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**DISSERTATION**

# THE EFFECT OF HIGH-FIBER OAT VERSUS WHEAT CEREAL ON FACTORS ASSOCIATED WITH CARDIOVASCULAR DISEASE RISK

Submitted by

Brenda Davy

Department of Food Science and Human Nutrition

In partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2001

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We hereby recommend that the dissertation prepared under our supervision by Brenda Davy entitled THE EFFECT OF HIGH-FIBER OAT VERSUS WHEAT CEREAL ON FACTORS ASSOCIATED WITH CARDIOVASCULAR DISEASE RISK be accepted as fulfilling in part requirements for the degree of Doctor of Philosophy.

Committee of Graduate Work:

Advisor

Department Head

## ABSTRACT OF DISSERTATION

## THE EFFECT OF HIGH-FIBER OAT VERSUS WHEAT CEREAL ON FACTORS ASSOCIATED WITH CARDIOVASCULAR DISEASE RISK

Foods rich in dietary fiber, particularly those high in soluble fiber, have been recognized by major health organizations as beneficial for cardiovascular disease prevention. According to the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001), major risk factors for cardiovascular disease include elevated blood total and low-density lipoprotein cholesterol (LDL-C) concentrations. Additionally, the American Heart Association (2000) reports that one in four adults in the United States have hypertension, a condition that significantly increases cardiovascular disease mortality. The purpose of this dissertation was to examine the effect of increased fiber-rich oat cereal consumption, as compared to fiber-rich wheat cereal consumption, on blood lipid and lipoprotein concentrations and casual resting and 24-hour arterial blood pressure in middle aged and older men.

Thirty-six overweight middle-aged and older men (BMI 25-35kg/m$^2$, aged 50-75 y) with elevated BP (systolic BP 130-160mmHg and/or diastolic BP 85-99mmHg) were randomly assigned to consume an additional 14 g of dietary fiber per day in the form of

oat (5.5g β-glucan, n=18) or wheat cereals (no β-glucan, n=18) for 12 weeks. Measurements of plasma lipids and lipoprotein subclasses using proton nuclear magnetic resonance (NMR) spectroscopy were performed before and after the intervention. Casual resting arterial BP was measured at baseline and after four, eight, and 12 weeks of the intervention. 24-hour ambulatory arterial BP was measured at baseline and after 12 weeks of the intervention.

There were significant ($P<0.05$) time-by-treatment interactions for LDL-C (Oat:-2.5%; Wheat:+8.0%), small LDL-C (Oat:-17.3%; Wheat: +60.4%), LDL particle number (Oat:-5.0%; Wheat:+14.2%) and LDL-C/HDL-C ratio (Oat:-6.3%; Wheat:+14.2%). There was a trend for a time-by-treatment interaction for TC (Oat: -2.5%; Wheat:+6.3%, $P=0.08$), TG (Oat:-6.6%; Wheat:+22.0%, $P=0.07$) and VLDL-TG (Oat:-7.6%; Wheat:+2.7%, $P=0.08$). There was no effect of the oat cereal on HDL-C, HDL-C subclasses, or LDL, HDL or VLDL particle diameter. Neither casual systolic or diastolic BP changed as a result of the 12-week intervention in the oat (138/89 vs. 135/88 mmHg) or wheat (142/90 vs. 140/91 mmHg) groups, respectively (all $P>0.05$). Further, 24-hour, daytime, and nighttime SBP and DBP did not decrease with the intervention.

In conclusion, the addition of two large servings of oat as compared to wheat cereal results in lower concentrations of small, dense LDL-C and LDL particle number without producing adverse changes in blood TG or HDL-C concentrations in middle-aged and older overweight men. These beneficial alterations may contribute to the cardioprotective effect of oat fiber. However the consumption of fiber-rich oat cereal (or fiber-rich wheat cereal) has no detectable effect on resting or 24-h ambulatory blood pressure in middle aged and older overweight men with elevated blood pressure. Thus,

our findings do not suggest that the cardioprotective effect of oat consumption is due to an arterial blood pressure-lowering effect.

Brenda M. Davy

Department of Food Science and Human Nutrition

Colorado State University

Fort Collins, CO 80523

Fall 2001

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**BD**

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# CHAPTER ONE

## INTRODUCTION

According to recent estimates, cardiovascular diseases (CVD), including coronary heart disease (CHD), hypertensive disease, rheumatic heart disease, and cerebrovascular disease, are responsible for more than 40% of all deaths in the United States and 12 million deaths world wide (American Heart Association, 2000). Of the estimated 60,800,000 Americans that have one or more form of CVD, 82% have high blood pressure and 20% have CHD (American Heart Association, 2000).

Coronary heart disease, also referred to as ischemic heart disease (IHD), is the leading cause of death in our country (American Heart Association, 2000), accounting for 49% of total CVD deaths. Major risk factors for CHD include elevated blood total and low-density lipoprotein cholesterol (LDL-C) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-94) indicates that 52% of non-Hispanic white men aged 20 to 74 have a blood cholesterol concentration over 200mg/dl (NHANES III, 1988-94). Almost 50% of non-Hispanic white men have low-

density lipoprotein cholesterol concentrations greater than or equal to 130 mg/dl, and are thus considered at increased risk for CHD (NHANES III, 1988-94).

While it only directly accounts for about 5% of total CVD deaths in the United States, one in four adults in the United States has hypertension (American Heart Association, 2000). This estimate translates to an economic cost of approximately $37.2 billion in direct medical expenses as well as lost productivity (American Heart Association, 2000). Elevated arterial blood pressure increases risk of death from stroke, which is responsible for approximately 17% of CVD deaths (American Heart Association, 2000).

Dietary and other lifestyle changes (e.g., increased physical activity and body weight control) are recommended as the "foundation" for primary prevention of CHD and CVD (AHA Scientific Statement, 2000; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Major health organizations continue to advocate a diet that is low in fat, saturated fat, and cholesterol, and high in fiber-rich foods including fruits, vegetables, and grains for reducing risk of CVD and other chronic diseases (AHA Scientific Statement, 2000; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; United States Department of Agriculture, 2000). Additionally, some organizations have recognized the potential cardiovascular benefit of increased soluble fiber consumption, such as β-glucan contained in oat products (AHA Scientific Statement, 2000; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). For this reason, the objective of this dissertation was to investigate the effect of fiber-rich oat versus wheat cereal consumption on factors associated with cardiovascular disease risk,

specifically, blood lipid and lipoprotein concentrations and casual resting and 24-hour arterial blood pressure, in middle aged and older men.

**Research Objectives:**

The main purpose of these studies was to examine the effect of high-fiber oat versus wheat cereal on factors associated with cardiovascular disease risk in middle-aged and older men. Specifically, the **primary objectives** were to:

1. *Determine the effect of increased high-fiber oat or wheat cereal consumption on plasma lipid and lipoprotein concentrations, lipoprotein subclasses, lipoprotein particle size, and LDL particle number in middle aged and older men;*
2. *Determine the effect of increased high-fiber oat or wheat cereal consumption on casual resting and 24-hour arterial blood pressure in middle aged and older men with high-normal to Stage 1 hypertension.*

Additionally, we compared multiple assessment reporting techniques for the quantification of dietary fiber intake. Since this was not a primary objective of these studies, this report is included as *Appendix A*.

**Research Hypotheses:**

The primary **research hypotheses** were as follows:

1. *The consumption of whole-grain oat cereal, rich in soluble fiber, will favorably modify blood lipid and lipoprotein concentrations and characteristics as compared to whole-grain wheat cereal in middle aged and older men;*

2. *Resting casual and 24-hour arterial blood pressure will be reduced by the consumption of fiber-rich oat or wheat cereal in middle aged and older men with high-normal to Stage 1 hypertension.*

**Delimitations:**

This investigation was **delimited** as follows:

1. Our study population included only sedentary, non-smoking men from Fort Collins and its surrounding community. They were between the ages of 50 and 75, with a body mass index (BMI) of 25 to 35 $kg/m^2$, with mild to moderate hypertension (systolic blood pressure (SBP): 130-159 mm Hg, diastolic blood pressure (DBP): 80-99 mm Hg), but in otherwise good health.

2. Only men whose reported habitual dietary fiber intake was less than 30g/day were included in the study.

3. Prior to enrollment, all subjects were given the opportunity to taste-test the cereal products used in the study; only those who agreed to comply with daily consumption of the products for twelve weeks were included.

4. Subjects were only included if they provided informed consent and agreed to comply with the study protocol.

5. The high-fiber cereal products used in this study were limited to two "hot" cereals and two "ready-to-eat (RTE)" cereals. The two oat cereals used were regular Quaker Oats and Quaker Oat Bran Squares; the two wheat cereals used were Mother's Whole Wheat Hot Natural Cereal and Kellogg's Frosted Mini-Wheats. Thus, our results can only be generalized to those types of fiber-rich cereals.

**Limitations:**

The **limitations** of these studies were:

1. This study was conducted as an outpatient intervention study, with subjects in the "free-living" state. We were not able to control dietary intake other than the daily inclusion of the cereal products during the intervention. The cereal combinations provided approximately 500 kcal per day, therefore subjects had to adjust their habitual intake to maintain a stable body weight. As a result, unintentional dietary changes occurred (e.g., a reduction in fat, saturated fat, and cholesterol intake). With the exception of dietary magnesium intake, these changes were not significantly different between the two groups.

2. Subjects were instructed to maintain a stable body weight throughout the study. Body weight was monitored on a biweekly basis; however, a significant increase in mean body weight of 0.8 kg was noted. This increase was not different between the two groups.

**Assumptions:**

It was assumed that:

1. Subjects accurately reported their dietary intake and activity level, and that the quantification of these factors was accurate.

2. A four-day period of recording dietary intake was representative of habitual dietary intake in these subjects.

3. Subjects accurately reported their compliance with the cereal consumption.

4. All clinical and laboratory measurements made as part of the study (e.g., body composition, arterial blood pressure, blood lipid and lipoprotein measurements, blood glucose and insulin measurements) were accurate.

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## CHAPTER TWO

# A Review of the Literature: The Effect of Fiber-Rich Carbohydrates on Features of Syndrome X

Outline:

*Introduction*

Part One

*Description of Syndrome X*
*Prevalence and Significance of Syndrome X*
*"Risk Factors" for Syndrome X*
*Features of Syndrome X*

Part Two

*What are "Fiber-Rich Carbohydrates"?*
*Beneficial Effects of Fiber-Rich Carbohydrates*
*Current Recommendations for Intake of Dietary Fiber vs. Current Intake*

Part Three

*Effect of Fiber-Rich Carbohydrates on Features of Syndrome X*
*Conclusions and Applications*

## *Introduction*

A high-carbohydrate, low-fat (HCLF) diet has traditionally been recommended by major health organizations to reduce chronic disease risk. Recently it has been suggested that a HCLF diet is inappropriate for individuals with the Insulin Resistance Syndrome, also referred to as the Metabolic Syndrome, or Syndrome X (Reaven, 2000). Two arguments against the use of a HCLF diet in this population are generally cited. First, there is evidence that an increase in carbohydrate intake with a concomitant decrease in fat intake produces adverse changes in blood lipid and lipoprotein concentrations, e.g. an

increase in blood triglyceride (TG) and small, dense low-density lipoprotein cholesterol (LDL-C) concentrations and a decrease in high-density lipoprotein cholesterol (HDL-C), in some individuals (Krauss and Dreon, 1995; Krauss, 2001; Mittendorfer and Sidossis, 2001; Parks and Hellerstein, 2000). Second, HCLF diets may cause greater postprandial glucose and insulin concentrations in insulin resistant individuals (Riccardi and Rivellese, 2000; Reaven 2000), possibly leading to further impairment in insulin action. This has led some to conclude that a higher fat diet in which saturated fat is replaced with mono- and poly-unsaturated fat is preferable to a HCLF diet (Reaven, 2000).

While this approach may be effective for some, maintaining a higher fat intake may contribute to "passive overconsumption" (Blundell and Macdiarmid, 1997). In this regard, most researchers in the area of weight management continue to recommend a HCLF diet (Wing and Hill, 2001). Importantly, studies showing adverse effects of HCLF diets have generally not taken into account the dietary fiber content of the diet. A HCLF diet that is *rich* in dietary fiber may not produce the same adverse changes in blood lipids and lipoproteins as a HCLF diet limited in dietary fiber (Anderson 2000). Additionally, the blood lipid and lipoprotein response to an increase in carbohydrate intake may differ depending upon the *type* of fiber-rich carbohydrate consumed, e.g. predominantly soluble versus insoluble fiber (Davy et al., 2001).

The purpose of this review is to discuss characteristics of Syndrome X and to present findings related to the effect of fiber-rich carbohydrates, particularly those high in soluble fiber, on metabolic abnormalities associated with this syndrome. Practical applications for the utility of a HCLF diet, which includes fiber-rich carbohydrates for individuals with Syndrome X, will be presented.

# Part One

## *Description of Syndrome X*

Syndrome X refers to a condition in which several specific abnormalities, depicted in Figure 2-1, are clustered together with insulin resistance as the primary defect. Increased intra-abdominal adipose tissue (e.g., visceral obesity) may be the initial culprit in the development of this syndrome, although a causal relationship has not yet been proven (Frayn, 2000). Elevated stress-related cortisol secretion has also been associated with this syndrome (Bjorntorp and Rosmond, 2000), as have abnormal uric acid metabolism and polycystic ovary syndrome (Reaven, 2000). Recently, elevated concentrations of C-reactive protein (CRP) were found to be strongly correlated with waist circumference and visceral fat (Lemieux et al., 2001), suggesting that this may be yet another abnormality associated with Syndrome X.

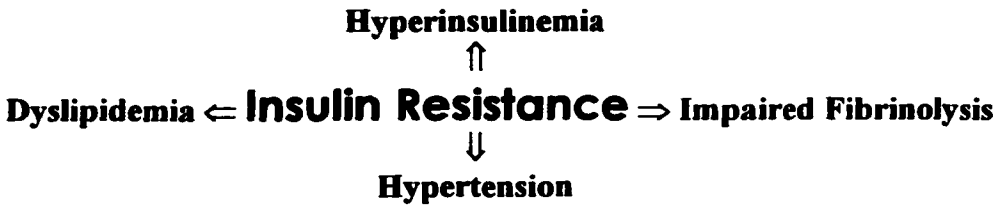


Figure 2-1. Syndrome X: The Insulin Resistance Syndrome

## *Prevalence and Significance of Syndrome X*

The prevalence of Syndrome X in the U.S. is unknown and estimates vary depending on the source. It has been reported to be 16% among Caucasians (Beck-Nielsen, 1999); 7% in Caucasian and African-American men and women (Schmidt et al., 1996); and 10% and 6% in Native American men and women, respectively (Greenlund et

al., 1999). Recent estimates from the Framingham Study suggest much higher prevalence rates of 22% for men and 27% in women (Kannel, 2000).

The presence of this clustering of abnormalities has been found to increase risk of coronary heart disease and stroke by factors of 1.28 and 1.64, respectively (Pyorala et al., 2000). Findings such as these have prompted The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) to recognize the disorders of the metabolic syndrome as a secondary target of therapy. The presence of abnormalities associated with Syndrome X increase coronary heart disease (CHD) risk "at any given LDL cholesterol level" (The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The Expert Panel suggests that by treating lipid and non-lipid risk factors, CHD risk may be further reduced.

## *"Risk Factors" for Syndrome X*

### Genetics versus behavior

The development of Syndrome X is likely due to interactions between and among genetic and behavioral factors, e.g. diet and physical activity (Ukkola and Bouchard, 2001). There is evidence of "familial aggregation" with respect to features of this syndrome (Bouchard, 1995). Ukkola and Bouchard (2001) report that abdominal obesity is strongly heritable, with estimates ranging 25-40%. It has been estimated that 50% of the variability in insulin-mediated glucose disposal in non-diabetic individuals is due to genetic factors, with the remaining 20-25% attributed to obesity and physical inactivity each (Bogardus et al., 1985). Krauss (2001) indicates that the atherogenic lipoprotein phenotype (e.g., pattern B, characterized by small, dense LDL particles) is under the

influence of several genes, either acting singly or in combination to influence LDL particle size. As an example of an interaction between genetics and behavior, diet composition plays a role in the expression of this trait (Krauss and Dreon, 1995). As reviewed by Ukkola and Bouchard (2001), heritability estimates for features of Syndrome X are 25-40% for blood TG concentrations, 50-60% for total cholesterol, 30-55% for HDL-C, and 50% for hypertension. These authors report that data from twins studies indicate that 59% of the clustering of hypertension, diabetes, and obesity is attributed to genetic factors with the remainder (41%) due to environmental factors. Concordance rates for the presence of all three conditions in monozygotic twin pairs were five times that of dizygotic twin pairs, suggesting a very strong genetic influence.

In conclusion, it appears that approximately half of the variability in the occurrence of Syndrome X is due to genetic factors. Another interpretation of these heritability estimates is that the expression of these traits is under substantial behavioral/environmental influence, such as dietary habits, physical activity, and weight control.

**Increased intra-abdominal fat accumulation**

The physical characteristic commonly associated with Syndrome X is excessive abdominal visceral adipose tissue. Several mechanisms have been suggested as to why visceral obesity might cause insulin resistance and Syndrome X (Frayn, 2000). First, visceral adipose tissue secretes factors (e.g., cytokines and hormones), which drain into the portal vein and may alter hepatic metabolism. Information related to this will be addressed later in the chapter. Second, visceral adipose tissue more readily releases non-esterified fatty acids (NEFA) compared to subcutaneous adipose tissue, thereby

increasing fatty acid flux to the liver. The increased hepatic NEFA uptake could increase hepatic glucose production while decreasing glucose oxidation, resulting in glucose intolerance (Belfiore and Iannello, 1998; Ferrannini et al., 1983); increase hepatic very low density lipoprotein triglyceride (VLDL-TG) secretion, causing hypertriglyceridemia (Frayn, 2000); and decrease hepatic insulin removal, leading to hyperinsulinemia (Wiesenthal et al. 1999). Thus, increased visceral fat accumulation is thought by many to be the initial factor leading to the development of Syndrome X.

Computed tomography (CT) scans are required to directly quantify this adipose tissue depot, waist circumference (>100cm) and abdominal sagittal diameter (>25cm) may be used in clinical practice to identify individuals at risk for Syndrome X-related metabolic disorders (Pouliot et al. 1994). Other factors used to identify individuals with Syndrome X are listed in Table 2-1.

**Table 2-1. Clinical Identification of the Metabolic Syndrome**

| Risk Factor | Defining Level |
|---|---|
| Abdominal Obesity (Waist Circumference) | |
| Men | >102 cm |
| Women | >88 cm |
| Triglycerides | ≥150 mg/dl |
| HDL-C | |
| Men | <40 mg/dl |
| Women | <50 mg/dl |
| Blood Pressure | ≥130/≥85 mm Hg |
| Fasting Glucose | ≥110 mg/dl |

Reprinted from:
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001). Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 285(19): 2486-2497.

## ***Features of Syndrome X***

### Insulin resistance and Dysglycemia

As is implied by the other name of this disorder (e.g., the Insulin Resistance Syndrome), a primary feature of Syndrome X is insulin resistance. Specifically, the ability of insulin to promote glucose disposal in peripheral tissues such as skeletal muscle is impaired. This can be detected clinically by reduced insulin sensitivity ($S_I$) (usually defined as a less than normal insulin-mediated glucose disposal), hyperinsulinemia, impaired glucose tolerance, and an elevation in fasting blood glucose concentration (Table 2-1).

The mechanism by which insulin resistance occurs is complex, but is appears to result from a defect in the phosphatidylinositol-3 (PI-3) kinase insulin signaling pathway. It has been suggested that an increased production of TNF-$\alpha$ and/or excessive accumulation of fatty acids in non-adipocytes, both potentially as the result of high levels of abdominal visceral adipose tissue, may cause this defect (Shepherd and Kahn, 1999). Circulating insulin binds to the insulin receptor at the cell surface, initiating a series of intracellular events that includes PI-3 kinase activation. This signaling pathway eventually results in the translocation of the GLUT4 transporter from intracellular vesicles to the cell membrane, allowing glucose to enter the cell (Shepherd and Kahn, 1999). With insulin resistance, there is a defect in one or more step(s) of this pathway so that GLUT4 translocation does not occur.

As $S_I$ worsens, hyperinsulinemia and hyperglycemia may occur due to several factors, including: 1) decreased glucose utilization at the muscle and liver, causing increased hepatic glucose production and output (Ferrannini et al., 1983); 2) insulin

hypersecretion; and 3) decreased hepatic insulin removal (Jones et al., 2000). An increase in blood glucose concentration would stimulate the β-cells of the pancreas to increase insulin secretion (e.g., compensatory hyperinsulinemia), while elevated concentrations of NEFAs may impair hepatic insulin extraction (Wiesenthal et al., 1999). Increased insulin release combined with a reduction in hepatic insulin clearance would lead to hyperinsulinemia. Impaired glucose intolerance will occur as pancreatic β-cells can no longer compensate for the insulin resistant state.

The mitogen-activated protein (MAP) kinase insulin signaling pathway does not seem to be impaired in insulin resistant individuals. This pathway is responsible for the mitogenic functions of insulin, e.g., cell division and differentiation. With the compensatory hyperinsulinemia resulting from insulin resistance, the signal through the MAP kinase pathway may be amplified. This upregulation could be significant with respect to cardiovascular disease; in that endothelial and vascular smooth muscle cell proliferation may be increased (Ginsberg, 2000) via this MAP kinase pathway, possibly resulting in increased vascular resistance and endothelial dysfunction. Increased signal transduction through this pathway may also increase the expression of plasminogen activator inhibitor-1 (PAI-1)(Ginsberg, 2000), causing abnormalities in the fibrinolytic system leading to blood hypercoagulability and thrombosis. Thus, an up regulation of this pathway may contribute to several of the abnormalities associated with Syndrome X.

**Dyslipidemia**

The dyslipidemia associated with Syndrome X is characterized by elevated blood triglyceride (TG) concentrations, low concentrations of high-density lipoprotein cholesterol (HDL-C), and elevated levels of small, dense low-density lipoprotein (LDL)

particles (Hulthe et al., 2000). In individuals with characteristics of Syndrome X, insulin resistance in the adipocytes results in failure of insulin to suppress lipolysis and as a result, lipolysis is "unregulated". The result is increased NEFA flux to the liver. Consequently, hepatic very-low-density lipoprotein (VLDL)-TG production and release is increased (Mittendorfer and Sidossis, 2001), while clearance of VLDL-TG may be decreased (Parks et al., 1999). As a result, lipoproteins become TG-enriched, making them a favorable substrate for hepatic lipase. Small, dense LDL and HDL particles result; the former are more susceptible to oxidation and are less readily cleared (Lamarche and Lewis, 1998), making them very atherogenic. The latter are more readily cleared from circulation, resulting in a decrease in HDL-C concentrations (Lamarche and Lewis, 1998). This sequence of events is depicted in Figure 2-2. A predominance of small, dense LDL particles has been termed LDL subclass "pattern B", or the atherogenic lipoprotein phenotype. Individuals with the pattern B phenotype typically have elevated concentrations of blood triglycerides, and low concentrations of HDL-C (Krauss, 2001).

Under normal circumstances, blood chylomicron concentrations increase as the result of food ingestion; these exogenous TG-rich lipoproteins compete with endogenous TG-rich lipoproteins (e.g., VLDL-TG) for clearance by the liver. With Syndrome X, chronically elevated levels of VLDL-TG may decrease chylomicron clearance and thus produce postprandial lipemia. If atherogenesis is a postprandial phenomenon, as some have suggested (Mamo et al., 1997), this feature of Syndrome X may be particularly detrimental to cardiovascular health.

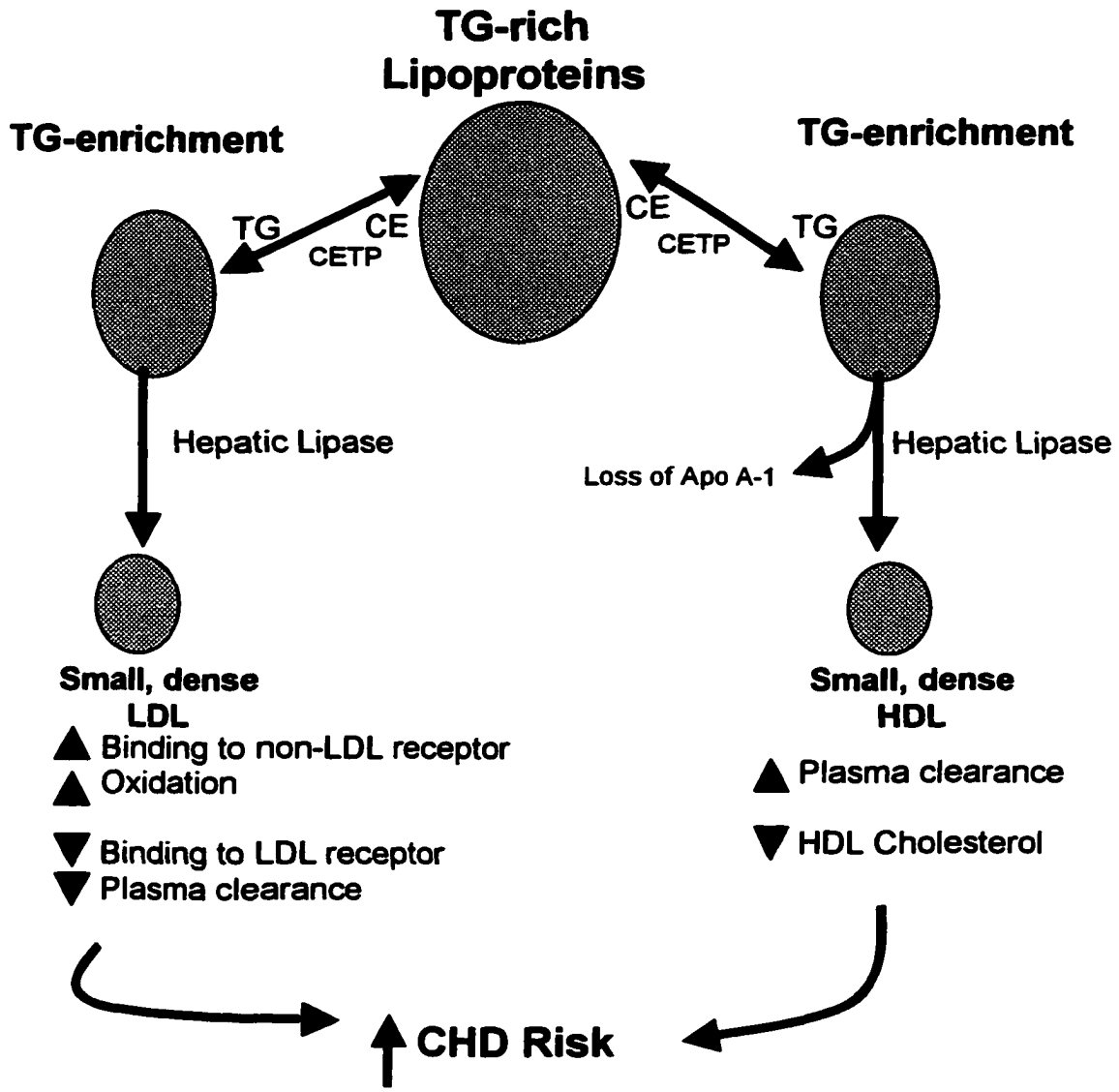


**Figure 2-2.** Triglyceride-enriched lipoproteins are a favorable substrate for hepatic lipase (HL); a higher HL activity results in increased formation of small, dense, atherogenic LDL particles. Research suggests that a high carbohydrate diet may elevate blood triglyceride concentrations in some individuals. As depicted in this figure, elevated blood triglycerides would result in triglyceride-enriched lipoproteins and thus, increased formation of small dense LDL and HDL particles.
Adapted from: Lamarche and Lewis, 1998.

**Hypertension**

The exact mechanism by which insulin resistance and/or hyperinsulinemia results in elevated arterial blood pressure is unclear (Mediratta et al., 1995), but several possibilities have been suggested. Reaven (2000) reports that that BP is elevated with Syndrome X due to one or more of the following: 1) impaired endothelial function with impaired vasodilation as the result of dyslipidemia; 2) increased renal sodium reabsorption, which would increase plasma volume and thus, cardiac output; or 3) increased sympathetic nervous system (SNS) activation due to hyperinsulinemia, which may also cause renal vasoconstriction and increased sodium retention (Scherrer and Sartorri, 1997).

Additionally, under normal circumstances insulin has vasodilatory effects. Since administration of the nitric oxide (NO) synthase inhibitor L-NMMA prevents insulin-induced vasodilation, the vasoactive actions of insulin are likely due at least in part to an increase in NO-induced endothelial vasodilation (Ferrannini 1999; Scherrer and Sartori, 1997). If peripheral insulin resistance leads to a loss in normal vasodilation (Mediratta et al., 1995; Ferrannini 1999), elevated arterial blood pressure could result.

Hyperinsulinemia may cause hypertrophy of blood vessel walls as the result of enhanced growth factor activity (via increased flux through the MAP kinase insulin signaling pathway), leading to a narrowing of the lumen of resistance vessels (Mediratta et al., 1995). Other hypothesized mechanisms include: an insulin-mediated reduction in plasma potassium concentrations which would decrease aldosterone concentrations, stimulate renin production, and increase the vasoconstrictor angiotensin II release to decrease urinary potassium excretion (Ferrannini, 1999); increased catecholamine

release; increased sensitivity to vasoconstrictors; decreased vascular sensitivity to vasodilators; and altered ionic composition (i.e. increased intracellular sodium and calcium) resulting from hyperinsulinemia and insulin resistance (Mediratta et al., 1995).

Finally, it has been suggested that the relationship between insulin resistance and blood pressure may be "largely circumstantial" and "parallel consequences", in that risk of both disorders increases with advancing age, obesity, and physical inactivity (Ferrannini 1999). Evidence of an indirect or weak causal relationship between insulin resistance and hypertension is a low correlation coefficient (0.15) between the two, after adjustment for age, gender, and BMI (Ferrannini 1999).

**Impaired Fibrinolysis**

Insulin resistance is associated with elevated concentrations of PAI-1(Landin et al., 1990), a key enzyme involved in the fibrinolytic system. Juhan-Vague et al.(1999) explain that in this system, the plasminogen activators t-PA and u-PA activate plasminogen, which in turn activate plasmin. Plasmin is a proteolytic enzyme that degrades fibrin and other extracellular matrix proteins. PAI-1 inhibits t-PA and u-PA, thus inhibiting the activation of plasminogen and decreasing fibrin degradation. In simple terms, this means that elevated levels of PAI-1 increase the likelihood of clot and plaque formation due to a decreased "clot-busting" ability.

Synthesis of PAI-1 is increased by cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)-$\alpha$ and hormones such as insulin (Juhan-Vague et al., 1999). Adipose tissue secretes PAI-1, with more PAI-1 secreted by visceral than subcutaneous adipose tissue (Alessi et al. 1997). A link between increased PAI-1 secretion and VLDL has been noted (Juhan-Vague et al., 1999).

Increased concentrations of fibrinogen and factor VII may also be related to the impaired fibrinolysis associated with Syndrome X, but will not be discussed here.

**C-reactive protein (CRP)**

As a blood marker of chronic inflammation, C-reactive protein (CRP) may be an indicator of endothelial stress and/or damage. Increased abdominal fat, as is found in individuals with Syndrome X, may result in increased cytokine flux (e.g., IL-6 and TNF-$\alpha$). This increased cytokine flux may produce an increase in hepatic CRP synthesis (Mohamed-Ali et al. 1998). In support of this, Lemieux et al. (2001) recently found that CRP concentrations were strongly correlated with waist circumference and visceral fat. These investigators found that CRP was correlated with insulin but not plasma lipoprotein concentrations, and suggest that obesity and abdominal adipose tissue are "critical correlates" of plasma CRP concentrations.

This section has discussed the prevalence and significance of Syndrome X, risk factors, and abnormalities associated with this syndrome. There has been debate as to the best dietary approach to recommend for this population. As mentioned previously, studies showing adverse effects of HCLF diets have generally not taken into account the type or amount of dietary fiber consumed. For example, the blood lipid and lipoprotein response to an increase in carbohydrate intake may differ depending upon the *type* of fiber-rich carbohydrate consumed, e.g. predominantly soluble versus insoluble fiber (Davy et al., 2001). The next section will clarify what is meant by "fiber-rich carbohydrates" including its classifications, briefly review the benefits of increased consumption of fiber-rich foods, and contrast current intake to recommendations.

# Part Two

## *What are "Fiber-Rich Carbohydrates"?*

### Description of Dietary Fiber

According to the American Dietetic Association (1997) and the American Association of Cereal Chemists (1999), dietary fiber is defined as the remnant of plant foods (e.g., storage and cell wall polysaccharides) that cannot be digested by human digestive enzymes.

### Classification of soluble vs. insoluble

Total dietary fiber consists of two major components, *soluble* and *insoluble* fiber, as well as resistant starch. Resistant starch is defined as starch and its degradation products that are not absorbed in the small intestine; for example, starch "trapped" within the plant cell by the cell wall (Delcour and Eerlingen, 1996). Legumes are a significant source of resistant starch, but information on the amount of resistant starch in Western diets is sparse.

As is indicated in Table 2-2, fiber-rich foods generally contain more insoluble than soluble fiber. Soluble fiber refers to the fiber that is "suspended in water upon analysis" (American Dietetic Association, 1997). Insoluble fibers are structural (e.g., lignins, cellulose, some hemicelluloses), while soluble fibers are gel-forming (e.g., β-glucan from oats, psyllium gum from psyllium seed hulls, pectin from the peel of fruits, guar gum from seeds of the guar plant) (Whistler and BeMiller, 1997). DeVries et al. (1999) provides a description of the technique used to determine total dietary fiber, as well as how to chemically distinguish between the two fiber fractions.

Examples of foods composed primarily of *insoluble* fiber are wheat, rye, and most grains. Oats contain a greater proportion of *soluble* fiber than any other grain; other sources of soluble fiber include barley, legumes, beans, and peas. The soluble fiber found in oats is β-glucan, a polysaccharide consisting of a linear chain of glucose units connected in β-(1,3) and β-(1,4) linkages. Characteristics of this gum include a high solubility and a moderate-to-high viscosity; it produces gel-like lumps when exposed to water (Bell et al., 1999).

**Table 2-2. Selected Sources and Amounts of Dietary Fiber**

| Food | Amount | Soluble Fiber, g | Total Fiber, g |
|---|---|---|---|
| Legumes, cooked: | | | |
| Kidney beans | ½ cup | 2.0 | 6.7 |
| Pinto beans | ½ cup | 2.0 | 6.7 |
| Vegetables, cooked: | | | |
| Brussels sprouts | ½ cup | 2.0 | 3.8 |
| Broccoli | ½ cup | 1.1 | 2.6 |
| Corn | ½ cup | 1.3 | 3.1 |
| Spinach | ½ cup | 0.5 | 2.1 |
| Zucchini | ½ cup | 0.2 | 1.6 |
| Fruits, raw: | | | |
| Apple | 1 medium | 1.2 | 3.6 |
| Banana | 1 medium | 0.6 | 2.2 |
| Cantaloupe | 1 medium | 4.4 | 7.4 |
| Orange | 1 medium | 1.8 | 2.9 |
| Grapefruit | ½ medium | 1.1 | 1.8 |
| Grapes | 1 cup | 0.3 | 1.1 |
| Prunes | 6 medium | 3.0 | 8.0 |
| Grains: | | | |
| Barley (dry) | ½ cup | 3.4 | 11.8 |
| Oatmeal (dry) | 1/3 cup | 1.3 | 2.8 |
| Oat bran (dry) | 1/3 cup | 2.0 | 4.4 |
| All-bran cereal | 1 cup | 2.2 | 13.0 |
| Corn flakes cereal | 1 ounce | 0.1 | 0.3 |
| Brown rice, cooked | ½ cup | 0.4 | 5.3 |
| Whole-wheat bread | 1 slice | 0.4 | 2.1 |
| White bread | 1 slice | 0.2 | 0.4 |
| Nuts: | | | |
| Cashews | 1 cup | 0.4 | 7.8 |
| Almonds | 1 cup | 1.6 | 15.9 |
| Peanuts | 1 cup | 4.8 | 12.7 |
| Sunflower seeds | 1 cup | 4.6 | 9.8 |

Adapted from:
Van Horn L (1997). Fiber, lipids, and coronary heart disease. A statement for healthcare professionals from the Nutrition Committee, American Heart Association. Circulation. 95:2701-4.
Spiller GA (1993). In: CRC Handbook of Dietary Fiber in Human Nutrition, 2nd edition. Dietary fiber values for common foods.

**Glycemic Index versus Glycemic load**

Interest in the health aspects of the amounts and types of dietary carbohydrate prompted the development of two indices of carbohydrate intake, "glycemic index" and "glycemic load". The *Glycemic index* (GI) quantifies the glycemic response (e.g., increase in blood glucose concentration) following the ingestion of a food. Specifically, following the ingestion of 50g of the food of interest, blood glucose concentrations are measured over a two-hour period. The blood glucose concentrations are then plotted graphically over time. The area under the glucose curve is quantified, and compared to that from 50g of glucose (or in some instances, white bread). The GI for the food of interest is expressed as a percentage of the area under the glucose curve for the test food compared to that for glucose (Walberg Rankin, 1997). The GI is thought by some to be superior to the traditional classification of carbohydrates as "simple" or "complex" (Liu et al. 2000).

*Glycemic load* is calculated as the GI of a food multiplied by the amount of the food (i.e., grams) consumed. The overall glycemic load of a diet is calculated as the sum of the glycemic load of the individual foods consumed. Thus, the dietary glycemic load is thought to represent the quality and quantity of carbohydrates consumed. A positive association between CHD risk and both GI and glycemic load has been reported (Liu et al., 2000).

These terms are somewhat related to dietary fiber in that fiber-rich carbohydrates have traditionally been classified as "complex" carbohydrates, which are thought to be more slowly absorbed and would thus produce a lower glycemic response as compared to foods traditionally classified as "simple" carbohydrates. However, in contrast to findings

related to dietary fiber (reviewed by Sharma, 1992), it is somewhat controversial (Coulton and Reaven, 1997; Wolever 1997) and unclear as to whether or not GI is important with respect to glucose tolerance (Jarvi et al., 1999; Liljeberg et al., 1999; Luscombe et al., 1999; Meyer et al., 2000). Inconsistent findings may at least in part be due to methodological issues, for example, the reference food used to determine GI (e.g., glucose or white bread), and the amounts of other macronutrients (e.g., fat and protein) consumed by study participants.

## ***Beneficial Effects of Fiber-Rich Carbohydrates***

There is a vast body of literature supporting the beneficial effect of fiber-rich carbohydrates for optimal health and disease prevention. While findings in some areas are inconsistent, it is generally accepted that consumption of fiber-rich carbohydrates is important for gastrointestinal health by decreasing constipation and reducing risk of diverticular disease (Anderson et al., 1994; Position of the American Dietetic Association, 1997). A high intake of fiber-rich carbohydrates is also thought to be helpful for weight management via its effect on satiety (Anderson et al., 1994; Sparti et al., 2000) and for reducing risk of cardiovascular disease (Liu et al., 1999; Van Horn, 1997), diabetes (Anderson et al., 1994; Salmeron et al., 1997; Salmeron et al., 1997) and stroke (Ascherio et al., 1998). Many believe that a high fiber intake will also reduce risk of certain types of cancer, specifically colorectal and breast cancer (Howe et al., 1990; Howe et al., 1992; Rose 1992). However, these relationships are still unclear (McKeowyn-Eyssen et al., 1994; Willett et al., 1992).

Due to the different physiologic and metabolic effects of various types/sources of fiber-rich carbohydrates, it is likely that health benefits differ according to specific type of fiber consumed (e.g., soluble versus insoluble). While studies sometimes do not distinguish between soluble versus insoluble fiber (Ascherio et al., 1998; Liu et al., 1999), others have documented the benefit of a specific type of fiber. For example, foods rich in *soluble* fiber (e.g., oats, beans, psyllium) have been shown to improve blood lipid and lipoprotein concentrations (Anderson et al., 1990; Anderson et al., 1991; Brown et al., 1999; Kashtan et al., 1992). Studies investigating the effects of wheat bran, rich in *insoluble* fiber, have had inconsistent effects on blood lipids and lipoproteins (Jenkins et al., 1999; Kashtan et al., 1992; Vuksan et al., 1999). Anderson et al. (1994) reports that while all fiber-rich foods help prevent constipation and diverticulosis, foods rich in soluble fiber delay gastric emptying and enhance satiety, while foods rich in insoluble fiber increase fecal bulk and decrease gastrointestinal transit time. Thus, it seems that while all types of fiber are beneficial, the specific benefit differs according to type of fiber-rich carbohydrate consumed.

Because of the documented benefits of various dietary fibers, the U.S. Federal Drug Administration (1998) currently allows four food labeling health claims related to dietary fiber:

1) Fiber containing grain products, fruits, and vegetables, help reduce risk of cancer;
2) Fruits, vegetables, and grain products that contain fiber, particularly soluble dietary fiber, may reduce risk of heart disease;
3) Whole oats may reduce risk of heart disease; and,
4) Psyllium seed husk may reduce risk of heart disease.

## *Current Recommendations for Intake of Dietary Fiber vs. Current Intake*

The American Dietetic Association (ADA) recommends an intake of 20 to 35g of dietary fiber per day for adults (Position of the ADA, 1997). In contrast to these recommendations, the mean dietary fiber intake of Americans is 15.1g per day, and 18.2g in males over age 50 (USDA's CSFII, 1997).

Major sources of fiber in the typical American diet include grains and breakfast cereals (~40% of total fiber intake), vegetables and vegetable juices (25% of total fiber intake), legumes, nuts and soy products (~14% of total fiber intake) and fruits and fruit juices (~11% of total fiber intake). Within the "grains" category, oats alone contribute approximately 4% of total fiber intake (US Food Supply Database, 2000).

This section presented classifications for types of fiber-rich carbohydrates, the benefits associated with increased consumption of fiber-rich carbohydrates, and contrasted current recommendations for fiber intake versus current intake level. The next section will discuss the effects carbohydrates rich in dietary fiber, particularly the soluble fiber from oats, on the abnormalities associated with syndrome X.

# Part Three

## *Effect of Fiber-Rich Carbohydrates on Features of Syndrome X*

This section will discuss the abnormalities of Syndrome X that may be affected by fiber-rich carbohydrates, specifically those high in soluble fiber. This will include the effect of fiber-rich carbohydrates on blood insulin and glucose parameters, dyslipidemia,

and arterial blood pressure. A limited number of studies have been conducted on the effect of dietary factors on blood coagulation, although there is some evidence that a diet rich in fiber *may* reduce thrombogenesis (Djousse et al., 1998; Marckmann et al., 1994; Mennen et al., 1997).

**Effect of Fiber-Rich Carbohydrates on Blood Insulin and Glucose Parameters**

It has been suggested that increased consumption of high-carbohydrate, low-fiber foods could increase blood insulin concentrations and reduce insulin action (Jenkins et al., 2000; Riccardi and Rivellese, 2000). Such foods may also increase risk of non-insulin dependent diabetes mellitus (Salmeron et al., 1997). Surprisingly, some critics of HCLF diets do not believe that dietary macronutrient composition will alter insulin action in individuals with insulin resistance (Reaven, 2000), despite earlier findings opposing this viewpoint (Reaven, 1997).

Supporting the belief that macronutrient composition may not influence blood insulin and glucose parameters are findings from several studies. Garg et al. (1994) did not find differences in fasting blood glucose or insulin concentrations in insulin resistant individuals after six weeks of consuming a diet with 55% of energy from carbohydrates and 30% from fat as compared to one containing 40% of energy from carbohydrates and 40% from fat, of which 20% were MUFA. In a similar study by the same group (Garg et al., 1992), insulin sensitivity ($S_I$) was not altered by a high-carbohydrate (60% of total energy) or low-carbohydrate (35% total energy) diet. Importantly, these two intervention diets were matched for dietary fiber content (25g/day). Findings from a pilot study conducted in individuals with characteristics of Syndrome X suggest that a HCLF diet

and a high mono-unsaturated fat (MUFA) diet have similar effects on postprandial glucose and insulin concentrations (Ginsberg, 1996).

Some suggest a HCLF diet may improve insulin sensitivity ($S_I$). A positive correlation between habitual fiber intake and $S_I$ (Lovejoy and DiGirolamo, 1992) has been reported, but these authors did not find a relationship between $S_I$ and habitual carbohydrate intake. Fukagawa et al. (1990) found that three to four weeks of a high-carbohydrate (68% of total energy), high-fiber (~33g/1000kcal) diet increased peripheral insulin sensitivity, and decreased fasting blood glucose and insulin concentrations in healthy young and old adults. In agreement with these findings are those of Strazinsky et al. (1999), who determined that $S_I$ was significantly higher after two weeks of a high fiber, HCLF diet, as compared to two weeks of a high-fat, low-carbohydrate diet. With respect to soluble fiber, there is evidence in animals that a high intake of soluble fiber may reduce fasting blood glucose concentrations and improve $S_I$ by increasing muscle GLUT-4 content (Song et al., 2000).

In conclusion, findings of the effect of fiber-rich carbohydrates on insulin resistance are inconsistent, leading some to question the effectiveness of dietary fiber in reducing insulin resistance (Jenkins et al., 2000). Some of the inconsistencies may be due to methodological differences including the type of individuals studied (e.g., insulin resistant versus insulin sensitive individuals), the types of dietary carbohydrates used (e.g., fiber content, whole foods versus liquid formulas), and the carbohydrate content of the test diets (e.g., 85% versus 50% carbohydrate).

**Effect of Fiber-Rich Carbohydrates on Dyslipidemia**

There is evidence that the dyslipidemia associated with Syndrome X (e.g., elevated TG and small, dense LDL concentration with low HDL-C concentration) may be exacerbated by a HCLF diet. This phenomenon, termed carbohydrate-induced hypertriglyceridemia (HTG), was recently reviewed extensively by Parks and Hellerstein (2000). It is controversial as to whether or not carbohydrate-induced HTG confers the same cardiovascular risk as compared to endogenous HTG. As suggested by Parks and Hellerstein (2000), if the metabolic mechanism is the same, then cardiovascular risk is likely increased. However, if the mechanism is different, then diet-induced HTG may not have negative health effects. Results of studies in this area are inconsistent, with some concluding that diet-induced HTG is the result of reduced VLDL-TG clearance and not increased VLDL-TG secretion or de novo lipogenesis (Parks et al., 1999) and others attributing it to increased VLDL-TG secretion (due to increased hepatic fatty acid availability resulting from decreased hepatic fatty acid oxidation)(Mittendorfer and Sidossis, 2001).

Regardless of this mechanistic controversy, it is generally accepted that elevated TG and small dense LDL concentrations and low HDL-C concentration are all important risk factors for CVD (Austin et al., 1988; Gardner et al., 1996; Gotto 2001; Lamarche et al., 1997; Mack et al., 1996; Stampfer et al., 1996). If blood TG concentrations are increased as the result of a HCLF diet, this may lead to (as depicted in Figure 2-2) increased concentrations of small dense LDL and decreased concentrations of HDL. Critics of HCLF diets often cite this phenomenon as a major reason against the use of this diet approach, particularly in individuals with Syndrome X.

Due to methodological differences between studies on the effect of HCLF diets on blood lipids and lipoproteins (e.g., type and forms of carbohydrates, length of intervention period, etc.), it is not clear if all HCLF diets will result in diet-induced HTG. Advocates of HCLF diets suggest that adequate amounts of fiber-rich carbohydrates will prevent carbohydrate-induced HTG. Anderson (2000) contends that his group has successfully used high-fiber, HCLF diets for treating hypertriglyceridemic individuals for 25 years. In support of this are findings from a recent study, which suggest that a HCLF diet with high levels of total (50g) and soluble fiber (25g) may prevent adverse lipid and lipoprotein changes in individuals with type 2 diabetes (Chandalia et al., 2000). Anderson (2000) extensively reviewed literature specifically related to this area, and reports that "the available literature persuasively documents that moderate to high levels of dietary fiber intake attenuate the carbohydrate-induced hypertriglyceridemia observed with HCLF diets". He maintains that carbohydrate-induced HTG indicates a state of "fiber-deficiency" which can be corrected with the consumption of moderate to large amounts of fiber-rich carbohydrates.

With respect to the various types of fiber-rich carbohydrates, considerable attention has been focused upon the lipid-lowering properties of soluble viscous fibers, including psyllium, oats, guar and pectin. The cholesterol-lowering effect of these types of fiber is generally attributed to their ability to decrease bile acid absorption in the small intestine and increase fecal bile acid excretion. As a result, endogenous cholesterol synthesis is diverted from lipoproteins to bile acid synthesis (Anderson and Hanna, 1999), which lowers the hepatic free cholesterol pool. A reduction in hepatic cholesterol concentration leads to upregulation of LDL receptors, which in turn increases clearance

of LDL-C. A recent meta-analysis of 67 controlled clinical trials indicates that increased consumption of soluble fiber produces small but significant decreases in blood total cholesterol and LDL-C concentrations without significantly changing triglyceride and HDL-C concentrations (Brown et al., 1999). The effective dose range appears to be between 3-10g soluble fiber.

A meta-analysis specifically on the lipid-lowering effect of oat products indicated that a dose of ~3g/day of β-glucan, the soluble fiber found in oats, reduced total cholesterol concentrations by approximately 5-6mg/dl (Ripsin et al., 1992). This investigation did not examine the effect of oats on blood TG or lipoprotein concentrations. In contrast, a recent intervention study did not find that this level of β-glucan (in the form of oat bran concentrate) significantly changed blood concentrations of total cholesterol, TG or LDL-C, but did find a significant decrease in HDL-C concentration (Lovegrove et al., 2000). This study did not detect differences in post-prandial TG measurements after the eight-week intervention period.

Insulin resistance has been linked to degree of postprandial lipemia (Jeppesen et al., 1995), as has the small, dense LDL phenotype (Lemieux et al., 2000). As discussed earlier, chronically elevated levels of VLDL-TG may decrease chylomicron clearance and contribute to postprandial lipemia in individuals with Syndrome X; this may be exacerbated by HCLF diets (Abbasi et al., 2000). However, one investigation found that four weeks of a high-fiber, HCLF diet could reduce the lipemic response to a high-fat test meal (Gerhard et al., 2000). Thus, the very limited available information suggests that a HCLF diet may not worsen postprandial lipemia if the diet is also high in fiber.

Research on the lipoprotein responses of individuals with LDL subclass pattern B to HCLF diets relates to the emerging area of diet-gene interactions. In contrast to the dietary approach sometimes recommended for treating the dyslipidemia associated with Syndrome X (e.g., a higher fat diet with saturated fat replaced largely by mono- and poly-unsaturated fat)(Reaven, 2000), some data suggests that "pattern B" individuals respond favorably to a HCLF diet. Specifically, concentrations of small, dense LDL particles and LDL-C will be reduced in these individuals in response to a HCLF diet (Dreon and Krauss, 1997). This seems counter-intuitive in that pattern B is one component of the dyslipidemia associated with Syndrome X. In a recent review, however, Krauss (2001) reports that the prevalence of the pattern B phenotype increases with an increase in carbohydrate and a decrease in fat consumption. In other words, a HCLF diet will induce the expression of the pattern B phenotype. Several studies published on this topic appear to have conflicting results, thus it is not clear if a HCLF diet is advisable or detrimental for individuals with the pattern B phenotype (Dreon et al., 1994; Dreon et al., 1995; Krauss and Dreon, 1995).

With respect to fiber-rich carbohydrates, data presented in Chapter 3 of this dissertation (Davy et al., 2001) indicate that individuals with the pattern B phenotype have a favorable lipid and lipoprotein response to an increased consumption of oat as compared to wheat cereal. This suggests that the lipid and lipoprotein response to increased carbohydrate consumption may depend on the type of dietary carbohydrate (e.g., carbohydrates rich in soluble versus insoluble fiber) as well as LDL subclass phenotype.

**Effect of Fiber-Rich Carbohydrates on Arterial Blood Pressure**

Epidemiological studies consistently report that increased dietary fiber and/or whole grain consumption is associated with a reduced risk of coronary heart disease (CHD) (Hu et al., 2000; Liu et al., 1999; Rimm et al., 1996; Wolk et al., 1999). Additionally, some have reported a significant inverse relationship with CHD risk and soluble fiber (Pietinen et al., 1996; Wolk et al., 1999) and oat consumption (Wolk et al., 1999), but this finding has not been universal (Liu et al., 1999; Rimm et al., 1996).

A negative association between dietary fiber intake and arterial blood pressure (BP) has been reported (Ascherio et al., 1992; Acherio et al., 1996). This relationship has also been noted specifically with oat intake (He et al., 1995). However, very few clinical trials have been done which support a direct effect of fiber on BP without weight loss. In a comparison of the consumption of three sources (wheat, rice, oat) of fiber-rich carbohydrates (an additional 12g fiber/day) on arterial BP, no significant effect of any fiber source on BP was found (Kestin et al., 1990). Consistent with this are findings by Swain et al., (1990) who report that BP was unchanged in individuals consuming an additional 18g dietary fiber per day from oat products, and Fehily et al. (1986), who did not find a BP-lowering effect of a diet containing 19g/day of additional cereal fiber. Our 12-week intervention study reported in Chapter 4, which did not find that the inclusion of high-fiber oat or wheat products was effective in reducing resting casual or 24-hour ambulatory BP, is also in agreement with these studies (Davy et al., 2001).

In contrast to these findings, a few published intervention studies report that a fiber-rich HCLF diet can lower arterial BP. Results from the DASH trial (Appel et al., 1997) suggest that a HCLF diet rich in fruits, vegetables, low-fat dairy products and

whole grains is effective in reducing BP. Similarly, Strazinsky et al. (1999) found that BP was lower after two weeks of a high-fiber, HCLF diet as compared to a low-carbohydrate, high-fat diet. With respect to soluble fiber, Saltzman et al. (2001) reported that a hypocaloric diet containing ~7g soluble fiber from oats decreased systolic BP as compared to a hypocaloric diet lower in fiber.

Thus, the available literature suggests that either weight loss or a whole-food HCLF diet containing multiple sources of fiber-rich carbohydrates (fruits, vegetables, and whole grains), and not just the addition of a single source of fiber (e.g., oats), may be necessary to significantly reduce arterial BP.

## ***Conclusions and Applications***

### Benefits of fiber-rich carbohydrates for weight management

Weight loss, specifically the reduction of body fat, may be the most effective strategy for improving abnormalities associated with Syndrome X in overweight individuals (Reaven, 2000; Ukkola and Bouchard, 2001). Of importance to the obese insulin-resistant individual, the degree of insulin resistance and/or hyperinsulinemia does not alter weight loss response to a hypocaloric diet (McLaughlin et al., 1999). A moderate weight loss of ~10% can significantly enhance insulin clearance, thereby reducing hyperinsulinemia, although greater degrees of weight loss *may* be required to reduce insulin secretion and improve insulin resistance (Jones et al., 2000).

Ad-libitum HCLF diets generally result in weight loss and would thus be preferable to a diet high in mono- or poly-unsaturated fat for insulin resistant individuals (Purnell and Brunzell, 1997). Additionally, diets containing adequate amounts of fiber

may be less energy-dense and may promote greater feelings of satiety (Position of the ADA, 1997). Regarding weight maintenance, weight management experts recommend a HCLF diet for most individuals (Wing and Hill, 2001). Fiber-rich carbohydrates, particularly those high in soluble fiber, should be included as part of the maintenance HCLF diet to prevent adverse lipid and lipoprotein changes in individuals with Syndrome X.

**How much dietary fiber?**

As stated previously, the ADA recommends a daily fiber intake of 20-35g/day for adults (Position of the ADA, 1997). Recommended intakes for amounts of specific fiber types are generally not made, although it has been recognized that foods rich in soluble fiber have beneficial properties (AHA, 2000; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; Position of the ADA, 1997). Our results are consistent with this, and suggest that the replacement of dietary fat with carbohydrate my have adverse effects on blood lipids and lipoproteins unless carbohydrates rich in soluble fiber are consumed (Davy et al., 2001). Data suggest that 3g soluble fiber in the form of β-glucan may not be sufficient to improve blood lipids and lipoprotein concentrations (Lovegrove et al., 2000), therefore an intake ranging 3g (Ripsin et al., 1992) to 8-10g (Brown et al., 1999; Davy et al., 2001) is recommended. Since individuals with the metabolic syndrome are characterized by the presence of dyslipidemia (eg, low HDL-C, elevated TG and small dense LDL-C), these individuals would benefit from a HCLF diet that includes sources of soluble fiber such as oats.

**"Dietary Fiber" versus "other" components of fiber-rich foods**

It is not clear if the health benefits of fiber-rich foods are directly attributable to their dietary fiber content alone, or if there are other components or properties of the foods that are responsible for their beneficial health effects. Such factors might include essential fatty acids, micronutrients, antioxidants and phytochemicals (Anderson and Hanna, 1999). In support of this are findings of epidemiological studies, which have found that even after adjusting for fiber intake; consumption of whole grains is independently associated with a reduced risk of CHD (Liu et al., 1999), total mortality (Jacobs et al., 1999) and IHD (Jacobs et al., 1998). Therefore, it seems likely that the beneficial effects of fiber-rich carbohydrates are due to not only their fiber content, but also to other properties of the food. This suggests that the emphasis of dietary recommendations be placed on the consumption of foods, rather than nutrients.

**Dietary fiber and Fiber-rich foods versus a high-fiber pattern of intake**

In recent years, major health organizations such as the American Heart Association and the USDA have made dietary recommendations that are more food- and dietary pattern-based and less nutrient-based. This approach is more consumer-friendly, allowing us to focus upon aspects of our diet other than grams or percentages of nutrients.

The strongest evidence in support of this approach is findings from the Dietary Approaches to Stop Hypertension (DASH) trial (Appel et al., 1997; Moore et al., 1999; Obarzanek et al., 2001). The primary objective of this trial was to assess the effects of dietary patterns on blood pressure. The DASH dietary pattern was high in fruits (~5 servings/day), vegetables (~4 servings/day), grains (~8 servings/day) and low-fat dairy products (~2 servings/day), emphasized fish and chicken rather than red meat, and was

low in total fat (~26%), saturated fat (~7%), cholesterol (~150mg), sugar, and refined carbohydrates. Sodium intake (~3g) and body weight were kept constant. The fiber content of the diet was approximately 30g per day. After eight weeks, the DASH diet significantly reduced resting systolic and diastolic blood pressure (Appel et al., 1997), 24-hour ambulatory blood pressure (Moore et al., 1999), blood total cholesterol and LDL-C concentrations (Obarzanek et al., 2001) as compared to a control diet (e.g., typical American diet). Despite the relatively high carbohydrate content of the diet (~57% of total energy), blood TG concentrations did not increase. A small but significant decrease in HDL-C concentration (3.7 mg/dl) was detected (Obarzanek et al., 2001). Authors concluded that the DASH diet would likely reduce coronary heart disease risk.

Due to the improvements in arterial blood pressure and blood lipid and lipoprotein concentrations (with the exception of the reduction in HDL-C), this type of dietary pattern may be beneficial for individuals with Syndrome X. The limited effectiveness of long-term weight loss maintenance might suggest that it would be worthwhile for future studies to investigate the effect of the DASH dietary pattern (without weight loss) on abnormalities associated with Syndrome X.

In summary, there is evidence that that HCLF diets limited in dietary fiber may exacerbate some of the abnormalities associated with syndrome X, particularly blood lipid and lipoprotein concentrations. There is also evidence suggesting a HCLF diet that includes a variety of fiber-rich carbohydrates, such as the DASH dietary pattern, is beneficial for reducing arterial blood pressure and improving blood lipids and lipoproteins. It is unclear if a high-fiber, HCLF diet will improve insulin sensitivity;

however, if this dietary pattern facilitates weight loss, the most effective treatment for all of the abnormalities associated with this syndrome, then this dietary approach would seem to be beneficial. However, at this time it is not clear if the *type* of dietary fiber consumed is important with respect to improvement in arterial blood pressure or blood lipid and lipoprotein variables beyond those traditionally measured (e.g., lipoprotein subclasses, LDL particles number, lipoprotein particle sizes). Thus, the purpose of our investigation was to determine the effect of fiber-rich oat versus wheat cereal on these factors associated with increased cardiovascular disease risk.

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## CHAPTER THREE

# A high-fiber diet containing oats as compared to wheat favorably alters low-density lipoprotein cholesterol subclass and particle number in middle-aged and older men


## ABSTRACT

**Background:** To date, no studies have examined the possibility that soluble oat fiber may favorably alter lipoprotein particle size and number, even in the face of added dietary carbohydrate.

**Objective:** We examined the effects of adding two large servings per day of either oat or wheat cereal on plasma lipids, lipoprotein subclasses, lipoprotein particle diameters and LDL particle number.

**Design:** Thirty-six overweight middle-aged and older men (BMI 25-35kg/$m^2$, aged 50-75 y) were randomly assigned to consume either oat or wheat cereals (total dose of 14g dietary fiber/day from cereals) daily for 12 weeks. Measurements of plasma lipids and lipoprotein subclasses using proton nuclear magnetic resonance (NMR) spectroscopy were performed before and after the intervention. To determine the possible influence of insulin and glucose metabolism on lipoprotein changes, whole-body insulin sensitivity

was estimated in the fasted state before and after the intervention using the frequently sampled intravenous glucose tolerance test.

**Results:** There were significant time-by-treatment interactions ($P<0.05$) for LDL-C (Oat:-2.5%; Wheat:+8.0%), small LDL-C (Oat:-17.3%; Wheat: +60.4%), LDL particle number (Oat:-5.0%; Wheat:+14.2%) and LDL-C/HDL-C ratio (Oat:-6.3%; Wheat:+14.2%). There was a trend for a time-by-treatment interaction for TC (Oat:-2.5%; Wheat:+6.3%, $P=0.08$), TG (Oat:-6.6%; Wheat:+22.0%, $P=0.07$) and VLDL-TG (Oat:-7.6%; Wheat:+2.7%, $P=0.08$). There was no significant time-by-treatment interaction for HDL-C and HDL-C subclasses; LDL, HDL, and VLDL particle diameter. Insulin sensitivity did not change with either intervention.

**Conclusions:** The addition of two large servings of oat as compared to wheat cereal results in lower concentrations of small, dense LDL-C and LDL particle number without producing adverse changes in blood TG or HDL-C concentrations. These beneficial alterations may contribute to the cardioprotective effect of oat fiber.

## INTRODUCTION

A diet high in fiber has been linked to a decreased risk of mortality from cardiovascular disease (CVD) independent of energy intake, dietary fat intake, and other dietary factors (Khaw et al., 1987; Wolk et al., 1999). Meta-analyses have shown that the consumption of soluble fiber, such as β-glucan found in oat products, reduces blood total cholesterol (TC) and LDL-C concentrations (Brown et al., 1999; Ripsin et al., 1992). Thus, the ability of soluble fiber to reduce CVD risk is in part related to its ability to favorably modify blood lipids and lipoproteins.

Many individuals with apparently "normal" blood lipid profiles will develop CVD (Miller et al., 1990; Miller et al., 1992). Examining blood lipid parameters beyond those traditionally measured may provide greater insight into an individual's actual CVD risk, as well as the effectiveness of an intervention to modify this risk. Such parameters might include lipoprotein subclasses, particle size (e.g., diameter) and particle number. For example, small, dense LDL particles appear to be more atherogenic than larger, less dense LDL particles (Gardner et al., 1996; Lamarche et al., 1997; Mack et al., 1996; Stampfer et al., 1996), and individuals with a predominance of small, dense LDL (pattern B lipoprotein profile) are at increased risk of coronary heart disease (CHD) as compared to those with a predominance of large LDL particles (pattern A) (Austin et al., 1988; Gardner et al., 1996; Lamarche et al., 1997; Stampfer et al., 1996). Small, dense HDL particles, more commonly referred to as $HDL_3$, appear to be less cardioprotective than the larger, less dense $HDL_2$ (Freedman et al., 1998). An elevated LDL particle number, often recognized by high apoprotein B concentrations, has also been linked to an increased CHD risk (Lamarche et al., 1997; Lamarche et al., 1996).

The adoption of a high-carbohydrate, low-fat diet sometimes produces unfavorable changes in blood lipids and lipoproteins, specifically an increase in plasma triacylglycerol (TG) and a reduction in HDL-C concentrations (Parks et al., 1999). This phenomenon was recently reviewed by Parks and Hellerstein (2000). Elevated TG concentrations may, in turn, contribute to increased concentrations of both small, dense LDL and HDL particles (Lamarche et al., 1998). Because of this phenomenon, some have suggested that the replacement of carbohydrate for fat is inappropriate (Connor et al., 1997). Recent evidence indicates that changes in lipoprotein profiles in response to a

high-carbohydrate, low-fat diet may be dependent on LDL subclass phenotype (Dreon et al., 1999).

To date, no studies have examined the effects of fiber-rich oat and wheat cereal consumption on lipoprotein subclasses, particle size and particle number. It is also not clear if adverse lipid and lipoprotein changes induced by an increase in carbohydrate are differentially altered by cereals rich in soluble (e.g., oat) versus insoluble (e.g., wheat) fiber. Thus, the purpose of this investigation was to determine the effects of adding two large servings per day of either oat or wheat cereal on plasma lipid parameters which have not been previously reported, including lipoprotein subclasses, lipoprotein particle diameters and LDL particle number.

## METHODS

### Subjects

Male subjects aged 50-75 y with a body mass index (BMI) between 25-35 $kg/m^2$ were recruited for this study from the surrounding community. Only subjects who were sedentary or minimally physically active (< two 30-minute aerobic exercise sessions per week) were included. Individuals were excluded if they reported or were observed to have any of the following: apparent cardiovascular disease, self-reported diabetes or fasting blood glucose $\geq$ 126 mg/dl, systolic blood pressure >160mmHg and/or diastolic blood pressure >99mmHg, asthma, tobacco use, history of eating disorders, history of thyroid gland disorders, or use of any medications known to affect any of the dependent variables in this study. Subjects were excluded if they reported a high habitual intake of dietary fiber (e.g., >30g/day), as determined by the Block Screening Questionnaire for

Fat and Fruit/Vegetable/Fiber Intake (Block 1994). Taste testing of the cereal products was conducted prior to enrollment to ensure that all subjects found the cereal palatable. Approximately 150 men were screened for this study, 39 of which were enrolled. Two men were excluded after enrollment due to detection of fasting blood glucose concentrations greater than 7.0 mmol/l, and another individual dropped out after enrollment due to a broken limb, which necessitated the use of medications. A total of 36 men completed the protocol; 18 per intervention group. This study was approved by the Human Research Committee at Colorado State University. All subjects provided written informed voluntary consent prior to participation.

**Experimental Design**

Following screening, subjects were randomly assigned to consume whole grain oat or wheat cereals containing a daily dose of 14g dietary fiber for 12 weeks (Oat group-60g dry Quaker Oatmeal and 76g Quaker Oat Bran ready-to-eat cold cereal, Quaker Oats Company, Barrington, Illinois; Wheat group-60g dry Mother's Whole Wheat Hot Natural Cereal, Quaker Oats Company, Barrington, Illinois and 81g Frosted Mini-Wheats, Kellogg Company, Battle Creek, Michigan). The combination of oat cereals provided 5.5g β-glucan as determined by manufacturer's analysis. The amount of cereal provided was matched between groups to achieve a similar amount of energy, macronutrients, and dietary fiber according to information provided by the manufacturer and USDA Nutrient Database for Standard Reference, Release 12 (Oat group-513 kcals, 8g fat, 95g carbohydrate, 13.5g simple sugar, 21g protein, 14g dietary fiber; Wheat group-480 kcals, 3g fat, 112g carbohydrate, 20.6g simple sugar, 14g protein, 14g dietary fiber). Subjects

were instructed not to alter their dietary habits other than the daily inclusion of the cereals for breakfast and a snack.

The cereal dose containing approximately 500 kcal per day increased the mean total carbohydrate intake in both grams and percentage of energy from carbohydrate by about 5% (Oat group: 47 to 52%, Wheat group: 50 to 55%) and significantly decreased the absolute and relative fat content by about 5% (Oat group: 35 to 30%, Wheat group: 33 to 28%). These dietary changes resulted in a mean fat intake $\leq$ 30% of total energy.

Subjects returned uneaten cereals packets to the investigators on a biweekly (eg, every other week) basis so that compliance could be determined. Compliance with the intervention was not significantly different between groups, with subjects consuming 96±4% and 95 ±5% of the required cereal servings in oat and wheat groups, respectively. Only one individual reported less than 88% compliance; exclusion of this individual from data analysis did not change any of the findings.

**Anthropometric Measurements**

Body weight with subjects wearing only light indoor clothing was determined to the nearest 0.1 kg using a balance scale (Detecto, Webb City, MO) and height (cm) without shoes was measured using a wall-mounted stadiometer. Body weight was re-assessed biweekly throughout the study. Skinfold thickness measurements (mm) were obtained at eight sites (chest, abdomen, triceps, suprailiac, midaxillary, subscapular, thigh, and medial calf) using calipers (Lange, Cambridge Scientific Industries, Cambridge, MD). Waist circumference was measured (cm) at the level of the umbilicus.using a nonstretchable tape (Gulick II Measuring Tape, Country Technology, Gays Mills, WI). Anthropometric measurements were repeated during the last week of the intervention.

**Dietary Assessment**

Each subject kept a four-day food intake record at baseline and during the final week of the study to assess dietary intake. Subjects were instructed by a research dietitian (BD) to accurately record food intake (e.g., portion sizes, food preparation methods, brand names of products) using two-dimensional food models. The dietitian reviewed all records with subjects upon completion for accuracy and sufficiency of detail. Subjects were asked to provide food labels for products used to determine appropriate substitutions when actual items consumed were not in the software database. Food intake records were analyzed using the Food Intake Analysis System (FIAS 3.98 nutrient analysis program, University of Texas School of Public Health, 1998). The FIAS database consists of the Primary Data Set (PDS) and the Survey Nutrient Data Base (Survey NDB) of the National Nutrient Data Bank, developed and maintained by the United States Department of Agriculture (USDA).

**Lipid and Lipoprotein Analysis**

Blood samples were obtained at baseline and after the 12-week intervention. Following an overnight fast, blood was obtained from an indwelling IV catheter into tubes containing EDTA. Samples were inverted, and then centrifuged to obtain plasma, which was then stored at –70° C until analysis.

Plasma lipid and lipoprotein concentrations and lipoprotein particle size were determined from plasma samples using nuclear magnetic resonance (NMR) spectroscopy (LipoMed, Inc., Raleigh, NC). This method is based on the principle that when plasma is exposed to the NMR magnet, the methyl group protons of each of the four types of lipids (phospholipid, cholesterol, cholesterol ester, and TG) in the lipoproteins together emit a

bulk NMR signal. The unique signal produced by the various lipoprotein particles of differing diameters (based on the phospholipid shell) contribute to this bulk signal, analogous to the sound produced by simultaneously ringing numerous bells of differing size and shape (Figure 3-1). This composite signal then undergoes deconvolution using linear least–squares regression analysis to separate the lipoprotein subclasses based on prior knowledge of the methyl signal frequency and shape emitted by individual lipoprotein subclasses. The plasma concentration of each lipoprotein subclass is then calculated based on knowledge about the known relationship between signal amplitude and subclass concentration (Otvos et al., 1992; Otvos 2000). To perform these calculations, software is used which contains a reference library of subclass spectra obtained by isolating lipoprotein particle size ranges from fasting plasma of normolipidemic and dyslipidemic subjects using ultracentrifugation and agarose gel filtration chromatography (Otvos 2000). This process allows the simultaneous measurement of 15 lipoprotein subclasses including VLDL-TG (V1-V6), LDL-C (IDL, L1-L3), HDL-C (H1-H5) and chylomicrons (Table 3-1). $HDL_2$ corresponds to the sum of H4 and H5, $HDL_3$ is the sum of H1, H2, and H3. Based on comparisons with the lipoproteins separated by flotation ultracentrifugation, "small" LDL corresponds to L1 and "large" LDL refers to the sum of L2 and L3 (Otvos et al., 1992; Otvos 2000). Individual lipoprotein lipid concentrations are then calculated based on the average measured lipid values for each of the lipoproteins, based on values previously determined from spectrophotometric analysis of lipids from reference samples (Otvos et al., 1992). Total plasma cholesterol, triacylglycerol, LDL-cholesterol, and HDL-cholesterol concentrations are then determined by summing the lipid concentrations of the various

subclasses. Values were expressed in mmol/l of cholesterol (LDL-C and HDL-C) and triacylglycerol (VLDL-TG). Strong correlations between NMR and chemical analysis for VLDL-TG, LDL-C, and HDL-C have been reported (r = 0.98, 0.91, and 0.93 respectively) (Otvos et al., 1992). LDL and HDL subclass distributions between NMR and gradient gel electrophoresis (GGE) also correlate well (Otvos et al., 1992).

Average particle size (diameter, nm) of VLDL, LDL, and HDL, and concentration (particle number) of the LDL particles (nmol/L) were also determined. Reference standards for VLDL and LDL subclass diameters for the NMR method are based upon electron microscopy and for HDL by polyacrylamide GGE (Otvos 2000). Correlations between NMR and GGE for LDL and HDL particle size have been reported to be 0.70-0.90 and 0.88 (Otvos et al., 1992), respectively. LDL subclass diameters obtained with the NMR method are ~5nm smaller than those obtained using GGE, but are in agreement with electron microscopy data and calculations based upon LDL chemical composition (Otvos 2000). Individuals were classified as LDL subclass phenotype pattern A if their mean particle size was > 20.5 nm and pattern B if they had a mean baseline LDL particle size ≤20.5 nm (Freedman et al., 1998), and lipoprotein responses to the intervention were analyzed by LDL subclass phenotype and cereal group.

Coefficients of variation using the NMR procedure have been reported to be 1.5-2.9% for standard lipid panel variables, 1.8% for LDL particle concentration, and about 0.5% for average LDL and HDL particle size (Otvos 2000). A more detailed treatment of the use of NMR for measuring plasma lipid and lipoprotein concentrations and lipoprotein particle size has been described previously (Otvos et al., 1992; Otvos 2000; Otvos 1999).

**Intravenous Glucose Tolerance Test**

An insulin-augmented frequently sampled intravenous glucose tolerance test (IVGTT) was administered to these subjects at baseline and after the intervention following an overnight, 12-hour fast. The test was performed with the subject in a supine position, after a 30-minute relaxation period. An intravenous (IV) catheter was placed in each antecubital vein, one for the administration of insulin and glucose, and one for collecting blood samples. Two blood samples were obtained at time (t) = -10, -5 minutes, with these two samples used for determination of the mean baseline insulin and glucose concentrations. At time zero, a bolus of glucose (0.3g/kg in a of 50% dextrose solution) was infused over a 90 second period. At t = 20 minutes, a bolus of insulin (0.03 U/kg) was injected. Blood samples were obtained at t = 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes and immediately centrifuged at 4°C and analyzed for glucose concentrations by the glucose oxidase method using a glucose autoanalyzer (Yellow Springs Instruments, Yellow Springs, Ohio). A sample of plasma was stored at –20°C for later determination of insulin concentrations by the ELISA method (Diagnostic Systems Laboratories, Inc., Webster, TX). Insulin and glucose values from the IVGTT were entered into the MINMOD program (version 3.0, R. Bergman, University of Southern California) for determination of insulin sensitivity ($S_I$), acute insulin response to glucose ($AIR_G$) and glucose effectiveness ($S_G$). This model uses measurements of plasma glucose and insulin concentrations over the 3-h period to deduce in vivo whole-body insulin sensitivity (Bergman et al., 1981).

**Statistical Analysis**

Kolmogorov-Smirnov normality tests were performed on independent and dependent variables prior to further statistical analysis. Treatment differences were initially assessed using a two (oat vs wheat) by two (pre vs post-treatment) ANOVA (General Linear Model, SPSS statistical software, SPSS 9.0 for Windows). A two by two ANCOVA procedure was used with changes in body weight, and changes in dietary macronutrient intake used as covariates where appropriate. Lipoprotein responses to the two cereals were compared in phenotype pattern A versus B using ANCOVA. When there was a significant pattern by time interaction, paired t-tests were used to determine pattern A vs B differences in lipid and lipoprotein responses to the intervention. Simple correlational analyses were performed to identify relationships among variables that could explain any treatment-related changes. Alpha was set at $P< 0.05$. All data are expressed as mean±SEM.

## RESULTS

The physical characteristics of the study participants are shown in Table 3-2. There were no significant group differences in subject characteristics at baseline. Mean body mass index (BMI=kg/m$^2$) and sum of skinfold thickness increased slightly but significantly in both groups over time ($P<0.05$). Body weight increased ~0.8 kg ($P<0.05$).

Despite the slight increase in body weight, no change in energy intake was detected in either cereal group over the 12-week intervention. However, significant changes in macronutrient intake were noted (Table 3-3), with similar increases in mean intakes of protein (g) and carbohydrate (g and % of total energy) and a decrease in fat

intake (g and % of total energy) occurring in both groups. This change was an increase of approximately 5% as a percentage of total energy for carbohydrate and a decrease of about 5% as a percentage of total energy for fat. Intake of cholesterol and saturated (SFA) and monounsaturated fat (MUFA) was reduced and dietary P:S ratio improved significantly in both groups. Unexpected baseline differences in dietary intake of saturated fat, myristic and palmitic acid were observed (P=0.02, 0.02, and 0.01, respectively).

The results of the lipid and lipoprotein analyses are shown in Table 3-4. One individual in the oat group had incomplete lipid data; data are for 17 individuals in the oat group and 18 in the wheat group. There were no significant differences in baseline lipid or lipoprotein concentrations between groups. There was a significant time-by-treatment interaction for LDL-C, the small LDL-C subclass, LDL particle concentration, and LDL-C/HDL-C ratio, with the oat group showing favorable changes, and the wheat group experiencing elevations in these lipid parameters. A significant reduction in mean HDL particle size across both groups was noted over time. A paired sample t-test indicated no significant change in HDL size in the oat group (P=0.32), but a significant reduction in the wheat group (P=0.03). Therefore, this significant time effect is attributed to the greater reduction in HDL particle size in the subjects consuming the high-fiber wheat cereals. There were trends for a decrease in concentration of TC (P=0.08), TG (P=0.07), VLDL-TG (P=0.08), LDL particle size (P=0.10), and TC/HDL-C (P=0.05) in the oat versus wheat group. Few individuals in either group had detectable concentrations of chylomicrons or intermediate-density lipoproteins, with the analyses indicating no significant changes in either group over time (data not shown). Correlational analyses

indicated a significant ($P<0.05$) relationship of change in TG concentrations to changes in LDL size ($r= -0.80$), small LDL-C ($r= 0.76$), TC ($r= 0.50$), LDL-C ($r= 0.36$), and $HDL_2$ ($r= -0.58$).

Because of baseline differences in dietary intake of saturated fat, myristic and palmitic acid, additional statistical analyses were performed using changes in these dietary variables as well as intake of total fat, polyunsaturated fat, cholesterol, and P:S ratio as covariates. All significant blood lipid/lipoprotein changes remained significant, even after adjustment. Additionally, TC levels were significantly different in the oat versus wheat group over time when changes in P:S ratio and polyunsaturated fat intake were used as covariates.

After covarying for LDL-subclass phenotype (patterns A and B), the significant time-by-treatment interactions indicated above remained significant. However, significant differences were noted in response to the intervention according to LDL subclass phenotype (Figures 3-2a-d). Pattern A individuals consuming oats ($n=5$) had a small but significant reduction in LDL size ($21.0\pm0.2$ to $20.8\pm0.2$ nm, $P=0.05$), as did pattern A individuals consuming wheat ($n=8$) ($21.1\pm0.1$ to $20.5\pm0.3$ nm, $P=0.05$). Pattern B individuals who consumed oats ($n=12$) had a significant reduction in small LDL-C ($2.41\pm0.39$ to $1.92\pm0.38$ mmol/L, $P=0.05$) while pattern A individuals consuming wheat had significant increases in small LDL-C ($0.13\pm0.1$ to $1.23\pm0.5$, $P=0.05$) and LDL particle concentration ($1385\pm89$ to $1746\pm137$, $P=0.01$). Pattern A individuals consuming wheat had a significant increase in TG concentration ($1.10\pm0.2$ to $1.93\pm0.4$, $P=0.05$). Pattern B individuals consuming wheat ($n=10$) did not exhibit significant changes in any of these variables.

Insulin and glucose parameters are shown in Table 3-5. There were no significant changes in fasting glucose or insulin concentrations, $S_I$ or $AIR_G$. There was a significant time-by-treatment interaction for $S_G$ (P=0.03), with the oat group exhibiting a reduction and the wheat group an elevation. Despite lack of significant group differences in $S_I$, among individuals in the entire sample, change in TG concentration was significantly associated with change in $S_I$ (r=0.40, P=0.03), as were changes in LDL particle number (r=0.46, P=0.01) and LDL-C (r=0.50, P=0.01).

## DISCUSSION

The major finding of this study is that the addition of two large servings of oat cereal as compared to wheat cereal results in lower concentrations of small, dense LDL and LDL particle numbers. Furthermore, despite the increase in carbohydrate intake and the decrease in total and saturated fat, mean plasma TG concentration did not increase in those subjects consuming high-fiber oat cereals. However, plasma TG increased along with other unfavorable changes in lipids and lipoproteins in those consuming the wheat cereal, as has been reported in some studies where dietary carbohydrate was increased and dietary fat decreased. (Parks et al., 1999). Because a low-fat, high-carbohydrate, high-fiber diet is frequently recommended for the prevention and treatment of CVD, it may be important to distinguish between the type of fiber recommended, e.g., soluble versus insoluble.

We found a trend toward reduced TG concentrations in those consuming oats and elevated TG concentrations in those consuming wheat ($p<0.07$). Even modest elevations in concentrations of blood TG are independently related to increased CVD risk (Austin et

al., 1998) possibly resulting from alterations in the lipid composition of HDL and LDL. The exchange of cholesterol esters for TG among these lipoproteins causes them to become relatively cholesterol-depleted and TG-enriched (Lamarche et al., 1998). These particles, then, are favorable substrates for hepatic TG lipase, with TG removal resulting in decreases in particle diameter and increases in density. In this investigation, changes in TG concentrations were significantly inversely correlated with change in LDL particle size and $HDL_2$ and positively correlated with change in concentration of small LDL-C. These findings provide support for a relationship between a decrease in TG concentrations accompanied by an increase in LDL particle size in those consuming oat but not wheat cereal.

The characteristics of small, dense LDL particles may relate to their increased atherogenic potential. Specifically, these particles may be more susceptible to oxidation and have a lower clearance rate as the result of a reduced affinity for the LDL receptor (Lamarche et al., 1998). LDL particle size is inversely correlated with CHD (Gardner et al., 1996; Stampfer et al., 1996). Studies have suggested that the highest risk for CHD may occur in individuals with a predominance of small LDL (pattern B) and a high LDL particle concentration (Lamarche et al., 1997). The LDL particle concentration provides some indication of apolipoprotein B levels, or the concentration of potentially atherogenic particles in the plasma. Anderson et al. (1991) found that supplemental oat bran (e.g., without an increase in dietary carbohydrate) lowered apolipoprotein B-100 levels by 13.7%; however, this could have been attributed to a decrease in body weight. Our data suggest that the type of fiber consumed may be an important factor in determining the concentration and number of small LDL particles.

Our findings also suggest that LDL subclass phenotype may be an important determinant of lipid and lipoprotein response to an increased intake of dietary carbohydrate and fiber. Among pattern B individuals, small LDL-C concentrations improved in those consuming oats but failed to improve in those consuming wheat. Among pattern A individuals, small LDL-C, LDL particle number, and TG were unchanged in those consuming oats but worsened significantly in those consuming wheat. Thus, the lipid and lipoprotein response to increased dietary carbohydrate appears to depend on both the LDL subclass phenotype and the type of dietary carbohydrate (eg, soluble versus insoluble fiber) consumed.

A positive correlation between habitual dietary fiber intake and $S_I$ has been reported (Lovejoy and DiGirolamo, 1992). Increased viscous dietary fiber intake may decrease gastric emptying and increase small intestinal transit time, modify the secretion or action of digestive enzymes, or alter other factors which decrease the rate of glucose absorption (Sharma 1992). This could flatten postprandial glucose and insulin curves and potentially increase $S_I$. We did not find a significant change in $S_I$ with an increased intake of soluble or insoluble dietary fiber. However, our measurements were made in the fasted state and it is possible that alterations in glucose and insulin metabolism may have occurred postprandially. The latter could impact lipoprotein subclasses.

These data indicate that increased carbohydrate consumption resulting from increased intake of high-fiber oat cereals does not reduce HDL-C concentrations or increase TG concentrations. This is in agreement with a recent meta-analysis indicating that soluble fiber does not raise blood TG concentration (Brown et al., 1999). Wheat bran supplements (eg, an increase in fiber without an increase in carbohydrate intake) may

decrease serum TG concentration (Anderson et al., 1991) but do not generally lower blood TC or LDL-C (Anderson et al., 1991; Jenkins et al., 1998; Jenkins et al., 1999; Kestin et al., 1990). However, this has not been a consistent finding (Kashtan et al., 1992; Vuksan et al., 1999). We found that high-fiber wheat cereal consumption (approximately 500 kcal) produced increases in TC, LDL-C, and TG, in a manner similar to what has been noted in studies substituting dietary carbohydrate for fat (Parks et al., 1999). The reason for these unfavorable lipoprotein changes in those consuming the wheat cereal is not readily apparent, however, the mechanism by which these alterations are produced does not occur with increased oat consumption. This difference may be related to characteristics of the cereal, eg, soluble versus insoluble fiber content. It is also possible that the difference in simple sugar content of the two cereal combinations (7.1 g) could have contributed to these differences, although this would seem unlikely as this amount represents a difference of only 1.4% of total reported energy intake between the two groups.

A potential caveat to this study is our use of NMR spectroscopy, rather than more conventional methods, to determine lipoprotein subclasses. However, there are several observations that support our use of NMR spectroscopy for this purpose. First, the analyses of subjects' pre- and post-intervention blood samples were performed in a single run by observers blind to subject group assignment. Second, the absolute levels of plasma lipid and lipoprotein concentrations and the reductions in LDL-C are within a range previously reported using more conventional methodology (Brown et al., 1999). Finally, the fact that in our sample, the correlation coefficients for change in the plasma lipid and lipoprotein concentrations and lipoprotein size with change in insulin sensitivity were

significant and in the expected direction, also lends support to the use of this technique to quantify plasma lipid and lipoprotein concentrations and lipoprotein particle size. Therefore we believe that comparisons of these values between groups and within subjects in our sample are meaningful and scientifically valid.

In conclusion, we found the addition of two large servings per day of oat cereal as compared to wheat cereal resulted in lower concentrations of small, dense LDL-C and LDL particle number without producing adverse changes in blood TG or HDL-C concentrations. These data suggest that the type of dietary fiber, such as that found in oat cereal, may be important when recommending a high-fiber, low-fat, high-carbohydrate diet for the improvement of blood lipids and lipoproteins.

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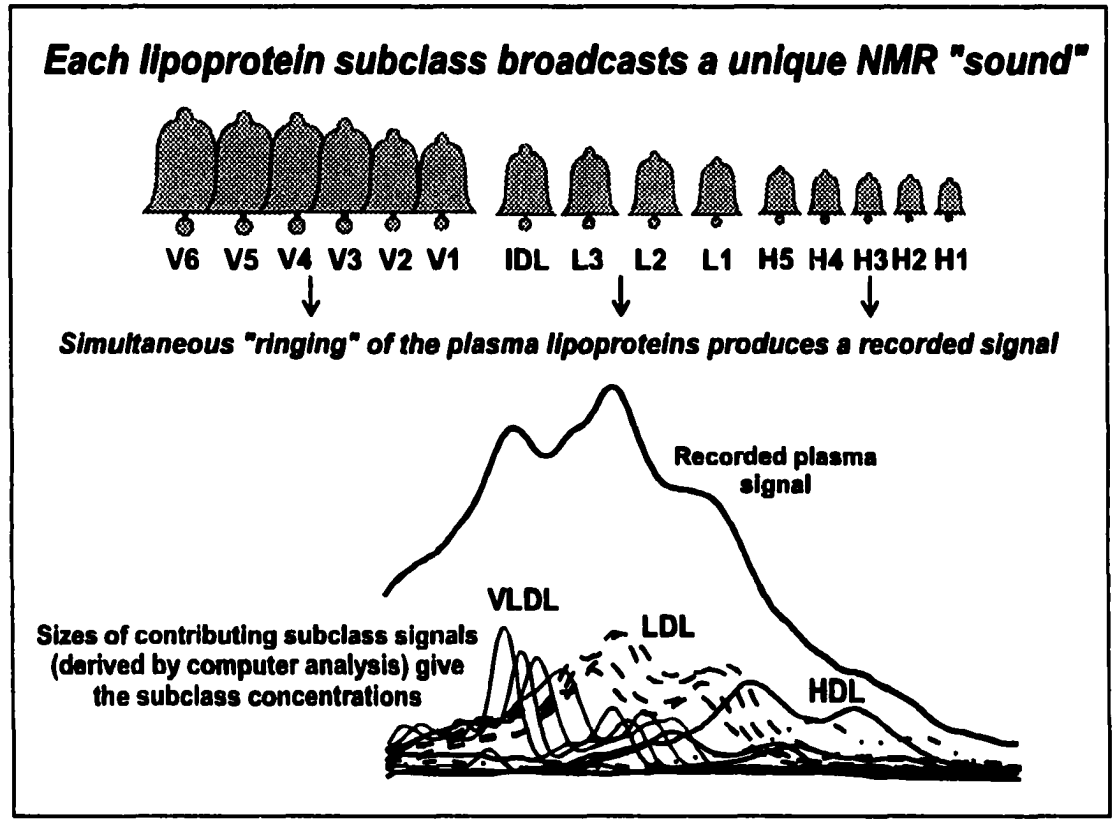
**Figure 3-1. Lipoprotein subclasses behave like bells in the NMR analyzer**

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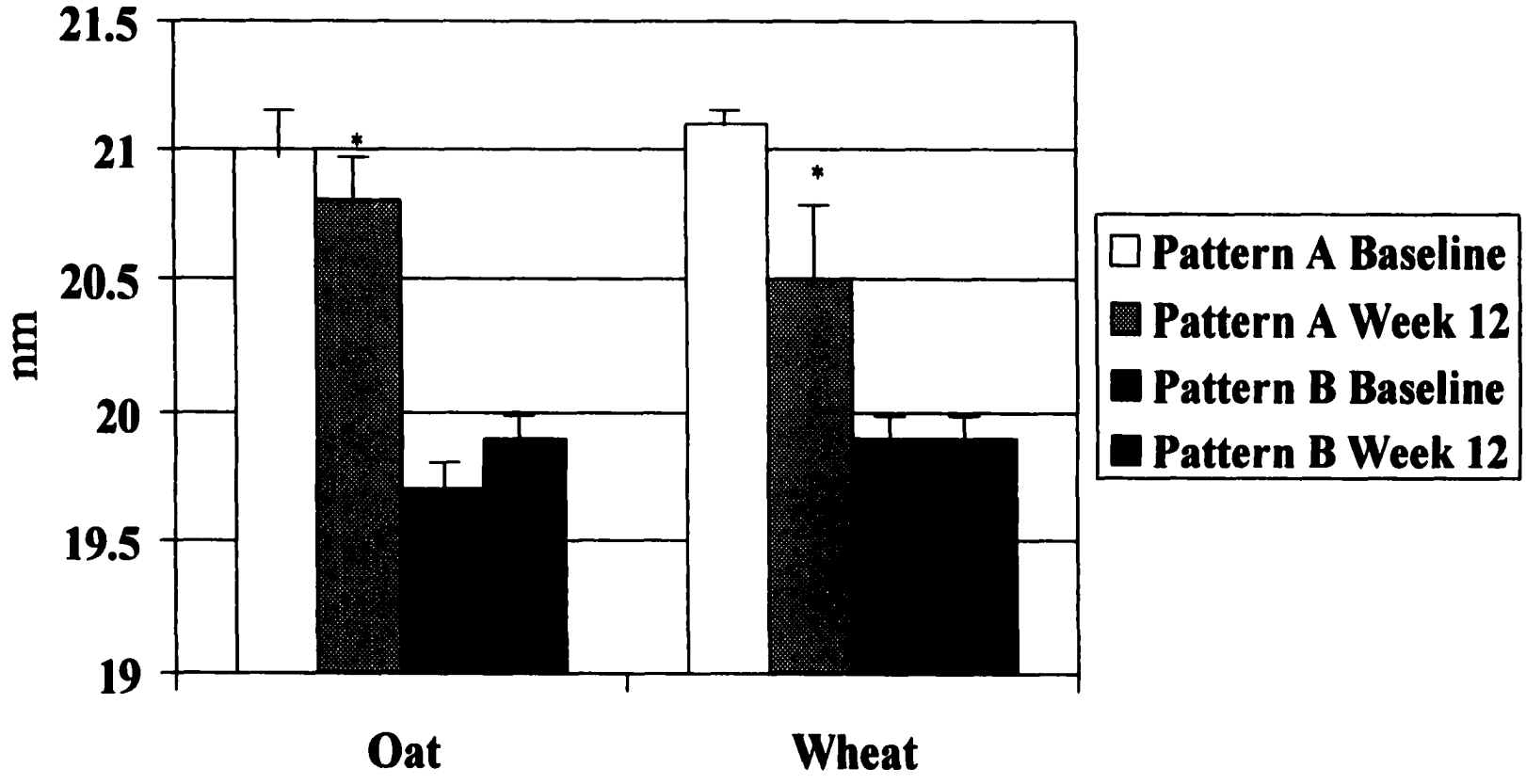
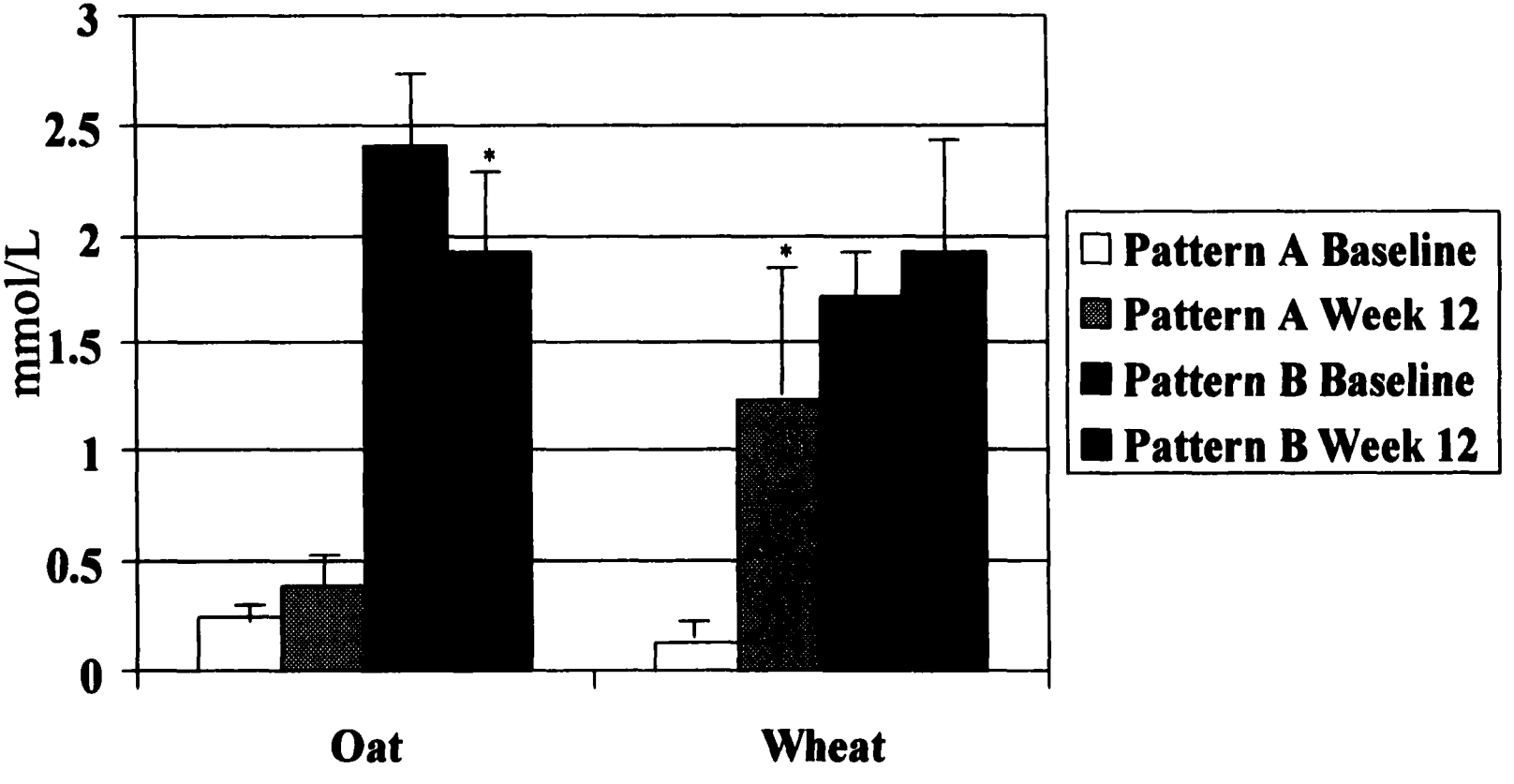
## Figure 3-2a. Change in LDL size in pattern A versus B individuals consuming oat or wheat cereal



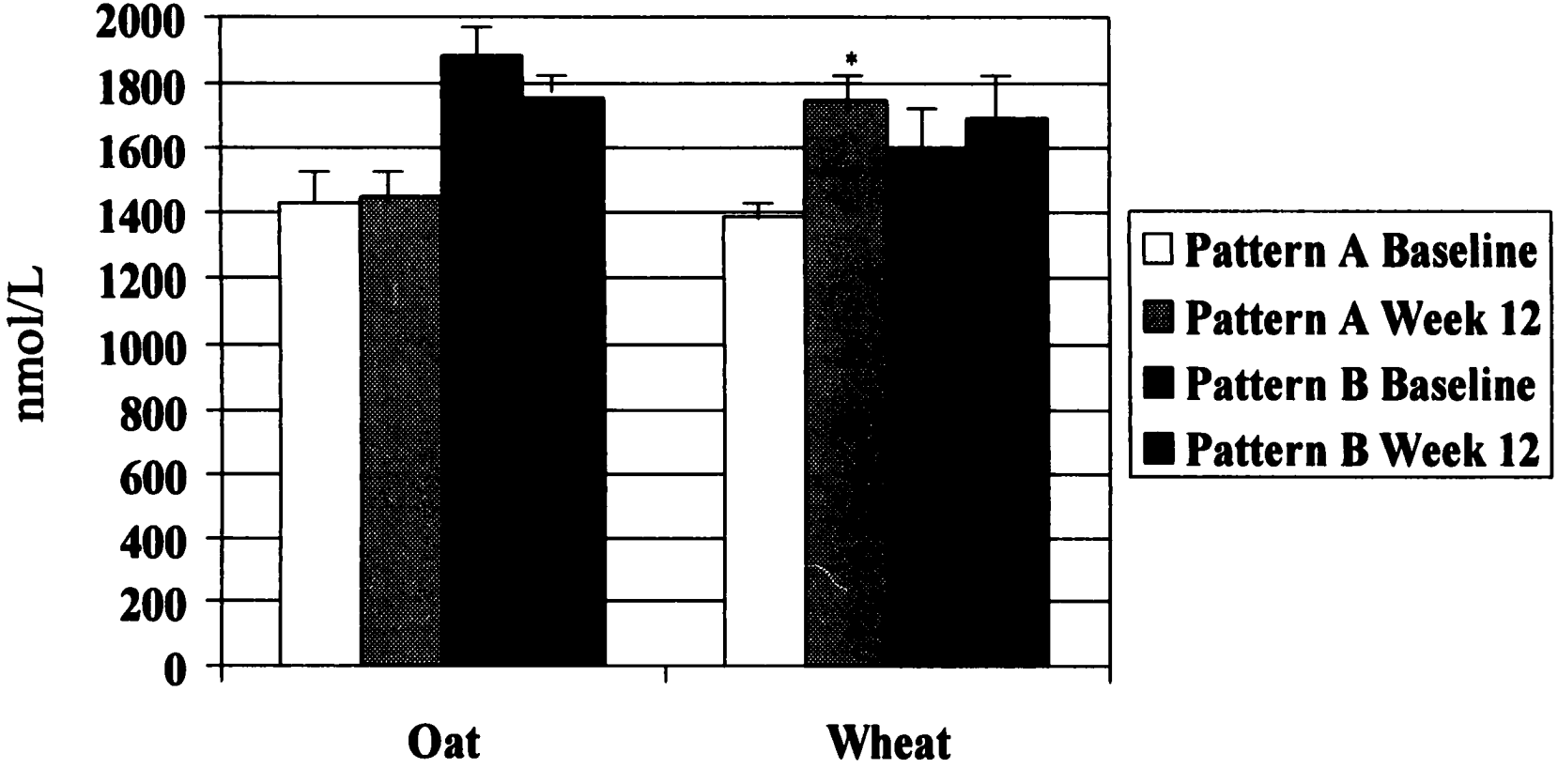

Values are Mean±SEM. *Significant within pattern difference in baseline versus week 12, $P \leq 0.05$.

# Figure 3-2b. Change in small LDL-C concentration in pattern A versus B individuals consuming oat or wheat cereal



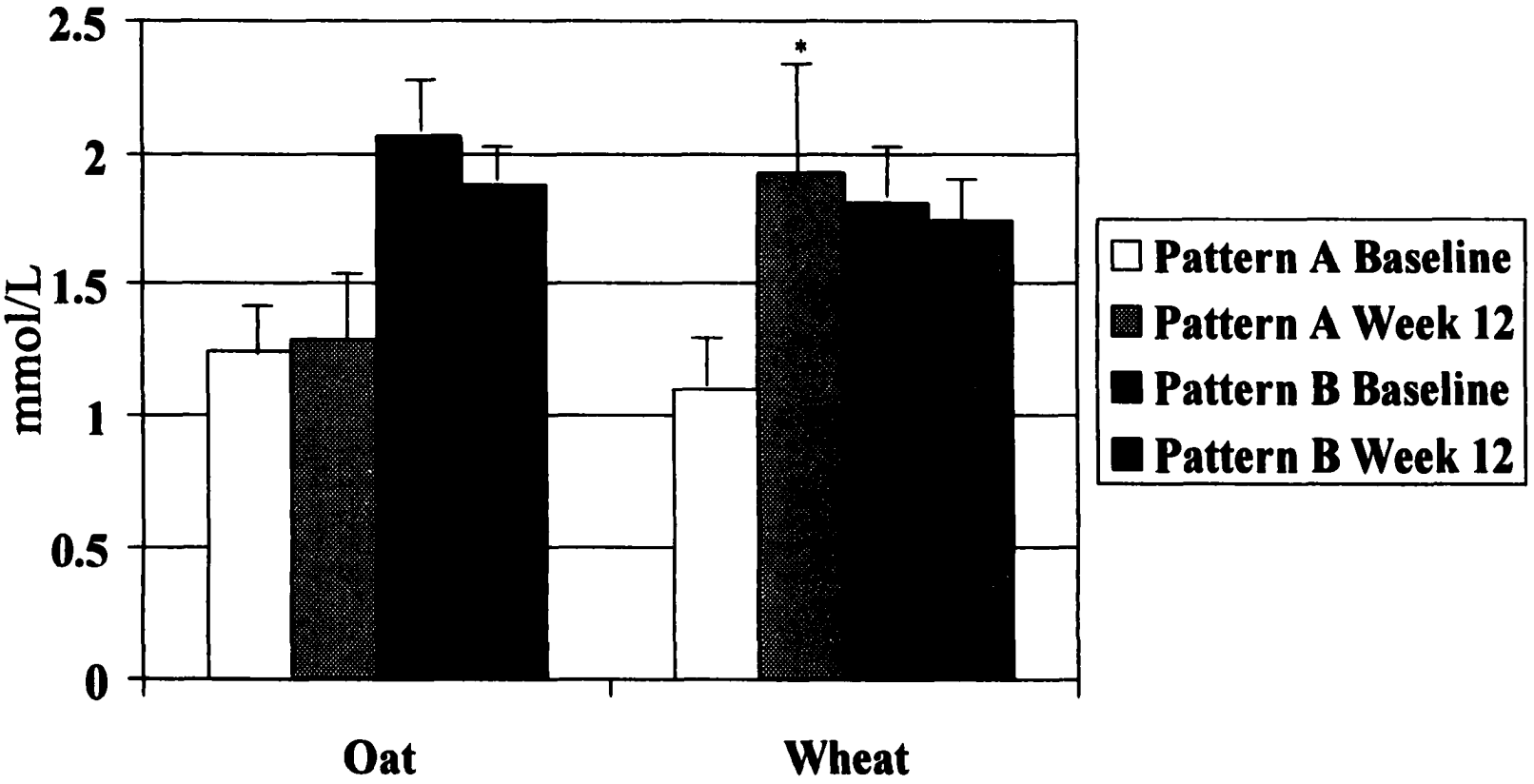

Values are Mean±SEM. *Significant within pattern difference in baseline versus week 12, P≤0.05.

Figure 3-2c. Change in LDL particle concentration in pattern A versus B individuals consuming oat or wheat cereal




Values are Mean±SEM. *Significant within pattern difference in baseline versus week 12, $P \leq 0.05$.

## Figure 3-2d. Change in triacylglycerol concentration in pattern A versus B individuals consuming oat or wheat cereal




Values are Mean±SEM. *Significant within pattern difference in baseline versus week 12, P≤0.05.

Table 3-1. Lipoprotein Subclasses Determined by Nuclear Magnetic Resonance Spectroscopy

| | Sub-Populations | Diameter Range (nm) |
|---|---|---|
| VLDL | V6 | 150±70 |
| | V5 | 70±10 |
| | V4 | 50±10 |
| | V3 | 38±3 |
| | V2 | 33±2 |
| | V1 | 29±2 |
| LDL | IDL | 25±2 |
| | L3 | 22±0.7 |
| | L2 | 20.5±0.7 |
| | L1 | 19±0.7 |
| HDL | H5 | 11.5±1.5 |
| | H4 | 9.4±0.6 |
| | H3 | 8.5±0.3 |

Table 3-1. Lipoprotein Subclasses Determined by Nuclear Magnetic Resonance Spectroscopy (continued)

| Sub-Populations | Diameter Range (nm) |
|---|---|
| H2 | 8.0±0.2 |
| H1 | 7.5±0.2 |

Table 3-2. Physical Characteristics Before and After 12 Weeks of the Intervention.

| | Oat Group (n=18) | | Wheat Group (n=18) | |
|---|---|---|---|---|
| | Baseline | Week 12 | Baseline | Week 12 |
| Age (years) | 57±2 | | 61±2 | |
| Height (cm) | 175.9±1.5 | | 177.4±1.5 | |
| Weight (kg)* | 91.4±3.0 | 92.1±3.0 | 92.3±3.0 | 93.2±3.0 |
| BMI ($kg/m^2$)* | 29.6±0.8 | 29.8±0.8 | 29.2±0.8 | 29.5±0.8 |
| Sum of skin folds (mm)* | 168.7±7.9 | 172.4±10.5 | 175.0±7.9 | 185.6±10.5 |
| Waist Circumference (cm) | 104.1±2.2 | 104.5±2.1 | 104.8±2.0 | 105.1±2.1 |

Data are expressed as mean±SEM. There was no significant difference in age or height between the groups. There were no significant group by time interactions for weight, BMI, sum of skin folds or waist circumference. *Significant main effect of time. ($P<0.05$).

Table 3-3. Dietary Intake at Baseline and After 12 Weeks of the Intervention.

| | | Oat Group | | Wheat Group | |
|---|---|---|---|---|---|
| | | Baseline | Week 12 | Baseline | Week 12 |
| Energy | (kJ) | 10620±560 | 10877±536 | 9398±544 | 9939±521 |
| | (kcal) | 2538±134 | 2599±128 | 2246±130 | 2375±125 |
| Protein* | (g) | 91.1±5.1 | 103.3±6.0 | 82.1±4.9 | 86.8±5.8 |
| | (%) | 14.8±0.7 | 15.9±0.6 | 14.8±0.7 | 14.4±0.6 |
| Fat* | (g) | 99.8±6.5 | 89.2±6.0 | 82.4±6.4 | 78.3±5.8 |
| | (%) | 35.3±1.5 | 29.6±1.2 | 33.3±1.4 | 28.0±1.2 |
| Carbohydrate* | (g) | 297.2±21.3 | 336.8±17.3 | 283.3±20.7 | 331.6±16.8 |
| | (%) | 47.0±2.2 | 51.5±1.6 | 49.6±2.1 | 55.0±1.5 |
| Dietary Fiber* | (g) | 20.9±1.9 | 30.2±1.6 | 18.9±1.9 | 29.2±1.6 |
| Cholesterol* | (mg) | 406.7±42.2 | 260.9±31.1 | 291.4±41.0 | 232.5±30.2 |

| | | | | | |
|---|---|---|---|---|---|
| Fatty Acids: | | | | | |
| Saturated* | (g) | 35.8±2.4 | 29.6±2.1 | 27.6±2.3 | 24.2±2.0 |
| Lauric Acid* | (g) | 1.3±0.3 | 0.7±0.1 | 0.6±0.3 | 0.5±0.1 |
| Myristic Acid* | (g) | 3.3±0.3 | 2.5±0.2 | 2.4±0.3 | 2.1±0.2 |
| Palmitic Acid* | (g) | 19.2±1.3 | 16.4±1.1 | 15.1±1.2 | 13.5±1.1 |
| Monounsaturated* | (g) | 38.2±2.7 | 34.3±2.4 | 32.0±2.6 | 29.6±2.3 |
| Polyunsaturated | (g) | 17.9±1.5 | 18.4±1.8 | 16.3±1.4 | 18.5±1.8 |
| P:S ratio* | | 0.5±0.1 | 0.7±0.1 | 0.6±0.1 | 0.8±0.1 |

Data are expressed as mean±SEM. There were no significant group by time interactions. *Significant main effect of time ($P<0.05$).

Table 3-4. Lipid and Lipoprotein Profiles At Baseline and After 12 Weeks of the Intervention.

| | Oat Group | | Wheat Group | | |
|---|---|---|---|---|---|
| | Baseline | Week 12 | Baseline | Week 12 | P for Interaction |
| Total cholesterol, mmol/L | 5.28±0.18 | 5.15±0.21 | 4.91±0.16 | 5.22±0.18 | 0.08 |
| LDL-C, mmol/L | 3.58±0.16 | 3.49±0.14 | 3.30±0.15 | 3.57±0.14 | 0.02* |
| Small LDL-C, mmol/L | 1.77±0.33 | 1.47±0.34 | 1.01±0.33 | 1.61±0.33 | 0.01* |
| Large LDL-C, mmol/L | 1.79±0.31 | 2.01±0.30 | 2.28±0.30 | 1.94±0.29 | 0.08 |
| HDL-C, mmol/L | 0.87±0.05 | 0.86±0.05 | 0.89±0.04 | 0.85±0.05 | 0.41 |
| $HDL_2$-C, mmol/L | 0.27±0.04 | 0.24±0.04 | 0.27±0.04 | 0.24±0.04 | 0.92 |
| $HDL_3$-C, mmol/L | 0.61±0.03 | 0.63±0.02 | 0.62±0.03 | 0.62±0.02 | 0.68 |
| Triacylglycerol, mmol/L | 1.83±0.17 | 1.71±0.18 | 1.50±0.17 | 1.83±0.17 | 0.07 |
| VLDL-TG, mmol/L | 1.44±0.17 | 1.33±0.17 | 1.13±0.16 | 1.44±0.17 | 0.08 |
| LDL size, nm | 20.08±0.2 | 20.15±0.2 | 20.41±0.2 | 20.16±0.2 | 0.10 |

| | | | | | |
|---|---|---|---|---|---|
| HDL size**, nm | 8.44±0.1 | 8.40±0.1 | 8.56±0.1 | 8.42±0.1 | 0.14 |
| VLDL size, nm | 50.7±2.0 | 50.3±1.8 | 50.1±1.9 | 50.1±1.8 | 0.89 |
| LDL particle concentration, nmol/L | 1752±102 | 1664±101 | 1503±99 | 1717±98 | 0.01* |
| LDL-C/HDL-C ratio | 4.3±0.3 | 4.1±0.3 | 3.8±0.3 | 4.3±0.3 | 0.02* |
| Total cholesterol/HDL-C ratio | 6.4±0.4 | 6.0±0.5 | 5.7±0.3 | 6.4±0.4 | 0.05 |

Data are expressed as mean±SEM. *Significant time-by-treatment interaction ($P<0.05$). **Significant main effect of time, $P=0.02$.

Table 3-5. Insulin and Glucose Metabolism At Baseline and After 12 Weeks of the Intervention.

| | Oat Group | | Wheat Group | | |
|---|---|---|---|---|---|
| | Baseline | Week 12 | Baseline | Week 12 | P for Interaction |
| Fasting glucose, mmol/L | 5.4±0.1 | 5.6±0.1 | 5.3±0.1 | 5.3±0.1 | 0.17 |
| Fasting insulin, pmol/L | 93.8±15.4 | 88.4±12.5 | 55.3±15.4 | 58.8±12.5 | 0.34 |
| $S_I$, $10^{-4}min^{-1}$ /uM/ml | 1.8±0.3 | 1.8±0.3 | 2.6±0.3 | 2.2±0.3 | 0.21 |
| $S_G$, $min^{-1}$ | 0.0198±0.0018 | 0.0187±0.0017 | 0.0188±0.0019 | 0.0224±0.0018 | 0.03* |
| $AIR_G$, pmol/ml/min | 527.6±45.2 | 471.9±54.5 | 410.6±47.9 | 406.1±57.8 | 0.30 |

Data are expressed as mean±SEM. *Significant time-by-treatment interaction, P<0.05.

# CHAPTER FOUR

## Influence of oat consumption on resting casual and ambulatory 24-hour arterial BP in men with high-normal to stage I hypertension


## ABSTRACT

The results of epidemiological studies suggest increased intake of dietary fiber is associated with lower levels of arterial blood pressure (BP). However, there is little information available addressing the possibility that increased oat consumption may reduce arterial BP in individuals with elevated arterial BP. To test this hypothesis, 36 male middle-aged and older men (BMI 25-35kg/m$^2$, aged 50-75) with elevated BP (systolic BP 130-160mmHg and/or diastolic BP 85-99mmHg) were randomly assigned to consume an additional 14 g of dietary fiber in the form of oat (5.5g β-glucan, n=18) or wheat cereals (no β-glucan, n=18) for 12 weeks. Casual resting arterial BP was measured at baseline and after four, eight, and 12 weeks of the intervention. 24-hour ambulatory arterial BP was measured at baseline and after 12 weeks of the intervention. There were no differences in casual resting or 24-hr ambulatory BP at baseline in the two groups. Casual systolic BP (SBP) did not change as a result of the 12-week intervention in the oat (138±2 vs. 135±3 mmHg) or wheat (142±2 vs. 140 ±3 mmHg) groups, respectively (all

P>0.05). Casual diastolic BP (DBP) also did not change in the oat (89±2 vs. 88±2 mmHg) or wheat (90±2 vs. 91±2 mmHg) group during this period (all P>0.05). Further, 24-hour, daytime, and nighttime SBP and DBP did not decrease with the intervention. Therefore, the results of the present study suggest that the cardioprotective benefit of regular oat consumption is not conferred by an arterial BP-lowering effect.

## INTRODUCTION

Approximately one in four adults in the United States have hypertension (American Heart Association, 2000). In 1998, high blood pressure (BP) caused the deaths of 44,435 Americans (American Heart Association, 2000). Importantly, dietary and other lifestyle changes are recommended as the initial approach for the treatment of high-normal (130-139/85-89) and Stage I hypertension (140-159/90-99) for individuals without target organ damage or clinical cardiovascular disease (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VI, 1997).

Epidemiological studies indicate that total dietary fiber intake is inversely related to arterial BP (Ascherio et al. 1992, Hallfrisch et al. 1995, Joffres et al. 1987, Ludwig et al. 1999). Other studies (He et al. 1995) have suggested that oat fiber intake, in particular, is inversely related to arterial blood pressure. However, previous clinical trials that have addressed the possibility that increased high-fiber oat cereal consumption lowers BP have been inconsistent. To our knowledge, there are only three published studies (Kestin et al. 1990; Swain et al. 1990; Saltzman et al. 2001) that address this issue. All of these studies were conducted in normotensive individuals. Of these, only one study (Saltzman et al. 2001) reported a reduction in arterial BP in individuals

consuming a *hypocaloric* diet high in oat fiber. These reductions in SBP were greater than observed in a control group exhibiting a similar amount of weight loss. Therefore, it is unclear whether fiber-rich oat cereal, independent of weight loss, lowers BP in individuals with elevated arterial blood pressure. To test this hypothesis, we measured resting seated and supine BP and 24-hr ambulatory BP in 36 middle-aged and older men before and after randomization to 12-weeks of increased oat (n=18) or wheat fiber (n=18) consumption.

## MATERIALS AND METHODS

### Subjects

Male subjects aged 50-75 y with a body mass index (BMI) between 25-35 $kg/m^2$ and elevated BP (systolic BP 130-160mmHg and/or diastolic BP 85-99mmHg) were recruited for this study from the surrounding community. Only subjects who were sedentary or minimally physically active (< two 30-minute aerobic exercise sessions per week) were included. Individuals were excluded if they reported or were observed to have any of the following: overt cardiovascular, metabolic, or pulmonary disease or use of any medications known to affect any of the dependent variables in this study. Subjects were excluded if they reported a high habitual intake of dietary fiber (e.g., >30g/day), as determined by the Block Screening Questionnaire for Fat and Fruit/Vegetable/Fiber Intake (Block 1994). This study was approved by the Human Research Committee at Colorado State University. All subjects provided written informed consent prior to participation.

**Experimental Design**

Following screening, subjects were randomly assigned to consume whole grain oat or wheat cereals containing 14g of dietary fiber for 12 weeks (Oat group, 60g Quaker Oatmeal and 76g Quaker Oat Bran ready-to-eat cold cereal, Quaker Oats Company, Barrington, Illinois; Wheat group, 60g Mother's Whole Wheat Hot Natural Cereal, Quaker Oats Company, Barrington, Illinois and 81g Frosted Mini-Wheats, Kellogg Company, Battle Creek, Michigan). The combination of oat cereals provided 5.5g β-glucan as determined by manufacturer's analysis. The amount of cereal provided was matched between groups to achieve a similar amount of energy, macronutrients, and dietary fiber according to the USDA Nutrient Database for Standard Reference, Release 12 (Table 4-1). Subjects were instructed to consume the cereals daily at breakfast and as a snack while substituting and adjusting their habitual intake to the increased cereal consumption to maintain weight stability. Compliance was assessed by measuring the uneaten portion of cereal that was returned to the investigators on a biweekly (eg, every other week) basis.

**Anthropometric Measurements**

Body weight was determined to the nearest 0.1 kg using a balance scale (Detecto, Webb City, MO) and height (cm) (without shoes) was measured using a wall-mounted stadiometer. Body weight was re-assessed biweekly throughout the study. Skinfold thickness measurements (mm) were obtained at eight sites (chest, abdomen, triceps, suprailiac, midaxillary, subscapular, thigh, and medial calf) using calipers (Lange, Cambridge Scientific Industries, Cambridge, MD). Waist circumference was measured (cm) at the level of the umbilicus using a Gulick II measuring tape (Country Technology,

Gays Mills, WI). Anthropometric measurements were performed again during the last week of the intervention.

**Dietary Assessment**

Each subject kept a four-day food intake record at baseline and during the final week of the study to assess dietary intake. Subjects were instructed by a research dietitian (BD) to accurately record food intake (e.g., portion sizes, food preparation methods, brand names of products) using two-dimensional food models. The dietitian reviewed all records with subjects upon completion for accuracy and sufficiency of detail. Subjects were asked to provide food labels for products used to determine appropriate substitutions when actual items consumed were not is the software database. Food intake records were analyzed using the Food Intake Analysis System (FIAS 3.98 nutrient analysis program, University of Texas School of Public Health, 1998). The FIAS database consists of the Primary Data Set (PDS) and the Survey Nutrient Data Base (Survey NDB) of the National Nutrient Data Bank, developed and maintained by the United States Department of Agriculture (USDA).

**Urinary Measurements**

24-hr urinary sodium, potassium and creatinine excretion were measured before and after the 12-week intervention using a VITROS Model 250 analyzer (Ortho-Clinical Diagnostics, Inc, Johnson & Johnson, Rochester, NY). Assays for measurement of urinary sodium, potassium and creatinine were performed according to manufacturer's instructions (Vitros Chemistry Products, Ortho-Clinical Diagnostics, Inc, Johnson & Johnson, Rochester, NY).

**Blood Pressure Measurements**

Resting supine and seated BP measurements were obtained before and after the intervention using both a Hawksley Random Zero (RZ) sphygmomanometer (Hawksley Technology, London, England) and an automated Dinamap XL vital signs monitor (model 9300, Johnson & Johnson Medical, Inc., Tampa, FL) to obtain independent and objective measurements. Prior to the intervention, BP measurements were obtained a minimum of three times over a two-week run-in period to ensure a stable baseline measurement. A stable BP was defined as three consecutive BP measurements on three separate occasions within 5mm Hg. On each occasion that BP was measured, care was taken to adhere to the identical protocol as follows: The subject was taken into a quiet room with the temperature kept at 23 degrees Celsius, where he rested quietly for exactly 5 min in a seated posture prior to the first BP measurement. Three measurements were obtained using the appropriate cuff size such that the bladder width was at least 40% of the subject's arm circumference and bladder length at least 80% of the arm circumference. The rate of cuff deflation was 2-3 mm Hg per second. The first and fifth Korotkoff sounds were used to determine systolic and diastolic BP, respectively. Each of the BP measurements was separated by a two-minute interval. Upon completion of the seated measurements, subjects were then placed in a supine position on a comfortable bed for 5 minutes, and supine blood pressure measurements were taken following the same protocol.

In order to eliminate interobserver bias from the measurements, blood pressure measurements for each individual were taken by the same observer throughout the study, and the observer was blind to subject group assignment. Subjects were blind to all

readings and were not informed of their blood pressure values until completion of the study. The mean of the three measurements was used for statistical comparison. Seated BP measurements were obtained using the RZ at weeks four and eight of the interventions, and again at during the last week of the intervention (week 12). Biweekly (eg, every other week) Dinamap measurements were also obtained. All BP measurements were made early in the morning after a 12-hour fast.

Ambulatory 24-hour BP measurements were obtained using a noninvasive ambulatory BP monitor (model 90207, Spacelabs, Redlands, WA) at baseline and after the 12-week intervention period. The cuff was programmed to inflate automatically every 15 minutes from 6 AM to 10 PM and every 30 minutes from 10 PM to 6 AM. For each subject, daytime was defined as the time from waking in the morning until going to bed in the evening. Nighttime was the remainder of the twenty-four hour period. Systolic BP (SBP) and diastolic BP (DBP) variability were defined as the standard deviation of each individual's 24-hr SBP and DBP recordings. Nocturnal dip (%) was defined as the product of daytime minus nighttime BP, divided by the daytime BP, multiplied by 100. SBP and DBP load was calculated as the percentage of BP's >140 mmHg and >90 mmHg, respectively, for 24-hr, daytime, and nighttime intervals.

**Intravenous Glucose Tolerance Test**

It has been hypothesized that if dietary fiber does reduce arterial BP, it may do so via an effect on blood insulin concentrations and/or insulin sensitivity, since insulin may increases sympathetic nervous system activity (Scherrer and Sartori, 1997). For this reason, an insulin-augmented frequently sampled intravenous glucose tolerance test (IVGTT) was administered to these subjects at baseline and after the intervention. The

test was performed in the supine position following an overnight, 12-hour fast, after a 30-minute relaxation period. An intravenous (IV) catheter was placed in each antecubital vein, one for the administration of insulin and glucose, and one for collecting blood samples. Two blood samples were obtained at time (t) = -10, -5 minutes, with these two samples used for determination of the mean baseline insulin and glucose concentrations. A bolus of glucose (0.3g/kg in a of 50% dextrose solution) was infused over a 90 second period at t=0. At t = 20 minutes, a bolus of insulin (0.03 U/kg) was injected. Blood samples were obtained at t = 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes and immediately centrifuged at 4°C and analyzed for glucose concentrations by the glucose oxidase method using a glucose autoanalyzer (Yellow Springs Instruments, Yellow Springs, Ohio). A sample of plasma was stored at –20°C for later determination of insulin concentrations by the ELISA method (Diagnostic Systems Laboratories, Inc., Webster, TX). The MINMOD program (version 3.0, R. Bergman, University of Southern California) was used for determination of insulin sensitivity ($S_I$). This model uses measurements of plasma glucose and insulin concentrations over the 3-h period to deduce in vivo whole-body insulin sensitivity (Bergman et al. 1981).

**Statistical Analysis**

Group, time, and group by time interaction effects were assessed using repeated measures analysis of variance (General Linear Model, SPSS statistical software, SPSS 9.0 for Windows). Group characteristics at baseline were compared using independent t-tests. Alpha was set *a priori at* $P< 0.05$. All data are expressed as mean±SEM.

## RESULTS

The characteristics of the study participants are shown in Table 4-2. These characteristics were similar at baseline between the oat and wheat cereal groups (all P>0.05). Compliance to the intervention was similar in the two groups (Oats=96±4% vs. Wheat=95 ±5%). One individual reported less than 88% compliance; exclusion of this individual from data analysis did not alter our findings. There were small but significant increases in body weight (~0.8 kg), body mass index and the sum of skinfold thickness in both oat and wheat groups over time (all P<0.05).

Self-reported mean dietary intake of protein, carbohydrate, fiber and magnesium increased significantly over the intervention period in both groups, while mean dietary intake of fat, alcohol, and cholesterol decreased in both groups over time (Table 4-3). No change in mean dietary intake of sodium, potassium, or calcium was observed (all P>0.05). A significant main effect of time and a group by time interaction was found for magnesium intake, with a slightly greater increase noted in the oat group. However, twenty-four hour urinary sodium, potassium, or creatinine excretion did not change in either group as a result of the intervention (all P>0.05, data not shown).

Casual seated and supine arterial SBP and DBP measured using the RZ sphygmomanometer did not change significantly over the twelve-week intervention period in either group (Table 4-4). SBP and DBP determined with the Dinamap automated sphygmomanometer also did not change (P>0.05) in either group as a result of the intervention (Figure 4-1).

The increased consumption of oat or wheat cereal and fiber did not significantly change 24-hour ambulatory SBP and DBP (Table 4-5). There was a small, but

significant, increase in nighttime DBP and MAP in both groups over time. However, no significant changes were noted in daytime or nighttime SBP, daytime DBP, 24-hour or daytime mean arterial pressure (MAP), SBP or DBP variability, SBP or DBP nocturnal dip, or SBP and DBP load (data not shown).

No significant change was noted over time or across groups in fasting blood glucose (Oat: 5.4±0.1 to 5.6±0.1 mmol/L; Wheat: 5.3±0.1 to 5.3±0.1 mmol/L) or insulin concentration (Oat: 93.8±15.4 to 88.4±12.5 pmol/L; Wheat: 55.3±15.4 to 58.8±12.5 pmol/L), or $S_I$ (Oat: 1.8±0.3 to 1.8±0.3 $10^{-4}min^{-1}$/uM/ml; Wheat: 2.6±0.3 to 2.2±0.3 $10^{-4}min^{-1}$/uM/ml).

## DISCUSSION

Epidemiological studies suggest a negative association between fiber consumption and arterial BP (Ascherio et al. 1992, Hallfrisch et al. 1988, He at al. 1995, Joffres et al. 1987, Ludwig et al.1999). However, randomized controlled trials are required to confirm a causal relationship. While the beneficial effect of increased oat consumption on blood lipids and lipoproteins has been well documented (Anderson et al. 1984, Anderson et al. 1990, Brown et al. 1999, Kestin et al. 1990), the effectiveness of increased oat consumption on arterial BP has yet to be confirmed.

The new finding of the present study is that increased high-fiber oat or wheat cereal consumption does not lower casual or 24-hr ambulatory BP in middle-aged and older men with high normal BP or stage I hypertension. Conclusions and applications of previous intervention studies in this area are limited due to use of a normotensive population and intervention periods of only four to six weeks (Swain et al. 1990, Kestin

et al. 1990). Our 12- week intervention study used individuals with high-normal and Stage I hypertension, in whom dietary and lifestyle modifications are recommended as the initial treatment approach (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VI, 1997). Additionally, other strengths of this study are an extended run-in baseline measurement period, meticulous measurements of seated and supine BP using two different instruments, BP measurements obtained at two week intervals, the blinding of both observers and participants to group assignment, and the use of the same observer for an individual participant on each occasion during the intervention to minimize interobserver bias.

Saltzman et al. (2001 ) recently reported a reduction in SBP in normotensive individuals following a six-week hypocaloric diet rich in oat fiber (7.2g soluble fiber). These reductions in SBP were greater than observed in hypocaloric lower fiber control group exhibiting a similar amount weight loss. The intake of oat fiber in these study participants was approximately 30% higher than the amount provided in our study. Possibly a higher level of soluble fiber from oats is necessary to produce a BP lowering effect. Alternatively, weight loss may be required to elicit a reduction in BP with oat fiber consumption. Importantly, differences in baseline BP levels between the Saltzman study and ours, e.g., normotensives versus individuals with high-normal to Stage 1 hypertension, is unlikely to explain the discrepancy because greater BP reductions would be expected in individuals with higher baseline levels.

We have consistently found in previous studies that Caucasian, African-American, and Hispanic adults who ingest a plant-based diet rich in dietary fiber, exhibit less hypertension than their nonvegetarian counterparts (Melby et al. 1989, Melby et al.

1994, Alexander et al. 1999). We have suggested that this phenomenon of less hypertension in vegetarians is likely explained by multiple nutrients acting in concert, rather than a single factor such as dietary fiber. Results from the Dietary Approaches to Stop Hypertension (DASH) trial (Appel et al. 1997) also suggest a combination of dietary factors has a favorable impact on blood pressure. Specifically, a high-fiber low-fat diet rich in fruits, vegetables, and low-fat dairy products elicited a mean 5.5 mm Hg reduction in resting casual SBP and 3.0 mm Hg in DBP as compared to the control group. Body weight was kept stable, and consumption of sodium and alcohol were similar across groups. Similar reductions were noted in 24-hr ambulatory BP. Both hypertensive and normotensive subjects experienced reductions in BP, with greater reductions evident among hypertensives. However, in contrast to the present study, the DASH trial was not designed to test the BP-lowering effect of particular foods, but rather to test the effectiveness of a specific dietary pattern in reducing BP.

We observed a small but significant increase in average body weight (~0.8kg) in both groups over time. We do not believe this magnitude of average weight gain confounded the interpretation of our findings because similar weight gain was observed in both the oat and wheat groups. Thus, our ability to detect a small reduction in BP with oat consumption should not have been compromised. However, it is possible that small reductions in BP in both groups might have been missed.

In conclusion, our results indicate that twelve weeks of increased oat or wheat fiber consumption has no effect on casual or 24-hour ambulatory arterial BP in middle aged and older men with mild to moderate hypertension. As suggested by findings from

Saltzman et al. (2001) and Appel et al. (1997), either weight loss or a combination of dietary factors, rather than a single food, may be required to effectively lower BP.

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**Figure 4-1. Casual resting arterial blood pressure (Mean±SEM) in men consuming fiber-rich oat or wheat cereals.**

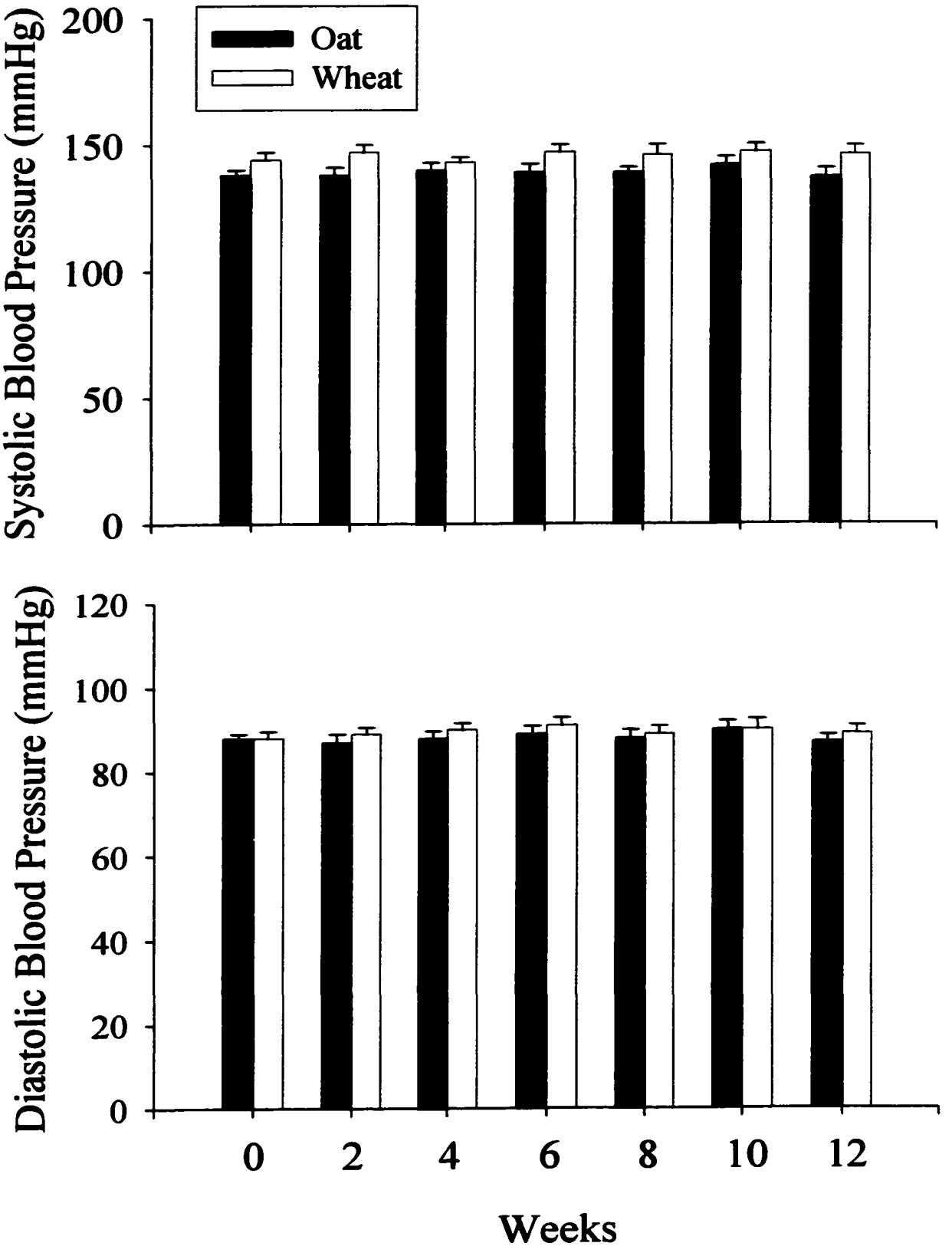

Table 4-1. Energy and Macronutrient Composition of the Cereal Combinations

| | Oat Group | Wheat Group |
|---|---|---|
| Energy, kcal | 513 | 480 |
| Carbohydrate, g | 95 | 112 |
| Simple Sugars, g | 14 | 21 |
| Fat, g | 8 | 3 |
| Protein, g | 21 | 14 |
| Dietary Fiber, g | 14 | 14 |

Table 4-2. Subject Characteristics

| | Oat Group (n=18) | | Wheat Group (n=18) | |
|---|---|---|---|---|
| | Baseline | Week 12 | Baseline | Week 12 |
| Age (years) | 57±2 | | 61±2 | |
| Height (cm) | 175.9±1.5 | | 177.4±1.5 | |
| Weight (kg)* | 91.4±3.0 | 92.1±3.0 | 92.3±3.0 | 93.2±3.0 |
| BMI ($kg/m^2$)* | 29.6±0.8 | 29.8±0.8 | 29.2±0.8 | 29.5±0.8 |
| Sum of skin folds (mm)* | 168.7±7.9 | 172.4±10.5 | 175.0±7.9 | 185.6±10.5 |
| Waist Circumference (cm) | 104.1±2.2 | 104.5±2.1 | 104.8±2.0 | 105.1±2.1 |

Data are expressed as mean±SEM.
There was no significant difference in age or height between the groups. There were no significant group by time interactions for weight, BMI, sum of skin folds or waist circumference.
*Significant main effect of time ($P<0.05$).

Table 4-3. Self-Reported Dietary Intake at Baseline and After 12 Weeks of the Intervention.

| | | Oat Group | | Wheat Group | |
|---|---|---|---|---|---|
| | | Baseline | Week 12 | Baseline | Week 12 |
| Energy | (kJ) | 10620±560 | 10877±536 | 9398±544 | 9939±521 |
| | (kcal) | 2538±134 | 2599±128 | 2246±130 | 2375±125 |
| Protein* | (g) | 91.1±5.1 | 103.3±6.0 | 82.1±4.9 | 86.8±5.8 |
| | (%) | 14.8±0.7 | 15.9±0.6 | 14.8±0.7 | 14.4±0.6 |
| Fat* | (g) | 99.8±6.5 | 89.2±6.0 | 82.4±6.4 | 78.3±5.8 |
| | (%) | 35.3±1.5 | 29.6±1.2 | 33.3±1.4 | 28.0±1.2 |
| Carbohydrate* | (g) | 297.2±21.3 | 336.8±17.3 | 283.3±20.7 | 331.6±16.8 |
| | (%) | 47.0±2.2 | 51.5±1.6 | 49.6±2.1 | 55.0±1.5 |
| Alcohol* | (g) | 18.2±5.6 | 12.3±4.9 | 11.9±5.4 | 10.4±4.8 |
| | (%) | 4.5±1.5 | 3.0±1.2 | 4.1±1.5 | 2.7±1.2 |
| Dietary Fiber* | (g) | 20.9±1.9 | 30.2±1.6 | 18.9±1.9 | 29.2±1.6 |
| Cholesterol* | (mg) | 406.7±42.2 | 260.9±31.1 | 291.4±41.0 | 232.5±30.2 |
| Sodium | (mg) | 4490±283 | 4022±301 | 3754±275 | 3386±292 |
| Potassium | (mg) | 3305±215 | 3639±231 | 3188±209 | 3294±225 |
| Magnesium* [A] | (mg) | 338±19 | 512±19 | 319±19 | 415±19 |
| Calcium | (mg) | 830±60 | 911±67 | 838±58 | 829±65 |

Data are expressed as mean±SEM. *Significant main effect of time ($P<0.05$).
[A]Significant group by time interaction ($P<0.05$).

Table 4-4. Casual Arterial Blood Pressure (Random Zero Sphygmomanometer)

| | Baseline | Week 4 | Week 8 | Week 12 | P* |
|---|---|---|---|---|---|
| Systolic Blood Pressure (SBP), seated, mmHg | | | | | |
| Oat group (n=18) | 138.2±2.4 | 133.7±2.8 | 137.0±2.0 | 134.6±3.1 | 0.859 |
| Wheat group (n=18) | 142.3±2.4 | 140.1±2.0 | 141.1±2.7 | 140.3±2.5 | |
| Diastolic Blood Pressure (DBP), seated, mmHg | | | | | |
| Oat group | 88.5±1.6 | 87.6±2.0 | 88.1±2.1 | 87.6±2.0 | 0.584 |
| Wheat group | 90.4±1.5 | 88.7±2.1 | 89.7±1.6 | 90.9±2.0 | |
| SBP, supine, mmHg | | | | | |
| Oat group | 132.6±2.3 | - | - | 131.6±3.1 | 0.401 |
| Wheat group | 139.2±2.4 | - | - | 135.3±2.8 | |
| DBP, supine, mmHg | | | | | |
| Oat group | 83.6±1.4 | - | - | 83.6±1.6 | 0.411 |
| Wheat group | 85.1±1.8 | - | - | 88.3±4.0 | |
| Pulse Rate, seated, beats per minute | | | | | |
| Oat group | 69.4±3.3 | - | - | 70.3±3.2 | 0.913 |
| Wheat group | 66.5±2.0 | - | - | 67.1±2.2 | |
| Pulse Rate, supine, beats per minute | | | | | |
| Oat group | 65.7±2.7 | - | - | 65.9±2.9 | 0.545 |
| Wheat group | 61.9±1.9 | - | - | 63.3±2.2 | |

Values are expressed as Mean±SEM. *P value for interaction.

Table 4-5. Ambulatory Arterial Blood Pressure Before and After 12 Weeks of the Intervention

| | Baseline | Week 12 | P[c] |
|---|---|---|---|
| 24-hr Systolic Blood Pressure (SBP), mmHg | | | |
| Oat group (n=16) | 133.3±1.5 | 132.8±2.0 | 0.403 |
| Wheat group (n=16) | 141.7±2.2 | 143.0±2.4 | |
| 24-hr Diastolic Blood Pressure (DBP), mmHg | | | |
| Oat group | 84.1±1.6 | 84.1±1.3 | 0.745 |
| Wheat group | 87.9±1.5 | 88.3±1.7 | |
| 24-hr Mean Arterial Pressure (MAP) | | | |
| Oat group | 100.7±1.5 | 100.0±1.4 | 0.410 |
| Wheat group | 106.1±1.6 | 106.7±2.0 | |
| Daytime SBP, mmHg | | | |
| Oat group | 137.5±1.6 | 136.3±2.0 | 0.304 |
| Wheat group | 146.4±2.2 | 147.4±2.7 | |
| Night-time SBP, mmHg | | | |
| Oat group | 117.4±2.1 | 116.6±4.7 | 0.386 |
| Wheat group | 126.2±2.5 | 129.8±2.6 | |
| Daytime DBP, mmHg | | | |
| Oat group | 86.1±1.9 | 87.0±1.4 | 0.887 |
| Wheat group | 91.0±1.9 | 91.6±1.9 | |
| Night-time DBP, mmHg* | | | |
| Oat group | 73.0±1.9 | 75.0±2.0 | 0.357 |
| Wheat group | 74.4±1.7 | 78.5±2.2 | |
| Daytime MAP | | | |
| Oat group | 104.1±1.5 | 103.2±1.6 | 0.547 |
| Wheat group | 110.1±1.6 | 110.3±2.3 | |

| Table 4-5. (cont.) | Baseline | Week 12 | P[C] |
|---|---|---|---|
| Night-time MAP** | | | |
| Oat group | 88.1±1.8 | 90.2±2.0 | 0.259 |
| Wheat group | 90.3±2.9 | 96.2±2.2 | |
| SBP Variability | | | |
| Oat group | 13.6±0.6 | 13.6±1.0 | 0.617 |
| Wheat group | 12.9±0.9 | 13.5±0.5 | |
| DBP Variability | | | |
| Oat group | 10.2±0.4 | 11.1±0.7 | 0.204 |
| Wheat group | 10.9±0.5 | 10.8±0.6 | |
| SBP Nocturnal Dip[A], % | | | |
| Oat group | 14.6±1.4 | 14.7±3.0 | 0.569 |
| Wheat group | 13.7±1.3 | 11.7±1.7 | |
| DBP Nocturnal Dip[B], % | | | |
| Oat group | 14.9±2.2 | 13.9±1.7 | 0.372 |
| Wheat group | 18.0±1.4 | 13.9±2.5 | |

Values are expressed as Mean±SEM.
[A] [(daytime SBP-nighttime SBP)/daytime SBP] x 100.
[B] [(daytime DBP-nighttime DBP)/daytime DBP] x 100.
[C] P value for interaction.
*Significant effect of time, P=0.01.
**Significant effect of time, P=0.02

# CHAPTER FIVE

## SUMMARY AND CONCLUSIONS

Cardiovascular diseases are responsible for causing almost 50% of all deaths in the world (American Heart Association, 2001). Elevated arterial blood pressure and dyslipidemia are contributing factors to cardiovascular disease morbidity and mortality. Dietary modification is one component of a healthy lifestyle that can help to prevent or delay the onset of cardiovascular diseases, particularly with respect to maintaining normal arterial blood pressure and blood lipid and lipoprotein concentrations. Major health organizations such as the American Heart Association (2000), the United States Department of Agriculture (2000), and the American Dietetic Association (1998) recommend that Americans consume diets rich in whole grains, fruits and vegetables, and moderate in fats, particularly saturated fats, for the prevention of chronic disease. As recently reviewed by Slavin et al. (2001), epidemiology and clinical studies support a negative association between consumption of whole grains and cardiovascular disease. While many beneficial components of whole grains have been identified (eg, micronutrients and phytochemicals), a common feature of these foods is their high fiber content. Foods rich in dietary fiber, particularly those high in soluble fiber, have been recognized as beneficial for cardiovascular disease prevention (Expert Panel on

Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001; American Dietetic Association 1997).

The objective of this dissertation was to examine the effect of increased fiber-rich oat cereal consumption on blood lipid and lipoprotein concentrations and casual resting and 24-hour arterial blood pressure in middle aged and older men. Our results may be summarized as follows:

1. *Primary Objective One: Determine the effect of increased high-fiber oat or wheat cereal consumption on plasma lipid and lipoprotein concentrations, lipoprotein subclasses, lipoprotein particle size, and LDL particle number in middle aged and older men.*

The results of our study suggest that the consumption of whole-grain oat cereal favorably modifies blood lipid and lipoprotein concentrations and lipoprotein characteristics as compared to whole grain wheat cereal. Specifically, we found that the oat as compared to wheat intervention resulted in significant reductions in LDL-C and small LDL-C concentrations, LDL particle number, and LDL-C/HDL-C ratio. We did not find significant effects of the intervention on HDL-C, HDL-C subclasses, or LDL, HDL or VLDL particle diameter. We concluded that the consumption of oats, rich in soluble fiber, may be a beneficial part of a high-fiber, low-fat, high-carbohydrate diet.

2. *Primary Objective Two: Determine the effect of increased high-fiber oat or wheat cereal consumption on casual resting and 24-hour arterial blood pressure in middle aged and older men with high-normal to Stage 1 hypertension.*

The results of our study suggest that the consumption of fiber-rich oat cereal (or fiber-rich wheat cereal) does not affect resting casual and 24-hour arterial blood pressure in this study population. Specifically, we did not find that the intervention reduced casual resting systolic or diastolic blood pressure, or 24-hour, daytime, or nighttime ambulatory blood pressure. From this, we concluded that given the conditions of this study, the cardioprotective effect of oat consumption is probably not due to an arterial blood pressure-lowering effect.

Additionally, in our comparison of multiple assessment reporting techniques for the quantification of dietary fiber intake (Appendix A), we determined that in situations where staff and financial resources are limited, a single 24-hour recall may be an acceptable method for assessing the mean dietary fiber intake of a group of individuals, as well as for detecting changes in the intake of groups of individuals. However, for detecting an individual's dietary fiber intake, a four-day food intake record is recommended.

## FUTURE DIRECTIONS

Our results can only be generalized to the population we studied, that is, middle aged and older men. While cardiovascular diseases (CVD) are the leading cause of death in men, they are also the primary cause of death in women. When the total number of CVD deaths is considered, more women than men die from CVD in the United States

(American Heart Association, 1999). For this reason, future studies on the effects of various dietary interventions on factors associated with CVD risk should consider including women, specifically postmenopausal women. Hormone replacement therapy, often advocated for the prevention of CVD and other chronic diseases in postmenopausal women, may interact with dietary patterns (e.g., a high intake of carbohydrates) to produce adverse lipids changes. This is important for studies investigating dietary interventions for dyslipidemia, since adverse changes in blood lipid/lipoprotein concentrations may be particularly detrimental in women (Bengtsson et al., 1993; Stensvold et al., 1993).

Our study focused upon the effects of consuming an individual food item (e.g., oats) rather than the effect of a dietary pattern, on factors associated with CVD risk. Due to research findings such as those from the DASH trial (1999), health organizations have recognized the importance of *dietary patterns* in disease prevention. A drawback of studying the health effects of an individual food item or even macronutrient (e.g., carbohydrate) is that the publication of the findings may lead individuals to lose sight of the importance and benefit of an "overall" healthy diet. While we may recognize the benefits of certain types of foods, we should frame our findings in the context of what is recommended for us to eat: a plant-based diet rich in fruits, vegetables, and whole grains, and low to moderate in fats. Also, we may be able to optimize the beneficial effects of a healthful diet by studying how foods and nutrients act together to promote good health. Thus, it may be beneficial for future studies to focus upon patterns of intake that promote optimal health.

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# APPENDIX A

## Assessment of Dietary Fiber Intake: A Comparison of Methods

Brenda Davy, MS, RD, Patricia Kendall, PhD, RD, Christopher Melby, DrPH

## Introduction

The American Dietetic Association and other prominent health organizations have recognized the importance of an adequate fiber intake for optimal health and disease prevention (American Cancer Society, 2000; American Dietetic Association, 1997; National Cancer Institute, 2000; Van Horn et al, 1997). While recommended levels are in the range of 20 to 35g/day (American Dietetic Association, 1997), most Americans fall short of these goals with a mean intake of 15.1g of dietary fiber for all individuals and 18.2g for males over age 50 (United States Department of Agriculture, 1997).

Accurate methods to assess dietary fiber intake in a variety of settings should be identified so that adherence to current recommendations and/or the effectiveness of interventions can be determined. Ideal methods may vary among populations and with study design and available resources. As indicated in a review by Block (1982), there is no gold standard to compare the validity of these methods; however, multiple days of food intake records (eg, four to seven days) are often used as comparison.

### *Food Intake Records*

Food intake records (FIR), which require an individual to record all foods and beverages consumed, serving size and preparation method, allow for better determination of portion size and account for day-to-day variation in intake while relying less on memory as compared to 24-hr recalls (Block, 1982). Trained nutrition personnel must instruct individuals in recording methods and utilize software for nutrient analysis. It has been recommended that lengthy recording periods (eg, more than four days) be avoided as this may contribute to inaccuracy (Gersovitz et al., 1978; Rebro et al., 1998). Four days are likely adequate for energy and macronutrients, although seven to 14 days may

be required to assess some nutrients (eg, vitamins A, C) (St. Jeor et al., 1983). With regard to assessment of fiber intake, the variability in intake appears to be low and is similar to that reported for carbohydrate (Hartman et al., 1990). Thus, a four day recording period is likely sufficient. Underreporting, a major issue for variables such as energy and fat, does not appear to be a significant problem for dietary fiber (Bingham, 1994).

***24-hour dietary Recalls***

The 24-hr recall method has advantages and disadvantages. As compared to a FIR, it has a greater ease of administration and lower respondent burden. When multiple days are used, this method may be the most effective and least costly method for assessing the dietary intake of groups (Morgan et al., 1987). Multiple telephone 24-hr recalls may be preferable to FIR for monitoring dietary change in intervention studies since individuals may be less likely to alter their habits (Buzzard et al., 1996). However, trained nutrition personnel are required to conduct dietary recalls and utilize nutrient analysis software. A slightly higher intake of some nutrients, but not fiber, has been noted when recalls are administered via telephone (Casey et al., 1999). The recall method may not be appropriate for assessing the nutrient intake of individuals, as it does not account for day-to-day variation in intake. Due to the reliance on memory, recalls may be an inappropriate assessment method for elderly populations (Brown et al., 1990). When utilizing the recall method, a variety of days of the week should be included since over-representation of certain days (eg, Fridays when individuals often eat meals out) could over/under estimate intake of some dietary variables (eg, fat, alcohol, protein).

### *Short Food Frequency Questionnaires*

Short dietary questionnaires that inquire about the frequency of consumption of a limited number of foods are a rapid, easily administered dietary assessment method with little subject burden. They are useful for rapidly screening individuals prior to study entry, for example on fat or fiber intake, or for tracking intake in large health promotion/public health programs, community health screenings, or situations in which "crude" methods are acceptable. They may be conducted over the phone or self-administered. Lower values for some nutrients, e.g., fiber, may be obtained as compared to other methods (Kristal et al., 1990). Also, some of these tools may become outdated with changes in the food supply, for example the increased availability of fat-modified foods.

The purpose of this investigation was to compare the efficacy of using a 24-hr recall and short self-administered screening questionnaire for fruit/vegetable and fiber intake (Block, 1994) versus a four-day FIR to assess baseline dietary fiber intake in a sample of middle-aged and older men, and to compare the ability of 24-hr recalls versus four-day FIR to detect changes in dietary fiber intake in men participating in an intervention study to increase dietary fiber intake.

## Methods

Participants were 36 middle-aged and older men aged 50-75 with a BMI between 25-35 who were recruited for a study on the impact of increased cereal fiber consumption on cardiovascular disease risk. All were in apparently good health and were not taking medications. At baseline, each completed a short self-administered Block Screening

Questionnaire for Fat and Fruit/Veg/Fiber intake (fiber screener)(Block, 1994), a 24-hr recall administered by a registered dietitian (BD), and a four-day FIR. The FIR included one weekend day and three weekdays. Participants used two-dimensional food models to determine portion sizes and were instructed in detailed recording methods (BD). The 24-hr recall and four-day FIR were repeated after a 12-week intervention during which 14g of dietary fiber in the form of two high fiber cereals (60g Quick Oats and 76g Oat Bran Cereal, Quaker Oats Company, Barrington Illinois or 60g Mother's Whole Wheat Hot Natural Cereal, Quaker Oats Company, Barrington Illinois, and 81g Frosted Mini-Wheats, Kellogg Company, Battle Creek Michigan) were provided. Compliance was determined at biweekly intervals by self-report. The Food Intake Analysis System (FIAS 3.98, University of Texas School of Public Health, July 1998) nutritional analysis software was used for analysis of the recalls and FIR (BD).

Nonparametric Spearman's rho correlation tests were performed on the three intake methods assessed at baseline and on change in fiber intake pre- and post intervention as assessed by the 24-hr recall and FIR using SPSS statistical software (SPSS 9.0 for Windows). T-tests were performed to determine differences between the three methods at baseline. General Linear Model Repeated Measures Analysis of Variance was used to analyze the pre- and post 24-hr recalls and four-day FIR's. Data are expressed as mean ±SEM.

## Results and Discussion

The mean age of participants in this study was 59 (±1) years with a mean BMI of 29.4 (±0.5) $kg/m^2$. Self-reported compliance with cereal consumption was 96 (±4)%.

Mean dietary fiber intake for 36 subjects with complete data at baseline was 22.4g (±2.1) with the 24-hr recall, 20.2g (±1.3) with the four-day FIR and 16.3g (±0.8) with the short screening questionnaire. T-tests indicated no significant difference in baseline fiber intake assessed by the 24-hr recall and the four-day FIR ($p=0.355$), but significant differences were found between the 24-hr recall and fiber screener ($p=0.018$) and the four-day FIR and fiber screener ($p=0.016$). As shown in Table A-1, baseline fiber intake assessed with the three methods was not correlated.

Baseline and post-intervention dietary fiber intake assessed by the 24-hr recall and four-day FIR ($n=35$) were significantly different (Table A-2). Thus, a significant change in mean fiber intake as a result of the high-fiber intervention was detected using either method. Correlations of pre-and post-values were also significant using either method, with r values of 0.395 ($p=0.010$) for the recalls and 0.679 ($p=0.001$) for the FIR. The correlations alone do not indicate whether or not values remained the same or changed similarly among individuals, but the ANOVA indicated a significant increase in mean fiber intake. Taken together, these findings suggest that both the FIR and recall method are capable of detecting an increase in fiber intake on an individual basis. However, the stronger correlation obtained with the FIR method suggests that it may be more appropriate for detecting change in individual intake.

The lack of correlation among methods used in this investigation was disappointing; however, others have not found strong correlations among dietary assessment methods (Kristal et al., 1990; Liu et al., 1992; Kroke et al., 1999). Correlations are based upon individual values. Because assessment methods were not correlated at baseline, one or more of these methods may be limited in their ability to

assess fiber intake on an individual basis. As discussed earlier, a single 24-hr recall may not be representative of an individual's habitual intake. The sample size and/or a limited range of intake values within this sample may also be factors contributing to the lack of significant correlations. However, pre- and post-intervention values using the four-day FIR or the 24-hr recall were correlated, indicating that an individual's baseline fiber intake was related to post-intervention fiber intake according to either method.

The lowest mean value for mean dietary fiber intake was obtained with the short fiber screener. Block (Block, 1998) reported that FFQ containing a greater number of food items would provide higher estimates of intake values. Since this short screener only includes nine categories of foods in the fruit/vegetable/fiber section, this may explain the low mean fiber value. Although this method did not provide values similar to the other methods used in this study, it may still have utility as a tool to rapidly screen individuals, to rank individuals into categories of intake or provide a "crude" estimate of intake in settings that have limited resources/nutrition personnel.

For some nutrients, biomarkers are available to validate dietary intake. Bingham et al. (Bingham et al., 1995) compared breath hydrogen, breath methane and stool frequency to dietary fiber intake assessed with FIR. Only stool frequency was even slightly related ($r=0.16$)(Bingham et al., 1995); thus it does not appear that an acceptable biomarker for dietary fiber intake exists.

Our findings can only be generalized to individuals similar to those participating in this study. For example, the ideal method for determination of fiber intake may vary with gender (Ritenbaugh et al., 1997) and with age (Brown et al., 1990).

In conclusion, the most significant finding of this investigation was that baseline fiber intake for this sample assessed by a single 24-hr recall compared to a four-day FIR was not significantly different. This indicates that either method may be useful for assessing fiber intake on a group basis. Also, significant differences between pre- and post-intervention fiber intake were detected using both the 24-hr recall and the four-day FIR method. Thus, the increase in fiber intake was captured regardless of assessment method used.

## Applications

- A 24-hr recall may be an adequate method to assess cross-sectional group dietary fiber intake, and to detect changes in the fiber intake of groups even in small intervention studies when the situation (staff, cost, time) does not permit use of four-day FIR.
- The FIR method may be more appropriate for detecting change in dietary fiber intake on an individual basis.
- Previous studies indicate that multiple 24-hr recalls (eg, four) are preferable to intake records in some situations. Multiple recalls better account for individual variability in intake.

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## Tables

Table A-1. Correlation Coefficients (r values) for Baseline Methods To Assess Fiber Intake*

| | 24-hr Recall | Four-day FIR | Fiber Screener |
|---|---|---|---|
| 24-hr Recall<br>(P value) | 1.0 | 0.032<br>(0.429) | -0.050<br>(0.388) |
| 4-day FIR<br>(P value) | | 1.0 | 0.058<br>(0.368) |
| Fiber Screener | | | 1.0 |

*n=36

Table A-2. Comparison of Pre- and Post Fiber Intake by 24-hr Recall and 4-day FIR*

| Method | Pre (Mean±SEM) | Post (Mean±SEM) | P value |
|---|---|---|---|
| 24-hr Recall | 22.4g±2.1 | 29.4g±1.6 | 0.008** |
| 4-day FIR | 19.8g±1.3 | 30.3g±1.2 | 0.0001** |

*n=35

** Significant difference in pre vs. post

# APPENDIX B

## Product Information

**Ingredient Lists For the Products Used**
**According to the Manufacturer's Label Information**

**Quaker Quick Oats:**

Ingredients: 100% Natural Rolled Oats.

**Quaker Ready-To-Eat Oat Bran Cereal:**

Ingredients: Oat Bran, Whole-wheat flour, sugar, corn flour, baking soda, calcium carbonate, salt, caramel color, reduced iron, sodium ascorbate, niacinamide, zinc oxide, vitamin E acetate, vitamin A palmitate, thiamin mononitrate, pyridoxine hydrochloride, riboflavin, folic acid.

**Mother's Whole Wheat Hot Cereal:**

Ingredients: 100% Natural Rolled Whole Wheat.

**Kellogg's Frosted Mini-Wheats:**

Ingredients: Whole grain Wheat, sugar, sorbitol, gelatin, reduced iron, niacinamide, zinc oxide, pyridoxine hydrochloride, riboflavin, thiamin hydrochloride, folic acid, vitamin $B_{12}$.

# Cereals, oats, regular and quick and instant, without fortified, dry

**NDB No:** 08120

| Nutrient | Units | Value per 100 grams of edible portion | Sample Count | Std. Error |
|---|---|---|---|---|
| **Proximates** | | | | |
| Water | g | 8.80 | 528 | 0.093 |
| Energy | kcal | 384 | 0 | |
| Energy | kj | 1607 | 0 | |
| Protein | g | 16.00 | 192 | 0.053 |
| Total lipid (fat) | g | 6.30 | 196 | 0.035 |
| Carbohydrate, by difference | g | 67.00 | 0 | |
| Fiber, total dietary | g | 10.6 | 0 | |
| Ash | g | 1.90 | 184 | 0.000 |
| **Minerals** | | | | |
| Calcium, Ca | mg | 52 | 33 | 0.923 |
| Iron, Fe | mg | 4.20 | 175 | 0.000 |
| Magnesium, Mg | mg | 148 | 31 | 0.038 |
| Phosphorus, P | mg | 474 | 140 | 0.044 |
| Potassium, K | mg | 350 | 48 | 0.032 |
| Sodium, Na | mg | 4 | 111 | 0.000 |
| Zinc, Zn | mg | 3.07 | 29 | 0.092 |
| Copper, Cu | mg | 0.343 | 31 | 0.033 |
| Manganese, Mn | mg | 3.630 | 5 | 0.001 |
| Selenium, Se | mcg | 34.0 | 12 | 4.469 |
| **Vitamins** | | | | |
| Vitamin C, total ascorbic acid | mg | 0.0 | 0 | |
| Thiamin | mg | 0.730 | 173 | 0.000 |
| Riboflavin | mg | 0.140 | 81 | 0.000 |
| Niacin | mg | 0.780 | 71 | 0.016 |
| Pantothenic acid | mg | 1.245 | 15 | 0.025 |
| Vitamin B-6 | mg | 0.120 | 19 | 0.000 |
| Folate, total | mcg | 32 | 24 | 3.485 |

| | | | | |
|---|---|---|---|---|
| Folic acid | mcg | 0 | 0 | |
| Folate, food | mcg | 32 | 24 | |
| Folate, DFE | mcg_DFE | 32 | 0 | |
| Vitamin B-12 | mcg | 0.00 | 0 | |
| Vitamin A, IU | IU | 101 | 5 | 5.635 |
| Vitamin A, RE | mcg_RE | 10 | 0 | |
| Vitamin E | mg_ATE | 0.700 | 0 | |
| **Lipids** | | | | |
| Fatty acids, total saturated | g | 1.110 | 0 | |
| 4:0 | g | 0.000 | 0 | |
| 6:0 | g | 0.000 | 0 | |
| 8:0 | g | 0.000 | 0 | |
| 10:0 | g | 0.000 | 0 | |
| 12:0 | g | 0.020 | 238 | |
| 14:0 | g | 0.010 | 238 | |
| 16:0 | g | 0.940 | 238 | |
| 18:0 | g | 0.060 | 238 | |
| Fatty acids, total monounsaturated | g | 1.980 | 0 | |
| 16:1 undifferentiated | g | 0.010 | 238 | |
| 18:1 undifferentiated | g | 1.970 | 238 | |
| 20:1 | g | 0.000 | 0 | |
| 22:1 undifferentiated | g | 0.000 | 0 | |
| Fatty acids, total polyunsaturated | g | 2.300 | 0 | |
| 18:2 undifferentiated | g | 2.200 | 238 | |
| 18:3 undifferentiated | g | 0.100 | 238 | |
| 18:4 | g | 0.000 | 0 | |
| 20:4 undifferentiated | g | 0.000 | 0 | |
| 20:5 n-3 | g | 0.000 | 0 | |
| 22:5 n-3 | g | 0.000 | 0 | |
| 22:6 n-3 | g | 0.000 | 0 | |
| Cholesterol | mg | 0 | 0 | |
| **Amino acids** | | | | |
| Tryptophan | g | 0.222 | 0 | |
| Threonine | g | 0.545 | 0 | |
| Isoleucine | g | 0.657 | 0 | |

| | | | | |
|---|---|---|---|---|
| Leucine | g | 1.216 | 0 | |
| Lysine | g | 0.664 | 0 | |
| Methionine | g | 0.295 | 0 | |
| Cystine | g | 0.386 | 0 | |
| Phenylalanine | g | 0.847 | 0 | |
| Tyrosine | g | 0.543 | 0 | |
| Valine | g | 0.888 | 0 | |
| Arginine | g | 1.129 | 0 | |
| Histidine | g | 0.383 | 0 | |
| Alanine | g | 0.835 | 0 | |
| Aspartic acid | g | 1.371 | 0 | |
| Glutamic acid | g | 3.517 | 0 | |
| Glycine | g | 0.797 | 0 | |
| Proline | g | 0.885 | 0 | |
| Serine | g | 0.711 | 0 | |
| **Other** | | | | |
| Caffeine | mg | 0 | 0 | |
| Theobromine | mg | 0 | 0 | |

**USDA Nutrient Database for Standard Reference, Release 14 (July 2001)**

New Search

# Cereals ready-to-eat, QUAKER, QUAKER Oat Bran Cereal

**NDB No:** 08216

| Nutrient | Units | Value per 100 grams of edible portion | Sample Count | Std. Error |
|---|---|---|---|---|
| **Proximates** | | | | |
| Water | g | 4.00 | 0 | |
| Energy | kcal | 373 | 0 | |
| Energy | kj | 1561 | 0 | |
| Protein | g | 14.98 | 0 | |
| Total lipid (fat) | g | 5.17 | 0 | |
| Carbohydrate, by difference | g | 72.62 | 0 | |
| Fiber, total dietary | g | 10.5 | 0 | |
| Ash | g | 3.21 | 0 | |
| **Minerals** | | | | |
| Calcium, Ca | mg | 53 | 0 | |
| Iron, Fe | mg | 28.00 | 0 | |
| Magnesium, Mg | mg | 174 | 0 | |
| Phosphorus, P | mg | 537 | 0 | |
| Potassium, K | mg | 451 | 0 | |
| Sodium, Na | mg | 360 | 0 | |
| Zinc, Zn | mg | 6.82 | 0 | |
| Copper, Cu | mg | 0.310 | 0 | |
| Manganese, Mn | mg | 3.960 | 0 | |
| Selenium, Se | mcg | 30.5 | 0 | |
| **Vitamins** | | | | |
| Vitamin C, total ascorbic acid | mg | 10.9 | 0 | |
| Thiamin | mg | 0.680 | 0 | |
| Riboflavin | mg | 0.770 | 0 | |
| Niacin | mg | 9.100 | 0 | |
| Pantothenic acid | mg | 0.850 | 0 | |
| Vitamin B-6 | mg | 0.910 | 0 | |
| Folate, total | mcg | 182 | 0 | |

| | | | | |
|---|---|---|---|---|
| Folic acid | mcg | 163 | 0 | |
| Folate, food | mcg | 19 | 0 | |
| Folate, DFE | mcg_DFE | 296 | 0 | |
| Vitamin B-12 | mcg | 0.00 | 0 | |
| Vitamin A, IU | IU | 910 | 0 | |
| Vitamin A, RE | mcg_RE | 273 | 0 | |
| Vitamin E | mg_ATE | 3.678 | 0 | |
| **Lipids** | | | | |
| Fatty acids, total saturated | g | 0.950 | 0 | |
| 4:0 | g | 0.000 | 0 | |
| 6:0 | g | 0.000 | 0 | |
| 8:0 | g | 0.000 | 0 | |
| 10:0 | g | 0.000 | 0 | |
| 12:0 | g | 0.015 | 0 | |
| 14:0 | g | 0.010 | 0 | |
| 16:0 | g | 0.795 | 0 | |
| 18:0 | g | 0.051 | 0 | |
| Fatty acids, total monounsaturated | g | 1.690 | 0 | |
| 16:1 undifferentiated | g | 0.009 | 0 | |
| 18:1 undifferentiated | g | 1.630 | 0 | |
| 20:1 | g | 0.000 | 0 | |
| 22:1 undifferentiated | g | 0.000 | 0 | |
| Fatty acids, total polyunsaturated | g | 2.130 | 0 | |
| 18:2 undifferentiated | g | 1.976 | 0 | |
| 18:3 undifferentiated | g | 0.091 | 0 | |
| 18:4 | g | 0.000 | 0 | |
| 20:4 undifferentiated | g | 0.000 | 0 | |
| 20:5 n-3 | g | 0.000 | 0 | |
| 22:5 n-3 | g | 0.000 | 0 | |
| 22:6 n-3 | g | 0.000 | 0 | |
| Cholesterol | mg | 0 | 0 | |

**USDA Nutrient Database for Standard Reference, Release 14 (July 2001)**

New Search

# Cereals, whole wheat hot natural cereal, dry

**NDB No:** 08144

| Nutrient | Units | Value per 100 grams of edible portion | Sample Count | Std. Error |
|---|---|---|---|---|
| **Proximates** | | | | |
| Water | g | 9.90 | 18 | 0.264 |
| Energy | kcal | 342 | 0 | |
| Energy | kj | 1431 | 0 | |
| Protein | g | 11.20 | 18 | 0.421 |
| Total lipid (fat) | g | 2.00 | 16 | 0.061 |
| Carbohydrate, by difference | g | 75.20 | 0 | |
| Fiber, total dietary | g | 9.5 | 0 | |
| Ash | g | 1.60 | 16 | 0.042 |
| **Minerals** | | | | |
| Calcium, Ca | mg | 40 | 2 | |
| Iron, Fe | mg | 3.39 | 17 | 0.108 |
| Magnesium, Mg | mg | 122 | 18 | 2.283 |
| Phosphorus, P | mg | 379 | 18 | 7.862 |
| Potassium, K | mg | 389 | 5 | 11.910 |
| Sodium, Na | mg | 2 | 17 | 0.442 |
| Zinc, Zn | mg | 2.66 | 27 | 0.066 |
| Copper, Cu | mg | 0.458 | 26 | 0.018 |
| Manganese, Mn | mg | 3.200 | 1 | |
| Selenium, Se | mcg | 70.7 | 0 | |
| **Vitamins** | | | | |
| Vitamin C, total ascorbic acid | mg | 0.0 | 0 | |
| Thiamin | mg | 0.400 | 16 | 0.023 |
| Riboflavin | mg | 0.300 | 16 | 0.043 |
| Niacin | mg | 4.900 | 16 | 0.183 |
| Pantothenic acid | mg | 0.915 | 10 | 0.014 |
| Vitamin B-6 | mg | 0.391 | 0 | |
| Folate, total | mcg | 78 | 10 | 1.562 |
| Folic acid | mcg | 0 | 0 | |

| | | | | |
|---|---|---|---|---|
| Folate, food | mcg | 78 | 0 | |
| Folate, DFE | mcg_DFE | 78 | 0 | |
| Vitamin B-12 | mcg | 0.00 | 0 | |
| Vitamin A, IU | IU | 0 | 0 | |
| Vitamin A, RE | mcg_RE | 0 | 0 | |
| Vitamin E | mg_ATE | 1.350 | 0 | |
| **Lipids** | | | | |
| Fatty acids, total saturated | g | 0.300 | 0 | |
| 4:0 | g | 0.000 | 0 | |
| 6:0 | g | 0.000 | 0 | |
| 8:0 | g | 0.000 | 0 | |
| 10:0 | g | 0.000 | 0 | |
| 12:0 | g | 0.000 | 0 | |
| 14:0 | g | 0.000 | 0 | |
| 16:0 | g | 0.292 | 0 | |
| 18:0 | g | 0.008 | 0 | |
| Fatty acids, total monounsaturated | g | 0.283 | 0 | |
| 16:1 undifferentiated | g | 0.000 | 0 | |
| 18:1 undifferentiated | g | 0.283 | 0 | |
| 20:1 | g | 0.000 | 0 | |
| 22:1 undifferentiated | g | 0.000 | 0 | |
| Fatty acids, total polyunsaturated | g | 1.008 | 0 | |
| 18:2 undifferentiated | g | 0.933 | 0 | |
| 18:3 undifferentiated | g | 0.075 | 0 | |
| 18:4 | g | 0.000 | 0 | |
| 20:4 undifferentiated | g | 0.000 | 0 | |
| 20:5 n-3 | g | 0.000 | 0 | |
| 22:5 n-3 | g | 0.000 | 0 | |
| 22:6 n-3 | g | 0.000 | 0 | |
| Cholesterol | mg | 0 | 0 | |
| **Other** | | | | |
| Caffeine | mg | 0 | 0 | |
| Theobromine | mg | 0 | 0 | |

**USDA Nutrient Database for Standard Reference, Release 14 (July 2001)**

# Cereals ready-to-eat, KELLOGG'S FROSTED MINI-WHEATS, regular

**NDB No:** 08031

| Nutrient | Units | Value per 100 grams of edible portion | Sample Count | Std. Error |
|---|---|---|---|---|
| **Proximates** | | | | |
| Water | g | 5.30 | 0 | |
| Energy | kcal | 339 | 0 | |
| Energy | kj | 1418 | 0 | |
| Protein | g | 9.40 | 0 | |
| Total lipid (fat) | g | 1.60 | 0 | |
| Carbohydrate, by difference | g | 82.50 | 0 | |
| Fiber, total dietary | g | 10.7 | 0 | |
| Sugars, total | g | 19.60 | 0 | |
| Ash | g | 1.20 | 0 | |
| **Minerals** | | | | |
| Calcium, Ca | mg | 36 | 0 | |
| Iron, Fe | mg | 28.00 | 0 | |
| Magnesium, Mg | mg | 101 | 0 | |
| Phosphorus, P | mg | 290 | 0 | |
| Potassium, K | mg | 333 | 0 | |
| Sodium, Na | mg | 3 | 0 | |
| Zinc, Zn | mg | 2.90 | 0 | |
| Copper, Cu | mg | 0.300 | 0 | |
| Manganese, Mn | mg | 2.788 | 0 | |
| Selenium, Se | mcg | 4.1 | 3 | 0.387 |
| **Vitamins** | | | | |
| Vitamin C, total ascorbic acid | mg | 0.0 | 0 | |
| Thiamin | mg | 0.700 | 0 | |
| Riboflavin | mg | 0.800 | 0 | |
| Niacin | mg | 9.800 | 0 | |
| Pantothenic acid | mg | 0.739 | 0 | |
| Vitamin B-6 | mg | 0.900 | 0 | |

| | | | | |
|---|---|---|---|---|
| Folate, total | mcg | 200 | 0 | |
| Folic acid | mcg | 181 | 0 | |
| Folate, food | mcg | 19 | 0 | |
| Folate, DFE | mcg_DFE | 327 | 0 | |
| Vitamin B-12 | mcg | 2.90 | 0 | |
| Vitamin A, IU | IU | 0 | 0 | |
| Vitamin A, RE | mcg_RE | 0 | 0 | |
| Vitamin E | mg_ATE | 0.902 | 0 | |
| **Lipids** | | | | |
| Fatty acids, total saturated | g | 0.300 | 0 | |
| 4:0 | g | 0.000 | 0 | |
| 6:0 | g | 0.000 | 0 | |
| 8:0 | g | 0.016 | 0 | |
| 10:0 | g | 0.000 | 0 | |
| 12:0 | g | 0.000 | 0 | |
| 14:0 | g | 0.243 | 0 | |
| 16:0 | g | 0.013 | 0 | |
| 18:0 | g | 0.012 | 0 | |
| Fatty acids, total monounsaturated | g | 0.200 | 0 | |
| 16:1 undifferentiated | g | 0.182 | 0 | |
| 18:1 undifferentiated | g | 0.000 | 0 | |
| 20:1 | g | 0.000 | 0 | |
| 22:1 undifferentiated | g | 0.000 | 0 | |
| Fatty acids, total polyunsaturated | g | 1.100 | 0 | |
| 18:2 undifferentiated | g | 1.001 | 0 | |
| 18:3 undifferentiated | g | 0.052 | 0 | |
| 18:4 | g | 0.000 | 0 | |
| 20:4 undifferentiated | g | 0.002 | 0 | |
| 20:5 n-3 | g | 0.000 | 0 | |
| 22:5 n-3 | g | 0.000 | 0 | |
| 22:6 n-3 | g | 0.000 | 0 | |
| Cholesterol | mg | 0 | 0 | |

**USDA Nutrient Database for Standard Reference, Release 14 (July 2001)**

New Search

# APPENDIX C

## Consent Form
## and
## Sample Questionnaires

COLORADO STATE UNIVERSITY
INFORMED CONSENT TO PARTICIPATE IN A RESEARCH PROJECT

Project Title: Influence of Oat and Wheat Fiber on Arterial Blood Pressure in Middle-Aged and Older Adults

Principal Investigators: Kevin P. Davy, Ph. D. and Christopher L. Melby, Dr. P.H..

Contact People and phone number(s) for questions/problems: Kevin P. Davy, Ph. D. (970) 491-5871 or Christopher L. Melby, Dr. P.H. (970) 491-6736

Purpose of the Research: To determine the influence of oat or wheat fiber on cardiovascular health in middle-aged and older, moderately hypertensive males.

Procedures/Methods To Be Used: If you agree to participate in this study, you will first be required to undergo some preliminary tests and complete two questionnaires in order to determine whether or not you are eligible for participation in this study. Based on our evaluation of these tests and the questionnaires you may then be eligible to participate in the study. You must be a male between the ages of 50-75 with elevated systolic blood pressure, with or without elevated diastolic blood pressure. You will not be eligible to participate in this study if you have any of the following health problems: heart problems, systolic blood pressure >160mmHg and/or diastolic blood pressure >99mmHg, asthma, tobacco use, diabetes, history of any eating disorders, severely overweight, or use medications, including prescription high blood pressure medication. You will also not be eligible to participate in this study if you indicate that you are not willing to eat wheat or oat fiber daily for a 12-week period.

Diet and Physical Activity Questionnaires- You will be asked to complete two questionnaires. The first is a food questionnaire, which will be used to determine your average intake of calories, fat, protein, carbohydrate, fiber, fruits, and vegetables, during the previous month. About 10 minutes is required to complete the food questionnaire and about 15 minutes of your time is needed to write down what you ate the previous day. The second questionnaire is to estimate your usual physical activity level which will require about 15 minutes to complete.

Anthropometric Assessment- Your height will be measured without shoes and your body weight will be measured on a standard balance scale. Your body mass index will be calculated as weight in kilograms divided by height in meter(squared). To qualify for the study, you body mass index must be between 25 and 35 $kg/m^2$. In addition, your body fat percentage will be estimated using skinfold calipers and by dual energy x-ray absorptiometer (DEXA). The skinfold procedure involves pinching your skin in several areas of your body and measuring the thickness of each individual site using a pair of metal calipers. The DEXA procedure uses two low energy x-rays to determine the amount of body fat you have. The amount of radiation exposure in this procedure is very low, about 1/1000 of the normal radiation exposure you

receive yearly from "background" radiation from the environment. The exposure is less than that in a normal flight from Denver to Chicago, and about 1/40$^{th}$ the exposure from a routine stomach x-ray you might receive in a hospital. This test is performed in rm. 219 in Moby. . You will be asked to lie quietly on a bed in shorts for about 15 minutes while the scan is performed.

Baseline Period- In order for the researchers to ensure that your blood pressure values are consistent over time, you will be asked to have your blood pressure monitored over a two week baseline period. You will be asked to report to room 216 of the Gifford Building at Colorado State University between 8-11am. three times to have your resting blood pressure taken, with each visit separated by at least one day. You will be asked to not ingest caffeine containing beverages for at least 4 hours before each of these three visits. Each visit will require about 45 minutes of your time. You will also be provided a device that automatically measures your blood pressure at pre-programmed intervals throughout the day and night. You will be asked to wear the device for one 24-hour period during the baseline period. You will be instructed as to the use and care of this device by one of the members of the investigative team during one of the first three visits. You will also be asked to collect your urine for one 24-hour period during this time.

You will also be asked to keep track of your dietary intake for 4 days during this two week period by writing down everything you eat and drink on the dietary recall forms provided. This will require approximately 10 minutes of your time each day, and one of the members of the investigator team will instruct you as to the proper use of these forms during this first visit.

The total time commitment required for the baseline period will be approximately 4 hours.

Preliminary Measurements : After this baseline period, you will be asked to report to room 216 of the Gifford Building at CSU in the morning for a series of tests. These tests require that you have not eaten for 12 hours before the tests, and also that you have not had any caffeine or alcohol containing beverages during the previous 12 hours. A registered nurse will place two hollow needle/plastic tubes, one in each forearm vein. Blood will first be drawn for lipid and lipoprotein level, vitamin levels, and clotting factors. These tubes will remain in your arms for the next four hours so that the nurse can repeatedly draw blood from the tube in your arm, while regular insulin and glucose (naturally occurring substances) will be infused into the tube in your other arm. To measure your insulin sensitivity (a test to determine how your body metabolizes glucose), an intravenous glucose tolerance test (IVGTT) will then be administered by a registered nurse. After a 30 minute resting period, you will have two baseline blood samples drawn from one arm (6ml each), and then a pre-determined amount of glucose and insulin will be injected through the plastic tube in your arm at two different time points. Over the next three hours, you will remain

laying down resting in a semi-darkened room during which time you will have blood drawn at certain time points. The total number of blood draws from the plastic tube for each IVGTT will be 33 (approximately one measuring cup). This visit requires approximately 4 hours of your time.

To determine the effects of the dietary intervention on your cardiovascular system, a member of the investigator team will measure several variables using non-invasive procedures. You will be asked to report to room 212C Moby Building for this session. The amount of blood pumped by your heart per minute will be assessed using an ultrasound machine. The ultrasound machine uses sound waves to measure the blood flow in your heart. This machine will also be used to measure the elasticity of the blood vessels in your neck (carotid arteries) and in your arms (brachial arteries).

The ability of your blood vessels to dilate will be measured by inflating a standard blood pressure cuff on your arm, below your elbow. After about 5 minutes, the cuff will be deflated and the change in the diameter of your arm blood vessels will be measured using the ultrasound machine. All of these measurements will be taken twice, once before the dietary intervention, and once after the 12-week dietary intervention. These measurements will require approximately 2 hours of your time and provide an estimate of the overall health of your blood vessels.

Collectively, these preliminary measurements will require about 6 hours of your time, which will be divided into two visits, one for 4 hours and one for 2 hours on a separate visit.

Twelve-week Intervention- During this 12-week time, you will be asked to report to room 216 of the Gifford Building at CSU between 8-11am. six to seven different times. Each visit you will have your body weight and resting blood pressure taken and you will pick-up a two week supply of a pre-determined weight of either wheat cereal or oat cereal that will be provided in one container for the two week period. You will be asked to consume a designated amount of cereal each day over the two week period. You will be asked to return any unfinished portions of food to us at your next visit. These visits will last approximately 45 minutes to one hour each. Twice during the 12-week intervention, you will be asked about your dietary intake on the previous day. This will require approximately 10 minutes of your time each day. It is very important that you do not change other aspects of your diet or your physical activity level over the course of this 12-week period. If you have questions about this at any time during the study, please ask one of the members of the investigator team. The total time commitment for this 12-week intervention will be approximately 7 to 10 hours.

Post-test Measurements: At the end of the 12-week intervention, you will be asked to return to room 212C of the Moby Building or room 216 of the Gifford Building (as indicated above) at CSU in the morning having not eaten for the past 12 hours and having not consumed any caffeine containing beverages for 4 hours before the tests. You will have the same pre-tests performed as explained above in the Pre-test

Measurements section, including the blood draws, the IVGTT, DEXA and the heart and blood vessel measurements. These post-test measurements will require about 6 hours of your time, which will be divided into two visits, one for 4 hours and one for 2 hours on a separate visit. The overall time commitment required for completion of the study will therefore be approximately 20 to 25 hours spread-out over the 14 to 16 week (approximately two week baseline plus 12 week intervention) study period. One of the members of the investigator team will provide you with your individual results and will discuss the meaning of these results (as well as the overall study findings) upon completion of the project.

RISKS INHERENT IN THE PROCEDURES:

Intravenous Glucose Tolerance Test- Any time blood is drawn there is a small risk that you may faint, experience local soreness, bruising or infection. You will experience pain for a short period of time when a needle is inserted into the arm veins for the placement of catheters for the IVGTT and blood draws. A small amount of bleeding under the skin may occur in about 1 in 10 subjects that will cause a bruise. The risk of significant blood loss or infection is about 1 in 1000. There is also a small risk of your blood glucose dropping too low. You may feel disoriented, irritable, and/or fatigued. You may also begin to perspire (sweat) excessively. If this happens, you will be provided with very sweet sugar containing food and/or drink to return your blood glucose to normal which will alleviate your symptoms.

Blood Pressure Measurements- There are no known risks associated with having your resting or ambulatory blood pressure taken using the methods described above. You may experience some discomfort as the blood pressure cuff is inflated but this goes away when the cuff is deflated.

DEXA- The risks associated with the DEXA are very low. The radiation exposure is extremely low, and other than lying on a bed, the measurement does not actually come into contact with you at any time during the testing.

Dietary Intervention- You may experience abdominal discomfort or irregular bowel movements as a result of the oat or wheat bran consumption. There are no known risks associated with the ingestion of the either wheat or oat fiber.

Doppler Echocardiography- There are no known risks associated with the use of doppler echocardiography (ultrasound). You may feel temporary and moderate discomfort as the tranducers (measuring device or probe) is placed and moved on your chest or arm to obtain the measurement.

It is not possible to identify all potential risks in an experimental procedures, but the researchers have taken reasonable safeguards to minimize any known and potential, but unknown, risks.

BENEFITS:

11. You will receive $500 upon completion of the entire study based upon the following amounts of compensation: $50 for completion of the baseline IVGTT completed; $25 for completion of the baseline ambulatory BP monitoring: and 25$ for completion of the baseline structural and functional determinants of BP. You will receive an additional $400 for completion of all other aspects of the study. No other specific monetary compensation will be provided. You will also receive and benefit from receiving information regarding your cardiovascular disease risk profile.

CONFIDENTIALITY: All the data obtained for you will be kept in a separate file in a locked cabinet, that will be accessible only to members of the investigator team. No publicly available information will include any data which can be linked to you as an individual.

LIABILITY: The Colorado Governmental Immunity Act determines and may limit Colorado State University's legal responsibility if an injury happens because of this study. Claims against the University must be filed within 180 days of the injury.

Questions about subjects' rights may be directed to Celia S. Walker at (970) 491-1563.

PARTICIPATION: You will be compensated for your participation in this research. Upon completion of the study, you will be paid $500. If you decide to participate in the study, you may withdraw your consent and stop participating at any time, however, you will not receive any compensation. Your signature acknowledges that you have read the information stated and willingly signed this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 5 pages.

_____ _____

Participant Name (printed) Date

_____ _____

Participant signature Date

_____ _____

Principal Investigator signature Date

_____ _____

Investigator or Co- Investigator signature Date

Colorado State University

Office of Regulatory Compliance
Office of Vice President for Research
and Information Technology
Fort Collins, CO 80523
(970) 491-1563
FAX (970 491-2293

MEMORANDUM

TO: Kevin Davy, Exercise and Sport Science

FROM: Celia S. Walker, Administrator
Human Research Committee

SUBJECT: PROJECT APPROVAL
Title – Influence of Oat and Wheat Bran on Arterial Blood Pressure in Middle-Aged and Older Adults
Protocol No.: 97-298H
Funding Agency: Quaker Oats Company
Funding Agency Deadline: 12/31/97

DATE: January 27,1998

I am pleased to inform you that the above-referenced project was approved by the Human Research Committee on January 9, 1998 for the period January 9, 1998 through January 9, 1999 with the condition that the attached consent form is signed by the subjects and each subject is given a copy of the form. It is the investigator's responsibility to obtain this consent form from all subjects. NO changes may be made to this document without first obtaining the approval of the Committee.

A status report of this project will be required within a 12-month period from the date of approval. The necessary form (H-101) will be mailed to you prior to that date.

It is the responsibility of the investigator to immediately inform the Committee of any serious complications, unexpected risks or injuries resulting from this research.

It is also the investigator's responsibility to notify the Committee of any changes in experimental design or consent procedures (file Form H-101).

Any questions about the Committee's action on this project should be directed to me.

Attachment

## Instructions for Keeping Your Food Intake Record

**When to keep record:**
**Dates of your FIR: _____ to _____.**
Your food intake record (FIR) should be kept for four consecutive days. This should include three weekdays and one weekend day, for example, either Wednesday through Saturday or Sunday through Wednesday.

**What to Record:**
**Write down everything that you eat and drink each day.** Include coffee, tea, diet sodas, and chewing gum. Include any additions to foods, such as sugar and creamer used in your coffee, mustard and mayonnaise spread onto your sandwich, etc. Remember to include all meals and snacks. Provide brand names of products whenever possible. It is also very helpful if you are able to provide **food labels** for items eaten. For beverages, indicate whether or not ice was included in the drink.

**Record portion sizes for all items**. The **Food Diagrams** (models) which have been provided should help you to accurately estimate your portion sizes. Refer to the example on the back of this page for how to record food portions using the diagrams. If you have access to an accurate scale, the item may be weighed (record whether the item was weighed raw or cooked). Measuring cups and spoons may also be used.

**Record how items were prepared.** For example, was the item baked or fried? If fried, what type of fat was used (e.g. corn oil, lard, crisco shortening, etc)? Was the poultry skin removed prior to cooking or was it left on? Was the item chopped or sliced? If you are able to provide a **recipe** for an item that was made at home or at a friend's house, please include this with your FIR.

**How to complete your Food Intake Record Form:**
Please record only one item per line. Record foods on your record as soon as they are eaten, otherwise it is easy to forget! Carry the record and the diagrams with you while you are keeping your FIR. For an

example, see the back of this page. Please call the study dietitian at 491-3373 if you have questions.

**What about food eaten at a restaurant or a friend's house?** Describe the food in as much detail as you can. Include portion sizes (please use the diagrams). Often you can get information from your server or from the menu. Indicate whether you ate the whole portion that was served to you, or the fraction that you did eat. Include the name of the restaurant on your record.

**Your efforts to carefully and accurately record the foods you eat will help us get better results. Your diligence is greatly appreciated!**

Subject ID Number _____ Page ___ of ___

Date _____

Day (circle): 1 2 3 4 Other (indicate) _____

# Food Intake Record

| Line # (office use) | Time | Place | **Food Description** (Please specify, if known: brand names, cooking method, type of product, and include labels when possible) | Portion Size : How many? | Portion Size : Food Model | Thicknes s/Ice in drink | Office Use Only |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
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# *Food Questionnaire*

***Think about your eating habits over the past year or so. About how often do you eat each of the following foods? Mark an "x" in one box for each food***

| | (0) Less than once per MONTH | (1) 2-3 times per MONTH | (2) 1-2 times per WEEK | (3) 3-4 times per WEEK | (4) 5+ times per WEEK | Points Score |
|---|---|---|---|---|---|---|
| Hamburgers or cheesburgers | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Beef, such as steaks, roasts | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Fried chicken | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Hot dogs, franks | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Cold cuts, lunch meats, ham, etc. | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Salad dressings, mayo (not diet) | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Margarine or butter | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Eggs | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Bacon or sausage | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Cheese or cheese spread | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Whole milk | ☐ | ☐ | ☐ | ☐ | ☐ | |
| French fries | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Potato chips, corn chips, popcorn | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Ice cream | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Doughnuts, pastries, cake, cookies | ☐ | ☐ | ☐ | ☐ | ☐ | |
| | | | | | ***Meat/Snacks Score =*** | |

| | (0) Less than once per WEEK | (1) About 1 time per WEEK | (2) 2-3 times per WEEK | (3) 4-6 times per WEEK | (4) Every day | Points Score |
|---|---|---|---|---|---|---|
| Orange juice | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Not counting juice, about how often do you eat any fruit? | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Green salad | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Potatoes | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Beans, such as baked beans, pintos, kidney beans or in chili | ☐ | ☐ | ☐ | ☐ | ☐ | |
| About how often do you eat any other vegetables? | ☐ | ☐ | ☐ | ☐ | ☐ | |
| High-fiber or bran cereal | ☐ | ☐ | ☐ | ☐ | ☐ | |
| Dark bread, such as whole wheat, rye | ☐ | ☐ | ☐ | ☐ | ☐ | |
| White bread, including french, italian, biscuits, muffins | ☐ | ☐ | ☐ | ☐ | ☐ | |
| | | | | | ***Fruit/Vegetable/Fiber Score =*** | |

# APPENDIX D

## ANOVA Tables (SPSS version 10.0)

## General Linear Model (Small LDL-C, in mg/dl)*

**Within-Subjects Factors**

Measure: MEASURE_1

| TIME | Dependent Variable |
|---|---|
| 1 | SMLDL |
| 2 | PSTSMLDL |

**Between-Subjects Factors**

| | | N |
|---|---|---|
| GROUP | 1.00 | 17 |
| | 2.00 | 18 |

**Descriptive Statistics**

| | GROUP | Mean | Std. Deviation | N |
|---|---|---|---|---|
| SMLDL | 1.00 | 68.6118 | 58.86971 | 17 |
| | 2.00 | 38.8667 | 47.38705 | 18 |
| | Total | 53.3143 | 54.60009 | 35 |
| PSTSMLDL | 1.00 | 56.6529 | 51.15671 | 17 |
| | 2.00 | 62.4222 | 56.43611 | 18 |
| | Total | 59.6200 | 53.22227 | 35 |

**Multivariate Tests[b]**

| Effect | | Value | F | Hypothesis df |
|---|---|---|---|---|
| TIME | Pillai's Trace | .022 | .729[a] | 1.000 |
| | Wilks' Lambda | .978 | .729[a] | 1.000 |
| | Hotelling's Trace | .022 | .729[a] | 1.000 |
| | Roy's Largest Root | .022 | .729[a] | 1.000 |
| TIME * GROUP | Pillai's Trace | .172 | 6.836[a] | 1.000 |
| | Wilks' Lambda | .828 | 6.836[a] | 1.000 |
| | Hotelling's Trace | .207 | 6.836[a] | 1.000 |
| | Roy's Largest Root | .207 | 6.836[a] | 1.000 |

* to convert mg/dl to mmol/L, divide by 38.6.

**Multivariate Tests[b]**

| Effect | | Error df | Sig. |
|---|---|---|---|
| TIME | Pillai's Trace | 33.000 | .399 |
| | Wilks' Lambda | 33.000 | .399 |
| | Hotelling's Trace | 33.000 | .399 |
| | Roy's Largest Root | 33.000 | .399 |
| TIME * GROUP | Pillai's Trace | 33.000 | .013 |
| | Wilks' Lambda | 33.000 | .013 |
| | Hotelling's Trace | 33.000 | .013 |
| | Roy's Largest Root | 33.000 | .013 |

a. Exact statistic

b.
Design: Intercept+GROUP
Within Subjects Design: TIME

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| Within Subjects Effect | Mauchly's W | Approx. Chi-Square | df | Sig. |
|---|---|---|---|---|
| TIME | 1.000 | .000 | 0 | . |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| Within Subjects Effect | Epsilon[a] | | |
|---|---|---|---|
| | Greenhouse -Geisser | Huynh-Feldt | Lower-bound |
| TIME | 1.000 | 1.000 | 1.000 |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b.
Design: Intercept+GROUP
Within Subjects Design: TIME

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Sphericity Assumed | 587.888 | 1 | 587.888 |
| | Greenhouse-Geisser | 587.888 | 1.000 | 587.888 |
| | Huynh-Feldt | 587.888 | 1.000 | 587.888 |
| | Lower-bound | 587.888 | 1.000 | 587.888 |
| TIME * GROUP | Sphericity Assumed | 5513.557 | 1 | 5513.557 |
| | Greenhouse-Geisser | 5513.557 | 1.000 | 5513.557 |
| | Huynh-Feldt | 5513.557 | 1.000 | 5513.557 |
| | Lower-bound | 5513.557 | 1.000 | 5513.557 |
| Error(TIME) | Sphericity Assumed | 26615.503 | 33 | 806.530 |
| | Greenhouse-Geisser | 26615.503 | 33.000 | 806.530 |
| | Huynh-Feldt | 26615.503 | 33.000 | 806.530 |
| | Lower-bound | 26615.503 | 33.000 | 806.530 |

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | F | Sig. |
|---|---|---|---|
| TIME | Sphericity Assumed | .729 | .399 |
| | Greenhouse-Geisser | .729 | .399 |
| | Huynh-Feldt | .729 | .399 |
| | Lower-bound | .729 | .399 |
| TIME * GROUP | Sphericity Assumed | 6.836 | .013 |
| | Greenhouse-Geisser | 6.836 | .013 |
| | Huynh-Feldt | 6.836 | .013 |
| | Lower-bound | 6.836 | .013 |
| Error(TIME) | Sphericity Assumed | | |
| | Greenhouse-Geisser | | |
| | Huynh-Feldt | | |
| | Lower-bound | | |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Linear | 587.888 | 1 | 587.888 |
| TIME * GROUP | Linear | 5513.557 | 1 | 5513.557 |
| Error(TIME) | Linear | 26615.503 | 33 | 806.530 |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | F | Sig. |
|---|---|---|---|
| TIME | Linear | .729 | .399 |
| TIME * GROUP | Linear | 6.836 | .013 |
| Error(TIME) | Linear | | |

**Tests of Between-Subjects Effects**

Measure: MEASURE_1
Transformed Variable: Average

| Source | Type III Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| Intercept | 224370.265 | 1 | 224370.265 | 45.417 | .000 |
| GROUP | 2512.871 | 1 | 2512.871 | .509 | .481 |
| Error | 163026.568 | 33 | 4940.199 | | |

# Estimated Marginal Means

**1. Grand Mean**

Measure: MEASURE_1

| Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 56.638 | 8.404 | 39.540 | 73.737 |

**2. GROUP**

Measure: MEASURE_1

| GROUP | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1.00 | 62.632 | 12.054 | 38.108 | 87.156 |
| 2.00 | 50.644 | 11.714 | 26.811 | 74.478 |

**3. TIME**

Measure: MEASURE_1

| TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1 | 53.739 | 9.007 | 35.414 | 72.064 |
| 2 | 59.538 | 9.121 | 40.980 | 78.095 |

**4. GROUP * TIME**

Measure: MEASURE_1

| GROUP | TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| 1.00 | 1 | 68.612 | 12.919 | 42.329 | 94.895 |
| | 2 | 56.653 | 13.083 | 30.036 | 83.270 |
| 2.00 | 1 | 38.867 | 12.555 | 13.324 | 64.409 |
| | 2 | 62.422 | 12.714 | 36.555 | 88.289 |

# General Linear Model (small LDL-C, by pattern)

**Within-Subjects Factors**

Measure: MEASURE_1

| TIME | Dependent Variable |
|---|---|
| 1 | SMLDL |
| 2 | PSTSMLDL |

**Between-Subjects Factors**

| | | N |
|---|---|---|
| GROUP | 1.00 | 17 |
| | 2.00 | 18 |
| PREPATT | 1.00 | 13 |
| | 2.00 | 22 |

**Descriptive Statistics**

| | GROUP | PREPATT | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| SMLDL | 1.00 | 1.00 | 9.7200 | 11.92275 | 5 |
| | | 2.00 | 93.1500 | 52.49673 | 12 |
| | | Total | 68.6118 | 58.86971 | 17 |
| | 2.00 | 1.00 | 4.9250 | 9.96160 | 8 |
| | | 2.00 | 66.0200 | 48.17802 | 10 |
| | | Total | 38.8667 | 47.38705 | 18 |
| | Total | 1.00 | 6.7692 | 10.54351 | 13 |
| | | 2.00 | 80.8182 | 51.27880 | 22 |
| | | Total | 53.3143 | 54.60009 | 35 |
| PSTSMLDL | 1.00 | 1.00 | 14.8600 | 18.41801 | 5 |
| | | 2.00 | 74.0667 | 50.58130 | 12 |
| | | Total | 56.6529 | 51.15671 | 17 |
| | 2.00 | 1.00 | 47.6875 | 56.23371 | 8 |
| | | 2.00 | 74.2100 | 56.65056 | 10 |
| | | Total | 62.4222 | 56.43611 | 18 |
| | Total | 1.00 | 35.0615 | 47.26550 | 13 |
| | | 2.00 | 74.1318 | 52.11107 | 22 |
| | | Total | 59.6200 | 53.22227 | 35 |

**Multivariate Tests[b]**

| Effect | | Value | F | Hypothesis df |
|---|---|---|---|---|
| TIME | Pillai's Trace | .056 | 1.822[a] | 1.000 |
| | Wilks' Lambda | .944 | 1.822[a] | 1.000 |
| | Hotelling's Trace | .059 | 1.822[a] | 1.000 |
| | Roy's Largest Root | .059 | 1.822[a] | 1.000 |
| TIME * GROUP | Pillai's Trace | .153 | 5.602[a] | 1.000 |
| | Wilks' Lambda | .847 | 5.602[a] | 1.000 |
| | Hotelling's Trace | .181 | 5.602[a] | 1.000 |
| | Roy's Largest Root | .181 | 5.602[a] | 1.000 |
| TIME * PREPATT | Pillai's Trace | .129 | 4.598[a] | 1.000 |
| | Wilks' Lambda | .871 | 4.598[a] | 1.000 |
| | Hotelling's Trace | .148 | 4.598[a] | 1.000 |
| | Roy's Largest Root | .148 | 4.598[a] | 1.000 |
| TIME * GROUP * PREPATT | Pillai's Trace | .005 | .142[a] | 1.000 |
| | Wilks' Lambda | .995 | .142[a] | 1.000 |
| | Hotelling's Trace | .005 | .142[a] | 1.000 |
| | Roy's Largest Root | .005 | .142[a] | 1.000 |

**Multivariate Tests[b]**

| Effect | | Error df | Sig. |
|---|---|---|---|
| TIME | Pillai's Trace | 31.000 | .187 |
| | Wilks' Lambda | 31.000 | .187 |
| | Hotelling's Trace | 31.000 | .187 |
| | Roy's Largest Root | 31.000 | .187 |
| TIME * GROUP | Pillai's Trace | 31.000 | .024 |
| | Wilks' Lambda | 31.000 | .024 |
| | Hotelling's Trace | 31.000 | .024 |
| | Roy's Largest Root | 31.000 | .024 |
| TIME * PREPATT | Pillai's Trace | 31.000 | .040 |
| | Wilks' Lambda | 31.000 | .040 |
| | Hotelling's Trace | 31.000 | .040 |
| | Roy's Largest Root | 31.000 | .040 |
| TIME * GROUP * PREPATT | Pillai's Trace | 31.000 | .708 |
| | Wilks' Lambda | 31.000 | .708 |
| | Hotelling's Trace | 31.000 | .708 |
| | Roy's Largest Root | 31.000 | .708 |

a. Exact statistic

b.
Design: Intercept+GROUP+PREPATT+GROUP * PREPATT
Within Subjects Design: TIME

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| Within Subjects Effect | Mauchly's W | Approx. Chi-Square | df | Sig. |
|---|---|---|---|---|
| TIME | 1.000 | .000 | 0 | . |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| Within Subjects Effect | Epsilon[a] | | |
|---|---|---|---|
| | Greenhouse -Geisser | Huynh-Feldt | Lower-bound |
| TIME | 1.000 | 1.000 | 1.000 |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b.
Design: Intercept+GROUP+PREPATT+GROUP * PREPATT
Within Subjects Design: TIME

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Sphericity Assumed | 1347.225 | 1 | 1347.225 |
| | Greenhouse-Geisser | 1347.225 | 1.000 | 1347.225 |
| | Huynh-Feldt | 1347.225 | 1.000 | 1347.225 |
| | Lower-bound | 1347.225 | 1.000 | 1347.225 |
| TIME * GROUP | Sphericity Assumed | 4142.429 | 1 | 4142.429 |
| | Greenhouse-Geisser | 4142.429 | 1.000 | 4142.429 |
| | Huynh-Feldt | 4142.429 | 1.000 | 4142.429 |
| | Lower-bound | 4142.429 | 1.000 | 4142.429 |
| TIME * PREPATT | Sphericity Assumed | 3400.279 | 1 | 3400.279 |
| | Greenhouse-Geisser | 3400.279 | 1.000 | 3400.279 |
| | Huynh-Feldt | 3400.279 | 1.000 | 3400.279 |
| | Lower-bound | 3400.279 | 1.000 | 3400.279 |
| TIME * GROUP * PREPATT | Sphericity Assumed | 105.349 | 1 | 105.349 |
| | Greenhouse-Geisser | 105.349 | 1.000 | 105.349 |
| | Huynh-Feldt | 105.349 | 1.000 | 105.349 |
| | Lower-bound | 105.349 | 1.000 | 105.349 |
| Error(TIME) | Sphericity Assumed | 22923.898 | 31 | 739.481 |
| | Greenhouse-Geisser | 22923.898 | 31.000 | 739.481 |
| | Huynh-Feldt | 22923.898 | 31.000 | 739.481 |
| | Lower-bound | 22923.898 | 31.000 | 739.481 |

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | F | Sig. |
|---|---|---|---|
| TIME | Sphericity Assumed | 1.822 | .187 |
| | Greenhouse-Geisser | 1.822 | .187 |
| | Huynh-Feldt | 1.822 | .187 |
| | Lower-bound | 1.822 | .187 |
| TIME * GROUP | Sphericity Assumed | 5.602 | .024 |
| | Greenhouse-Geisser | 5.602 | .024 |
| | Huynh-Feldt | 5.602 | .024 |
| | Lower-bound | 5.602 | .024 |
| TIME * PREPATT | Sphericity Assumed | 4.598 | .040 |
| | Greenhouse-Geisser | 4.598 | .040 |
| | Huynh-Feldt | 4.598 | .040 |
| | Lower-bound | 4.598 | .040 |
| TIME * GROUP * PREPATT | Sphericity Assumed | .142 | .708 |
| | Greenhouse-Geisser | .142 | .708 |
| | Huynh-Feldt | .142 | .708 |
| | Lower-bound | .142 | .708 |
| Error(TIME) | Sphericity Assumed | | |
| | Greenhouse-Geisser | | |
| | Huynh-Feldt | | |
| | Lower-bound | | |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Linear | 1347.225 | 1 | 1347.225 |
| TIME * GROUP | Linear | 4142.429 | 1 | 4142.429 |
| TIME * | Linear | 3400.279 | 1 | 3400.279 |
| TIME * GROUP | Linear | 105.349 | 1 | 105.349 |
| Error(TIME) | Linear | 22923.898 | 31 | 739.481 |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | F | Sig. |
|---|---|---|---|
| TIME | Linear | 1.822 | .187 |
| TIME * GROUP | Linear | 5.602 | .024 |
| TIME * | Linear | 4.598 | .040 |
| TIME * GROUP | Linear | .142 | .708 |
| Error(TIME) | Linear | | |

**Tests of Between-Subjects Effects**

Measure: MEASURE_1
Transformed Variable: Average

| Source | Type III Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| Intercept | 145521.923 | 1 | 145521.923 | 40.987 | .000 |
| GROUP | 1.076 | 1 | 1.076 | .000 | .986 |
| PREPATT | 52147.850 | 1 | 52147.850 | 14.688 | .001 |
| GROUP * PREPATT | 2977.484 | 1 | 2977.484 | .839 | .367 |
| Error | 110063.627 | 31 | 3550.440 | | |

# Estimated Marginal Means

**1. Grand Mean**

Measure: MEASURE_1

| Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 48.080 | 7.510 | 32.763 | 63.397 |

**2. GROUP**

Measure: MEASURE_1

| GROUP | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1.00 | 47.949 | 11.214 | 25.079 | 70.819 |
| 2.00 | 48.211 | 9.993 | 27.830 | 68.591 |

**3. TIME**

Measure: MEASURE_1

| TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1 | 43.454 | 7.333 | 28.498 | 58.410 |
| 2 | 52.706 | 9.084 | 34.179 | 71.233 |

**4. GROUP * TIME**

Measure: MEASURE_1

| GROUP | TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| 1.00 | 1 | 51.435 | 10.949 | 29.104 | 73.766 |
| | 2 | 44.463 | 13.564 | 16.799 | 72.127 |
| 2.00 | 1 | 35.472 | 9.757 | 15.572 | 55.373 |
| | 2 | 60.949 | 12.087 | 36.296 | 85.601 |

## General Linear Model (Systolic BP, Random Zero)

**Within-Subjects Factors**

Measure: MEASURE_1

| TIME | Dependent Variable |
|---|---|
| 1 | BASESBPZ |
| 2 | V12SBPZ |

**Between-Subjects Factors**

| | | N |
|---|---|---|
| GROUP | 1.00 | 18 |
| | 2.00 | 18 |

**Descriptive Statistics**

| | GROUP | Mean | Std. Deviation | N |
|---|---|---|---|---|
| BASESBPZ | 1.00 | 138.1667 | 10.13584 | 18 |
| | 2.00 | 142.2778 | 10.15646 | 18 |
| | Total | 140.2222 | 10.21515 | 36 |
| V12SBPZ | 1.00 | 134.5556 | 13.28963 | 18 |
| | 2.00 | 140.2778 | 10.35718 | 18 |
| | Total | 137.4167 | 12.09575 | 36 |

**Multivariate Tests[b]**

| Effect | | Value | F | Hypothesis df |
|---|---|---|---|---|
| TIME | Pillai's Trace | .097 | 3.638[a] | 1.000 |
| | Wilks' Lambda | .903 | 3.638[a] | 1.000 |
| | Hotelling's Trace | .107 | 3.638[a] | 1.000 |
| | Roy's Largest Root | .107 | 3.638[a] | 1.000 |
| TIME * GROUP | Pillai's Trace | .009 | .300[a] | 1.000 |
| | Wilks' Lambda | .991 | .300[a] | 1.000 |
| | Hotelling's Trace | .009 | .300[a] | 1.000 |
| | Roy's Largest Root | .009 | .300[a] | 1.000 |

**Multivariate Tests[b]**

| Effect | | Error df | Sig. |
|---|---|---|---|
| TIME | Pillai's Trace | 34.000 | .065 |
| | Wilks' Lambda | 34.000 | .065 |
| | Hotelling's Trace | 34.000 | .065 |
| | Roy's Largest Root | 34.000 | .065 |
| TIME * GROUP | Pillai's Trace | 34.000 | .588 |
| | Wilks' Lambda | 34.000 | .588 |
| | Hotelling's Trace | 34.000 | .588 |
| | Roy's Largest Root | 34.000 | .588 |

a. Exact statistic

b.
Design: Intercept+GROUP
Within Subjects Design: TIME

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| Within Subjects Effect | Mauchly's W | Approx. Chi-Square | df | Sig. |
|---|---|---|---|---|
| TIME | 1.000 | .000 | 0 | . |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| Within Subjects Effect | Epsilon[a] | | |
|---|---|---|---|
| | Greenhouse -Geisser | Huynh-Feldt | Lower-bound |
| TIME | 1.000 | 1.000 | 1.000 |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b.
Design: Intercept+GROUP
Within Subjects Design: TIME

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Sphericity Assumed | 141.681 | 1 | 141.681 |
| | Greenhouse-Geisser | 141.681 | 1.000 | 141.681 |
| | Huynh-Feldt | 141.681 | 1.000 | 141.681 |
| | Lower-bound | 141.681 | 1.000 | 141.681 |
| TIME * GROUP | Sphericity Assumed | 11.681 | 1 | 11.681 |
| | Greenhouse-Geisser | 11.681 | 1.000 | 11.681 |
| | Huynh-Feldt | 11.681 | 1.000 | 11.681 |
| | Lower-bound | 11.681 | 1.000 | 11.681 |
| Error(TIME) | Sphericity Assumed | 1324.139 | 34 | 38.945 |
| | Greenhouse-Geisser | 1324.139 | 34.000 | 38.945 |
| | Huynh-Feldt | 1324.139 | 34.000 | 38.945 |
| | Lower-bound | 1324.139 | 34.000 | 38.945 |

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | F | Sig. |
|---|---|---|---|
| TIME | Sphericity Assumed | 3.638 | .065 |
| | Greenhouse-Geisser | 3.638 | .065 |
| | Huynh-Feldt | 3.638 | .065 |
| | Lower-bound | 3.638 | .065 |
| TIME * GROUP | Sphericity Assumed | .300 | .588 |
| | Greenhouse-Geisser | .300 | .588 |
| | Huynh-Feldt | .300 | .588 |
| | Lower-bound | .300 | .588 |
| Error(TIME) | Sphericity Assumed | | |
| | Greenhouse-Geisser | | |
| | Huynh-Feldt | | |
| | Lower-bound | | |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Linear | 141.681 | 1 | 141.681 |
| TIME * GROUP | Linear | 11.681 | 1 | 11.681 |
| Error(TIME) | Linear | 1324.139 | 34 | 38.945 |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | F | Sig. |
|---|---|---|---|
| TIME | Linear | 3.638 | .065 |
| TIME * GROUP | Linear | .300 | .588 |
| Error(TIME) | Linear | | |

**Tests of Between-Subjects Effects**

Measure: MEASURE_1
Transformed Variable: Average

| Source | Type III Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| Intercept | 1387500.347 | 1 | 1387500.347 | 6737.336 | .000 |
| GROUP | 435.125 | 1 | 435.125 | 2.113 | .155 |
| Error | 7002.028 | 34 | 205.942 | | |

# Estimated Marginal Means

**1. Grand Mean**

Measure: MEASURE_1

| Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 138.819 | 1.691 | 135.382 | 142.256 |

**2. GROUP**

Measure: MEASURE_1

| GROUP | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1.00 | 136.361 | 2.392 | 131.500 | 141.222 |
| 2.00 | 141.278 | 2.392 | 136.417 | 146.138 |

**3. TIME**

Measure: MEASURE_1

| TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1 | 140.222 | 1.691 | 136.786 | 143.659 |
| 2 | 137.417 | 1.986 | 133.381 | 141.452 |

**4. GROUP * TIME**

Measure: MEASURE_1

| GROUP | TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| 1.00 | 1 | 138.167 | 2.391 | 133.307 | 143.027 |
| | 2 | 134.556 | 2.808 | 128.849 | 140.262 |
| 2.00 | 1 | 142.278 | 2.391 | 137.418 | 147.138 |
| | 2 | 140.278 | 2.808 | 134.571 | 145.985 |

# General Linear Model (Diastolic BP, Random Zero)

**Within-Subjects Factors**

Measure: MEASURE_1

| TIME | Dependent Variable |
|---|---|
| 1 | BASEDBPZ |
| 2 | V12DBPZ |

**Between-Subjects Factors**

| | | N |
|---|---|---|
| GROUP | 1.00 | 18 |
| | 2.00 | 18 |

**Descriptive Statistics**

| | GROUP | Mean | Std. Deviation | N |
|---|---|---|---|---|
| BASEDBPZ | 1.00 | 88.5000 | 6.80182 | 18 |
| | 2.00 | 90.3889 | 6.19429 | 18 |
| | Total | 89.4444 | 6.48270 | 36 |
| V12DBPZ | 1.00 | 87.5556 | 8.63796 | 18 |
| | 2.00 | 90.9444 | 8.57131 | 18 |
| | Total | 89.2500 | 8.65324 | 36 |

**Multivariate Tests[b]**

| Effect | | Value | F | Hypothesis df |
|---|---|---|---|---|
| TIME | Pillai's Trace | .002 | .071[a] | 1.000 |
| | Wilks' Lambda | .998 | .071[a] | 1.000 |
| | Hotelling's Trace | .002 | .071[a] | 1.000 |
| | Roy's Largest Root | .002 | .071[a] | 1.000 |
| TIME * GROUP | Pillai's Trace | .030 | 1.060[a] | 1.000 |
| | Wilks' Lambda | .970 | 1.060[a] | 1.000 |
| | Hotelling's Trace | .031 | 1.060[a] | 1.000 |
| | Roy's Largest Root | .031 | 1.060[a] | 1.000 |

**Multivariate Tests[b]**

| Effect | | Error df | Sig. |
|---|---|---|---|
| TIME | Pillai's Trace | 34.000 | .791 |
| | Wilks' Lambda | 34.000 | .791 |
| | Hotelling's Trace | 34.000 | .791 |
| | Roy's Largest Root | 34.000 | .791 |
| TIME * GROUP | Pillai's Trace | 34.000 | .310 |
| | Wilks' Lambda | 34.000 | .310 |
| | Hotelling's Trace | 34.000 | .310 |
| | Roy's Largest Root | 34.000 | .310 |

a. Exact statistic

b.
Design: Intercept+GROUP
Within Subjects Design: TIME

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| Within Subjects Effect | Mauchly's W | Approx. Chi-Square | df | Sig. |
|---|---|---|---|---|
| TIME | 1.000 | .000 | 0 | . |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

**Mauchly's Test of Sphericity[b]**

Measure: MEASURE_1

| | Epsilon[a] | | |
|---|---|---|---|
| Within Subjects Effect | Greenhouse -Geisser | Huynh-Feldt | Lower-bound |
| TIME | 1.000 | 1.000 | 1.000 |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b.
Design: Intercept+GROUP
Within Subjects Design: TIME

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Sphericity Assumed | .681 | 1 | .681 |
| | Greenhouse-Geisser | .681 | 1.000 | .681 |
| | Huynh-Feldt | .681 | 1.000 | .681 |
| | Lower-bound | .681 | 1.000 | .681 |
| TIME * GROUP | Sphericity Assumed | 10.125 | 1 | 10.125 |
| | Greenhouse-Geisser | 10.125 | 1.000 | 10.125 |
| | Huynh-Feldt | 10.125 | 1.000 | 10.125 |
| | Lower-bound | 10.125 | 1.000 | 10.125 |
| Error(TIME) | Sphericity Assumed | 324.694 | 34 | 9.550 |
| | Greenhouse-Geisser | 324.694 | 34.000 | 9.550 |
| | Huynh-Feldt | 324.694 | 34.000 | 9.550 |
| | Lower-bound | 324.694 | 34.000 | 9.550 |

**Tests of Within-Subjects Effects**

Measure: MEASURE_1

| Source | | F | Sig. |
|---|---|---|---|
| TIME | Sphericity Assumed | .071 | .791 |
| | Greenhouse-Geisser | .071 | .791 |
| | Huynh-Feldt | .071 | .791 |
| | Lower-bound | .071 | .791 |
| TIME * GROUP | Sphericity Assumed | 1.060 | .310 |
| | Greenhouse-Geisser | 1.060 | .310 |
| | Huynh-Feldt | 1.060 | .310 |
| | Lower-bound | 1.060 | .310 |
| Error(TIME) | Sphericity Assumed | | |
| | Greenhouse-Geisser | | |
| | Huynh-Feldt | | |
| | Lower-bound | | |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | Type III Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| TIME | Linear | .681 | 1 | .681 |
| TIME * GROUP | Linear | 10.125 | 1 | 10.125 |
| Error(TIME) | Linear | 324.694 | 34 | 9.550 |

**Tests of Within-Subjects Contrasts**

Measure: MEASURE_1

| Source | TIME | F | Sig. |
|---|---|---|---|
| TIME | Linear | .071 | .791 |
| TIME * GROUP | Linear | 1.060 | .310 |
| Error(TIME) | Linear | | |

**Tests of Between-Subjects Effects**

Measure: MEASURE_1
Transformed Variable: Average

| Source | Type III Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| Intercept | 574770.681 | 1 | 574770.681 | 5381.345 | .000 |
| GROUP | 125.347 | 1 | 125.347 | 1.174 | .286 |
| Error | 3631.472 | 34 | 106.808 | | |

# Estimated Marginal Means

**1. Grand Mean**

Measure: MEASURE_1

| Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 89.347 | 1.218 | 86.872 | 91.822 |

**2. GROUP**

Measure: MEASURE_1

| GROUP | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1.00 | 88.028 | 1.722 | 84.527 | 91.528 |
| 2.00 | 90.667 | 1.722 | 87.166 | 94.167 |

**3. TIME**

Measure: MEASURE_1

| TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1 | 89.444 | 1.084 | 87.241 | 91.648 |
| 2 | 89.250 | 1.434 | 86.336 | 92.164 |

**4. GROUP * TIME**

Measure: MEASURE_1

| GROUP | TIME | Mean | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| 1.00 | 1 | 88.500 | 1.533 | 85.384 | 91.616 |
| | 2 | 87.556 | 2.028 | 83.434 | 91.677 |
| 2.00 | 1 | 90.389 | 1.533 | 87.273 | 93.505 |
| | 2 | 90.944 | 2.028 | 86.823 | 95.066 |