damage. Hyperglycemia is also associated with increased production of nitrotyrosine, a marker of oxidative stress[18].

Mortality and Morbidity

Those with type 2 diabetes suffer from increased risk of cardiovascular disease, kidney failure, retinopathy, poor wound healing, periodontal disease, gallstone disease, certain cancers and death[1]. Cardiovascular disease contributes to a 75% mortality rate in those with type 2 diabetes. This is linked to hyperglycemia, dyslipidemia, hypertension, inflammation and oxidative stress – all risk factors that are increased in type 2 diabetes. Glucose reduction to sorbitol, glycation end products, impaired antioxidant defenses, compromised mitochondrial function and activated NADPH oxidase may all contribute to increased oxidative stress in subjects with type 2 diabetes[27]. Li et al. found that subjects with Type 2 Diabetes have higher cardiovascular risk than subjects without the disease even when blood glucose is under control[2]. However, blood glucose control significantly reduces risk in those with type 2 diabetes. Blood glucose control can help to improve the

lipid profile, decrease blood pressure and reduce inflammation and oxidative stress via the pathways mentioned above, as well as through mechanisms yet undefined[27].

Oxidative Stress & Inflammation

Oxidative stress leads to hypertension, cognitive impairment and increased inflammation[29]. Additionally, markers of inflammation such as C-reactive protein (CRP), IL-6 and TNF-alpha have been associated with diabetes pathogenesis and development, increasing the risk for developing type 2 diabetes in women by an average of 64%[30].

Oxidative stress is caused by reactive oxygen species such as peroxides. As mentioned, stable biomarkers of oxidative stress include isoprostanes and nitrotyrosine. CRP, IL-6, and TNF-alpha are markers of inflammation. NO is a major endothelium-derived vasodilator. Increased scavenging of NO by O_2^- due to oxidative stress diminishes the effects of NO. This exacerbates oxidative stress and inflammation characteristic of diabetes and causes hypertension. NO produces anti-oxidant, anti-inflammatory and anti-apoptotic effects in the endothelium[28].

Disulfide bonds are present in thiol-containing molecules such as cysteine, methionine and glutathione. These are an expendable source of plasma antioxidants and are preferentially consumed in the presence of free radicals. Reduction in protein thiol concentration is therefore an additional marker of oxidative stress[18].

Oxidative Stress and Inflammation Caused by Diabetic States

Hyperglycemia in diabetes creates oxidative stress in vascular endothelium and leads to inflammation. In the endothelium, hyperglycemia generates reactive oxygen

species such as superoxide (O_2^-). Superoxide reacts with nitric oxide (NO) to produce peroxynitrite ($ONOO^-$). $ONOO^-$ is extremely reactive, producing proinflammatory posttranslational modifications of cellular proteins such as nitrotyrosine. Nitrotyrosine is a marker of nitrative stress and a surrogate marker of $ONOO^-$ concentrations. Nitrotyrosine can in turn produce isoprostanes which are more stable downstream markers of $ONOO^-$ concentrations. The products resulting from this modification have been linked to enhanced expression of inflammatory molecules, cell death and impaired endothelial function[28]. Cardiovascular disease accounts for more than 70% of morbidity and mortality among individuals with type 2 diabetes[2].

Almonds

Chemical Composition

Almonds contain many components that are known to have beneficial effects in both human and animal models of diabetes and cardiovascular disease. These compounds include dietary fiber, magnesium, arginine, plant sterols, polyphenols, copper and many others[2].

Almonds also have high levels of mono-unsaturated fatty acids (MUFAs). MUFAs may enhance the secretion of GLP-1, a gut hormone known to increase insulin secretion in response to glucose intake, promote insulin sensitivity and decrease food intake[20]. Oleic acid in particular might have a beneficial effect on body fat, a risk factor for type 2 diabetes and cardiovascular disease, by enhancing mitochondrial fatty acid oxidation and thermogenesis by means of up-regulating uncoupling protein genes[2].

A single 1-ounce serving contains approximately 3.3 grams insoluble fiber, 6 grams protein, an average of 25.01 mg flavonoids, and 8.9 mg phytosterols. Almonds have also been reported to contain significant amounts of other phytochemicals including phytates, lignans, sphingolipids, proanthocyanins, and polyphenols[19,31]. Phytosterols have been linked with lower cholesterol levels and polyphenols show ferric-reducing antioxidant power. In addition, almonds have approximately 30 different antioxidants in their skin alone, including catechin, epicatechin, isohamnetin, quercetin, kampferol[18], and alpha-tocopherol (vitamin E)[2]. The antioxidant capacity of almonds may help to reduce oxidative stress caused by diabeters. Phytates and phenolics have been linked to lower postprandial glycemia in vivo and reduced amylolytic digestion (enzymatic starch breakdown to sugar) in vitro. Phytates bind to calcium, which is a necessary cofactor for amylase activity, and phenolics may bind directly to amylase thereby inhibiting its activity. Studies have also demonstrated that insoluble fiber lowers hyperinsulinemia, improves glycemic control and lowers plasma lipid concentrations in subjects with type 2 diabetes[19]. Arginine, monounsaturated and polyunsaturated fat, and vitamin E, have all been suggested as bioactive agents underlying the ability of almonds to produce cardioprotective effects, however the amount of these substances varies by variety[5].

As much as 20% of the energy from almonds is typically lost in the stool. The parenchymal cell wall of almonds is resistant to microbial and enzymatic breakdown in the gastrointestinal tract. Therefore, liberation of almond lipids for digestion is dependent upon the mechanical disruption that occurs with mastication. A study by Cassady et al. found that almonds exert effects on fullness, fecal fat losses, and hormone responses.

These effects were highly correlated with and dose dependent of the number of chews subjects took[23].

Potential Health Benefits Exerted by Almonds for Type 2 Diabetes

Many studies have suggested a benefit for nut consumption in both healthy and unhealthy populations. Epidemiological data from the Nurses' health Study indicate that women who consumed nuts at least 5 times per week had a 29% reduced risk of diabetes compared to those who never or almost never ate nuts[32].

Josse et al. found that almonds added to a high carb meal (white bread) decreased postprandial glycemia in a dose-response manner for 9 healthy non-diabetic subjects with normal fasting blood glucose levels. The authors hypothesized that this was due to the ability of almonds to decrease glucose absorption and slow gastric emptying rate when ingested with the meal, rather than affecting mechanisms for long-term glucose control[19]. Li et al. found that the addition of 60 g almonds per day for 4 weeks to prepared meals decreased fasting insulin, HOMA-IR and glucose by 4.1%, 9.2% and 0.8%, respectively in 20 dyslipidemic patients with type 2 diabetes ($p = 0.0238, 0.0184, 0.0039$). Although glucose concentrations were not lowered to the unimpaired range, reductions of this magnitude may still be clinically significant. The intervention also lowered body fat by 0.8% and improved the lipid profiles of these patients, lowering total cholesterol and LDL cholesterol and raising HDL cholesterol over the 12-week intervention period[2].

Similar results were found by Wien et al. in a study involving 65 subjects with prediabetes. Subjects were provided instructed to follow a standard ADA diet plan, or the same diet plan with 20% of energy from almonds, averaging approximately 57 g daily for

16 weeks. Results showed improvements in blood lipids, fasting insulin, HOMA-IR and HOMA-beta. However, reductions in HbA_{1C} were not greater than those in the control group, which were not statistically significant ($p = 0.070$) [20].

In a 3-arm crossover trial involving 13 healthy subjects, Cassady et al. found that 55 g of almonds increased GLP-1 and decreased insulin concentrations postprandially in a dose-response manner relative to the amount of mastication each subject performed on the almonds[23].

Conversely, a free-living study done by Lovejoy et al. did not find a significant correlation between almond intake and insulin sensitivity in healthy individuals after 4 weeks of 100 g almonds per day. However, insulin sensitivity improved modestly for women in the study and neared significance ($p = 0.09$). Moreover, the addition of almonds to the diet of 30 subjects with type 2 diabetes in a related controlled feeding trial did not significantly alter glycemia relative to control diets. They also found statistically significant increases in body weight of 0.9 kilograms in men, which may have masked or diminished any changes in insulin sensitivity. Additionally, subjects from Lovejoy et al. were excluded if fasting blood glucose was less than 140 mg/dL or greater than 200 mg/dL[21]. As previous studies have shown that almonds may affect blood glucose control by reducing postprandial glucose[18,19,22], it is likely that fasting blood sugar in these ranges is indicative that this particular population may not have responded well to a dietary intervention. Both studies revealed that almond consumption had beneficial effects on lipid values in both studies, improving all major types of cholesterol, with the most significant changes being an increased HDL cholesterol[21].

Cohen and Johnston reported similar reductions in postprandial glycemia of 30% following almond ingestion prior to a mixed meal among subjects with type 2 diabetes, but no reduction in postprandial glycemia among healthy subjects. In a separate pilot study with 13 subjects with type 2 diabetes, they also reported an additional significant reduction of 4% for HbA_{1C} and BMI in subjects in the almond group compared to a 1% increase in HbA_{1C} and no change in body mass index (BMI) for the control group[22].

Health Benefits on Oxidative Stress and Inflammation

In addition to lowering postprandial serum insulin and glucose responses to bread, the addition of almonds to a standard meal also reduced oxidative damage as measured by increases in serum thiol concentrations[18] and reduced DNA damage as measured by urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine, even among smokers. Reductions in urinary malondialdehyde, a marker of lipid peroxidation, and higher superoxide dismutase and glutathione peroxidase activity have also been observed with almond intake, suggesting that almonds confer antioxidant benefits as well[31].

Rajaram et al. concluded that almond ingestion at 10% or 20% of total energy intake was able to reduce CRP by 4.5-9% in healthy subjects compared to the control. However they observed no change in IL-6[33]. A crossover trial with varying supplemental doses of almonds (37-78g) and control supplement (muffin) found no difference between baseline and 4-week intervention period measures of CRP in 27 hyperlipidemic subjects[34].

Liu et al. compared a control National Cholesterol Education Program (NCEP) step II diet to a 56 g daily almond intervention diet for four weeks in subjects with type 2

diabetes using a crossover randomized control design. They found that compared to the control diet, IL-6 and CRP were significantly reduced by medians of 10.3%, each[27].

Metabolic Sex Differences & Treatment Responsiveness

Considering metabolic differences between men and women is paramount to designing treatment interventions for the different genders at each stage of life. It has been suggested that treatment and diagnosis of women's heart disease is followed less strictly by physicians. Additionally, women are often underrepresented in clinical trials regarding heart disease and gender-specific analyses are not always present in older large trials[35].

Differing fat deposition patterns between men and women may also affect responses to insulin, adrenaline, norepinephrine and sex hormones[7]. Women have a greater percentage of body fat even though they typically have smaller energy intake per kilogram lean body mass than men and preferentially use fat as fuel during exercise. Women also have more efficient fat storage during sedentary time, especially postprandially, while men tend to oxidize a greater percentage of ingested fat than women. Estrogen is thought to be at least partially responsible for this difference in fat metabolism. Studies suggest that estrogen may influence the hepatic processing of dietary fats[14].

Treatment responses to interventions also frequently differ between men and women. In one study, six months of flax lignin supplementation decreased metabolic syndrome composite scores in men, but not in women[29].

In addition to estrogen and testosterone, other hormone levels vary between men and women. Leptin is higher per kilogram body weight in women than in men. Leptin is an important appetite-regulating hormone produced in adipocytes and has been shown to be inhibited by androgens and promoted by estrogens. Estrogens may also alter hypothalamic sensitivity to leptin by binding to estrogen receptors found in the hypothalamus. However, this relationship is unclear because leptin does not appear to be affected in menopause or by estrogen replacement therapy[14].

Presentation of diabetes differs substantially between men and women. Men with diabetes show impaired fasting glucose more frequently than women, and impaired glucose tolerance presents more often in women than in men. In fact, post-challenge hyperglycemia is the only symptom of diabetes in 72% of women, but only 48% of men. Using fasting or postprandial glucose exclusively as criterion for diabetes screening and diagnosis would miss metabolic abnormalities in a substantial subset of the population[7].

Women typically enjoy relative cardioprotection prior to menopause compared to men. However, it appears that this protection disappears in those with diabetes as acute myocardial infarction incidence is three times higher for diabetic men than men without diabetes, but five times higher for diabetic women compared to nondiabetic women. Additionally, mortality from acute myocardial infarction was more than seven times greater among females with diabetes, and four times greater among men than among nondiabetic individuals[6]. Inflammation increases cardiovascular risk to a greater extent in women than in men[7]. This may be due to the effects that diabetes may have on estrogen action, particularly at the estrogen receptors.

A steep increase in myocardial infarction is observed in women ages 55-64 years when compared to the previous decade of life. This may be due to an interaction between diabetes and postmenopausal estrogen loss that adds a particularly high risk for these subjects. Prior to this, the 35-44 year age group displays the highest incidence and rate of recurrent acute myocardial infarctions among diabetic women. This early increased risk may be due to a mean onset age for diabetes of 11.8 years, which is significantly younger than the mean onset age of 24.7 years in men[6].

Estrogen

Estrogen may be an integral cause of differences in chronic disease development, presentation and treatment effectiveness between men and women. In heart failure and hypertrophy, estrogen receptors within the heart are upregulated, possibly modulating the progression of the disease[35]. Estrogens are involved in the regulation of insulin sensitivity, energy balance, blood pressure and body composition, impacting appetite, insulin release, glucose transport in hepatocytes and skeletal myocytes, adipocyte differentiation, and vascular tone and structure[36].

Endogenous estrogens exist in three subtypes: estrone, estriol and estradiol. Each has slightly different actions that may be antagonistic or synergistic. Estradiol is the most potent of these and has the highest binding affinity for both alpha and beta estrogen receptors, but it does not exist in the highest concentrations. Relative concentrations of each subtype vary by life cycle stage. Each of these estrogens is likely to produce differential activation of the ERs[37].

ERs exist in two different isoforms: alpha and beta. ER-alpha is expressed primarily in the uterus, pituitary, kidney and adrenal gland[38] and appears to influence aromatase expression, adiposity and hepatic adiposity[39]. ER-alpha is also involved in the estrogen stimulation of NO synthase[40]. ER-beta is expressed primarily in prostate, ovary, bladder and lung cells. The two isoforms are almost identical, differing only in the change from a serine to a methionine in ER-beta[38]. The function of the beta receptor is uncertain as no overt phenotype has been described from studies on animals lacking this receptor[39].

Testosterone

Associations of Testosterone with Type 2 Diabetes

Hypogonadism, characterized by low testosterone levels, is associated with several conditions including obesity, cardiovascular disease and mortality, liver cirrhosis, chronic renal failure, metabolic syndrome and type 2 diabetes. It is widely under-recognized and under-diagnosed and particularly prevalent in type 2 diabetes. Lower testosterone levels increase risk of cardiovascular disease and mortality; and testosterone concentrations are associated with decreases in insulin sensitivity, dyslipidemia and increased body fat[41].

Testosterone treatment of subjects with type 2 diabetes has been associated with improved insulin sensitivity. One study reported that a two-week withdrawal of testosterone replacement therapy resulted in impaired insulin sensitivity without affecting body composition. Other studies involving type 2 diabetic subjects, investigated the effects of testosterone therapy and found that testosterone undecanoate improved fasting

glycemia, postprandial glycemia, insulin sensitivity, mean HbA_{1C}, total cholesterol, fat mass and reduced visceral adiposity[17]. Additionally, treatment of isolated stem cells with testosterone increased their development into myocytes rather than adipocytes while testosterone deficiency had the opposite effect[41].

The hypogonadal obesity cycle hypothesis suggests that these associations may be self-perpetuating. Excess adipocytes release aromatase, which metabolizes testosterone to 17beta-estradiol. Decreased testosterone levels then allow increased lipoprotein lipase activity, which in turn causes increased fatty acid uptake and storage by adipocytes. The increased fat mass leads to increased insulin resistance and even greater breakdown of testosterone. A second hypothesis, the hypogonadal obesity adipocytokine hypothesis suggests that a normal hypothalamic-pituitary-testicular response to hypotestosteronemia is inhibited by 17beta-estradiol, leptin and the adipocytokines IL-6 and TNF alpha[41].

Links between Testosterone and Inflammation and Oxidative Stress

Levels of IL-6 and CRP have been significantly inversely correlated with total and bioavailable amounts of plasma testosterone concentrations, suggesting that low testosterone is linked to inflammation. Additionally, testosterone replacement therapy in hypogonadal individuals resulted in the ex vivo reduction of proinflammatory cytokines. Treatment with testosterone prior to intracoronary stenting procedures has also been shown to reduce the concentrations of inflammatory markers such as IL-6 and CRP[41].

Conclusion

Diabetes prevalence is increasing rapidly throughout the United States and in other parts of the world with high rates of mortality and morbidity. Relative risk, presentation and treatment outcomes for diabetes and its related complications differ markedly between men and women. These differences likely relate to differing sex hormone concentrations, specifically estrogen and testosterone. Conditions of low estrogen or low testosterone are related to type 2 diabetes pathology, oxidative stress and inflammation.

Almonds are a promising treatment option for subjects with type 2 diabetes, but treatment results may differ between the sexes. A limited number of studies suggest that almonds may improve glucose control, insulin sensitivity, and markers of oxidative stress and inflammation. The mechanism for their beneficial actions may be any number of favorable compounds they contain, namely insoluble fiber, flavonoids, phytates, arginine, monounsaturated and polyunsaturated fatty acids, and phenolic acids.

CHAPTER 3

MATERIALS AND METHODS

Subjects

The enrollment goal for this study was fifty subjects between the ages of 25 and 75 years of age who had been previously diagnosed with type 2 diabetes mellitus at least 6 months prior to study enrollment. The n for this study was determined by collaboration with colleagues in addition to the use of sample size calculation software developed by David Shoenfield of Harvard University. We estimated a standard deviation in HbA_{1C} of 1.01 based on the mean of a compilation of 43 studies found in a meta-analysis by Giugliano et al. [42] and a difference between means of 0.63 based upon an average reduction in HbA1c from two similar dietary interventions[20,43], using a significance level of $P = 0.05$ and power of 0.8. This calculation yielded n = 84. However, due to the unattainability of this number and agreement with the California Almond Board, along with consultation with experts, we determined to recruit an n of 50. Participants were recruited from college campuses, diabetes support groups and treatment centers, healthcare centers, community centers and shopping areas in the Phoenix metropolitan area. One hundred fifty-five individuals responded to our pre-screening survey administered online through SurveyMonkey over the course of a 9 month enrollment period. Of these, 82 met inclusion criteria and were screened for study eligibility. Of the 82 screened, 56 were excluded due to failure to meet exclusion criteria and the remaining 26 were enrolled in the study. Three subjects withdrew before study completion, leaving 23 subjects that were included in all analyses.

Inclusion criteria for participation in the study were that subjects could not be prescribed insulin, must not have a history of tree nut allergy, and must not be pregnant or lactating. Exclusion criteria were HbA_{1C} less than 6.50%, and a dietary intake of greater than 12% monounsaturated fatty acids. Prescription medication use was required to be consistent throughout the duration of the study with no intention of attempting weight loss or gain or plans to change eating habits or physical activity.

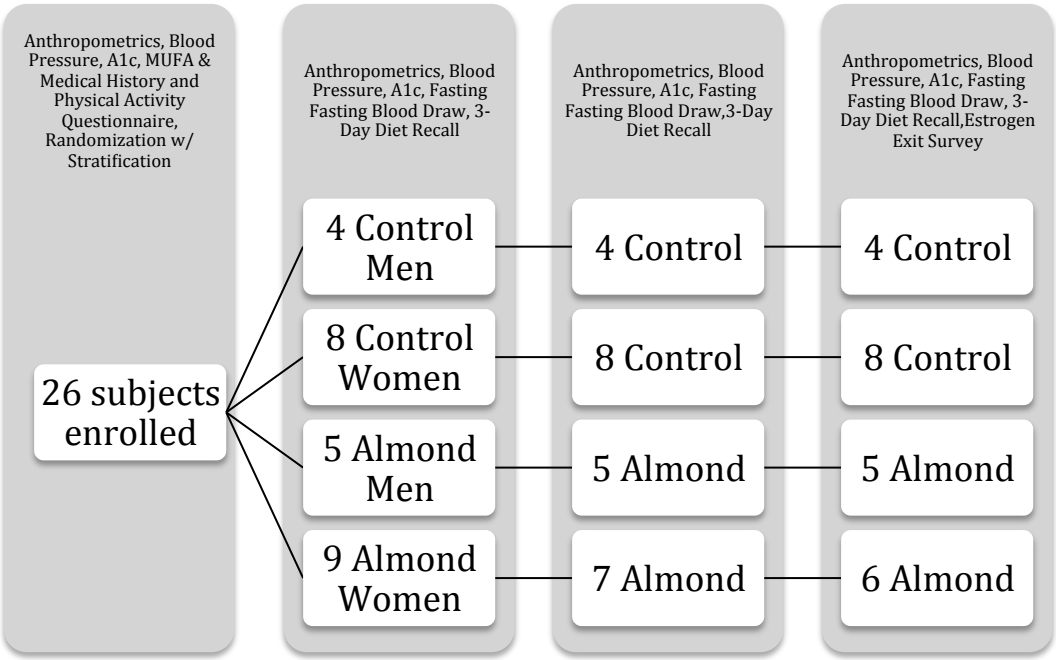
Study Protocol

Participants were asked to meet with researchers on four separate occasions during the course of the study. The first visit was a screening designed to determine whether participants met certain exclusion criteria, including HbA_{1c} greater than 6.50%, to provide participants with study information, and to obtain informed consent. Weight, height, waist circumference, and body mass index (BMI) were measured. Body composition was measured using bioelectrical impedance analysis. HbA_{1C} and blood pressure were also assessed and a monounsaturated fatty acid food frequency questionnaire and medical questionnaire were administered. Participants were instructed to complete a 3-day diet record prior to the second, third and final appointments and to restrict intake of all tree nuts to less than 2 servings per week, except for the almonds provided. Participants were then instructed to come in the following week and every 6 weeks thereafter for the duration of the 12-week study, for a total of 4 visits. Participants were to fast overnight (for at least 8 hours) prior to visits 2, 3 and 4. At each visit fasting blood was drawn. Aliquots of plasma were stored at -80°C for the analyses of glycemia, plasma insulin, oxidative stress and inflammatory markers at the conclusion of the study.

HbA_{1C}, blood pressure and all anthropometric measures were reassessed. Analysis of the three-day dietary recall and physical activity assessment was also performed (See Figure 1).

Participants were stratified by age, BMI, HbA_{1C}, duration of diabetes, and gender. They were then randomly assigned to either the intervention group or the control group. The intervention group received 60 ounces of almonds and was instructed to consume 1.5 ounces (43 g) 5 to 7 days per week for the 12-week trial period. The control group was instructed to maintain their current diet and physical activity levels.

Figure 1
Study Outline



Laboratory Analysis

HbA_{1C} was measured using capillary electrophoresis (COBAS Analyzer, Roche, Indianapolis, ID). It is a measure of the percent hemoglobin in red blood cells with

glucose attached and an indirect measure of long-term blood glucose control. Poor blood glucose control is associated with cardiovascular disease, nephropathy, retinopathy and other disease conditions. Because red blood cells have an average 120-day life cycle, it is necessary to measure HbA_{1C} throughout the 12-week study duration. However, glycated hemoglobin is believed to be most representative of the previous 2 to 4 weeks[44]. Fasting serum insulin and glucose concentrations were also measured by enzyme immunoassay and COBAS Analyzer, respectively. HOMA-IR was calculated as (insulin μU/mL x glucose mM)/22.5.

4-hydroxynonenal (4-HNE) is a marker of oxidative stress. 4-HNE may be involved in the development of diabetes, atherogenesis, cancer and other disease conditions[45]. This was measured using a commercially available kit according to the manufacturer's instructions.

Tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) are important inflammatory cytokines. TNF-alpha induces fever, controls immune cells by apoptosis, triggers IL-1 and IL-6 production, induces cachexia, and inhibits tumor growth and viral replication. Irregular concentrations are linked to Alzheimer's disease, cancer, irritable bowel disease, depression, asthma, type 2 diabetes, arthritis, cancer and Crohn's disease[30]. IL-6 increases acutely following infection, trauma, and exercise. Concentrations are increased during chronic inflammatory conditions such as obesity, insulin resistance, inflammatory bowel disease, arthritis and others. Additionally, IL-6 contributes to atherosclerotic plaque development and destabilization. IL-6 can serve as both a pro- and anti-inflammatory cytokine as in exercise and its modulation of bone

resorption[46]. Plasma concentrations of TNF-alpha and IL-6 were quantified using commercially available kits according to the manufacturer's protocols.

A lipid panel was also performed using nuclear magnetic resonance spectrophotometry and quantitative enzymatic testing. Because almonds are a rich source of tocopherols, serum tocopherol was measured using HPLC as they have potent antioxidant properties; they were also used to verify compliance with the study protocol.

Statistical Analyses

The data was analyzed using SPSS Statistical software. Data were analyzed once including all data points, and a second time excluding all subject data with baseline HbA_{1C} greater than 9.00%. Two-way repeated measures ANOVA was used to compare men and women in all biological parameters including HbA_{1C}, insulin, glucose, HOMA-IR, anthropometric measures, lipids, inflammatory markers, oxidative stress markers, and tocopherols. Two-way repeated measures ANOVA was used to compare compliance, dietary intake, and all other measures. Reported baseline physical activity was used to calculate estimated MET hours per week. Independent T-tests were used to compare HbA_{1C} concentrations, and changes in all variables between men and women subjects. Mann-Whitney U Tests were used to determine statistical significance of all data. Pearson correlation was used to identify possible covariates that may have confounded data including physical activity, age, baseline anthropometrics, and baseline variables of glucose control, oxidative stress and inflammation. Correlations with a $p < 0.05$ were considered to be significant confounding variables. Mean, median, mode and standard

deviation were measured for all variables. For all comparisons, $P<0.05$ were considered statistically significant.

The study was approved by the Arizona State University Institutional Review Board (IRB) that oversees all studies involving human subjects. Informed consent was administered at the first study visit when subjects were notified of potential risks and benefits for participating in the study. Potential risks included bruising or a feeling of faintness during blood draws, or an allergic reaction to the almonds. There were no conflicts of interest involved in this study and confidentiality was maintained throughout the study by assigning each subject an ID number and keeping consent forms separate from data.

CHAPTER 4

RESULTS

Descriptive characteristics

TABLE 1. Baseline Characteristics of Subjects[1]

	Women (n = 15)	Men (n = 9)	*p-value*
Age (y)	56.3 ± 8.6[1]	59.56 ± 4.0	*0.455*[2]
BMI (kg/m^2)	35.87 ± 9.60	34.00 ± 6.2	*0.835*
HbA1c (%)	7.3 ± 1.1	7.1 ± 0.7	*0.529*
Fasting insulin (mg/dL)	27.92 ± 14.4	35.91 ± 32.7	*0.713*
Fasting glucose (mg/dL)	152.4 ± 42.1	160.7 ± 34.6	*0.548*
METs	177.8 ± 338.1	197.5 ± 311.6	*0.172*

[1]Data are mean ± SD; n = 23

[2]P values were obtained from independent samples Mann-Whitney Test

As shown in table 1, the age of participants ranged from 44 to 70 years with a mean age of 57.5. The average body mass index (BMI) for subjects was 35.2 kg/m^2. Subjects had an average HbA_{1C} of 7.3%, and a fasting insulin and fasting glucose of 31.187 mg/dL and 155.77 mg/dL, respectively. Mean METs per week performed by participants was 185.0.

BMI was significantly correlated to IL-6 (r = 0.566, p = 0.005) and CRP (r =0.629, p = 0.002) at baseline. Age and insulin were negatively correlated (r = -0.501, p = 0.013). HNE and HbA1c were positively correlated at baseline (r = 0.423, p = 0.044). IL-6 and CRP were correlated (r = 0.544, p = 0.009), as were HNE and TNF-alpha (r = -0.521, p = 0.011). Baseline characteristics were not significantly different between men and women p>0.05.

Anthropometrics

There were no significant differences in BMI, weight, waist circumference, or percent body fat in either men or women. However, anthropometric measures tended to improve in men in the almond group compared to women, in whom measures tended to become worse or remain the same over time. (See tables 2 and 3.)

TABLE 2. Mean Change in BMI, Weight, Waist Circumference and Percent Body Fat in Men

		0 Weeks	**12 Weeks**	**Change**	***p-value***[1]
BMI (kg/m^2)	ALM = 5	34.7	32.3	**-2.4**	*0.803*
	CON = 4	33.2	32.8	**-0.4**	
Weight (lbs.)	ALM	239.93	237.49	**-2.44**	*0.806*
	CON	215.86	214.36	**-1.50**	
Waist (in.)	ALM	46.3	45.8	**-0.5**	*0.325*
	CON	41.3	41.9	**-.6**	
Body Fat (%)	ALM	34.4	38.1	**3.7**	*0.327*
	CON	34.0	33.2	**-0.8**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 3. Mean Change in BMI, Weight, Waist Circumference and Percent Body Fat in Women

		0 Weeks	**12 Weeks**	**Change**	***p-value***[1]
BMI (kg/m^2)	ALM = 6	36.9	37.1	**0.2**	*0.474*
	CON = 8	34.7	34.2	**-0.68**	
Weight (lbs.)	ALM	213.84	214.64	**0.80**	*0.604*
	CON	202.48	198.54	**-3.95**	
Waist (in.)	ALM	44.3	44.9	**0.6**	*0.135*
	CON	43.7	42.7	**-.09**	
Body Fat (%)	ALM	45.9	45.3	**-0.6**	*0.948*
	CON	43.9	42.9	**-1.0**	

[1]P values were obtained from independent samples Mann-Whitney Test

Energy and nutrient intake was estimated using 3-day food records collected at each fasting blood draw. Food Processor software was used to estimate intake and nutrient distribution and standardized food lists were used for ambiguous food listings. Total kcals decreased and macronutrient distribution changed over time in women, but not in men (Tables 4 and 5). Total kcals decreased by a net total of 583 kcals between the almond and control groups (p = 0.042). Percent energy from carbohydrate decreased by 15.14% while percent energy from protein increased by 2.43% (p = 0.017 and 0.062, respectively). Changes in energy and calorie distribution were not statistically different between the control group and the almond group in men.

TABLE 4. Mean Change in Energy and Macronutrient Distribution for Women

		0 Weeks	12 Weeks	Change	*p-value*[1]
Energy (kcals)	ALM = 6	2205	1520	**-686**	***0.042***
	CON = 8	1645	1541	**-103**	
Carbohydrate (%)	ALM	52.69	37.54	**-15.14**	***0.017***
	CON	43.97	44.71	**.74**	
Protein (%)	ALM	15.09	17.52	**2.43**	*0.062*
	CON	17.20	14.95	**-2.25**	
Fat (%)	ALM	43.29	45.98	**2.68**	*1.000*
	CON	35.73	37.56	**1.83**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 5. Mean Change in Energy and Macronutrient Distribution for Men

		0 Weeks	12 Weeks	Change	*p-value*[1]
Energy (kcals)	ALM = 5	1839	1916	**77**	*0.827*
	CON = 4	1596	1776	**180**	
Carbohydrate (%)	ALM	37.95	39.45	**1.49**	*0.275*
	CON	36.08	48.62	**12.54**	
Protein (%)	ALM	17.72	22.50	**4.78**	*0.127*
	CON	19.15	17.21	**-1.95**	
Fat (%)	ALM	44.04	38.36	**-5.68**	*0.827*
	CON	42.62	35.33	**-7.29**	

[1]P values were obtained from independent samples Mann-Whitney Test

Insulin Resistance

No significant changes were observed in markers of insulin sensitivity over the 12-week intervention period in either men or women (see Tables 6-9). Markers of insulin resistance more closely neared statistical significance in men compared to women for every marker except for HbA_{1C}.

TABLE 6. Overall Mean and Mean Changes in Markers of Insulin Resistance

		0 Weeks	**12 Weeks**	**Change**	***p-value***[1]
Glucose	ALM = 11	156.8	152.7	**-4.1**	*0.768*
	CON = 12	154.8	161.6	**6.8**	
Insulin	ALM	28.9	30.42	**1.53**	*0.279*
	CON	33.48	35.52	**2.04**	
A1c	ALM	7.4	7.4	**0.0**	*0.510*
	CON	7.4	7.2	**-0.2**	
HOMA-IR	ALM	11.43	11.97	**0.54**	*0.622*
	CON	10.53	15.64	**5.1**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 7. Mean and Mean Changes in Markers of Insulin Resistance in Men

		0 Weeks	**12 Weeks**	**Change**	***p-value***[1]
Glucose	ALM (n = 5)	174.5	150.1	**-24.4**	*0.462*
	CON (n = 4)	143.5	126.9	**-16.6**	
Insulin	ALM	28.02	32.75	**4.74**	*0.142*
	CON	45.77	37.41	**-8.37**	
A1c	ALM	7.2	7	**-0.1**	*0.805*
	CON	7.2	7.1	**-0.1**	
HOMA-IR	ALM	12.16	12.82	**-0.66**	*0.462*
	CON	11.78	11.13	**-0.66**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 8. Mean and Mean Changes in Markers of Insulin Resistance in Women

		0 Weeks	12 Weeks	Change	*p-value*[1]
Glucose	ALM = 6	142	154.8	**12.8**	*0.886*
	CON = 8	161.2	181.5	**20.3**	
Insulin	ALM	29.63	28.48	**-1.14**	*0.775*
	CON	26.45	34.43	**7.98**	
A1c	ALM	7.6	7.6	**0.1**	*0.566*
	CON	7.6	7.3	**-0.2**	
HOMA-IR	ALM	10.83	11.27	**0.44**	*0.886*
	CON	9.82	18.21	**8.39**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 9. Change in Markers of Glucose Control, Comparison Between Men and Women

		M	F
Glucose	ALM = 11	**-24.4**	**12.8**
	CON = 12	**-16.6**	**20.3**
Insulin	ALM	**4.74**	**-1.14**
	CON	**-8.37**	**7.98**
A1c	ALM	**-0.1**	**0.1**
	CON	**-0.1**	**-0.2**
HOMA-IR	ALM	**-0.66**	**0.44**
	CON	**-0.66**	**8.39**

Oxidative Stress and Inflammation

There were no significant differences in change in markers of oxidative stress and inflammation over the 12-week intervention period (Tables 10-13). However, CRP neared significance in the almond group (men and women combined) compared to the control group (p = 0.053). When outliers were removed (HbA_{1C} >9.0%), CRP reached significance (p = 0.017).

TABLE 10. Overall Mean and Mean Changes in Markers of Oxidative Stress and Inflammation over 12 Weeks (outliers removed)

		0 Weeks	12 Weeks	Change	*p-value*[1]
CRP	ALM = 11	4.31	3.11	**-1.20**	***0.017***
	CON = 12	5.68	9.75	**4.08**	
IL-6	ALM	1.128	1.008	**-0.120**	*0.373*
	CON	1.585	1.749	**0.164**	
HNE	ALM	84.13	81.41	**-2.72**	*0.742*
	CON	102.39	98.60	**-3.79**	
TNFa	ALM	33.76	35.01	**1.25**	*0.767*
	CON	25.81	26.80	**1.00**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 11. Overall Mean and Mean Changes in Markers of Oxidative Stress and Inflammation over 12 Weeks in Men

		0 Weeks	12 Weeks	Change	*p-value*[1]
CRP	ALM = 5	3.01	1.97	**-1.03**	*0.221*
	CON = 4	1.87	2.07	**0.198**	
IL-6	ALM	0.795	0.812	**0.017**	*1.000*
	CON	1.468	1.453	**-0.015**	
HNE	ALM	78.19	75.97	**-2.23**	*0.806*
	CON	80.04	78.82	**-1.22**	
TNFa	ALM	32.02	34.13	**2.11**	*0.539*
	CON	32.97	33.61	**0.64**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 12. Overall Mean and Mean Changes in Markers of Oxidative Stress and Inflammation over 12 Weeks in Women (outliers removed)

		0 Weeks	12 Weeks	Change	*p-value*[1]
CRP	ALM = 6	5.62	4.25	**-1.37**	*0.088*
	CON = 8	7.85	14.14	**6.29**	
IL-6	ALM	1.461	1.205	**-0.256**	*0.306*
	CON	1.644	1.898	**0.254**	
HNE	ALM	90.06	86.85	**-3.20**	*0.661*
	CON	113.56	108.48	**-5.08**	
TNF-alpha	ALM	35.50	35.90	**0.40**	*1.000*
	CON	22.22	23.4	**1.17**	

[1]P values were obtained from independent samples Mann-Whitney Test

TABLE 13. Change in Markers of Oxidative Stress and Inflammation, Comparison of Men and Women (outliers removed)

		M	F
CRP	ALM	**-1.03**	**-1.37**
	CON	**0.198**	**6.29**
IL-6	ALM	**0.017**	**-0.256**
	CON	**-0.015**	**0.254**
HNE	ALM	**-2.23**	**-3.20**
	CON	**-1.22**	**-5.08**
TNF-alpha	ALM	**2.11**	**0.40**
	CON	**0.64**	**1.17**

CHAPTER 5

DISCUSSION

No significant difference was observed in markers of glucose control. Changes in IL-6, HNE and TNF-alpha also did not reach statistical significance. However, when subjects with a baseline HbA_{1C} >9.0% were removed, CRP was reduced by an average of 1.20 mg/dL (27.8%), which was statistically significant ($p = 0.017$, both sexes combined; see Table 10). CRP is a major biomarker of inflammation. Chronic low-grade inflammation has been linked to increased risk for obesity, cancer and atherosclerosis. Long-term dietary patterns have been linked to elevations in CRP; however, few individual randomized control trials have been able to link specific foods to reductions in CRP[47]. Our results are consistent with the results from other studies demonstrating that almond ingestion can effectively reduce CRP concentrations in a variety of populations[27,33], however not all studies have demonstrated significant differences in CRP with almond ingestion[34]. This is the second study to show that CRP can be reduced by almond ingestion in a diabetic population. Therefore, this study demonstrates that a simple dietary intervention of consuming 1.5 oz. almonds daily is effective at reducing inflammation among those with type 2 diabetes.

The ability of almonds to reduce CRP has been attributed to their high MUFA content (although previous studies with alternative sources of MUFA have not consistently affirmed this mechanism[33,48]) via a decrease in *E*-selectin that could lower the inflammatory response, thus reducing CRP[33]. Magnesium has also been inversely

correlated with serum CRP concentrations[27,49]Arginine, alpha-tocopherol and other phytonutrients may also play a role in modifying inflammatory responders[27,33].

In spite of the significant response of CRP to almond ingestion, suggesting decreased inflammation, changes in IL-6 were not statistically significant in this study. Mean change data suggested that women in the almond group had average declines in IL-6 of -0.256 compared to women in the control group, which experienced average increases in IL-6 of 0.254 ($p = 0.306$; see figure 7).

Other studies have shown mixed results regarding the response of IL-6 to almond ingestion. In similar studies, one study showed that CRP and IL-6 concomitantly decreased with daily almond ingestion[27], while another found significant differences only in CRP reduction with almond intake[33]. These discrepancies may have been due in part to the small sample size, or lack of internal controls. In the Liu et al. study, all subjects were involved in both arms of the study, providing their own controls, a placebo diet was provided, and all meals were provided by a metabolic kitchen, decreasing interindividual variations in diet and all other individual measures[27]. However, providing meals to subjects would have decreased the generalizability of this study. The inability of this study to demonstrate significant changes in IL-6 may also be related to the nature of IL-6. IL-6 is subject to diurnal variations and is lower in the morning than it is at night; CRP does not exhibit such diurnal variations. CRP is a better predictor of cardiovascular disease than IL-6 when morning-extracted blood samples are used, as was the case in this trial[33].

Figure 2.

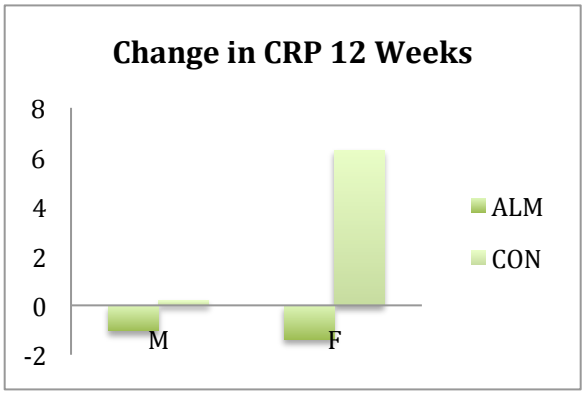
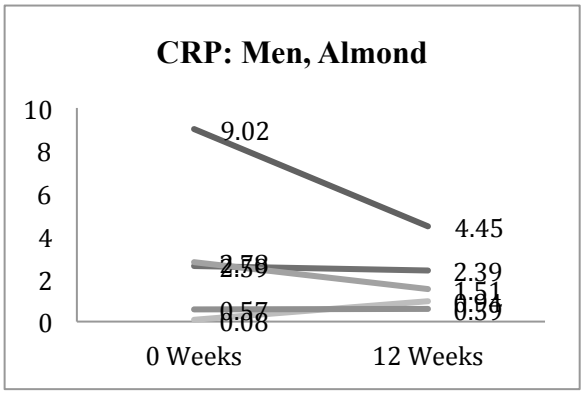


Figure 3.



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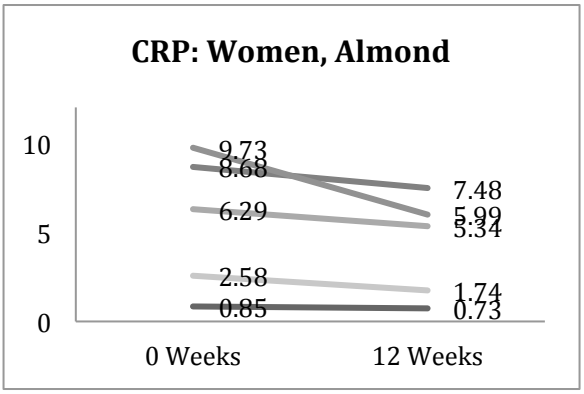

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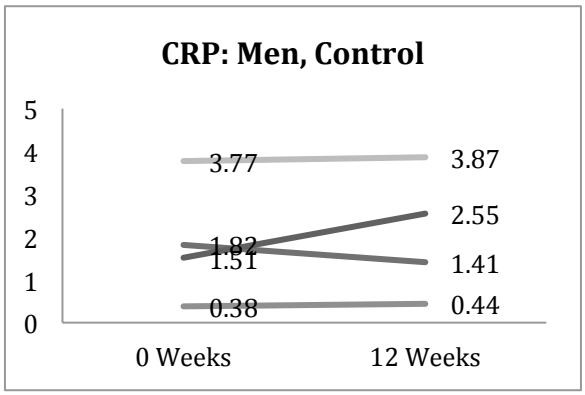

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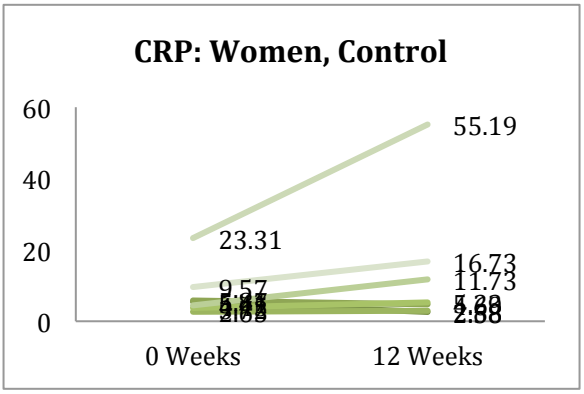
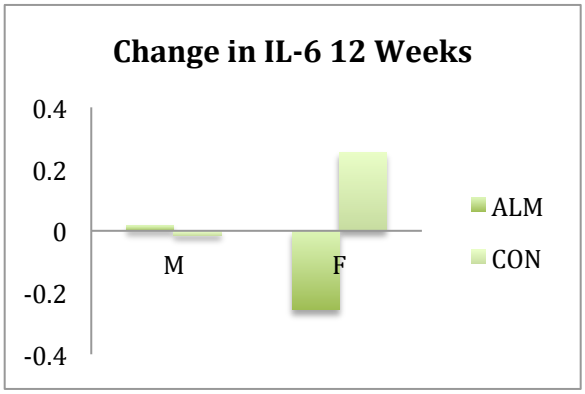


Figure 7.



Women in the intervention group had significant changes in their dietary patterns according to 3-day dietary recalls. Total calories decreased over time from an average of 2520 daily to 2205 ($p = 0.042$). Additionally, macronutrient composition of the diet changed with a decrease in carbohydrate composition from 52.69% to 37.54% compared to 43.97% to 44.71% in the control group ($p = 0.017$) and an increase in dietary composition of protein from 15.09% to 17.52% in the almond group and a decrease from 17.20% to 14.95% in the control group. Dietary changes were not significant for men. The decreased caloric intake and improved macronutrient profile observed for women in the almond group may be due to the composition of almonds. Almonds are a good source of protein and have a satiating quality[27], thereby reducing caloric intake. Wien et al. showed similar changes in dietary macronutrient composition, with a significant decrease in percent calories from carbohydrate. These results were significant in spite of concentrated attempts to maintain dietary consistency within subjects throughout the study period through the employ of a registered dietitian and double blinding. While Wien et al. did not report sex differences in their data, 69% and 79% of almond intervention and control subjects, respectively were female[20]

While no change was observed in HbA_{1c} over the intervention period, nonsignificant changes were observed for blood glucose and insulin. HOMA-IR combines these values to provide a reliable estimate of actual glucose control. All groups remained largely unchanged except for women in the control group, in which HOMA-IR worsened significantly. In observing individual changes in HOMA-IR, it can be seen that 4 of the 6 women in the almond group had decreased or unchanged values, whereas among men in the almond group, no trend is seen (see Figures 8-11). From this, it was

observed that almond ingestion in women may have produced better protections from deteriorating blood glucose control while glucose control in men remained largely unchanged by almond ingestion. This may be at least partly due to the observation that women with type 2 diabetes are more likely to have impaired glucose tolerance when presented with a glycemic challenge, while men with type 2 diabetes are more likely to exhibit impaired fasting glucose[7]. If almond ingestion improves glucose control by affecting postprandial glucose, the effect would be expected to be more prominent in women.

Figure 8.

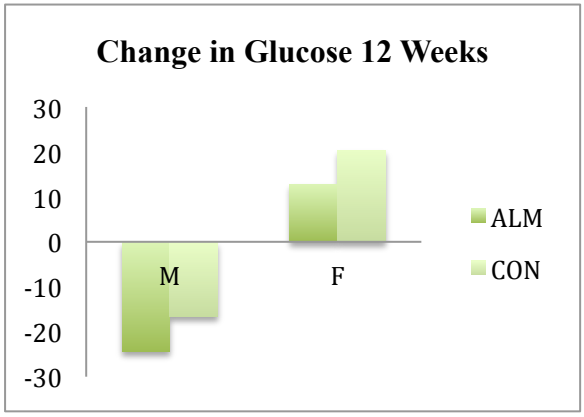


Figure 9.

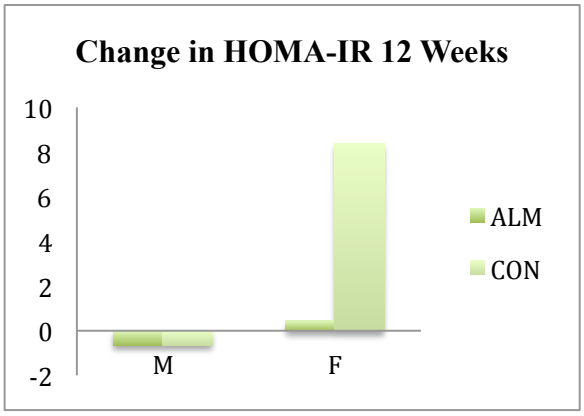


Figure 10.

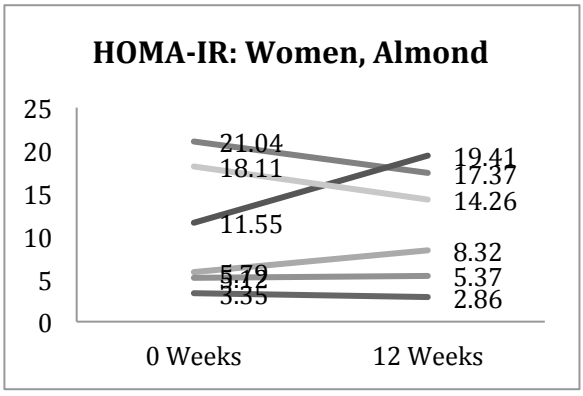
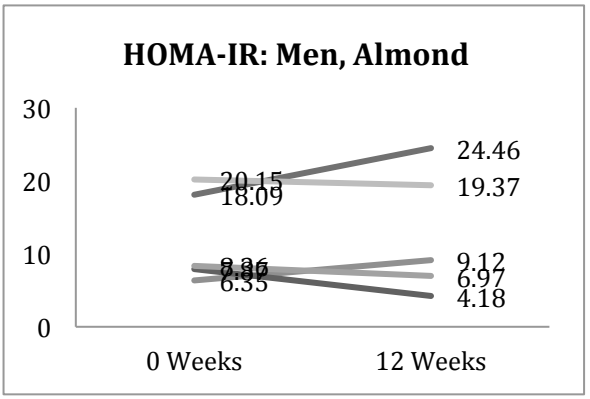


Figure 11.



The lack of significant change in glycemic control observed in this population has not been demonstrated in other studies[2,18,19,22]. This may in part be due to the exclusion criteria that may have unintentionally excluded the population that would be most sensitive to dietary intervention – those with better glucose control. Subjects with poorly controlled diabetes have not been studied in this context before and may be less sensitive to dietary interventions, especially those designed to lower postprandial glucose. As Monnier et al. points out, average daily plasma glucose is better predicted by postprandial plasma glucose than by fasting plasma glucose concentrations among subjects with type 2 diabetes, whereas in subjects with higher HbA_{1C}, fasting plasma concentrations were a better predictor of average daily plasma glucose concentrations[50]. Previous studies have suggested that almonds are able to improve postprandial blood glucose concentrations[18,19,22], but not fasting glucose concentrations[20-22], but only one study has demonstrated that almonds may also reduce fasting glucose concentrations[2]. Additionally, this study used a much lower dose of almonds than has been used in previous studies[2,18,20,21] and was subject to the placebo effect as no placebo was used and subject blinding was not possible.

This study had excellent controls, which allowed for high external validity. However, largely due to restrictive exclusion criteria that required an $HbA_{1C} \geq 6.50\%$, the goal number of participants were not recruited. This may have contributed to an inability of the results to demonstrate statistical significance in the results. Additionally, METs and dietary intake, as well as total estimated MUFA intake were measured via subject report. Dietary and physical activity may have been misreported.

Previous studies have suggested that almond ingestion may minimize postprandial glucose excursions, however this study was unable to demonstrate statistically significant improvements in blood glucose control with almond ingestion. Future studies should include subjects with a wider range of glucose control including those with diabetes who have excellent glucose control and those with prediabetes in order to delineate whether only particular diabetic populations may benefit from a dietary intervention that includes almonds. Future studies should also aim to include a higher number of subjects with diabetes.

CHAPTER 6

CONCLUSION

While data is too preliminary to suggest standardized supplementation recommendations to regulate blood glucose for individuals with type 2 diabetes, results of previous studies in combination with this study suggest that almond supplementation may be beneficial in this and other populations for reducing inflammation. It seems clear that almond ingestion is beneficial for ameliorating inflammation and improving the lipid profile in at risk individuals, as well as in healthy populations. Additional larger-scale studies are needed in order to delineate the potential benefits of almond supplementation on blood glucose control, oxidative stress and inflammation. Future studies should include individuals with greater variety in blood glucose control and seek to determine whether this dietary intervention could have varying impacts on individuals with greater or lesser blood glucose control than those studied in this study.

REFERENCES

1. US Department of Health and Human Services. Diabetes, type 2 fact sheet. http://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=121&key=D#D Web site. . Updated 2011. Accessed June/20, 2012.

2. Li SC, Liu YH, Liu JF, Chang WH, Chen CM, Chen CY. Almond consumption improved glycemic control and lipid profiles in patients with type 2 diabetes mellitus. *Metabolism*. 2011;60(4):474-479.

3. American Diabetes Association. The cost of diabetes. www.diabetes.org Web site. http://www.diabetes.org/advocate/resources/cost-of-diabetes.html. Accessed 09/21, 2012.

4. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: New and future developments in treatment. *Lancet*. 2011;378(9786):182-197.

5. Milbury PE, Chen CY, Dolnikowski GG, Blumberg JB. Determination of flavonoids and phenolics and their distribution in almonds. *J Agric Food Chem*. 2006;54(14):5027-5033.

6. Lundberg V, Stegmayr B, Asplund K, Eliasson M, Huhtasaari F. Diabetes as a risk factor for myocardial infarction: Population and gender perspectives. *J Intern Med*. 1997;241(6):485-492.

7. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. *Clin Res Cardiol*. 2006;95(3):136-147.

8. Manjoo P, Joseph L, Pilote L, Dasgupta K. Sex differences in step count-blood pressure association: A preliminary study in type 2 diabetes. *PLoS One*. 2010;5(11):e14086.

9. Homko CJ, Zamora L, Santamore WP, Kashem A, McConnell T, Bove AA. Gender differences in cardiovascular risk factors and risk perception among individuals with diabetes. *Diabetes Educ*. 2010;36(3):483-488.

10. Louet JF, LeMay C, Mauvais-Jarvis F. Antidiabetic actions of estrogen: Insight from human and genetic mouse models. *Curr Atheroscler Rep*. 2004;6(3):180-185.

11. Faulds MH, Zhao C, Dahlman-Wright K, Gustafsson JA. The diversity of sex steroid action: Regulation of metabolism by estrogen signaling. *J Endocrinol*. 2012;212(1):3-12.

12. Mukhopadhyay S, Mukherjee TK. Bridging advanced glycation end product, receptor for advanced glycation end product and nitric oxide with hormonal replacement/estrogen

therapy in healthy versus diabetic postmenopausal women: A perspective. *Biochim Biophys Acta*. 2005;1745(2):145-155.

13. Fineberg SE. Glycaemic control and hormone replacement therapy: Implications of the postmenopausal estrogen/progestogen intervention (PEPI) study. *Drugs Aging*. 2000;17(6):453-461.

14. Wu BN, O'Sullivan AJ. Sex differences in energy metabolism need to be considered with lifestyle modifications in humans. *J Nutr Metab*. 2011;2011:391809.

15. Moulana M, Lima R, Reckelhoff JF. Metabolic syndrome, androgens, and hypertension. *Curr Hypertens Rep*. 2011;13(2):158-162.

16. Grossmann M. Low testosterone in men with type 2 diabetes: Significance and treatment. *J Clin Endocrinol Metab*. 2011;96(8):2341-2353.

17. Corona G, Mannucci E, Forti G, Maggi M. Following the common association between testosterone deficiency and diabetes mellitus, can testosterone be regarded as a new therapy for diabetes? *Int J Androl*. 2009;32(5):431-441.

18. Jenkins DJ, Kendall CW, Josse AR, et al. Almonds decrease postprandial glycemia, insulinemia, and oxidative damage in healthy individuals. *J Nutr*. 2006;136(12):2987-2992.

19. Josse AR, Kendall CW, Augustin LS, Ellis PR, Jenkins DJ. Almonds and postprandial glycemia--a dose-response study. *Metabolism*. 2007;56(3):400-404.

20. Wien M, Bleich D, Raghuwanshi M, et al. Almond consumption and cardiovascular risk factors in adults with prediabetes. *J Am Coll Nutr*. 2010;29(3):189-197.

21. Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC. Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. *Am J Clin Nutr*. 2002;76(5):1000-1006.

22. Cohen AE, Johnston CS. Almond ingestion at mealtime reduces postprandial glycemia and chronic ingestion reduces hemoglobin A(1c) in individuals with well-controlled type 2 diabetes mellitus. *Metabolism*. 2011;60(9):1312-1317.

23. Cassady BA, Hollis JH, Fulford AD, Considine RV, Mattes RD. Mastication of almonds: Effects of lipid bioaccessibility, appetite, and hormone response. *Am J Clin Nutr*. 2009;89(3):794-800.

24. Gropper SS, Smith JL, Groff JL, eds. *Advanced nutrition and human metabolism.* 5th ed. Beltmont, CA: Wadworth, Cengage Learning; 2009. Adams Peter, Lustig Anna and Feldman Elisha, eds.

25. Shepherd PR, Kahn BB. Glucose transporters and insulin action--implications for insulin resistance and diabetes mellitus. *N Engl J Med*. 1999;341(4):248-257.

26. Thorens B, Mueckler M. Glucose transporters in the 21st century. *Am J Physiol Endocrinol Metab*. 2010;298(2):E141-5.

27. Liu JF, Liu YH, Chen CM, Chang WH, Chen CY. The effect of almonds on inflammation and oxidative stress in chinese patients with type 2 diabetes mellitus: A randomized crossover controlled feeding trial. *Eur J Nutr*. 2013;52(3):927-935.

28. Chakrabarti S, Cheung CC, Davidge ST. Estradiol attenuates high glucose-induced endothelial nitrotyrosine: Role for neuronal nitric oxide synthase. *Am J Physiol Cell Physiol*. 2012;302(4):C666-75.

29. Adolphe JL, Whiting SJ, Juurlink BH, Thorpe LU, Alcorn J. Health effects with consumption of the flax lignan secoisolariciresinol diglucoside. *Br J Nutr*. 2010;103(7):929-938.

30. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;53(3):693-700.

31. Bolling BW, Chen CY, McKay DL, Blumberg JB. Tree nut phytochemicals: Composition, antioxidant capacity, bioactivity, impact factors. A systematic review of almonds, brazils, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. *Nutr Res Rev*. 2011;24(2):244-275.

32. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002;288(20):2554-2560.

33. Rajaram S, Connell KM, Sabate J. Effect of almond-enriched high-monounsaturated fat diet on selected markers of inflammation: A randomised, controlled, crossover study. *Br J Nutr*. 2010;103(6):907-912.

34. Jenkins DJ, Kendall CW, Marchie A, et al. Dose response of almonds on coronary heart disease risk factors: Blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: A randomized, controlled, crossover trial. *Circulation*. 2002;106(11):1327-1332.

35. Regitz-Zagrosek V, Lehmkul E. Heart failure and its treatment in women. *Herz*. 2005;30(5):356-367.

36. Manrique C, Lastra G, Habibi J, Mugerfeld I, Garro M, Sowers JR. Loss of estrogen receptor alpha signaling leads to insulin resistance and obesity in young and adult female mice. *Cardiorenal Med*. 2012;2(3):200-210.

37. Turner JV, Agatonovic-Kustrin S, Glass BD. Molecular aspects of phytoestrogen selective binding at estrogen receptors. *J Pharm Sci*. 2007;96(8):1879-1885.

38. Steffan RJ, Matelan E, Ashwell MA, et al. Control of chronic inflammation with pathway selective estrogen receptor ligands. *Curr Top Med Chem*. 2006;6(2):103-111.

39. Cederroth CR, Nef S. Soy, phytoestrogens and metabolism: A review. *Mol Cell Endocrinol*. 2009;304(1-2):30-42.

40. Arnal JF, Laurell H, Fontaine C, et al. Estrogen receptor actions on vascular biology and inflammation: Implications in vascular pathophysiology. *Climacteric*. 2009;12 Suppl 1:12-17.

41. Jones TH. Effects of testosterone on type 2 diabetes and components of the metabolic syndrome. *J Diabetes*. 2010;2(3):146-156.

42. Giugliano D, Maiorino MI, Bellastella G, Chiodini P, Esposito K. Multiple HbA1c targets and insulin analogues in type 2 diabetes: A systematic review. *J Diabetes Complications*. 2011;25(4):275-281.

43. Lu T, Sheng H, Wu J, Cheng Y, Zhu J, Chen Y. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in chinese patients with type 2 diabetes. *Nutr Res*. 2012;32(6):408-412.

44. Michigan Diabetes Research and Training Center. Hemoglobin A1c fact sheet. University of Michigan Health system Web site. http://www.med.umich.edu/mdrtc/cores/ChemCore/hemoa1c.htm. Updated 2012. Accessed 9/23, 2012.

45. Mattson MP. Roles of the lipid peroxidation product 4-hydroxynonenal in obesity, the metabolic syndrome, and associated vascular and neurodegenerative disorders. *Exp Gerontol*. 2009;44(10):625-633.

46. Karaduman M, Oktenli C, Musabak U, et al. Leptin, soluble interleukin-6 receptor, C-reactive protein and soluble vascular cell adhesion molecule-1 levels in human coronary atherosclerotic plaque. *Clin Exp Immunol*. 2006;143(3):452-457.

47. Julia C, Meunier N, Touvier M, et al. Dietary patterns and risk of elevated C-reactive protein concentrations 12 years later. *Br J Nutr*. 2013;110(4):747-754.

48. Jenkins DJ, Kendall CW, Marchie A, et al. Direct comparison of dietary portfolio vs statin on C-reactive protein. *Eur J Clin Nutr*. 2005;59(7):851-860.

49. Song Y, Li TY, van Dam RM, Manson JE, Hu FB. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. *Am J Clin Nutr*. 2007;85(4):1068-1074.

50. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26(3):881-885.

APPENDIX A

INFORMED CONSENT

BENEFIT OF PLANT FAT FOR REDUCING CARDIOVASCULAR RISK FACTORS IN INDIVIDUALS WITH TYPE 2 DIABETES

INTRODUCTON
The purposes of this form are (1) to provide you with information that may affect your decision as to whether or not to participate in this research study, and (2) to record your consent if you choose to be involved in this study.

RESEARCHERS
Drs. Karen Sweazea and Carol Johnston, Nutrition professors at Arizona State University Downtown Campus, and Kristin Ricklefs, a nutrition doctoral student, have requested your participation in a research study.

STUDY PURPOSE
The purpose of the research is to examine the effects of almonds on heart disease risk factors in individuals with type 2 diabetes.

DESCRIPTION OF RESEARCH STUDY
You have indicated to us that you are 25-75 years of age and have been diagnosed by a physician with type 2 diabetes. It is our understanding that you do not take insulin for your condition but you may take other prescription medications. If there is a change to your prescription medication use during the 12-week study, please notify study personnel. This study will initially involve the completion of a brief medical history questionnaire and a short dietary questionnaire. At this time, your weight, height, and girth will be measured; your blood pressure will be taken; and, a drop of blood from a finger prick will be used to measure hemoglobin A1c. You will be instructed to record all food and beverage intake on 12 days during the 12-week study. This first meeting will take about 30 minutes. You will be randomly assigned to the 'almond' group or to the 'no dietary change' group. Participants in the almond group will consume 1.5 oz almonds daily during the trial. There are three additional visits (study visits 2, 3, and 4) that will last about 30 minutes and scheduled six weeks apart. On test days, you will travel to ASU (the Nutrition labs at the ASU Downtown campus or the Tempe campus) early in the morning and in a fasted state (no food or drink with the exception of water for >8 hours.)

On the test days, you will have a blood sample drawn from an arm vein, and we will measure blood pressure, weight, and girth. Food records will be collected at each test visit, and study foods will be provided. About 50 subjects will participate in this study. A research nurse will draw blood using standard, sterile techniques. Finger pricks will be conducted under sterile conditions using disposable, retractable lancets. Blood samples will be analyzed for biomarkers that are associated with the diabetic condition including glucose, insulin, cholesterol, and inflammation.

RISKS
Bruising of the skin or a feeling of faintness is possible during the blood draws. A registered nurse will draw the venous blood sample under sterile conditions and is trained to minimize these risks. Although participants are screened for food allergies, it is possible that individuals may have allergic reactions to the almonds used in the study.

BENEFITS
This study will provide information regarding the usefulness of simple diet alterations for improving markers of heart disease risk in individuals with type 2 diabetes. If desired, you will be provided with study results and your personal blood data at the end of the study. Almonds will be provided at no charge.

NEW INFORMATION
If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

CONFIDENTIALITY
All information obtained in this study is strictly confidential unless disclosure is required by law. The results of this research study may be used in reports, presentations, and publications, but your name or identity will not be revealed. In order to maintain confidentiality of your records, the investigators will use subject codes on all data

collected, maintain a master list separate and secure from all data collected, and limit access to all confidential information to the study investigators. Plasma from blood samples will be stored for 5 years in freezers in the laboratories of the Nutrition Program at Arizona State University Downtown Campus after which time they will be disposed of as biohazard waste.

WITHDRAWAL PRIVILEGE
You may withdraw from the study at any time for any reason without penalty or prejudice toward you. Your decision will not incur negative treatment to you by the researchers.

COSTS AND PAYMENTS
All study foods will be given to you during the study free of charge. You will also receive a cash incentive ($25, $35, and $50) on study visits 2, 3 and 4 (total amount, $110).

COMPENSATION FOR ILLNESS AND INJURY
If you agree to participate in the study, then your consent does not waive any of your legal rights. However, in the event of harm, injury, or illness arising from this study, neither Arizona State University nor the researchers are able to give you any money, insurance coverage, free medical care, or any compensation for such injury. Major injury is not likely but if necessary, a call to 911 will be placed.

VOLUNTARY CONSENT
Any questions you have concerning the research study or your participation in the study, before or after your consent, will be answered by Dr. Karen Sweazea [480-965-6025] or Dr. Carol Johnston [602-827-2265].

If you have questions about your rights as a subject/participant in this research, or if you feel you have been placed at risk, you can contact the Chair of the Human Subjects Institutional Review Board, through the ASU Research Compliance Office, at 480-965 6788.

This form explains the nature, demands, benefits and any risk of the project. By signing this form you agree knowingly to assume any risks involved. Remember, your participation is voluntary. You may choose not to participate or to withdraw your consent and discontinue participation at any time without penalty or loss of benefit. In signing this consent form, you are not waiving any legal claims, rights, or remedies. A copy of this consent form will be given to you.

Your signature below indicates that you consent to participate in the above study.

_____	_____	_____
Subject's Signature	Printed Name	Date

_____	_____
Contact phone number	Email

INVESTIGATOR'S STATEMENT
"I certify that I have explained to the above individual the nature and purpose, the potential benefits, and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Human Research Protections to protect the rights of human subjects. I have provided the subject/participant a copy of this signed consent document."

Signature of Investigator_____ Date_____

APPENDIX B

IRB APPROVAL

ASU Knowledge Enterprise Development

Office of Research Integrity and Assurance

To:	Carol Johnston ABC 132
From:	Carol Johnston, Chair Biosci IRB
Date:	06/11/2012
Committee Action:	**Expedited Approval**
Approval Date:	06/11/2012
Review Type:	Expedited F2 F4 F7
IRB Protocol #:	1206007903
Study Title:	Almond Ingestion to Reduce Hemoglobin A1C in Individuals with Type 2 Diabetes
Expiration Date:	06/10/2013

The above-referenced protocol was approved following expedited review by the Institutional Review Board.

It is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date. You may not continue any research activity beyond the expiration date without approval by the Institutional Review Board.

Adverse Reactions: If any untoward incidents or severe reactions should develop as a result of this study, you are required to notify the Biosci IRB immediately. If necessary a member of the IRB will be assigned to look into the matter. If the problem is serious, approval may be withdrawn pending IRB review.

Amendments: If you wish to change any aspect of this study, such as the procedures, the consent forms, or the investigators, please communicate your requested changes to the Biosci IRB. The new procedure is not to be initiated until the IRB approval has been given.

Please retain a copy of this letter with your approved protocol.

APPENDIX C

RECRUITMENT ADVERTISEMENTS

ASU *TYPE 2 DIABETES* NUTRITION STUDY

THE NUTRITION PROGRAM AT ASU IS RECRUITING VOLUNTEERS (25-75 y of age)
THIS STUDY WILL TEST HOW ALMONDS AFFECT HEART DISEASE RISK INDICATORS IN INDIVIDUALS WITH TYPE 2 DIABETES. IF YOU ARE A TYPE 2 DIABETIC AND GENERALLY HEALTHY YOU MAY QUALIFY FOR THIS TRIAL.

Participation will include:

- Enrolling in a 12-week trial and consuming almonds daily if randomly assigned to this group. One-half of participants will be assigned to a 'no dietary change' group.
- Traveling to the ASU research site (either the downtown or Tempe campus) for 4 visits that will take about 30 minutes each to complete.
- Fasting 12 hours and restricting exercise the night before three of the test visits. On these 3 visits blood samples will be collected. A finger prick will be performed on the initial visit.
- There is a dietary nut restriction (aside from the study treatments) during the trial.

All study foods will be given to you during the study free of charge.
You will also receive cash incentives ($25, $35, and $50) on study visits 2, 3 and 4

INTERESTED?? Please visit our recruitment site:
https://www.surveymonkey.com/s/ASU_Diabetes_Study

APPENDIX D

SURVEY MONKEY SCREENING QUESTIONNAIRE

Almond Study

Exit this survey

***1. Please provide your email address.**

2. Has your physician diagnosed you with type 2 diabetes?

Yes

No

Not sure

3. If you have been previously diagnosed with type 2 diabetes (answered yes to question 2, above), was this diagnosis prior to April 2012?

Yes

No

4. Do you know your glycosylated hemoglobin A1c level?

Yes

No

Not sure

If yes, what is it?

5. Are you between 25 and 75 years old?

Yes

No

6. Are you currently taking insulin?

Yes

No

Not sure

7. Are you currently taking any oral diabetic medications (e.g., metformin)?

Yes

No

8. Do you take any of the following medications: e.g. beta-blockers, ACE inhibitors, diphenhydramine or cyproheptadine (allergy medications), lithium carbonate, corticosteroids, thiazolidinediones (Actos, Avandia or Avandamet), sulfonylureas, biguanides, meglitinides, incretins, sodium valproate, or thyroid replacement therapy?

Yes

No

Not sure

9. Are you currently pregnant or breast-feeding?

Yes

No

10. Do you have a nut allergy?

Yes

No

Not Sure

11. Do you have any other food allergy?

Yes

No

Not Sure

If yes, please specify

12. Do you consume any of the following foods items daily: nuts (almonds, macadamia nuts, etc.), nut butters, avocados, olives, cooking or salad oils, margarine spread?

Yes

No

13. Will you be able to maintain your current diet and physical activity for a

consecutive 12 weeks?

Yes

No

Not sure

14. Do you train athletically to compete?

Yes

No

15. Are you willing and are able to travel to the ASU Downtown Campus or Tempe Campus to meet with the research investigators on four separate mornings?

Yes

No

If yes, which campus is preferred?

16. Are you willing to have a fasting blood draw (fast 10-12 hours prior to blood draw) on 3 separate occasions?

Yes

No

Not Sure

17. Where did you hear about this survey?

Done

APPENDIX E

MEDICAL HISTORY QUESTIONNAIRE

Medical History Questionnaire

ID#_____

Age:_____

_____in.

Gender (please circle): Female Male

Smoker (please circle): Yes No

To be completed by investigator

Height:_____ft.

Weight:_____lbs.

Waist:_____in.

1. Are you taking any medications regularly? (including aspirin, steroids, birth control, etc.)

Y N

If yes, what medications and how often?

---

2. Do you currently take supplements? (vitamins, minerals, herbs, etc.)

Y N

If yes, what supplements and how often?

---

3. Do you take insulin or an oral diabetic control medication (e.g., metaformin)?

Y N

4. Do you know what your glycosylated hemoglobin A_1C level is?

Y N

If so, what is it?_____

5. Has a doctor ever told you that you have any of the following conditions?

Heart disease? Y N

Kidney disease? Y N

Liver disease? Y N

Thyroid problems?

Y N

Cancer?

Y N

High blood pressure?

Y N

TURN OVER

Food Allergy? Y N (if yes, what type?)_____

Type 2 Diabetes? Y N (if yes, when were you diagnosed?)_____

Other chronic conditions?_____

6. Are you pregnant or planning on becoming pregnant in the next 16 weeks?

Y N

7. Are you currently breast-feeding?

Y N

8. Have you ever fainted at a blood draw?

Y N

Are you willing to participate in a blood draw?

Y N

Have you donated blood in the past 8 weeks?

Y N

9. Will you be willing to consume 1.5 ounces of almonds 5-7 times per week for 12 weeks?

Y N

10. Would you be able to restrict nut consumption (aside from that pertaining to the study to 2 servings per week for 12 weeks?

Y N

11. Do you follow a specific diet? (weight loss/gain, vegetarian, low-fat, etc.)

Y N

12. Are you willing to drive or take the Phoenix light rail (metro system) to either the ASU Tempe or downtown Phoenix campus for a fasting blood draw on 3 separate occasions?

Y N

13. Will you have a problem fasting overnight (10-12 hr) prior to the blood draw?

Y N

14. Will you be able to maintain your typical lifestyle/activities during the trial?

Y N

15. Over a 7 day period, how often do you engage in any regular activity long enough to work up a sweat

(e.g., heart beats rapidly)?_____ How often do you exercise moderately per week?_____

16. Please circle the total time you spend in each category for an average week.

Light activities such as: slow walking, golf, easy swimming, gardening, etc.

Hours per week: 0 1 2 3 4 5 6 7 8 9 10+

Moderate activities such as: moderate walking, cycling, swimming, weight lifting, etc.

Hours per week: 0 1 2 3 4 5 6 7 8 9 10+

Vigorous activities such as: fast walking, jogging, cycling, heavy/intense weight lifting, etc.

Hours per week: 0 1 2 3 4 5 6 7 8 9 10+

17. Please describe any other medical conditions or situations that may affect you ability to participate

in a research trial (i.e., pregnancy, infections, travel, deadlines, etc.).

APPENDIX F

MONO-UNSATURATED FATTY ACID QUESTIONNAIRE

n-3 FFQ Calculation Template

Ritter-Gooder PK, Lewis NM, Heidal K, et al. Validity and Reliability of a Quantitative Food Frequency Questionnaire Measuring Omega-3 Fatty Acid Intakes in Cardiac Patients in the Midwest. JADA 2006;106:1251-1255

Possible values		**0,0.5,1,1.5****	**1,3,6,14,22,30,60*****		
Food Item	MUFA Content in Grams/Medium Serving*	Portion Size	Frequency		Total value
Pickled Herring	5.500	0	0		0
Halibut, baked	5.000	0	0		0
Mackerel	2.400				
Sablefish	3.800				
Catfish, baked	3.400	0	0		0
Vegetable oil, sunflower or safflower, high oleic 70%	12.000	0	0		0
Hazelnut oil	12.000	0	0		0
Olive Oil	10.000	0	0		0
Shortening	9.000	0	0		0
Avocado oil	10.000				
Almond oil	9.000				
Margarine, hard	9.000				
Peanut Oil	7.100	0	0		0
Cream substitute	1.830	0	0		0
Egg yolk, raw	2.450	0	0		0
Whipping Cream	2.100	0	0		0
Macadamia nuts	12.780	0	0		0
Hazelnuts or Filberts	10.480	0	0		0
Pecans	9.020	0	0		0
Almonds	7.500	0	0		0
Mixed Nuts without Peanuts	7.660	0	0		0
Cahsew butter	10.000	0	0		0
Cashew nuts	6.770	0	0		0
Pistachio nuts	5.600	0	0		0
Sesame Seeds	5.200	0	0		0
Brazilnuts	5.600	0	0		0
Tahini	7.000	0	0		0
Peanut butter with Omega-3	12.000	0	0		0
Peanuts	6.770	0	0		0
Peanut butter, chunky style (regular)	8.000	0	0		0
Peanut butter , smooth (regular)	6.000	0	0		0
Kidney beans	4.370	0	0		0
Falafel	5.400	0	0		0
Olives, black	4.900				
Olives, green from jar	5.750				

Avocado, fresh, 1 whole	14.040				
Foie gras	3.300	0	0		0
Beef, ribs, short ribs	5.600	0	0		0
Beef, ground 70% lean	8.800	0	0		0
Beef, corned beef, brisket	8.400	0	0		0
Pork, salt pork, cured	3.570	0	0		0
Pork, cured ham	5.300	0	0		0
Pork, bacon (2 pieces)	3.780	0	0		0
Bacon drippings	5.140	0	0		0
Pork chop, loin, shoulder	4.110	0	0		0
Bologna	2.200	0	0		0
Hot dogs, beef or pork	5.880	0	0		0
Hormel Spam	8.110	0	0		0
Bratwurst, pork	11.340	0	0		0
Beef, smoked sausage	8.800	0	0		0
Polish sausage	10.300	0	0		0
Itailian pork sausage	8.420	0	0		0
Lamb, chop lean and fat	7.440	0	0		0
Lamb, ground	9.940	0	0		0
Lamb, roasted	7.200	0	0		0
Beef sticks	5.230	0	0		0
Potatos chips, made with partially hydrogenated oil	4.800	0	0		0
Trail mix with chocolate chips, nuts, and seeds	7.500	0	0		0
Trail mix, regular	6.250	0	0		0
Beef jerky	2.700	0	0		0
Pork skins	2.010	0	0		0
Puff pastry	6.290	0	0		0
Nabisco, nilla pie crust	3.400	0	0		0
Cookies, shortbread	3.320	0	0		0
Doughnuts	4.130	0	0		0
Danish pastry	3.100	0	0		0
Pie crust, made with enriched flour	2.400	0	0		0
Cookies, chocolate sandwich	4.800	0	0		0
Cookies, peanut butter	4.800	0	0		0
Pecan pie	8.430	0	0		0
Cookies, sugar	3.900	0	0		0
Pumpkin seeds	0.020	0	0		0
Ground Flaxseeds	2.000	0	0		0
Chia seeds	1.110	0	0		0
Poppy seeds	0.030	0	0		0
Banana bread	0.090	0	0		0
Pumpkin bread	0.480	0	0		0
Whole wheat bread	0.010	0	0		0
White bread	0.130	0	0		0
Oatmeal	0.020	0	0		0
Uncle Sams Cereal	1.200	0	0		0

All-bran	0.040	0	0		0
Special K	0.010	0	0		0
Cream of Wheat	0.010	0	0		0
Wheat Germ	0.800	0	0		0
Miracle whip	0.290	0	0		0
Flax oil	2.510	0	0		0
Soybeans	1.450	0	0		0
Garbanzo beans	0.040	0	0		0
Navy beans	0.190	0	0		0
Lentils	0.040	0	0		0
Tofu	0.300	0	0		0
Soy milk	0.240	0	0		0
Pinto beans	0.340	0	0		0
Baked beans	0.160	0	0		0
Baked beans with pork	0.040	0	0		0
Refried Beans/frijoles	0.040	0	0		0
Red Kidney beans	0.080	0	0		0
Blackeyed peas	0.170	0	0		0
Great Northern beans	0.020	0	0		0
Lima beans	0.010	0	0		0
Fresh Spearmint	0.020	0	0		0
Fresh Peppermint	0.010	0	0		0
Monthly total					**0**
Daily total					**0**
* Food ProcessorVersion 8.1, 2003, ESHA Research					
** 0.5= 1/2 portion 1.0= 1portion 1.5= 1 1/2 portion					
*** 1= once a month					
3= less than once a week					
6= 1-2 times/week					
14=3-4 times/week					
22= 5-6 times/week					
30= daily					
60= more than once/day					

APPENDIX G

3-DAY DIET RECORD SHEET

DIETARY INTAKE RECORD

Name: _____ Date: _____Weight (lbs): _____

TIME OF MEAL	FOOD ITEM	DESCRIPTION	AMOUNT

TIME OF MEAL	FOOD ITEM	DESCRIPTION	AMOUNT

TIME OF MEAL	FOOD ITEM	DESCRIPTION	AMOUNT

Supplements Taken – List brand, dosage (potency), number of tablets/amount:

APPENDIX H

DEFAULT FOOD ITEMS FOR DIET ANALYSES

Food Item	Food Processor Name	ESHA Code
SAUCES, OILS, JAMS, CONDIMENTS		
Alfredo Sauce	Alfredo Sauce-Cnd	9103
Balsamic vinegar	Vinegar, balsamic	53457
BBQ sauce	Sauce, barbecue, original	4936
Butter, regular		8000
Butter, unsalted	Butter, unsalted	8025
Caramel topping	Caramel topping	23070
Creamy garlic dressing	Salad dressing, Italian, garlic, creamy, rducd cal	8538
Curry sauce	Sauce, curry, prep f/recipe	53016
Dijon mustard	Mustard, dijon	27058
Extra virgin olive oil	Oil, olive, extra virgin	8361
Fat free ranch dressing	Salad dressing, ranch, fat free	8493
Ginger dressing	Salad dressing, lemongrass ginger	12931
Grape jelly	Jelly, grape (1T = 1 svg)	91451
Green sauce	Sauce, green	13486
Honey	Honey, strained/extracted	25001
Honey mustard	Mustard, honey, squeeze btl	92240
Hot Sauce	Hot pepper sauce	53470
Jelly	Jelly	23003
Ketchup	Ketchup	27000
Ketchup, packet	Ketchup, pkt	9153
Lemon juice	Juice, lemon, fresh	3068
Marinara Sauce	Marinara pasta sauce-jar	53336
Margarine	Margarine, hard	44966
Mayonnaise	Dressing, mayonnaise type	8021
Miracle whip	Dressing, miracle whip	8479
Miso sauce	Sauce, miso	7563
Mustard	Mustard, deli, squeeze btl	91811
Non-dairy creamer	Creamer, non-dairy	517
Oil and vinegar	Salad dressing, vinegar & oil, classic, D-5, FS	8191
Poppy seed dressing	Salad dressing, poppy seed, creamy	44949
Ranch dressing	Salad dressing, ranch	8555
Red Wine Vinaigrette	Red Wine Vinegar & oil dressing	8595
Salsa	Salsa	53676
Seasoned Salt	Season-all Seasoned salt	91928
Soy Sauce	Soy sauce f/soy	53063
Soybean oil	Oil, soybean	44893
Spicy brown mustard	Mustard, spicy brown	93388
Splenda pkt	Sweetener, sucralose, pkt, consumer use only	63253
Sriracha	Hot Chili Sauce f/Mature Red Peppers	92173
Strawberry jelly	Jelly, strawberry	23294
Sugar	White granulated sugar	25006
Sweet and Sour dressing	Salad dressing, sweet and sour	44701
Syrup, light	Syrup, pancake, light, rducd cal	25223
Teriyaki sauce	Marinade, teriyaki sauce	53004
Thousand island dressing	Salad dressing, thousand island	8024

Vegan mayonnaise	Dressing, mayonnaise, light, eggless	44859
Worcestershire Sauce	Worcestershire sauce	53099

BEVERAGES		
Aloe Vera Juice	Juice, aloe vera	7385
Beer, Amber Ale	Beer, Amber Ale	34066
Beer, Hefeweizen	Beer, Hefeweizen	22845
Beer, Light	Beer, light	22621
Chai tea	Tea, chai, original brewed w/water only	20883
Chamomile tea	Tea, herbal, chamomile, brewed	20118
Coffee	Coffee, brewed w/tap water	20012
Cola	Soda, cola	20147
Cranberry Juice	Juice, cranberry	4986
Creamer	Half and half	500
Diet Cola	Soda, cola, diet	20150
Diet Dr. Pepper	Soda, Dr Pepper, diet	4797
Dr. Pepper	Soda, Dr Pepper	4796
Green tea	Tea, green, brewed	20887
Herbal tea, caffeine free	Tea, herbal, caffeine free, brewed	20909
Hot chocolate		33290
Iced tea, Diet	Diet lemon iced tea w/Asp	20540
Iced tea, Sweetened	Sweetened lemon iced tea	21031
Iced tea, Unsweetened	Tea, iced, unswtnd, pitcher style, can/btl	20542
Izze Esque	Juice drink, lemon, sparkling	14127
Latte, lowfat	Latte w/lowfat milk	20668
Lemonade	Drink, lemonade	20745
Long Island iced tea	Mixed drink, Long Island iced tea	22568
Monster Energy Drink	Energy drink w/Caff & Vit B	63337
Protein Drink, Canned or Bottle	HiProtein Van Supplement Drink-Can/Btl	62795
Red wine	Wine, red	22501
Seltzer soda	Soda, seltzer	4791
Soy latte	Coffee, soy latte	20921
Sports Drink	Sports Drink-Btl	20142
Sports Drink, Blue	MountainBlast Sports Drink-Can/Btl	20560
Sports Drink, Lemon-Lime	Lemon-lime Sports Drink-Btl	20646
Sports Drink, Low Calorie	Low Calorie Fruit Sports Drink	62967
Sports Drink, Orange	Orange Sports Drink-Can/Btl	20561
Sugar free Red Bull	Drink, energy, sugar free, can	63628
Tap water	Water, tap	21134
Vitamin Water	Vitamin Supreme Juice	20718
Vodka	Vodka, 94 proof	22641
Whiskey	Whiskey, 80 proof	22670
White wine	Wine, white, med	22504

MEAT, EGGS, NUTS, SOY AND BEANS		
Almonds	Nuts, almonds, dry rstd, salted, whole	4571
Bacon	Cured bacon-microwaved	92207
Bean Burrito with Cheese	Bean Burrito w/cheese	57576
Beef, ground	Beef ground hamburger 20% fat- pan browned	58124

Black bean burger	Vegetarian meat, burger, soy, black bean & salsa	7718
Black beans	Beans, black, cnd	7168
Blueberry soy yogurt	Yogurt, soy, blueberry	71579
Carne Asada Steak	Beef skirt steak	58095
Cashews	Nuts, cashews, lightly salted, whole, svg	14504
Chicken Breast, Grilled, Diced	Grilled Chicken breast-Dice	81203
Chicken, Sauteed, Skinless	Chicken lt meat w/o skin- fried	15031
Chicken Breast, Baked	Original chicken breast-bkd, original, crispy	49168
Chicken Breast, breaded	Breaded chicken breast patty	81223
Chicken, Chipotle	Chicken thigh Broil/Fry w/o skin- roasted	15012
Chicken Strips, breaded	Chicken strips-breaded	81318
Edamame	Soybeans, edamame, ckd	9342
Egg, hard boiled	Hard Boiled Eggs, Lrg	19510
Egg, fried	Fried whole egg- Large	19509
Egg, fried in vegetable oil	Egg- fried with vegetable oil	19573
Egg, white, cooked	Egg whites-cooked	19522
Garbanzo beans	Beans, garbanzo, cnd	9982
Ham, deli sliced	Deli cooked ham lunchmeat	11814
Hot Dog, Beef	Beef hot dog	58153
Hummus	Spread, hummus	7081
Lamb	Lamb chop	13512
Lentil salad	Dish, rice pilaf, lentil, dry	38639
Light vanilla soy milk	Soy milk, vanilla, light	7779
Liquid eggs	Egg substitute, new	19581
Low fat vanilla soy milk	Soy milk, vanilla, low fat	21068
Mixed nuts	Nuts, mixed, deluxe	14358
Pastrami, beef, lunchmeat	Cured beef pastrami- thin slc	57955
Peanut butter	Peanut butter, natural, creamy	62944
Peanut butter, chunky, reduced fat	Peanut butter, crunchy, reducd fat (2T = 1 svg)	62939
Peanut butter, chunky, regular	Natural peanut butter, chunky	62945
Peanuts	Nuts, peanuts, dry rstd, salted (5.3 oz/cup)	4541
Pine nuts	Nuts, pine, pignolia, dried	4529
Pinto beans	Beans, pinto, cnd	7124
Pistachio	Nuts, pistachio, raw	4521
Pot Roast	Beef rib pot roast select Ln 1/4" tr-Rstd	10977
Protein Drink, Vanilla, Canned	HiProtein Van Supplement Drink	62795
Protein Powder, Soy	Soy Protein Powder-DryScp (1 scp [1/3 cup]=35g)	62696
Protein Powder, Whey	Vanilla Whey Protein Isolate Pwd (1/4 cup = 26.4g)	63320
Raspberry soy yogurt	Yogurt, soy, raspberry	71585
Refried beans	Dish, refried beans, cnd	7160
Roast Beef, Deli Sliced	Deli Medium Roast Beef Lunchmeat	11818
Salami	Genoa Salami	17344
Shrimp	Shrimp, mixed species, raw, med.	19125
Soy bacon	Vegetarian meat, Canadian bacon, soy, sliced	8838
Soy creamer	Creamer, soy milk, plain	54315
Soy latte	Coffee, soy latté, 11 fl. oz svg	20926
Soy meat	Vegetarian, protein, textured, TVP, Nutrisoy	52259
Soy milk, chocolate	Soy milk, chocolate	20920
Soy milk, plain	Soy milk, plain	20916
Soy nuts, salted	Soy nuts, salted	8877

Soy yogurt	Yogurt, soy	71572
Sunflower seeds	Seeds, sunflower	4038
Tofu	Tofu, firm	12888
Trail mix	Regular Trail Mix	44058
Tuna	Fish, tuna, light, w/water, chunk, cnd	19163
Turkey, deli sliced	Oven rst turkey breast lunchmeat- deli sliced	58173
Vegan mozzarella cheese	Cheese, substitute, mozzarella	13388
Vegetarian baked beans	Beans, baked, plain/vegetarian, cnd	7038
Vegetarian chicken	Vegetarian meat, protein, pces, svg	7528
Vegetarian ham	Vegetarian meat, veggie Ham, deli sliced, svg	91656
Vegetarian sausage	Vegetarian meat, sausage, breakfast links, fzn	57436
Veggie burger	Vegetarian meat, burger, Garden Veggie Patties, fzn	7722
Veggie griller	Vegetarian meat, burger, soy Griller	7751
Vegetarian chicken nuggets	Vegetarian meat, protein, nuggets, svg	8829
Walnuts, raw	Nuts, walnuts, English, dried, halves	4557
Whey protein	Protein, whey, conc	52260
White kidney beans	Beans, cannellini/white kidney, unsalted, cnd	9732
Yellowfish tuna	Fish, tuna, yellowfin, fillet, bkd/brld	17177

GRAINS		
Bagel	Bagel, plain, classic	8846
Banana Nut cereal	Cereal, Banana Nut Crunch	40278
Biscuit	Biscuit	9069
Blue corn tortilla chips	Chips, tortilla, blue corn	44301
Blueberry bagel	Bagel, blueberry	62740
Blueberry Morning cereal	Cereal, Blueberry Morning	40279
Blueberry muffin	Muffin, blueberry	8868
Broccoli and cheese rice	Dinner, rice, white & wild, broccoli & cheese sauce	57753
Brown Rice	Rice, brown, med grain, ckd	38082
Butter Croissant, small	Butter croissant-sml	71298
Cereal Bar, Strawberry	Strawberry filled cereal bar	40253
Couscous	Couscous, ckd (1/2c = svg)	38076
Dinner roll	Rolls, dinner, lrg	71351
English muffin	English muffin	28146
Flaxseed, ground		63636
Flour tortilla, x-large	Flour tortilla, rtb, 12" (4 oz) = 3C	90650
Flour tortilla, large	Flour tortilla, rtb, 10" (2.54 oz) = 2.5C	42025
Flour tortilla , medium	Tortilla, flour, rtb, 7" to 8" (1.73 oz) = 1.75C	42026
Flour tortilla, taco size	Tortilla, flour, soft taco	42703
Fried rice	Fried rice w/bean sprouts & scallions	23938
Granola bar	Bar, granola, oats 'n honey (1C)	47592
Granola bar, chocolate	Chewy chocolate chip granola bar	47103
Granola	Oats & Honey Granola	61528
Hamburger bun	Buns, hamburger	42020
Hot dog bun	Hotdog/frankfurter bun	42021
Kashi cereal	Cereal, Autumn Wheat	61388
Oatmeal, blueberry	Cereal, hot, oatmeal, blueberry, inst, pkt	14288
Oatmeal, plain	Cereal, hot, oatmeal, plain, inst, pkt	40468
Oatmeal, dry	Quick hot oats oatmeal-dry (20g=1C)	40467
Pancake, blueberry	Pancakes, blueberry, prep f/recipe, 6"	45118

Pancakes	Pancakes, plain, prep f/recipe, 6"	45117
Panini/Ciabatta bread	Italian bread- med slc	71219
Peanut butter granola bar	Soft peanut butter granola bar	23108
Pita bread	Bread, pita, white, unenrich, 6 1/2" (2.12 oz)	42286
Popcorn	Popcorn, low fat, microwave	14973
Pretzels, tiny twists, classic	Pretzels, tiny twists, classic style	14390
Puffins Peanut Butter cereal	Cereal, Puffins, peanut butter	61495
Rice cake	Rice cake, plain	44016
Rye bread	Bread, rye, Jewish	72292
Shredded Wheat cereal	Cereal, Shredded Wheat, spoon size	40287
Sourdough	Bread, sourdough, med slice	71210
Spanish rice	Dish, rice, spanish	53670
Strawberry Fields cereal	Cereal, Strawberry Fields	61389
Sun Chips, French onion	Snack, multigrain, french onion, svg	44257
Taco salad shell	Taco Salad Shell	13474
Taco shells	Taco shells	71544
Tater tots	Tater tots, abc's, fzn	70598
Top Ramen	Soup, Ramen noodles, miso flvr, dry pkg	91729
Tortilla Chips		44264
Tortilla, corn	Tortilla, corn, white, 6”	33419
Tortilla chips, plain		53695
Tortilla Chips, Doritos	Nacho flavored tortilla chips (1 oz= 12 chips)	44005
Triscuit crackers	Crackers, whole wheat, original	43584
Vanilla Almond cereal	Cereal, Shredded Oats, Vanilla Almond	61488
Waffles, whole grain	Waffles, 8 grain, fzn	12460
Wheat crackers	Crackers, wheat, original	43581
Wheat dinner roll	Rolls, dinner, wheat	42160
Wheat hoagie roll	whole wheat hoagie roll-med (3.32 oz)	71358
Wheat pita bread		42080
White bread	Bread, white, hearty	42475
White rice	Rice, white, long grain, ckd	38013
White sub roll, 5"-6"	Italian /white bread-6" SUB (2.5 oz)	91792
Whole grain bread		62798
Whole grain bread, ezekiel	Bread, sprouted, whole grain, flourless, svg	72930
Whole wheat bread	Bread, whole wheat, 100%	72301
Whole wheat pasta	Pasta, macaroni, whole wheat, ckd	38110
Whole wheat tortilla	Tortilla, whole wheat (1.65 oz) = 1.7C	71938
Wild long grain rice	Dish, rice pilaf, long grain & wild, dry	38614
Yakisoba noodles	Japanese soba noodles	38094

DAIRY		
American cheese	Cheese product, American, past, proc, slice	47824
Cheddar cheese, sliced	Cheddar cheese-slc	47864
Cheddar cheese, shredded	Cheddar chesse-shredded	1008
Cheese, mixed	Cheese, cheddar & monterey jack, shredded	47771
Chocolate ice cream, low fat	Ice cream, chocolate, 98% fat free	72151
Colby cheese, slice	Cheese, colby jack, slice	47784
Colby and Jack cheese, shredded	Colby & Monterey Jack cheese-Shred	1333
Cottage cheese	Cottage cheese, 1% fat	1047
Cream cheese	Cream cheese	1015

Cream cheese, low fat	Cream cheese low fat	1098
Fat free half and half	Cream, half and half, fat free	54378
Feta cheese	Cheese, feta, crumbled	1238
Goat cheese	Cheese, goat, hard	1078
Half and Half	Cream, half and half	500
Light Swiss cheese	Cheese, wedge, creamy swiss original light	48339
Milk 1%	Milk, 1%, w/add Vit A & D	4
Milk 2%	Milk, 2%, w/add vit A & D	2
Milk-skim	Milk, nonfat/skim, w/add Vit A	6
Milk-whole	3.25% whole milk	1
Mixed berry ice cream, low fat	Ice cream, strawberry, old fash, low fat	1738
Mozzerella Cheese, shredded		1058
Parmesan cheese	Cheese, parmesan, dried, grated	1252
Pepper Jack Cheese		48294
Provolone cheese	Cheese, provolone, slice	47900
Pudding, banana	Pudding, banana, snack cup	57989
Sour cream	Sour cream	555
Soy butter	Butter substitute, plain, soy, vegetarian	90961
Soy cheese	Cheese substitute, cheddar, soy	47983
String cheese, Low Fat	Cheese, mozzarella, string, low moist, part skim	48255
Swiss cheese	Cheese, swiss, aged, Deli Thin, slice	48245
Vanilla frozen yogurt	Frozen yogurt, vanilla	71517
Vegan cheddar cheese	Cheese substitute, cheddar	13387
Vegan sour cream	Sour cream sub, Sour Supreme, Better Than (3T = 1 oz wt)	13697
Yogurt, blueberry	Yogurt, blueberry mist, lowfat, indv	72536
Yogurt, lemon custard	Lowfat lemon burst yogurt	72506
Yogurt, peach	Yogurt, peach cobbler, lowfat	72467
Yogurt, strawberry	Lowfat classic strawberry yogurt	72809
Yogurt, strawberry, fat-free	Light Nonfat Strawberry Yogurt	13350
Yogurt, vanilla	Lowfat Vanilla Yogurt	2015

VEGETABLES		
Artichoke	Artichoke, French, ckd, drained, med	4436
Artichoke heart	Artichoke, hearts, w/water, cnd	319
Asparagus	Asparagus, cnd, drained, 5" long	5007
Avocado	Avocado, medium	3658
Baby potatoes	Potatoes, white, baby, ckd	9366
Beet	Beets, fresh, whole, 2"	5572
Broccoli	Broccoli, florets, fresh	5556
Broccoli, cooked	Broccoli chopped cooked	5028
Broccoli, sauteed	Stir fried broccoli	5654
Brussel sprout	Brussel Sprouts, fresh	5032
Cabbage, red	Cabbage, red, fresh, chpd	6766
Carrot	Carrots, fresh, lrg, 7 1/4" - 8 1/2" long	90423
Carrots, baby	Carrots, fresh, baby, med (14 ea = 1 cup)	5439
Carrots, shredded	Carrots, fresh, grated	5046
Carrots, sliced (4.2 oz/cup)	Smooth sliced carrots	1799
Carrots, whole, cooked	Whole carrots cooked-drnd (1F=78g)	5048
Celery stalk	Celery, stalk, fresh, med	5704
Cherry tomatoes	Tomatoes, red, cherry, fresh, year round avg	90530

Coleslaw	Cole Slaw, classic	69200
Corn on the cob	Corn, cob, 5.5", Simply Sweet, 80% ckd, iqf, FS	1812
Cucumber	Cucumber, fresh, med	5705
Cucumber, sliced (6 slices=.33 cup)	Fresh sliced cucumber w/peel	5071
Fennel bulb	Fennel, bulb, fresh	5449
French Fries, medium	French fries, medium (1 med=1.5 cup)	81439
French Fries, small	French fries, small	81438
French Fries, Waffle	Waffle French Fries, Sml (Med=1.5, Lrg=2)	7973
Frozen Vegetables	Vegetables, fzn	6391
Garlic	Garlic, cloves, fresh	26005
Green beans	Snap beans, green, cnd, drained	6750
Green beans, cooked	Green snap beans ckd w/salt-drnd	5856
Green bell pepper, chopped	Peppers, bell, green, sweet, fresh, chpd	5124
Green bell pepper, medium	Fresh green bell pepper-med (1/2 ea=1F)	6846
Iceberg, leaf	Fresh Iceberg Lettuce-Med Leaf (7 leaf=1F)	90446
Iceberg, shredded	Shredded iceberg lettuce	9316
Kale (4oz) = 1 bunch?	Cabbage, kale, fresh, chpd (1 stalk = 1 cup)	5208
Kettle potato chips	Chips, potato, original, svg	14316
Lettuce, Shredded	Shredded Lettuce Leaf	9328
Mashed potato	Mashed Potatoes, fast food	6185
Mushroom	Mushrooms, brown, fresh	440
Mushroom, Diced, Cooked	Mushroom pieces- stir fried w/o oil	5658
Mushroom, Sliced, Raw		5090
Onion, chopped	Onion, white, fresh, chpd (1/2 cup = 68.8g)	5101
Onion, white, cooked	White onion cooked drained whole-med (1F=105g)	5110
Onion, white, sliced	Fresh whit onions med slce-1/8" (5slices=1F; .5 cup=68g)	90460
Peas, frozen	Peas, green, ckd f/fzn, drained	5118
Pico de gallo	Salsa, pico de gallo (1 svg = 1/2 c)	28103
Potato	Potatoes, baked, med, 2 1/4" to 3 1/4"	5334
Potato chips	Chips, potato, original, svg	44236
Potato chips, BBQ	BBQ potato chips	61064
Potato, diced, cooked	Peeled potato, diced-ckd	5136
Radish	Fresh red radish- med (2 ea=1F)	5143
Red Bell Pepper, medium	Peppers, bell, red sweet, med 2 3/4" x 2 1/2"	6989
Red Bell Pepper, sliced	Peppers, bell, red sweet, fresh, sliced (61g=1/2 cup)	5295
Red onion	Onion, red, fresh, med slice, 1/8" (5sl=1F;.5cup=68g)	90465
Romaine lettuce	Lettuce, romaine, fresh, leaf	9331
Salsa	Salsa, prep from recipe	27020
Salad	Salad, leaf & romaine	69204
Snap peas (2.2 oz/cup)	Peas, sugar snap, stir fry blend, 80% ckd, iqf, FS	1845
Spinach, chopped	Spinach, fresh, chpd	5146
Spinach leaves, fresh	Fresh spinach leaves	6863
Sprouts	Sprouts, alfalfa, fresh	5010
Sweet potato	Sweet potato, dark orange, fresh, 5"	5809
Tomato	Tomatoes, fresh, med	5718
Tomato, diced	Fresh red tomatoes YearRoundAvg-Chpd/Slc	5170
Tomato, sliced	Fresh Red Tomatoes YrRndAvg Med Slc-1/4"(5 slices=1F)	5173
Tomato sauce	Tomato sauce, cnd	5180
Vegetables, mixed, thai blend	Thai stirfry mixed vegetables (1/2 cup= 2oz)	9670

Vegetables, roasted	Vegetables, peppers & onions, flame rstd, 80% ckd, iqf, FS	715
Zucchini	Squash, zucchini, baby, med, fresh	90604

FRUIT		
Apple, Large	Fresh Apples w/Peel-Lrg 3 1/4" (1.5F)	3001
Apple, Medium	Apples, fresh, med, 3"	3000
Apple, Small	Fresh apples w/peel-sml 2 1/2" (.75F)	71077
Apple juice	Juice, apple	793
Applesauce	Applesauce, gravenstein, unswtnd, cnd	3924
Apricot, fresh	Apricots, fresh, whole	14909
Apricots, dried	Apricots, dried	71688
Avocado, medium	Avocado, fresh, med, FDA	3852
Banana, large	Fresh lrg banana-8" to 8 7/8" long (1.25F)	3659
Banana, medium	Banana, fresh, med, 7" to 7 7/8" long	3020
Blackberries	Blackberries, fresh	3024
Blueberries	Blueberries, fresh	3029
Blueberries, frozen	Blueberries-fzn	9647
Cantaloupe	Melon, cantaloupe, fresh, cubes	3075
Cherries	Cherries, fresh	3373
Cranberries	Cranberries, fresh, whole	3039
Cucumber	Cucumber, fresh, med	5705
Cucumber, sliced	Fresh sliced cucumber w/peel (52g=1F;6 sli=.25cup)	5071
Dates, fresh	Dates, fresh	3374
Frozen peaches	Peaches, sliced, fzn	9650
Fruit leather	Fruit leather, sunberry burst	61581
Fruit salad	Salad, fruit, chilled, FS	52010
Grapes	Grapes, fresh, FDA (8 ea = 1/2 c)	3844
Grapefruit	Grapefruit, pink 3 ¾”	4888
Grape Juice	Concord grape juice	4985
Guava	Guave, fresh	3634
Honeydew	Melon, honeydew, fresh, 5 1/4"	71102
Kiwi	Kiwi, fresh, med, FDA (6.2 oz/cup) (2 ea=1F)	3858
Lemon	Lemon, fresh, med, FDA	3853
Lime	Limes, fresh, med, FDA	3857
Mango	Mango, fresh (5.82 oz/cup)	71980
Mango, frozen	Mango, chunks, fzn	9801
Nectarine	Nectarines, fresh, med, FDA	3849
Olive	Olives, black, large, cnd	27009
Orange	Oranges, all types, fresh, med, 2 5/8"	3082
Orange, small		3086
Orange juice	Juice, orange	1854
Orange juice with Calcium	Orange juice w/Calcium	3480
Peach	Peaches, fresh, med, FDA	3847
Pear	Pears, fresh, asian, 2 1/4" x 2 1/2"	3272
Pineapple	Pineapples, chunks, cnd, w/water	3737
Pineapple/orange/banana juice	Juice, pineapple orange banana, rtd	3992
Plum	Plums, fresh, med, FDA	3851
Raspberries	Fresh	3648
Strawberries	Strawberries, fresh, med, FDA (3 whole=1/4 cup)	3846
Strawberries, frozen	unsweetened strawberries-fzn (75g=1F)	3137

Tangerine	Tangerines, fresh, med	71989
Watermelon	Watermelon, diced, fresh	3385

MISCELLANEOUS		
Apple cinnamon toaster pastry	Pastry, apple cinnamon, toaster style	12455
Artichoke and spinach bites	Dish, ravioli, spinach and artichoke filled, brd, FS	60769
Bean Burrito w/cheese	Bean burrito w/cheese (5C)	57576
Bean and Rice Burrito	Organic bean & rice burrito-fzn	83097
Beef Taco		56642
Broccoli and cheddar soup	Soup, broccoli cheddar cheese, rts, cnd	50895
Broccoli soup	Soup, broccoli, creamy	1790
California Roll	California Sushi roll	91813
Cheeseburger	Cheeseburger plaing-lrg	56648
Cheese & spinach tortellini	Dish, pasta, tortellini, spinach cheese, refrig	83187
Cheese quesadilla	Quesadilla, cheese	12866
Chicken Quesadilla	Chicken Quesadilla (2.5C)	72589
Chicken Soft Taco	Chicken Soft Taco (1C,.5F)	7204
Cheez-It reduced fat	Crackers, cheese, rducd fat (10ea = 1 svg)	43812
Chex Mix	Snack, mix, bold party blend	44205
Coconut milk	Coconut, milk, fresh	4528
Corn Dog	Corn dog (1.5C)	56668
Crab cakes	Crab cakes, make w/blue crab	19420
Curry dinner	Dish, tofu w/sour curry, Thai, prep f/recipe, svg	2997
Egg roll	Dish, egg roll, vegetable, ckd	15272
Falafel	Dish, falafel, prep f/recipe, patty, 2 1/4"	16138
French Fries		23958
Grilled cheese sandwich	Sandwich, cheese, grilled	12818
Guacamole	Guacamole, California	44423
Instant breakfast shake	Instant Breakfast, French vanilla, no sug add, rtd, cnd	14722
Lasagna	Stouffer's	21501
Luna Bar, nutz over chocolate	Bar, energy, nutz over chocolate	43709
Macaroni & cheese	Dish, macaroni & cheese	56681
Minestrone soup	Soup, minestrone	4835
Mocha w/soy, small	Coffee, mocha, w/soy milk	20923
Pad Thai vegetarian	Dish, pad Thai, w/rice noodles, vegetarian, rth	92069
Pickle, sandwich slice	Pickles, bread & butter, sandwich slice	9688
Pizza for one	Pizza, cheese, for one, fzn (2.25C,.5F)	56782
Pizza, cheese, large	Cheese 16" large Pizza- slice (2C, .5F)	831
Pizza, cheese, med	Pizza, cheese, med, 12" (1C, .25F)	56485
Pizza, chicken,grn pepper & onion	ChickenOn&GrnPpr 12"med slice (1C, .5F)	92479
Pizza, individual 6"	Pizza, cheese, 6"	57787
Pizza, pepperoni, 14"	Pepperoni 14" Lrg pizza-slc (1C,.25F)	92458
Pizza, pepperoni, 1/6 of 12"	Pepperoni pizza- 1/6 of 12" (1.25C, .25F)	90795
Pizza, pepperoni, 12", med	Pepperoni pizza- 12" slice (.9C, 2 slices=.25F)	56490
Pizza, spinach mushroom garlic	(1.25C, .75F)	90787
Pizza, thin crust	Pizza, cheese, thin crust, 14"	93262
Pizza, veggie	Pizza, Veggie Lover's, med, 12" (1.5C,1.25F)	57811
Potato chips		53695
Potato salad	Salad, potato, picnic, FS	4842
Spaghetti with meatballs	Canned	92765

Spring roll	Dish, spring roll, vegetable, Thai, prep f/recipe	2995
Subway veggie sandwich, 6"	Sandwich, veggie delite, w/white, 6"	69109
Tortilla soup	Tortilla soup w/toppings (1C,1F)	50713
Vegetable burrito	Burrito, veggie	56620
Vegetable lasagna	Dish, lasagna, vegetable, Mona's, FS	57841
Vegetable quiche	Dish, quiche, spinach, vegetarian	57514
Vegetable sandwich, grilled	Sandwich, rstd vegetable, pocket, fzn	81193
Vegetable soup	Soup, vegetable, vegetarian, cond, cnd	50509
Vegetable summer rolls	Thai vegetable spring roll (1C,.5F)	2995
Vegetable stir fry	Dish, stir fry, rice & veg	70470
Vegetarian baked beans	Beans, baked, plain/vegetarian, cnd	7038
Vegetarian bratwurst	Vegetarian meat, sausage, bratwurst	91495
Vegetarian chili	Chili, vegetarian, cnd	7609
Vegetarian corn dog	Corn dog, vegetarian, fzn	8869
Vegetarian sushi roll	Sushi, vegetarian roll	92384

DESSERT		
Baby Ruth, Funsize	Candy bar, Baby Ruth, fun size	23269
Brownie (2" square)	Brownie, 2" square, fast food	47150
Butterfinger, Funsize	Candy bar, Butterfinger, fun size	23067
Carob cookies	Cookies, carob	47076
Carrot cake	Cake, carrot	12760
Chocolate cake with frosting	Cake, chocolate, w/chocolate icing, 1/8th of 18oz	16392
Chocolate chip cookie	Cookies, chocolate chip	47520
Chocolate, Dark	Candy, dark choc	92662
Fortune cookie	Fortune Cookie	91667
Frozen Yogurt, Chocolate	Frozen yogurt, chocolate, nonfat	72784
Frozen Yogurt, Vanilla	Vanilla frozen yogurt soft serve	2064
Ice Cream, Cookies & Cream	All Nat Cookies N cream ice cream	71482
Ice Cream, Vanilla	Vanilla ice cream	2004
Kit Kat	Candy bar, Kit Kat, 1.5oz bar	23060
Licorice	Candy, licorice	92656
M & M candies	Candy, milk chocolate	23045
Mango ice cream	Ice cream, mango	72700
Oatmeal chocolate chip cookie	Cookies, oatmeal, w/choc chip	92327
Oatmeal cookie	Cookies, oatmeal raisin	47656
Popsicle, cherry	Frozen dessert pop, cherry	72238
Rice Krispies Treats	Rice Krispies Treats, squares	44219
Shortbread cookie, sugar free	Cookies, shortbread, sugar free	93010
Skittles candies	Candy, Skittles, original, bite size	23431
Small banana split	Frozen dessert, banana split, sml	72140
Sorbet	Sorbet, strawberry	49197
Sugar, brown		19334
Tootsie, lollipop	Candy, hard, lollipop, Tootsie Pop, asrtd flvrs, mini	92708