THE EFFECTS OF FLAXSEED ON THE GLUCOSE PROFILE IN NATIVE AMERICAN POSTMENOPAUSAL WOMEN

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DEDICATION

My thesis is dedicated to three circles of special people in my life. Firstly, to my beloved parents for giving me life in the first place, for molding me in to a sensible human being, for their effective counseling in my times of despair and for their unconditional love and support to pursue my aspirations when they went ahead of the limitations of language, culture and countries. Secondly, to my dearly loving friend Dr. K. Andy Prasad, a source of my inspiration and who is always there to listen to my complaints, frustration and confusions. His compassionate words offered me so much comfort in times of loneliness. Thirdly, to the Ford Foundation for its exceptional contribution to the outstanding individuals who require absolute access to higher education in the developing countries.

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TABLE OF CONTENTS

LIST OF TABLES

Table Pages

NOMENCLATURE

Adult Treatment Panel	ATP
Behavioral Risk Factor Surveillance	BRFS
Body mass index	BMI
Carbohydrate	CHO
Cardiovascular disease	CVD
Central nervous system	CNS
Complementary alternative medicine	CAM
Estrogen receptor	ER
Expert Panel	OEI
Fasting blood glucose	FBS
Food and Drug administration	FDA
Free fatty acids	FFA
Generally recognized as safe	GRAS
Glucose transporter	GLUT
Hepatocyte nuclear factor	HNF
High density lipoprotein	HDL
Homeostasis assessment model of insulin resistance	HOMA-IR
Hormone Replacement Therapy	HRT
Hormone sensitive lipase	HSL

Impaired glucose tolerance	IGT
Indian Health Service	IHS
Indulin dependent diabetes mellitus	IDDM
Instititutional Review Board	IRB
International Diabetes Foundation	IDF
Low density lipoprotein	LDL
Maturity onset diabetes of the youth	MODY
Mitochondrial syndrome	MLEAS
National Cholesterol Education Program	NCEP
National Heart, Lung Blood institute	NHLBI
Non insulin dependent diabetes	NIDDM
Non-esterified free fatty acids	NEFFA
Proliferator-activated receptor gamma expression	PPAR
Secoisolarirecinol diglucoside	SDG
Sex Hormone Binding Globulin	SHBG
Strong Heart Study	SHS
Total Triglyceride	TGL
Tumor necrosis factor	TNF
Visceral adipose tissue	VAT

CHAPTER I

INTRODUCTION

Currently, it is estimated that over 6.3 million men and 8.7 million women in the US have diabetes (1). Furthermore, the prevalence of diabetes in US is higher among the minority ethnic populations than whites (2) and it is one of the major causes of mortality and morbidity in American Indians (3). Approximately 38 to 72% of the Native Americans with diabetes are from Oklahoma, South Dakota, North Dakota (2). It is excessively affecting women than in men (4) and there are reports (5-8) suggesting that age associated with menopause has adverse effect on lipid metabolism and visceral obesity which both contributes to the development of insulin resistance and type 2 diabetes. Although, hormone replacement therapy (HRT) alleviates postmenopausal symptoms (9), reduce bone resorption (10), rheumatoid arthritis (11) and schizophrenia (12), decrease the risks of cardiovascular disease (CVD) (13) its effect on carbohydrate metabolism is less clear (14). However, maintaining near-normal blood glucose level can retard the progression of diabetes-associated macro vascular complications (5, 16). Diet restriction, modest exercise, lifestyle interventions, and pharmacotherapy even though maintains near normal glycemic profile in diabetics but, sometimes may not succeed (17).

It is also affirmed that prolonged usage of antidiabetic drugs can produce adverse effects such as hypoglycemia, weight gain, lactic acidosis and flatulence (18, 19).

Therefore, women in developed countries such as those living in the US and West European countries can particularly benefit from the use of complimentary and alternative medicine (CAM)such as functional foods and dietary supplements in order to prevent and/or reduce chronic diseases including but not limited to diabetes, cardiovascular disease, and osteoporosis (20).

Although there are a number of studies that have shown the effectiveness of lignans and isoflavones in preventing cancer, there are a limited number of studies that suggests (20) phytoestrogens may play a role in the treatment of obesity and diabetes. Isoflavones**,** lignans**,** and coumestans (coumestrol) are the three major classes of phytoestrogens. Phytoestrogens are diphenolic compounds found in plants that is similar in structure to estrogens found in humans (21, 22). Phytoestrogens are often considered in broader terms, referring to compounds that exert hormonal effects including binding to the estrogen receptor (ER), induction of specific hormone-responsive gene products, and inhibit stimulation of ER-positive cancer cell growth (21, 22).

Lignans, another type of phytoestrogens, are found in a wide range of plant foods with flaxseed being the most concentrated source. When plant lignans and isoflavones reach the gut, they are structurally modified by colonic microflora to mammalian lignans and isoflavonoids (23). It has been suggested that isoflavones and lignans may have a protective role as antipromotional compounds during growth of hormone-dependent cancers. In vitro*,* lignans and/or isoflavones have been shown to inhibit estrogen synthesis, bind to estrogen receptors, and inhibit estradiol-stimulated breast cancer cell growth (24-27). Furthermore, lignans may increase sex hormone binding globulin

(SHBG) synthesis suggesting that lignans can reduce the biological activity of the sex steroid hormones by lowering the concentrations of the free fractions (28). In humans, there is some evidence of an association between phytoestrogens, endogenous sex steroid hormones, and hormone-dependent cancers (21). Studies (21, 29-31) have reported that postmenopausal women with breast cancer, as compared to omnivorous and vegetarian controls, excrete lower amounts of urinary lignans. Significant positive correlations have been observed between urinary total lignans, and plasma sex hormone binding globulin (SHBG) concentrations, while negative correlations between lignans and plasma free-estradiol concentrations have been reported (32). In terms of cancer studies, quantity of flaxseed consumed or length of dietary flaxseed intervention could be important modulators in controlling SHBG secretion and/or estrogen bioavailability and the outcome of the investigation.

There are also a small number of studies in which the positive effects of these compounds on carbohydrate metabolism have been investigated (20). In terms of wholefood, flaxseed (a rich source of lignans) with estrogenic (33), anti estrogenic (34), antitumergic (35), and antioxidant (36) properties may also be effective in normalizing blood sugar levels. Therefore, we hypothesized that daily consumption of flaxseed has a beneficial effect on the glucose status of postmenopausal women. This hypothesis is based on two lines of observations: 1) ovarian hormone deficiency due to menopause negatively affect glucose status and increase the risk of diabetes in women (5-8, 2) lignanic compounds present in flaxseed have resemblance to 17β-estradiol (20) that somehow mimics the action of estrogen in improving the glycemic profile of postmenopausal women (5-8, 20). To my knowledge, the present study is the first to

investigate the effect of intake of ground flaxseed on the glucose status of the Native American postmenopausal women.

Hypothesis and specific aims:

The hypothesis of this study was that the daily consumption of flaxseed improves the glycemic profile in Native American postmenopausal women. To test this hypothesis we had two specific aims as follows:

Aim 1: To determine the extent to which the daily consumption of an approximately 30 g flaxseed regimen reduces fasting blood glucose and glycated hemoglobin levels in Native American postmenopausal women.

Aim 2: To determine the extent to which the daily consumption of an approximately 30 g flaxseed reduces fasting insulin levels in Native American postmenopausal women.

CHAPTER II

REVIEW OF LITERATURE

Prevalence of Diabetes among Native Americans in the US

Diabetes poses a significant health problem in the US. It is estimated that 6.3million men and 8.3 million women have diabetes (1). Epidemiological data show that, diabetes is disproportionately affecting the minority and disadvantaged population in the westernized countries (37). Diabetes in the US is 2-6 times greater in minority ethnic groups such as Blacks, Hispanics, and Native Americans than whites (38).

Recent data from Indian Health Service (HIS), Behavioral Risk Factor Surveillance System (BRFSS) (39) indicate that the incidence of diabetes is alarming among the Native Americans and Alaskan Natives. An epidemiological study (40) also has found similar trends in prevalence of diabetes among Native Americans and Alaskan Natives in the Atlantic, Alaska, Northern Plains, Southern plains and South West region. The findings of this study (40) have indicated a tremendous increase in the number of diabetic cases among Native Americans and Alaskan Natives from 43,262 to 64,474 during the 8 year period of the study (1990-1997). There was also a significant increase in prevalence of diabetes by 76% in Alaskan region and 28 to 37% in other regions. Additionally, it was documented that the prevalence of diabetes mellitus (DM) was more prevalent in women compared to men in all the regions. Forty-nine percent of the diabetic Native

Americans and Alaskan Natives were in the age group of 45-64 years. Since, this study was a cross sectional study, the variables for the increased prevalence of diabetes was not determined. According to many population–based studies, it was well recognized that the adaptable risk factors such as obesity, physical inactivity, and exposure to diabetes in uterus increase the risk of diabetes (40, 41). In Native Americans, obesity is highly prevalent and this is associated with increased risk of glucose intolerance and diabetes in this population (42).

Similar findings were reported by The Strong Heart Study (SHS) (3). The main objective of that study was to determine the incidence and factors that increase the risk of diabetes in Native American population. The incidence of diabetes increased excessively in Native Americans aged between 45 and74 years residing in the regions of Arizona, Oklahoma, South and North Dakota. The results indicated that the participants who had higher body mass index (BMI), with higher waist to hip ratio, fasting glucose and fasting insulin levels at baseline developed diabetes during the study. Also, the participants who had, impaired glucose tolerance (IGT), high percentage body fat, total triglyceride (TGL), Albumin urea and lower levels of HDL, apoprotein A1 develop diabetes. Additionally, the incidence of diabetes was higher in women than men. The results also indicated that diabetes was one of the major causes of morbidity and mortality among the Native American population (3). Other studies (38, 43)have also identified diabetes to be the leading cause for the micro vascular such as neuropathy (44), nephropathy (45) and macro vascular complications such cardio myopathy (44) and neuropathy as those seen in Native Americans, Mexican Americans, Pima Indians, and Hispanics. The SHS (43) findings also suggested that diabetes is one of the underlying risk factors for coronary

heart disease in Native Americans in Oklahoma, South Dakota, North Dakota and with its prevalence being greater by 2 to 3 times than other regions of the country. A cohort study intended to determine the mortality rate and causes of death in 1012 non-insulin dependent diabetic Native Americans in Oklahoma showed that the mean annual mortality rate was higher in diabetic Oklahoma Indians than the general population with and without diabetes(46). The above findings suggest that diabetes is the underlying risk factor for the excess mortality and morbidity rates among the Native American population.

In short, the reasons for the higher prevalence of diabetes among the minorities are diet (e.g. high calorie, high fat diet) (47), life style factors (e.g. physical inactivity, alcohol intake) (48, 49), and genetic predisposition (50).

Risk Factors for Diabetes

Metabolic syndrome and diabetes

Non insulin-dependent diabetes (NIDDM) is accelerating in both developing and developed nations and disproportionately affecting ethnic groups such as Native Americans, African Americans, and Mexican Americans (51). Diabetes is associated with both micro-vascular related disorders, e.g. retinopathy, nephropathy,and neuropathy and macro-vascular complications, e.g. cardiovascular and cerebrovascular diseases. Cardiovascular disease (CVD) is the leading cause of death in ethnic groups suffering from type 2 diabetes (52). Acording to the National Survey Data (53), metabolic syndrome is the underlying risk factor for the development of CVD and NIDDM in the US and is affecting 25% of adults aged between 20 to 70 years and also

affecting ethnic groups such as Mexican Americans (32%), African Americans (22%) and other racial ethnic groups (20%). Metabolic syndrome is increasing the risk of CVD and NIDDM by 2 to 3 fold.

Metabolic syndrome is a group of metabolic abnormalities such as visceral obesity, dyslipidaemia, glucose intolerance, impaired fasting glycemia, insulin resistance, hypertension that alters glucose and lipid homeostasis and increase the risk of NIDDM and CVD (54). In 1988, it was identified by Kim and Reaven (55) thatinsulin -resistance played a key connecting role in the development of metabolic abnormalities and it was determined as a major tool to identify individuals at greater risk of CV. Hence, metabolic syndrome is, otherwise, known as insulin-resistance syndrome or syndrome X or deadly quartet. A conspicuous increase in the prevalence of metabolic syndrome has been observed for the past two decades, but at the same time it has been coupled with worldwide rise in obesity and NIDDM (56). Recently, there is evidence that it is obesity and not insulin-resistance that plays a detrimental role in influencing other metabolic abnormalities that constitute metabolic syndrome (57-60). The Italian Longitudinal Study on Aging which was conducted during 1992 to 1996 intended to investigate the affiliation between the variables of metabolic syndrome and their impact on the development of NIDDM. The study was conducted employing 2295 subjects aged between 65-84 years. This was the first study to utilize factor analysis to find out the underlying risk factor for the cluster of the metabolic abnormalities. This study recognized new factors such as body mass index (BMI), waist circumference (indicators of obesity) that overlie with lipid, insulin, blood pressure, glucose factors in both sexes. It was documented that 3.8% of men and 6.0% of women who were non diabetic at baseline became diabetic during the

four-year period of this study. Body size factor was positively associated with development of metabolic syndrome (59). Therefore, it has been recently justified that prevalence of obesity and its associated risk factors form the cluster of metabolic syndrome (61).

Accordingly, based on this concept several definitions were framed depending on a set of criterion such as visceral obesity, dyslipidaemia, glucose intolerance, impaired fasting glycemia, insulin resistance, and hypertension by World Health Organization (WHO) consultation (62), National Cholesterol Education Program: Adult Treatment Panel III (NCEP ATP III) (63), and European Group for the Study of Insulin Resistance (64). Nevertheless, each definition does have the same opinion on some variables but fluctuate on some others. For instance, the NCEP ATP III and International Diabetes Federation (IDF) do not include glucose intolerance tolerance and insulin resistance in the set criteria and mainly emphasize on obesity and its importance in the predisposition of many metabolic abnormalities (65). In 2004, a new definition was framed by International Diabetes Federation (61), with the following recommendations: "Central obesity considered by waist circumference and is ethnicity specific, in addition the presence of any two of the following variables for instance raised triglycerides (> 150mg/dl or 1.7 mmol /L), elevated blood pressure (systolic ≥ 130mm Hg and diastolic ≥ 85 mm Hg), raised fasting plasma glucose (≥ 100 mg/dL or 5.6 mmol/L) represent metabolic syndrome".

The mechanism by which obesity involves in developing insulin-resistance and other metabolic abnormalities is by the distribution of fat. The excess accumulation of fat in the visceral adipose tissue drains free fatty acids (FFA) into the portal vein (66). This

causes increase in the plasma concentration of the FFA leading to ectopic fat storage (fat in liver, muscle) (67).Thus elevations of FFA induce insulin resistance by hampering hepatic insulin clearance (68).This inhibits insulin mediated uptake of glucose by skeletal muscle and causes intramyocellular accumulation of triglycerides and diacylglycerol (67). Thus, elevated intramyocellular lipid levels slow down insulin signaling molecules and reduce the insulin mediated glucose transport into the muscle by down regulating insulin responsive glucose transporter (GLUT4) (69) and inhibits suppression of hepatic glucose production and results in hyperglycemia and insulin resistance (70) and dyslipdaemia (65). Insulin resistance has been reported to occur due to obesity/ FFA which can induce-hypertension by stimulating the sympathetic nervous system leading to high concentrations of noradrenalin which is a vasoconstrictor and causes hypertension (71). Thus, obesity, distribution of fat, concentration of FFA allengage in the a ccrual of metabolic abnormalities to form metabolic syndrome that leads to pathogenesis of NIDDM and CVD.

More recently, according to IDF (61), there are other components such as "tomographic assessment of visceral obesity, liver fat, biomarkers of adipose tissue, apolipoprotein B, LDL particle size, endothelial dysfunction, urinary albumin, inflammatory markers, and thrombotic markers that influence the development of metabolic syndrome, CVD and NIDDM and can be included as part of metabolic syndrome criteria".

Since, the incidence of metabolic syndrome is escalating rapidly in the world, it has been recognized that lifestyle intervention, including low calorie diet, physical activity, and weight loss and drug therapies improve all features of metabolic syndrome.

Lifestyle modifications are the guiding principlesand include effectual management of stress, proper diet, and positive attitudeall of which help individuals triumph over this syndrome (72).

Obesity and diabetes

Obesity is one of the major risk factors for the development of type 2 diabetes (73). Its prevalence is increasing at an alarming rate in both developed and developing countries leading to various metabolic disorders such as, hypertension, heart disease, gallstones, colon cancer, stroke (74), osteoarthritis, work disability, and sleep apnea, insulin resistance (75). It was estimated from the data of 5 prospective cohort studies (76-80) and the Nurses' Health Study (81) in combination with 1991 national statistics on body mass index (BMI) distributions, population size, and overall deaths, 300,000 adult Americans die every year due to obesity and its co-morbidities such as diabetes, hypertension, dyslipidemia (82, 79). According to data from 2001 Behavioral Risk Surveillance system (BRFSS), it was recognized that, along with hike in the prevalence of obesity (5.6%), its co morbid condition, diabetes is also increased by 8.2 % from 2000 to 2001. Unfortunately, the prevalence continues to increase in US adult population, irrespective of age, sex, race, and educational background. Therefore, to overcome over obesity and its associated risks have become one of the important health challenges in the 21st century (83).

Behavioral (84), environmental (85), and genetic factors (86) all influence obesity and adversely affect the physical, mental and social well being (87) of the individual. Although, there is abundant evidence that obesity alters glucose homeostasis and

contributes to insulin-resistance type 2 diabetes, the underlying mechanism is not clearly elucidated (88).One noteworthy finding is that inappropriate anatomical distribution of body fat adds to impaired insulin sensitivity, insulin resistance, dyslipidemia, and type 2 diabetes in both men and women (89). Usually, 80% of the fat is stored in the subcutaneous adipose tissue (SCAT) which is further classified in to abdominal and gluteofemoral fat. The remaining is stored in visceral adipose tissue (VAT) and others such as retroperitoneal, perirenal and orbital (90).

In obese men, along with accumulation of excess abdominal subcutaneous fat, deposition of visceral fat also increases which leads to android or apple-shaped obesity (90). In obese women, gluteofemoral subcutaneous fat accumulates more so than men and contributes to peripheral obesity or gynoid obesity. The accumulation of visceral fat is less compared to obese men, but it is the android obesity in women that leads to metabolic complications (90). Studies have demonstrated that, it is the visceral fat that disrupts glucose homeostasis by increasing insulin resistance and decreasing insulin sensitivity (91-94) because visceral fat cells are less receptive to antilypolytic result of insulin.

Insulin, an antilypolytic hormone (95) plays a major role in the utilization of fat stored in adipose tissue, and non adipose tissues such as liver and skeletal muscle. It facilitates in the uptake of glucose and aids in the formation of glycogen in the liver. It also inhibits hepatic gluconeogenesis and glycogenolysis. It also induces lipoprotein lipase activity in peripheral tissues and in turn hydrolyses triglycerides (TG) into free fatty acids (FFA), monoglycerides and sent to adipose tissue for further re esterification

into TG (96). Insulin inhibits the activity of hormone sensitive lipase (HSL) and hampers the hydrolysis of TG and inhibits the release of FFA in to the circulation (97).

In obese individuals, due to excess accumulation of fat in the visceral adipose tissue, insulin mediated suppression of HSL is seized and increases in the flux of FFA take place and drains into hepatocytes through portal vein (98) . Excess drain of FFA in liver increases gluconeogenesis, decreases hepatic insulin clearance and decreases glucose uptake from blood leading to constant rise in insulin secretion ultimately ends up in hyperinsulemic condition resulting in insulin resistance (99). Due to increased HSL acitivity in adipose tissue, the size of the adipocytes increases with the accumulation of FFA and decreases the storage space by reducing the adipocyte number (100). This results in diversion of FFA to extra adipose tissues such as liver, muscles, and heart (ectopic fat storage) and produces insulin resistance (100). Apart from the fat distribution, there are several other factors such as increased levels of leptin (101), tumor necrosis factor-α (TNF –α) (102), plasminogen activator factor inhibitor (PAI-1) (103) and decreased levels of adinopectin (104) are involved in the development of obesity and insulin resistance (105). These factors are known as adipocytokines (hormone-like substances) secreted by adipocytes in the adipose tissue (106). Therefore, adipose tissue is not only long-term energy storehouse but also is an energetic endocrine organ (107).

Many studies in mice carrying the recessive mutations, obese (ob) and diabetes (db), predicted the subsistence of a circulating endocrine hormone that are able to communicate information from the periphery to the CNS with regard to the adequacy of energy stores (108-110). It has been reported the involvement of leptin, an “ob gene” product, in regulation of appetite, energy expenditure and insulin sensitivity by acting on

the satiety center of hypothalamus (111). Studies (112-114) demonstrated that a genetic mutation on "ob" gene caused hyperphagia in mice, but this condition was reversed when leptin was infused (61). The presence of leptin receptors in hypothalamus encoded by "db" gene has also been demonstrated in a study by Chen and colleagues (110). Leptin secreted from adipocytes reach the hypothalamus crossing the blood brain barrier through leptin receptors and activate satiety center by inhibiting the action of neuropeptide Y (NPY) a potent stimulator of food intake (115). Studies (116, 117) have demonstrated that, a mutation in "db gene" interferes with the signals of leptin to hypothalamus and negative feed back mechanism is disrupted resulting in stimulation of NPY causing hyperphagia (115).

A study conducted on Polynesians by Zimmet and colleagues (118), a population with high incidence of diabetes and obesity, found that leptin levels were remarkably increased in both sexes and was directly associated with BMI, waist circumference, potent indicators of obesity (118). Several animal (119-121) and human (121, 118) studies also have demonstrated that resistance of hypothamus to leptin, stimulated insulin secretion, further contributing to insulin resistance.

To sum up, before getting into intervention approaches, it is important to have enhanced understanding about genetic and environmental factors that contributes to obesity-induced insulin-resistance and type 2 diabetes.

Genetics and diabetes

Type 2 diabetes is a multifactorial disorder which is influenced by both genetic and environmental factors (122). There are studies that have demonstrated that type 2 diabetes is affects certain populations more such as the Native Americans (38, 37). This

raised a question that genetics may contribute to type 2 diabetes in these populations (123). In 1962, it was documented that in periods of surplus availability of food, there was an abnormal increase in the secretion of insulin in non-agricultural Native Americans. Since, insulin is lipogenic, it resulted in hyperglycemia and excessive deposition of fat in this population. This condition favored them during the times of famine by utilizing excess fat as a source of energy and fuel to the body (124). Abnormal secretion of insulin was assumed to be due to "thrifty gene". Thus thrifty gene hypothesis came in to existence and it proved that some genetic background helped this population to live on during times of famine (124). Unfortunately, due to modernization, change in the composition of traditional diet, decrease in physical inactivity, excess accessibility to food misused thrifty gene hypothesis and added to the development of obesity and insulin resistance and ultimately type 2 diabetes (123, 124). Although, there is considerable evidence about the role of genetics in the development of type 2 diabetes, only 10% of the genetic risk factors have been identified. In view of the fact that, type 2 diabetes is a polygenic disorder, only a few numbers of cases of NIDDM are due to mutations in single gene (122). Maturity onset diabetes of the young (MODY) is the common form that results due to single gene mutation. It contributes only 2-5% in the development of type 2 diabetes (125). Genetically MODY is considered heterogenous due to defect in the gene expression of glucokinase (glycoltic enzyme) (126), insulin promoting factor-1(IPF-1) (involve in embryonic development of pancreatic islets) and hepatic nuclear factors such as hepatocyte nuclear factor- 4α (HNF-4α), hepatocyte nuclear factor -1α (HNF-1α), hepatocyte nuclear factor-1β (HNF-1β) (126) which are disseminated on the pancreatic beta cells and engage in carbohydrate metabolism by

controlling glucose transporters and enzymes concerned with glucose metabolism (122).Thus mutations in these genes result in the inefficiency of the beta cells of the pancreas to secrete sufficient insulin (122). Because of its prevalence in diverse forms such as MODY 1, MODY 2, MODY 3, MODY 4, MODY 5, MODY, it is considered heterogenic (125). Other monogenic forms of type 2 diabetes include mutation in mitochondrial $tRNA^{leu}$ which can cause maternally inherited type 2 diabetes (127) and mitochondrial syndrome (myopathy, encephalopathy, lactic acidosis, and stroke) (MELAS) (128).

As there are many factors involve in the progression of type 2 diabetes such as obesity, insulin sensitivity, and beta cell function, therefore, the genetic constituent of type 2 diabetes is multifarious rather than homogenous. Studies demonstrated that mutations in multiple genes that adjust insulin secretion, action, and insulin signaling add more to the advancement of type 2 diabetes rather than single gene mutations (122). Nearly 200 candidate genes were identified by candidate gene approach which investigates the connection between a particular gene that involve in the regulation of insulin secretion, carbohydrate and fat metabolism and type 2 diabetes. But, their predisposition to type 2 diabetes is very small. Candidate gene approach was unsuccessful to recognize the genes that are more vulnerable to progression of type 2 diabetes (122). Further research with large sample sizes are needed to explore the genetic contribution of type 2 diabetes in general as well as in ethnic populations. Hence, research with a novel tool “genome wide scans” is lending a hand to the researchers to identify the genes that are more liable to common forms of type 2 diabetes.

Diet and diabetes

In the US, obesity is the predisposing factor for type 2 diabetes and is disproportionately affecting women, minority ethnic groups such as Native Americans (129-131), African Americans (132), and children with less than high school education (133). Though most of the Americans are health conscious and aware of diet-related disorders like overweight and obesity-induced diabetes, they continue to gain weight. The proportions of overweight individuals gradually have increased from 24.3% in 1960 to 33.3% in 1991 (134, 135). Although there is a large body of evidence that overweight is a risk factor leading to diabetes (73-80) unfortunately the US population is becoming more obese as time passes. Aside from excess caloric intake and reduced physical activity, numerous other factors influence the prevalence of diabetes and obesity (136, 137). These factors include low intake of dietary fiber (138), increased consumption of refined carbohydrate (137), and inadequate consumption of fruits and vegetables (139, 140). Although there has been a consistent decline in the intake of dietary fat from 40% to 33% in recent decades in the US, this level remains to be higher than the recommended daily allowance of (30%). Nearly, 58 million Americans are affected with obesity and its related disorders due to high fat diet (135, 141). It has been found that for addition of every one kg of weight above the ideal body weight, the risk of diabetes increases by 4.5% (1). During the past several decades, fast food has played a major role in the American diet. It is defined as the "food purchased in self service or carryout eating places without wait service". Fast foods are rich in calories, proteins, carbohydrates, saturated fats, total fat, and cholesterol and are usually low in fiber, calcium and vitamins such as A, and C. French fries, hamburgers are the rich income sources for fast food out

let owners (142). According to a survey by USDA , 56% of US adults eat away from home and out of these 33% go to the fast food restaurants and fast food accounted for 14% of the total energy intake in the year 1995 (142). It was reported that women are the frequent eaters in fast food outlets and a direct relation existed between total energy and fat intake (142).French et al.(2000) investigated the relationships between demographic, behavioral and dietary factors and the frequency of using fast food restaurants in a community based sample of 891 adult women aged 20-45. The results showed that the frequency of using fast food restaurants was considerably higher in young women, in individuals with low income, particularly among the ethnic groups, and people with greater body weight. High consumption of fast foods is directly associated with excess weight gain and obesity. Thus fast food plays a dominant role in the excess accumulation of calories in the body predisposing to obesity and diabetes (143).

The findings of a number of epidemiological studies (37, 2, 40) suggest that the prevalence of DM in the US is greater among the minority ethnic populations than Caucasians. Adaptation of western life-style has resulted in an increase in the prevalence of type 2 diabetes in ethnic groups as evident by migration of ethnic groups to the US which has resulted in change in the composition of traditional diet (132). Environmental factors such as excess accessibility to food, low cost of fast foods, change in the composition of conventional diet style, sedentary life, and television advertisements of fast foods all can be considered contributing factors to obesity and thereby leading to diabetes especially in ethnic groups (132, 140, 144).By projecting the available immigration data, 50% of the US population would be Hispanics and Asian origin by the year 2030. Therefore, the prevalence of type 2 diabetes would reach its maximum in US,

provided the influence of western life style continues on these populations (1). Several (132, 140, 144) studies on many ethnic groups like Native Americans, African Americans (145), Hispanic Americans (146), Pima Indians(38) , have reported that excess caloric intake and physical inactivity contribute to type 2 diabetes in US. Hence, westernization, migration, and acculturation all play a significant role in changing traditional dietary habits and contribute to high intake of fat, calories, predisposing to DM and obesity.

Physical inactivity and diabetes

Epidemiological evidence suggests that physical inactivity is one of the important determinants for the higher prevalence of type 2 diabetes among the minority ethnic groups such as Native Americans (144), Asian Indians (147), Chinese (148), Creoles (149), Polynesians (150), Micronesians (151), and Melanesians (152). Physical inactivity is a predisposing factor to obesity (153-155) and according to many longitudinal and cross sectional studies obesity is determined as a primary contributing factor to NIDDM among Native Americans, Asian Indians, Chinese, Creoles, Polynesians, Micronesians and Melanesians (144, 147-152). Therefore, in brief, “obesity associated with physical inactivity is the primary risk factor in the causation with type 2 diabetes mellitus”.

Insulin resistance (IR) is the characteristic feature of type 2 diabetic patients (156). Studies have demonstrated that obesity (Visceral obesity) (157), sedentary life style, lack of physical fitness (158) can aggravate IGT and insulin resistance. Therefore, studies advocate” physical activity” as one of the effective strategies to prevent underlying risk factors such as obesity, reducing the risk of developing diabetes (159-161).

It is well known that exercise can improve insulin sensitivity (162, 163) in type 2 diabetics and reduce the incidence of mortality in both men and women from ischemic heart diseases (164). Exercise enhances the utilization of glucose by muscles and reduces hyperglycemia in IGT individuals suffering from type 2 diabetis. It also stimulates the release of catabolic hormones such as glucagons and catecholamine that inhibit insulin action and improve insulin sensitivity and lipid metabolism (164, 165). Many studies have documented the existence of significant inverse relation between the amount of exercise and disorders such as type 2 diabetes (159), obesity (154), hypertension (166) (167), hyperlipidemia (168) and ischemic heart disease (169). Epidemiological studies have also recognized similar phenomenon between diabetes and physical inactivity among Mexican Americans (170), blacks (171), Pima Indians(172) , Asian Americans (173). However, interestingly the inverse association predicted between physical activity and occurrence of diabetes was found to be higher in Mexican and black men and surprisingly not in these two ethnic groups of women (170, 174). On the contrary, another study by Harris and colleagues (175) did not reveal such variations between men and women. It was also found that white women were more physically active than Native American, Hispanic, black women (176).

In addition to exercise, weight reduction would be an effective measure in reducing the risk diabetes and obesity (177, 178). According to the present weight management program, increased physical activity and reduced caloric intake by about 500 to1000 cal/day will produce a weight loss of 0.6 kg (1.5 lb) per week, and 7 to10% reductions in body weight over 6 to12 month period (65). Intervention trials have demonstrated that reduced intake of calories and increased physical activity produce a

negative energy balance which in turn reduces the risk of developing type 2 diabetes (179, 180). The Finnish Diabetes Prevention Study (181) documented that effective individual counseling resulted in 58% reduction in the risk of type 2 diabetes in subjects who received high fiber/low fat diet along with exercise. This supports the hypothesis that life style modifications are directly related to the incidence of type 2 diabetes (181).

Diabetic Prevention Program Research Group (182) also demonstrated a 58% reduction in the incidence of diabetes in impaired glucose tolerance individuals with body mass index (BMI) of 34.0 who were assigned a lifestyle modification program when compared with the group assigned metformin and placebo. Also, a meta analysis of controlled clinical trials proposed an inverse relation between exercise and blood levels of glycated hemoglobin (Hb A1c) (a predictor of type 2 diabetes (183).

As type 2 diabetes is a lifestyle-related disease, current guide lines (184) advocate the incorporation of regular and physical activity combined with weight loss to improve the metabolic syndrome variables such as insulin sensitivity, insulin resistance, glucose tolerance, and lipid profile that contribute to the causation of type 2 diabetes.

Prevention and Treatment of Diabetes in Postmenopausal Women

Lifestyle modification and diabetes

Life style modification plays a significant role in the prevention and treatment of type 2 diabetes and its related complications (185). A change in life style includes weight reduction, physical exercise, and calorie reduction (186).

Obesity is one of the major risk factors for the development of type 2 diabetes (73). A strong correlation exists between obesity and diabetes in both the sexes (187). In

obese individuals, the occurrence of type 2 diabetes is 3-7 folds higher (188, 74). Body mass index is a strong indicator of obesity and potential determinant of the development of diabetes. Progression of type 2 diabetes increases 20-fold in adults whose BMI is greater than 35 kg/m2 (188, 74). The rationale of this statement is to highlight the importance of weight reduction, a life style modification in the prevention and treatment of type 2 diabetes. Many studies (189-192) have been carried out to investigate the beneficial effects of weight loss in individuals with type 2 diabetes and insulin resistance. Weight loss have been shown to improve glycemic control, insulin action, reduce serum levels of fasting glucose (189, 190), total cholesterol, triglyceride, low-density lipid protein (191, 192) in patients with type 2 diabetes. Therefore, weight reduction is considered to be the main strategy for overweight, obese individuals and diabetics as well. Weight loss can be achieved through reduced caloric intake and increased physical activity.

Reduction in total caloric intake is an important component in the treatment of obesity and diabetes. According to National Heart, Lung, Blood Institute (NHLBI) (193)and Obesity Education Initiative Expert Panel (OEI) (194), a diet that supplies 1000-1200 K Cal/day for women and 1200 to1600 Kcal/day for men provides an energy deficit of 500-1000 Kcal /day and is considered low calorie diet. Low fat diet recommendation is a common remedy for both overweight and obese individuals. The findings of short-term intervention trials (195, 196) and randomized controlled trails (197, 198) suggest that fat restricted diet (25-30% of calories) results in decreased energy intake with subsequent weight loss. However, the long-term effect of fat restricted diet on weight loss is unclear and the evidence is insufficient. Aside from high fat diet,

excessive intake of carbohydrate aggravates dyslipidemia, which is often associated with insulin resistance in type 2 diabetes (199). Although there are studies (200-205) that have demonstrated the efficacy of low carbohydrate (CHO) and high protein/high fat diet in reducing body weight in short-term basis, the long-term efficacy and safety of these types of dietary approaches are questionable. One possible explanation for the beneficial effects of low carbohydrate may be unrelated to the amount of carbohydrate consumed, rather has to do with the type of carbohydrate (198). For instance, a study by Heilbronn LK and colleagues (199) has shown that adults who have consumed low glycemic index foods have experienced weight loss. Therefore, this and similar questions are needed to be answered in well-designed clinical trials.

To date based on the existing body of information; it is improbable to conclude that one particular diet is appropriate for all overweight, obese/diabetic individuals. Dietary recommendations should be based on a number of factors including individual's individual food preferences, circumstances, cultural ethnic preferences and his/her motive towards weight management should be taken in to consideration (206). Multiple approaches are available for an efficient management of energy intake and weight loss. For instance, fat and carbohydrate restricted diets will reduce the caloric intake (207) (199), diets rich in fiber, whole grains and fruits will increase the volume of food and improve satiety (208)

The current dietary guidelines of the American Diabetes Association (209), the American Heart Association (210) , and the National Cholesterol Education Program (NCEP)–Adult Treatment Panel (ATP III) (193), include a diet rich in vegetables, whole grains, low fat or non fat dairy products, fish, legumes, poultry, lean meats and limit the

intake of saturated fat, trans fatty acids, cholesterol, salt intake of 6 grams or less per day and alcohol intake (no more than 2 drinks per day for men and one drink for women). One drink equals to 12 oz of beer, 5 oz of wine or 1.5 oz of distilled spirits. Each drink contains 15 g of alcohol. Additionally, weight loss should be gradual with following moderate and practical dietary recommendations, e.g. reduction in total caloric intake, approximately 500-1000 kcal on a daily basis while receiving a well balanced diet in terms of macro- and micro-nutrients. These dietary guidelines are based on the risk factors for coronary heart disease (CHD), which is an important consideration for individuals with type 2 diabetes; because the risk of developing CHD is 3 to 7 fold higher in type 2 diabetics than non-diabetic individuals (193).

Apart from diet restriction, exercise also plays an important role achieving ideal body weight. Many epidemiological studies (211, 162, 212), have provided evidence that physical inactivity can lead to type 2 diabetes and suggested that regular physical activity improves insulin sensitivity, glycemic control (163) and delays the development of type 2 diabetes, and reduces the overall mortality rate as a consequence of DM (164). It has been shown that 30-minute moderate intensity exercise on a daily basis lower the risk of metabolic syndrome (213). Hence, diet therapy together with exercise can act synergistically to reduce the incidence of type 2 diabetes. Nonetheless, it is essential for the individuals with type 2 diabetes with or without other associated risks to receive professional advice before initiating exercise (206). To sum up, strict adherence to diet restriction and moderate intensity exercise will help in the efficient management of diabetes and cardiovascular diseases and their underlying risk factors.

Antidiabetic drugs and diabetes

Diet restriction, modest exercise, lifestyle intervention sometimes fails to control blood sugar and do not enhance the production of endogenous insulin and responsiveness of a specific tissue to insulin. Hence, pharmacotherapy is effective, if calorie restriction and physical activity proves to be ineffective (17).

The drugs used in the management of diabetes are categorized into insulin augmenting agents and insulin assisting agents (214). Insulin augmenting agents include sulfonyl ureas (glimepride, tolbutamide) and meglitinides (repaglinide) (214). Sulfonylurea derivatives bind to the receptors on the β-cells and close the potassium channels that will instigate the production of endogenous insulin and inhibit β-cell apoptosis (214). There are long–acting sulfonylurea ureas (glimepiride) (215) and short–acting: sulfionyl ureas (tolbutamid) (216). The treatment effects of these drugs depend on the site and duration of their actions.

These drugs are contraindicated when there is severe hypoglycemia due to inefficient renal clearance, renal impairment, hepatic dysfunction and cardiac failure (19, 217). A recent retrospective cohort study reported by Bell DS and colleagues(2 18) reported that sulfonyl monotherapy exposure resulted in heart failure. On the other hand, there is conflicting evidence by a UK prospective diabetes study (219, 220), that micro- and macro-vascular complications were noticed to be diminished with sulfonylurea derivative treatments. Maru et al (2005) (221) reported that the risks of heart failure exist due to any kind of antidiabetic drugs within the first year of diagnosis. It has also been suggested that, the risk of heart failure depends not only on the therapy itsself but also on the severity of the disease and duration of the preclinical condition and the need for drug

therapy (221). Biguanide (metformin), a –glucosidase inhibitors (acarbose), and insulin sensitizers like thiazolidinediones (rosiglitazone) are another group of drugs that come under insulin assisting agents (222). Each drug has specific site of action and specific function in the control of hyperglycemia.

Thiazolidinediones mainly act on the adipose tissue. These drugs activate proliferator–activated receptor gamma expression (transcription factor) (PPAR γ). Activation of (PPAR γ) regulates the relocation of triglyceride deposits in visceral and subcutaneous depots and reduces the circulation of non-esterified free fatty acids (NEFFA) and glycerol. This will prevent excess accumulation of fat in hepatic adipocytes and intramyocytes and alleviate hepatic and skeletal muscle insulin resistance (223) (224). Thiazolidinediones also play a vital anti-inflammatory role by reducing the production of proinflammatory cytokines such as tumor necrosis factor -α TNF α and interleukin 6. It also increases the concentration of adenopectin, an adipokine that in turn inhibits hepatic gluconeogenisis, reduces plasma glucose and stimulates lipid oxidation and glucose uptake by skeletal muscles (225).

Beguanides (Metformin) acts on the liver and prevents fasting hypoglycemia by decreasing hepatic glucose output (226). Treatment with this drug prevents weight gain, which is a common feature in type 2 diabetics (222). Glucosidase inhibitors such as Acarbose increase the volume of the food by absorbing moisture and reduce satiety. They also delay digestion and absorption of complex carbohydrates and prevent hyperglycemia (227). Sometimes, oral anti-diabetic drugs can be ineffective in severe hyperglycemic conditions and the need for exogenous insulin may be necessary. Hence, insulin alone or

combined therapy with oral anti-diabetic drugs is prescribed depending on the severity of the condition (18).

Although anti-diabetic drugs exert many beneficial effects in control of hyperglycemia, the prolonged use of these drugs can produce adverse effects such as severe hypogyglycemia (228), weight gain (229), lactic acidosis (230), flatulence with sufonyl urea, thiazolianediones , biguanides , glucosidase inhibitors (231). Therefore, the use of complimentary and alternative medicine (CAM) and the incorporation of natural supplements in the diet to prevent diseases such as Diabetes, cardiovascular diseases, osteoporosis, cancer are becoming more prevalent (232). Currently, there are numerous studies being conducted to investigate the health benefits of bioactive-rich food sources such as flaxseed and soy on hyperlipidemia, hyperglycemia and other chronic diseases.

Role of Bioactive Food Components in Preventing Chronic Diseases

Phytoestrogens

Phytoestrogens are naturally occurring plant compounds, which either exerts estrogenic and antiestrogenic activity depending on specific tissue or estrogen level (21) (22). These compounds are heterocyclic phenols and exhibit structural similarities to estrogens. They are classified in to three main groups – isoflavones, coumestans and lignans . Genestin and diadzein are the bioactive isoflavones while biochanin A and formononetin are the precursors for these isoflavones. Lignans are widely present in the plant kingdom and helps in lignin formation in plant cell walls. Secoisolariciresinol and matairesinol are the precursors for enterolactone and enterodiol. Coumestrol and 4'-methoxy coumesterol are biosynthetically similar to isoflavones. Legumes, seeds and

whole grains are the rich sources of phytoestrogens (21, 22). Soybeans and soybean products are abundant sources of isoflavones (233). Chickpeas, legumes, cloverleaves, toothemelic and blue grass are also good sources of isoflavones (234). Coumestans are found in alfalfa and sprouts of clover, split peas, kala chana seeds, pinto beans, lima beans, and soybean sprouts also contain small amounts of coumestrol . Plant foods such as flaxseed, oil seeds are rich in lignans (234).

Phyoestrogens exist in plants as glycosides. Once ingested, glycosides undergo hydrolysis and subjected to fermentation by intestinal bacterial beta- glucosidases and converted in to bioactive aglycones (23). In the distal part of the intestine, specific metabolities are formed. These uncongugated specific metabolites (aglycones) are absorbed in the intestinal tract and reach the liver to form glucoronides, which are then either re -excreted through bile and urine or enter enterohepatic circulation (23). The production of specific metabolites varies depending on gastrointestinal flora, antibiotic use and diet (235). The Biological effect of phytoestrogens depends on the time of exposure. For example, in premenopausal women, the intake of phytoestrogens may produce adverse effects such as increased risk of breast cancer. This is due to the presence of natural estrogen and intake of estrogen rich diet. For normal postmenopausal women, because of lack of production of natural estrogen, estrogen rich diets have beneficial effects in relieving postmenopausal symptoms, breast cancer, cardiovascular diseases (CVD) (22).

The type of food consumed, the level of intake and the specificity of the compound in the diet influence the biological activity of phytoestyrogens (236, 237). The diet of an individual varies depending on the geographical area. For instance, western diet

is different from the Asian diet (238). Therefore, the incidence of breast (239, 240), ovarian cancers (241), prostate carcinomas (242), CVD (243) is less in Asian population compared to westerners. This might be due to the intake of phytoestrogen-rich diet by Asians. Lately, due to change of life style and dietary habits because of westernization in Asian countries, the risk of cancers (239-242), cardiovascular diseases (243), and similar chronic diseases are towards the rise.

A number of beneficial effects are associated with the intake of phytoestrogens, with regard to postmenopausal symptoms such as hot flashes. In Asian women the incidence of hot flashes are lower than the Caucasian women (244). Phytoestrogens have also been reported to protect loss of bone mass in pre- (245) and post-menopausal (246) women. Studies have reported that the intake of soy protein in overectomised rat prevented bone loss as indicated by an increase in bone formation markers (e.g. serum alkaline phosphotase, and osteocalcin levels) compared with the control animals (247, 248).

A number of studies (249 -252) support the hypothesis that adequate intake of isoflavones and lignans reduce the risk of cancer. Epidemiological data have shown that soy consumption reducesthe risk of prostate cancer in Japanese men (253). Similarly, several studies have established a negative association between consumption of soy/soy protein and the development of lung cancer (254), stomach cancer (255), breast cancer (256) and rectal cancer (257).

It has also been shown that phytoestrogens exert beneficial effects in postmenopausal women by improving lipid profile and reducing the risk of developing CVD (258). Many studies (259, 260) supportthis notion by showing the positive effect of

intake of soy protein on the total cholesterol and low-density lipoprotein concentrations in humans. Further, meta analysis of 38 controlled clinical trials also reported that intake of soy protein decreased blood cholesterol, LDL and triglyceride concentrations (TGL) (261).

Phytoestrogens exert either estrogenic or antiestrogenic effect on a variety of tissues depending upon the availability of ER-alpha and ER–beta receptors through the classical genomic effects (24, 25). However, the affinity of phytoestrogens to binding to ER-beta receptors is far greater than those of ER- alpha (262). ER-beta receptors are more expressed in tissues such as bone, breast, cardiovascular system (263) and hence, phytoestrogens may show greater beneficial effects in preventing breast cancer, osteoporosis, CVD diseases in postmenopausal women in the absence of substantial level of circulating estrogen.

Thus phytoestrogen influences different tissues depending on the length of the exposure, dose, and metabolites (264). The field as a whole is relatively new and further studies are underway to shed light on numerous health benefits of phytoestorgens,

Lignans

Lignans are a class of phytoestrogens that are found in seeds, whole grains, legumes and vegetables. However, among edible plant foods, flaxseed is the richest sources of lignans (265). Secoisolariresinol and matairesinol are the major components of plant lignans. These are the precursors for the production of mammalian lignans namely enterodiol and enterolactone (266). These precursors undergo hydrolysis, dehydroxylation and demethylation in the gut to form mammalian lignans (267). Plant lignans are absorbed

and utilized in the small intestine by a series of deconjugation and conjugation reactions. Following the absorption process, hepatic phase II enzymes (UDP-glucoronosyl transferates and sulphotransferases) involve in conjugation of lignans with glucoronic acid and sulphate to form conjugates. These conjugates either enter enterohepatic circulation or get excreted through urine or bile-like natural estrogens (268). Later, the intestinal bacteria for further re- absorption, and metabolism of metabolites, deconjugate the conjugated lignans in the intestine. Thus, intestine serves as the primary site for biotransformation of plant lignans to mammalian lignans (268). It is well documented that biotransformation is affected in patients with ileostomies, because of the decrease in the enzymatic and fermentative capacity of the intestine (269). Determinants such as quantity and quality of the lignans, (270), and presence of constipation will hasten the process of biotransformation (271, 272) whereas increase in body mass index, smoking (271, 272), high fat diet (273), will lower biotransformation process. Thus, thelevels of enterolactone in blood and urine are influenced by a number of variables which may cause the findings of one study to be different from another study.

A close association has also been observed between enterolactone concentrations in blood and hormone-related diseases such as osteoporosis (274), cancer of breast (275) and prostate (276). This has lead researches to investigate the process of absorption and biotransformation of lignans and their influence on the hormone-related diseases.The hormone-like compounds, enterolactone and enterodiol, are found to be weakly estrogenic and therefore being able to influence the production, metabolism and activity of biological estrogen and cell proliferation, differentiation, adhesion and angiogenesis, thereby acting as natural anti-carcinogens (270).

Many human (278, 279) and animal studies (281, 289) have depicted that intake of lignan-rich foods reduce the risk of developing breast, and prostate cancers. Classical and nested case control studies have examined urinary, serum and plasma enterolactone as biomarkers of lignan intake and have found that the higher the concentration of enterolactone in blood and urine, can be interpreted as lower risk of acquiring breast cancer in pre- and post-menopausal women and in patients with breast cancer (27, 272, 277). A study by Serraino and Thompson (278) also revealed a significant reduction in epithelial cell proliferation by 38.8 - 55.4% and nuclear aberrations by 58.8 - 65.9% in mammary gland of female rats fed with lignan-rich flaxseed flour or defatted flaxseed meal (5% or 10%) and the effect was significant at 5% level of flaxseed flour/defatted flaxseed meal.

Thus, dose dependent studies have provided significant insight as how lignans prevent various types of cancers.

Much evidence has accumulated in support of protective effect of lignans against the risk of prostrate cancer in men. In a study by Mills et al. (1989) (279), high intake of beans and lentils, rich sources of lignans, and dried fruits resulted in decreased risk of prostate cancer in men. Animal studies including those of rats and mice also have exhibited similar results (280, 281). In the studies, for instance, when animals were fed with high rye bran diet (a good source of lignans), they experienced apoptosis of prostate tumor cells.

Overall, it can be assumed that, not only the estrogenic/antiestrogenic properties of lignans (282), but also the antioxidant (283, 284) properties have some protective

effect against diseases associated with free radicals such as cancer, cardiovascular disease and diabetes (282).

Flaxseed

Flax (Linum usitatissimum) is a blue flowering crop that was identified in Near East some 10000 years ago (285). Presently, researchers are focusing on the health benefits of flaxseed components such as lignans, omega 3 fatty acids and soluble fiber. Whole flaxseed contains approximately 41% fat, 28% dietary fiber, and 21% protein. It also contains minerals and vitamins in considerable quantities. Flax contains an average of 35% of its mass as oil and is a rich source of omega 3 fatty acids (alfa linolenic acid) (286).

Until now, most of the research on flaxseeds has focused on its estrogenic and antioxidant characteristics, the former having influence on hormone related diseases like cancer of breast, prostate and colon, and the latter showing considerable effect on free radical-associated diseases of cardiovascular system, diabetes and inflammatory diseases.

Animal and cell culture studies have shown that dietary flaxseed and its components reduce the growth and metastasis of established estrogen receptor negative (ER-ve) human breast cancer cells in nude mice (287). Flaxseed has also been shown to inhibit the growth of tumor cells in the human colon by anti estrogenic property (288), decreases the number of aberrant crypt cell fociproliferation, and increase apoptotic index in the distal colon of male rats with colon carcinogensis (289) and prostatic carcinoma in transgenic mice (289). Similarly, flaxseed has been shown to be effective in inhibiting the growth of melanoma cells and tumors in the lungs of C57BL/6 mice (290).

Additionally, several human studies (291, 292) have confirmed the anticarcinogenic effects of flaxseed and its components. For instance, in a study by Thompson et al. (291) showed that consumption of 25g flaxseed daily for 39 days reduced tumor cell proliferation, and increased apoptosis of breast cancer cells in postmenopausal patients with recently diagnosed breast cancer. A similar finding was reported among clients with prostate cancer who were put on 30 grams of flaxseed/day with low fat meal (20% of Kcal or less) (293). In that study, the biomarkers of prostate neoplasma (eg: prostate specific antigen, testosterone, free androgens) have shown a decline. The results suggested that fat restriction and flaxseed supplementation decreased epithelial cell proliferation and its associated biomarkers.

Further, much evidence has accumulated on the effect of flaxseed on the levels of lipid parameters and biomarkers of cardiovascular diseases. A randomized clinical trial by Dodin et al.(2005) (294) found that consumption of 40 grams of flaxseed/day by French Canadian postmenopausal women (n=101) for 12 months reduced serum total and high density lipoprotein cholesterol concentrations compared to those who were put on wheat germ placebo (n=98). Another study by Nestel et al (295)established a remarkable association between intakes of 29 grams of alpha linolenic acid from margarine products based-on flaxseed and arterial compliance, an important index of circulatory system. The findings of that study (295) suggested that there was a significant improvement in arterial compliance in obese subjects, regardless of raise in LDL oxidizability and diminished insulin sensitivity.

Prasad et al.(1999) (286) established the potential effect of flaxseed as antioxidant and its role in the prevention of hypercholesterolemic atherosclerosis, a condition that

occurs due to over production of free radicals resulting from stimulation of polymorphonuclear leucocytes by hypercholesterolemic condition. Their findings demonstrated that secoisolariciresinol diglucoside (SDG) reduced total cholesterol by 33%, LDL-C by 33% and there was a significant increase in HDL-cholesterol of greater than 140% in rabbits. Furthermore, there were considerable decreases in malondialdehyde chemiluminescence (lipid peroxidation product) and perceptible increase in antioxidant reserve in rabbits fed with 1% cholesterol + 15 mg of SDG/kg body weight compared to control group. Thus, oxidative stress plays a major role in the pathogenesis of cardiovascular disease.

Several lines of evidence indicate that oxidative stress is one of the underlying factors of diabetes. Increase in plasma free radical concentration increases fasting plasma insulin in type 2 diabetic patients (296). It has also been reported that increased levels of reactive oxygen species (ROS) impairs glucose tolerance, decreases insulin sensitivity and increases insulin resistance in patients with type 2 diabetes (297). Increased levels of ROS adversely affect the function of islet cells of pancreas and hampers glucose absorption resulting in hyperglycemia. The concentration of malondialdehyde increases and alters cell impermeability and cell apoptosis (297).

Based on this concept and the potential antioxidant activity of SDG, Prasad et al. (2000) (2001)(298, 299) conducted a study evaluating the ability of SDG in preventing type 1 and type 2 diabetes. His findings indicated a positive association between oxidative stress and non insulin-dependent diabetes (NIDDM) and insulin-dependent diabetes (IDDM). Treatment with SDG prevented NIDDM in female Zuncker rat model of type 2 diabetes and IDDM in diabetic prone Biobreeding rats (Bbdprats).

The studies in which the effects of flaxseed or its bioactive components have been investigated in relation to diabetes are sparse. Further research is needed using human volunteers and animal models to confirm the beneficial effects of intake flaxseed and its lignans on glucose metabolism. Thus the present research mainly focused on how hormone deficiency hampers glucose metabolism and investigated the extent to which flaxseed consumption improved fasting blood glucose levels in Native American postmenopausal women. Future clinical trials are needed to investigate the role of lignans, a class of phytoestrogens found in flaxseed, in individuals with hyperglycemia.

CHAPTER III

MATERIALS AND METHODS

Subject Recruitment

A total of fifty-five mild to moderate hyperglycemic fasting blood glucose (FBS) $\geq$ 110 mg/dL but less than 126 mg/dL) and hypercholesterolemic (total cholesterol level $\geq$200 but less than 380 mg/dL) Native American postmenopausal women with mean age 47 to 63 yearsof age who were not on hormone replacement therapy (HRT), for at least six months prior to study, were enrolled for this study. The study protocol was approved by the Institutional Review Board (IRB) at Oklahoma State University. Volunteers were accepted into the study by meeting the following criteria: being postmenopausal as determined by at least 1 year of amenorrhea, FBS levels of more than 110 mg/dL but less than 126 mg/dL, not taking any medications known to alter carbohydrate and lipid metabolism, no history of hypo- and hyperthyroidism, liver or kidney diseases. Potential candidates were recruited from health fairs conducted by Native American tribes and advertisement at large. Participants were provided with a verbal and written explanation of the study. They were assured that their participation in the study was completely voluntary and their information would be kept confidential. After signing the consent form approved by the IRB, detailed medical and diet histories were obtained.

Experimental design

The experimental design was a randomized controlled design. Eligible subjects were randomly assigned to one of the following three treatment groups (n=18 per treatment group): 1) control; 2) flaxseed; and 3) flaxseed+additional fiber for a period of 3 months. Approximately, thirty grams of flaxseed was provided to each of the subjects in the flaxseed and flaxseed + fiber groups in the form of bread, muffins, and powder as part of their daily diet. The baked products were stored at -20^{o} C prior to distribution to subjects. They were provided to the subjects frozen and subjects were instructed to keep them frozen until ready for consumption. Subjects thawed the products overnight in the refrigerator or defrosted them in a microwave oven for an immediate consumption. The treatment regimens were distributed to subjects on a biweekly basis. The participants in the flaxseed and flaxseed+fiber treatment groups were asked to consume 2 muffins (~10 g of flax), 2 slices of bread (~3 g of flax) and 2 tablespoon of flax powder (~16 g) per day, whereas the participants in control group consumed 2 oat muffins and 2 slices of bread per day. Additional ~ 8g dietary fiber was added to the flaxseed+fiber treatment group. The flaxseed+fiber treatment regimen was included to determine if the combination of these two components will have synergistic or additive effect in improving glucose profile compared to flaxseed alone. The treatment regimens provided similar amounts of calories, and protein. Participants were advised to adjust their daily food intake in order to maintain their caloric intake. Composition of the study products is presented in Table 1.

Dietary assessment and anthropometric measurement

Height, weight, hip and waist circumferences were measured and the waist to hip ratio was calculated at baseline and at the end of the study. The total body fat, and lean mass content was measured using bioelectric impedance (Biodynamic Model 310e, Biodynamics Corp., Seattle) which measures the impedance to the electric current through the body. Higher impedance means greater body fat content. With the exception of height, all other measurements were repeated at monthly visits. If weight gain was observed during the course of the study, the participants were counseled regarding their daily food intake and were advised to make simple adjustments in their daily caloric intakes.

To ensure compliance, the following steps were taken 1) a monthly calendar was given to the participants to record their intake of regimens daily; 2) participants were asked to return unused dietary regimens and were given new supplies and a new calendar during their monthly visits; 3) a bi-monthly 24 hr food recall over the phone was done on a random basis to check for compliance; 4) after three months of treatment blood draw, anthropometric measurements, physical activity and dietary assessment were repeated. An additional 7-day physical activity questionnaire enquiring about the activities of the participants was also noted down.

Blood collection and processing

Fasting venous blood samples, approximately 20 mL, were obtained from each participant in ethylendiaminetetraacetic acid (EDTA) and non-EDTA vacutainer tubes at

the beginning and at the end of study. All blood samples were placed on ice until processing. Plasma and serum were separated by centrifuging the samples at 2500 g for 20 minutes at 4 ^{o}C. Serum and plasma were aliquoted and stored at -80 ^{o}C until analyses. At the end of the study all samples were run together to minimize variability.

Serum analyses

Fasting blood sugar and glycated hemoglobin from serum and whole blood were analyzed using ACE Clinical Analyzer (Monclair, NJ). The clinical analyzer was calibrated using Gemcal reference serum (Alfa Wassermann, Inc; West Caldwell, NJ) before each test. Alfa Wassermann quality control (QC)-1 and (QC-2) were used as control in all test.

In serum glucose reacts with ATP in the presence of hexokinase and magnesium. Hexokinase helps in catalyzing phosphorylation reaction and converts glucose to glucose -6-phosphate. In the presence of glucose-6-phosphate dehydrogenase and (NAD^{+}), oxidation of glucose-6-phosphate to glucose-6-phosphogluconate and nicotinamide adenine dinucleotide (NADH) takes place. The NADH produced is absorbed at 340 nm which was measured bichromatically at 340 nm/378 nm is directly proportional to the initial amount of glucose.

Glycated hemoglobin in whole blood was estimated by the agglutination inhibition assay method. It determines the quantity of hemoglobin A_{1c} (HbA_{1c}) and total hemoglobin (THB) in whole blood. Hemoglobin A_{1c} agglutinator agglutinates with hemoglobin A_{1c} (HbA_{1c}) antibody in deficiency of hemoglobin A_{1c} (HbA_{1c}) in the whole blood. If the (HbA_{1c}) concentration is more in the blood it competes with agglutinator to bind with the (HbA_{1c}) antibody binding sites and inhibits agglutination of Hemoglobin

A_{1c} agglutinator. The absorbance is monitored monochromatically at 592 nm and is indirectly proportional to the (HbA_{1c}) in the whole blood sample. Then (THB) is measured by alkaline hematin D-575 method. In this test, all the hemoglobinic derivatives are transformed in to alkaline hematin. A green colorsolution is produced and measured bichromatically at 573 nm and 692 nm. The concentration of the color produced is directly proportional to the (THB) concentration. Then percent hemoglobin is calculated by the following equation:

HbA_{1c} * 26.44/THB

Fasting serum insulin was analyzed by radioimmuneassay (RIA) method using human insulin-specific RIA kit from LINCO Research (St.Charles, MO). Human insulin-specific RIA kit is used to quantitatively determine insulin in blood or serum by double antibody technique. In RIA procedure, a known concentration of a labeled antigen (^{125}I-labeled human insulin) is incubated with a constant diluted antiserum (Human Insulin Antiserum) with a purpose to limit the binding sites of antigen on the antibody. If an unlabelled antigen is added to the sample constantly, it competes with the labeled antigen to bind to the limited binding sites on the antibody. Therefore, there will be a decrease in binding of labeled antigen to the antibody binding sites as the concentration of unlabelled antibody increases. Thus, a standard curve is created with an increase in the concentrations of the standard unlabeled antigens. From this curve, the amount of unknown samples can be calculated. This method measures the true insulin levels.

Data management and statistical analysis

All data obtained about the subjects were kept in lock cabinets with limited accessibility. Upon completion of the study the data from laboratoryanalyses and questionnaires w ere entered into spreadsheets and double checked for accuracy.

The experiment was a completely randomized design with repeated measures. Treatment is the main plot factor and was applied to each subject, while baseline andfinal values were considered the repeated measures. Results were expressed as mean ± SE. The significance of percentage differences between and within treatments was assessed with Student's *t* test for paired data (two-tailed). Data were analyzed using PC SAS version 8.2 (SAS Inst., Cary, NC) using PROC GLM MIXED. The primary outcome variables were the change from baseline in fasting blood glucose, insulin and glycated hemoglobin values and homeostasis assessment model of insulin resistance (HOMA-IR.). Analysis of variance technique was used to assess treatment (flaxseed vs. flaxseed with additional fiber vs. control) differences. Significant differences were determined using alpha level as 0.05

CHAPTER IV

RESULTS

Subject participation

Out of the 55 participants recruited, 13 dropped out of the study. Nine women completed the control regimen, 17 completed the flaxseed regimen and 16 completed flaxseed + additional fiber regimen. One woman dropped out of flaxseed treatment group complaining of gastrointestinal discomfort. Subjects complaining of gastrointestinal problem and unpalatability of study food were given suggestions to incorporate the study food into their diet to reduce these problems. Four of the participants from the control group relocated and hence could not continue with the study. Eight subjects, 4 from control regimen, and 2 each from the flaxseed treatment groups did not give any reason for dropping out of the study.

Nutrient intake

The baseline daily nutrient intake was determined using a food frequency questionnaire validated by the National Institutes of Health (NIH). There were no differences in the baseline caloric intake as well as protein, carbohydrate, fiber, total fat, saturated fat, polyunsaturated fat and calcium intake (Table 2) among the groups. The nutrient intake of the subjects during the study was monitored by a 24-hr food recall conducted over the phone. There were no changes in caloric intake, carbohydrate and

polyunsaturated fat consumptions among the groups while they were takingthe study regimen (Table. 3). There was a tendency for an increase in protein (P=0.074) total fat (P=0.062), and saturated fat (P=0.099) intake in the flaxseed groups. Dietary fiber (P=0.000) and calcium (P=0.015) intake were significantly increased in the flaxseed group.

Anthropometric measurements

The results of the anthropometric measurement are shown in Table 4. Age range for the study participants was 47-62 yrs. There were no significant changes in body weight after 3 months of consuming the dietary regimens. However, body weight of subjects in the control group tended (P=0.066) to decrease after 3 months of being on the study regimen. The body mass index (BMI) did not change among the subjects in any of the treatment groups but when compared to the baseline values there was a decrease in mean body weight of subjects in all three treatment groups. But, there was a significant difference in the mean waist circumference in the flaxseed group (P=0.01) but not in control and flaxseed+fiber group. The hip circumference was decreased significantly from baseline in the flaxseed group (P= 0.03), but the other groups showed no such a change. The percent body fat increased significantly among women in the flaxseed with additional fiber treatment group (P= 0.02).

Serum analyses

The glucose parameters are presented in Table 5. Consumption of 25-30 grams of flaxseed had no significant effects on blood glucose, insulin and HbA1 when baseline values were compared with their corresponding final values of the treatment groups. On

the average, women in the flaxseed + additional fiber experienced a 5% increase in final values of glucose compared to their baseline values (P=0.20). But there was a significant increase in the final fasting blood glucose values in control group (P = 0.0147). Also, insulin tended to increase in the control group but not in flaxseed groups. According to our homeostasis assessment model of insulin resistance HOMA-IR data, there were no improvements in insulin resistance in any of the treatment groups.

CHAPTER V

DISCUSSION

The findings of the present study indicate that daily consumption of approximately 30 grams of whole ground flaxseed incorporated in to bread, muffins and energy drink did not show any change in final values of the fasting blood glucose (FBS) , insulin and glycated hemoglobin levels in Native American postmenopausal women. A significant increase in the FBS and insulin values were observed in the control group which were fed white bread and muffins. This finding shows that, although flaxseed and flaxseed + fiber treatment did not enhance the glycemic profile, still it has some treatment effect by maintaining the glycemic profile constant from baseline until the end of the study in the. Thus, it is reasonable to postulate that incorporation of flaxseed might improve hyperglycemia and hyperinsulinemia, if it is integrated in other foods rather than bread which in general has high glycemic index (308).

Since no study was conducted on the effect of flaxseed on glucose status in Native American postmenopausal women, it is difficult to compare the consistency of the results of our study with similar studies. However, the sustaining effect of flaxseed on glucose homeostasis to some extent agrees with the findings of an earlier study by Lemay et al (300) in which twenty five menopausal women were randomized to a crossover treatment with either 40 grams of crushed flaxseed, or 0.625 mg of conjugated equine estrogen or

combined with 100 mg of micronized progesterone daily for two months. The findings of that study (300) indicated that intake of 40 grams crushed flaxseed improved the glucose and insulin levels as successful as oral estrogen-progesterone administration. Intake of crushed flaxseed without incorporating it in bread and muffins, unlike in our study, might have significantly improve glucose profile of postmenopausal women who participated in the present study.

In a study by Cunnane et al. 1993 (301) on six healthy volunteers (five males and two females) with average age of 30 ± 4 years were randomly assigned to 50 grams carbohydrate from either flaxseed or wheat flour in the form of bread. After an over night fast, blood samples were collected and analyzed for every 15 minutes for one hour. The results showed that there was a 28% decrease in the incremental area under the blood glucose curve in the flaxseed group compared to the wheat regimen. Nonetheless, the study by Cunnane and colleagues (301) had a very small sample size of healthy human subjects and it makes difficult to draw firm conclusions from their findings. The bioavailability of sex hormones in addition to estrogenic properties of flaxseed might have added to the lowering effect of glucose levels in their study (302). In the earlier clinical trials, the amount of flaxseed used was approximately 40-50 grams. It was suggested that daily incorporation of 50 grams high α- linolenic acid flaxseed, produce encouraging effects in humans regarding glucose responses. However, according to the United States Food and Drug Administration (FDA) incorporation of 12 grams of flaxseed into 100 grams of food is generally recognized as safe (GRAS) (303). The FDA recommendation may a bit out of data and its recommendation is based on older varieties of flaxseed which contained much higher cynogenic compounds. More recent human data

suggest that inclusion of up to 50 grams of flaxseed can be considered safe and may enhance the glycemic profile of postmenopausal women, particularly the Native American postmenopausal women as is the case in the present study.

There are also studies that are consistent with our findings (304, 305, 306). In a randomized cross over trial study by Juntunen KS and colleagues (304), twenty postmenopausal women were assigned to rye bread, rich in lignans, (307) and wheat bread for 8 weeks with an 8-week washout period. No significant differences were observed in the baseline and final values of fasting plasma glucose and insulin which were the main measures of insulin-resistance in rye bread and wheat bread groups. Although, decrease in plasma insulin values were observed with rye bread period, but not significant (p=0.993).The effects of flaxseed and flaxseed + fibereffects in our study were similar to rye bread in sustaining glycemic profile. On the other hand, there was a significant increase in the final values of fasting glucose (P=0.0147) in the control regimen group of our study which is in contrast to the findings of earlier studies by Jutntunen et al. (304) and Leinonen et al. (305). Therefore, collective review of literature advocates that, inclusion of foods with high glycemic index (308, 309, 310) in the daily diet may increase fasting blood glucose levels. Hence, the consumption of wheat bread may have added to the elevated fasting glucose levels in the control group in our study. Although, the types of bread seemed to have an effect on the fasting glucose values in the control group, there were no changes in the fasting glucose, glycated hemoglobin and insulin levels in the flaxseed and flaxseed +fibergroups. This suggests that there might be some treatment effects due to flaxseed and fiber in maintaining the glycemic profile.

In the present study, although, there was not a significant difference in the intake of protein (P=0.718) and fat (P=0.613) in all the three groups at baseline, an increased tendency in protein (P= 0.074) and total fat (P=0.062), saturated fat (P=0.09) intakes were detected in flaxseed and flaxseed + fiber groups when assessed by 24-hr food recall during the treatment period. Promising data put forward that both quantity and quality of protein (311) and fat (312) intake influence carbohydrate metabolism Protein intake stimulates the production of glucogenic substrates such as glutamine, alanine and lactate which undergo oxidation to produce glucose. Excess availability of amino acids alters the ratio of glucoregulatory hormones (glucagon and insulin) in diabetics. The glucagons response to amino acids will be high in diabetics and results in the hepatic gluconeogenesis and glycogenolysis and inhibits the ability of insulin to suppress the endogenous production of glucose contributing to hyperglycemia and stimulating the pancreatic beta cells to secrete more insulin resulting to hyper insulinemia and insulin resistance (311, 313, 314,). Thus, an increased trend in the protein intake could be one possibility of not finding improvement in the glycemic profile of women receiving the flaxseed regimens.

Similarly, high intake of total fat and saturated fat also worsens carbohydrate metabolism by increasing the production of free fatty acids which in turn compete with the glucose uptake by the muscles. Surplus availability of plasma free fatty acids through diet accumulates in the adipose tissue and non- adipose tissues such as liver and muscle and decreases the intracellular concentration of glucose resulting in hyperglycemia. To maintain euglycemic condition, pancreatic beta cells are stimulated to produce excess insulin resulting in hyperinsulinemia and finally deteriorating the function of beta cells

resulting in insulin-resistance (315-317). Recent literature suggests that it is the quality of fat that influences insulin sensitivity and insulin resistance(312) . Many studies have demonstrated that intake of saturated fat deteriorates insulin sensitivity and increases insulin resistance (318, 319, 320), whereas polyunsaturated fatty acids (PUFA) enhances insulin sensitivity (321, 322, 323). It has also been identified that saturated fat is one of the most important dietary variables contributing to the progression of type 2 diabetes in ethnic populations such as Native Americans (324, 325), Japanese Americans (326), Mexican Americans (327). In our study, the high intake of total fat and saturated fat might have gone beyond the effect of flaxseed and flaxseed + fiber in the treatment groups.

The glycemic index of plant foods, particularly grains, are lower when they are less refined and it is generally believed that incorporation of whole kernels in the baking products such as bread and muffins improve their glycemic and insulin profile rather than high fiber alone (305). Method of processing such as heating, cooking, baking, size of the grain and grain structure (304, 308, 328) may also affect their glycemic index (305). Thus baking process may rise the GI of breads and control the post prandial and fasting glucose levels. However, baking breads at low temperatures for longer time might produce better results in controlling glucose by hampering the digestion of bread and increasing the formation of resistant starch and retrogradation of amylase (305). Therefore, processed flaxseed in the form of breads and muffins in our study theoretically should have been more effective in reducing glucose and improving insulin levels ground flaxseed. However, results from earlier study by Leininen et al (305) using whole kernel rye bread suggest that intact structure of the kernel ruptures during the baking process

and gets uncovered to enzymatic hydrolysis of starch. This might be a possibility in our study that ground flaxseed during baking process might have been subjected to the above mentioned process and resulted in no improvement of the glycemic profile in the treatment groups.

As it was discussed earlier, it has been demonstrated that, physical form of food is an important factor in controlling glycemic response (329). Jenkins and his colleagues reported that intake of pasta (white spaghetti) reduced blood glucose level remarkably compared to white and whole meal bread. It was also documented in another study (330), thatwhite spaghetti and whole meal spaghetti were able to significantly lower glycemic responses compared to white bread and Semolina bread. Therefore, many non nutrients factors influence the glycemic index of food which in turn affects the glycemic profile. Our study might have produced pronounced results, if we had used ground flaxseed in conjunction with low glycemic index foods such as pasta, spaghetti rather than high glycemic index foods like bread and muffins.

Overall, the findings of our study suggest that intake of 25 to 30 grams of flaxseed incorporated into baked products by postmenopausal Native American for 3 months can sustain their glycemic profile.

Table 1: Nutrition facts of the study products

	Bread			Muffin			Powder	
Treatment	A	B	C	A	B	C	B	C
Serving size		**1 slice**			**1 piece**		**2 Tbsp**	
Energy (kcal)	70	80	70	150	160	130	55	16
Flaxseed (g)	-	1.5	1.5	-	5	5	9	
Carbs (g)	12	16	7	25	22	21	5	
Protein (g)	2	3	8	5	4	4	3	
Fat (g)	1	1	4	4.5	6	4.5	6	
Fiber (g)	0.5	3	4	1	2	5		

A= Control group, B= Flaxseed group, C= Flaxseed + fiber group. Values are as mentioned on the product labels provided by Natural oven of Manitowic,WI.

Table 2: Baseline food intake measured with food frequency questionnaire

Measures	Control (A)	Flaxseed (B)	Flaxseed with additional fiber (C)	*P* Value
Total energy (kcal)	1123± 104	1683± 300	1784 ±684	0.541
Nutrients (g)				
Protein	47 ±14	65± 47	59± 25	0.718
Carbohydrates	136± 42	195±106	229±91	0.285
Dietary fiber	13 ±2	18 ±13	16 ±6	0.658
Total fat	45±16	77± 67	74± 31	0.613
Saturated fat	11± 3	23±17	23±11	0.399
Polyunsaturated fat	10± 2	17± 16	17± 8	0.685
Minerals (mg)				
Calcium	366 ±129	661± 417	648± 449	0.529

Data represent least square mean ± SE. Differences were considered significant at value <0.05.

Table 3: Food intake during the study by 24hr food recall

Measures	Control (A)	Flaxseed (B)	Flaxseed with additional fiber (C)	*P* Value
Total energy (kcal)	1511± 193	1994± 161	1967± 161	0.195
Nutrients (g)				
Protein	46± 8	67± 5	69± 6	0.074
Carbohydrates	195± 32	252± 26	218± 19	0.325
Dietary fiber	12± 5[c]	22± 8[b]	30± 10[a]	0.000
Total fat	49± 27	78± 24	71± 28	0.062
Saturated fat	12± 3	20 ±2	20± 3	0.099
Polyunsaturated fat	5± 2	8± 1	10± 2	0.230
Minerals (mg)				
Calcium	476± 72[c]	814 ±68[a]	654± 66[b]	0.015

Data represent least square mean ± SE. Differences were considered significant at P value <0.05.

Table 4: Subject characteristics and anthropometric measurements

	Control (A)			Flaxseed(B)			Flaxseed+Fiber (C)		
	Baseline	Final	*P* Value	Baseline	Final	*P* Value	Baseline	Final	*P* Value
n	17	9	-	20	17	-	18	16	
Age, *yrs*	50.8 ±3.1	-	-	57.0±2.2	-	-	60.4±2.5	-	-
Weight, *kg*	75.0±5.5	72.1±7.0	0.06	82± 3.6	81.5 ±4.3	0.61	79.1±4.2	78.5 ±4.0	0.51
BMI	28.9±1.9	28.1±1.9	0.17	30.8±1.4	31.1±1.4	0.42	30.8±1.4	30.5±1.4	0.39
Hip* *inches*	42.4 ±1.2	43.3±1.4	0.30	45.2±1.3^{a}	43.8 ±1.5^{b}	0.03	43.5±1.2	42.7 ±1.2	0.16
Waist*, *inches*	36.7± 2.3	36.3± 2.6	0.62	39.8± 1.4^{a}	38.4 ±1.5^{b}	0.01	39.3 ±1.1	39.1 ±1.1	0.60
Waist/ hip ratio	0.86	0.83	0.47	0.88	0.88	0.45	0.95	0.91	0.38
Body Fat*, %	38.2 ±1.6	35.7 ±2.5	0.20	39.9 ±1.2	39.1 ±1.5	0.56	40.1± 1.4^{b}	43.3± 1.5^{a}	0.02
Fatbody wt	29.2 ±2.3	26.5± 2.6	0.10	33.5 ±1.45	32.7 ±1.5	0.50	32.3 ±1.1	34.2 ±1.1	0.12
Lean Body Wt	45.7± 2.7	45.8 ±3.0	0.93	48.8 ±1.7	49.0 ±2.0	0.77	45.6± 2.1	44.9 ±2.6	0.31

Data represent least square mean ± SE. Differences were considered significant at *P* value <0.05. In each groups the values that do not share the same superscript letters are significantly different. BMI=Body mass index

Table: 5 Effects of three-month flaxseed supplementation on serum glucose parameters in postmenopausal women

A (Control)					B (Flaxseed)				C (flaxseed+fiber)			
	Base line	final	P value	% change from base line	Base line	final	P value	% change from base line	Base line	final	P value	% change from base line
Glucose (mg/dl)	91.4± 4.9	102± 5.1	0.0147	12.47	104.3± 2.6	104± 2.9	0.30	0	101± 4.5	106± 4.9	0.20	5
Insulin (µU/ml)	19.38± 5.3	31.44± 5.6	0.12	62.22	14.4±4.20	17.62± 4.20	0.59	22.36	16.97±4.6	17.14± 4.8	0.9	1.001
P_A_{1c}	5.8±0.16	5.8±0.1	0.9115	0	5.7±0.1	5.9±0.1	0.4669	3.5	5.6±0.14	5.7±0.14	0.7702	1.78
HOMA-IR	5.80± 0.34	6.55± 0.35	0.13	12.93	5.79± 0.26	5.872± 0.26	0.84	1.38	5.64± 0.32	5.86± 0.38	0.66	3.9

Data represent least square mean $\pm$ SE. Differences were considered significant at *P* value <0.05.; n= 9 for control group, n= 17 for flaxseed group, n= 16 for flaxseed with additional fiber group. P_A_{1c} = Percentage Hemoglobin, HOMA-IR= Homeostatic Model Assessment of Insulin Resistance

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APPENDIX

Oklahoma State University
Institutional Review Board

Protocol Expires: 2/3/2004

Date : Monday, July 28, 2003 IRB Application No HE0345

Proposal Title: DOES FLAXSEED REDUCE THE RISK OF CVD IN NATIVE AMERICAN WOMEN?

Principal
Investigator(s) :

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Reviewed and
Processed as: Expedited

Approval Status Recommended by Reviewer(s) : Approved **Modification**

Please note that the protocol expires on the following date which is one year from the date of the approval of the original protocol:

Protocol Expires: 2/3/2004

Signature Carol Olson

Carol Olson, Director of University Research Compliance

Monday, July 28, 2003
Date

Approvals are valid for one calendar year, after which time a request for continuation must be submitted. Any modifications to the research project approved by the IRB must be submitted for approval with the advisor's signature. The IRB office MUST be notified in writing when a project is complete. Approved projects are subject to monitoring by the IRB. Expedited and exempt projects may be reviewed by the full Institutional Review Board.

VITA

Kiranmayi Korlagunta

Candidate for the Degree of

Master of Science

Thesis: THE EFFECTS OF FLAXSEED ON GLUCOSE PROFILE IN NATIVE AMERICAN POSTMENOPAUSAL WOMEN

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Name:Kiranmayi Korlagunta Date of Degree: July, 2006

Institution: Oklahoma State University Location: Stillwater, Oklahoma

Title of Study: THE EFFECTS OF FLAXSEED ON GLUCOSE PROFILE IN NATIVE AMERICAN POSTMENOPAUSAL WOMEN

Pages in Study: 84 Candidate for the Degree of Master of Science

Major Field: Nutritional Science

Scope and Method of Study: The onset of menopause can indirectly disturb glucose homeostasis and increase the risk of diabetes. Evidence has shown that diabetes markedly affect minority ethnic populations particularly American Indians. A small number of studies documented that phytoestrogens play a favorable role in controlling hyperglycemia and reduce the risk of menopause induced diabetes. The purpose of the present study was to examine the effects of intake of flaxseed (a rich source of phytoestrogens) on the glucose status of Native American postmenopausal women. Fifty five Native American postmenopausal women aged 47-63 years who were not on hormone replacement therapy and had boarder line hyperglycemia (> 110 and < 126 mg/dl) were enrolled and assigned randomly to one of the three dietary regimens (control, flaxseed, flaxseed +fiber) for three months. Treatment regimens were in the form of bread, muffins, and flaxseed powder.

Findings and conclusions: Daily intake of flaxseed given in the form of bread, muffin and flaxseed powder did not demonstrate any significant effects in the baseline and final values of glucose, glycated hemoglobin and insulin levels in both the treatment groups. Incorporation of ground flax seed in low glycemic index foods might produce beneficial effects in maintaining glucose profile

ADVISER'S APPROVAL: Dr. Bahram H. Arjmandi