4. CORONARY DISEASE AND METABOLIC SYNDROME

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Data from the Framingham Offspring Study indicate that the risk of coronary heart disease (CHD) in men and women, who were followed for 16 years, was directly related to the number of coronary heart disease risk factors (high cholesterol, low HDL-cholesterol, high body mass index, high systolic blood pressure, high triglyceride levels, and high blood glucose). Each of these risk factors also is associated with obesity (Wilson et al. 1999). Data from the Framingham Offspring Study also demonstrate that small changes in body weight are associated with significant changes in the sum of CHD risk factors. A gain in weight of 2.25 kg or more over 16 years significantly increased the sum of risk factors for CHD by 20% in men and 37% in women. Conversely, a reduction in weight by 2.25 kg or more significantly decreased the risk factor sum by 48% in men and 40% in women.

The metabolic syndrome is also known as the insulin resistance syndrome, dysmetabolic syndrome, and syndrome X. There is no precise definition of this syndrome, but it represents a specific body phenotype in conjunction with a group of metabolic abnormalities that are risk factors for coronary heart disease (CHD). Characteristics of this syndrome include abdominal obesity, insulin-resistant glucose metabolism (hyperinsulinemia, high fasting plasma glucose concentrations, impaired glucose tolerance), dyslipidemia (hypertriglyceridemia, low serum HDL-cholesterol concentration), and hypertension. Recently, additional metabolic abnormalities associated with abdominal obesity that are also risk factors for coronary heart disease have been identified, such as increased serum concentrations of apolipoprotein B, small, dense low-density-lipoprotein (LDL) particles, increased C-reactive protein, increased plasminogen activator inhibitor 1 (PAI-1), and impaired fibrinolysis (Lemieux et al. 1999, 2001, Landin et al. 1990). Obesity itself is not a requirement for the metabolic syndrome, and metabolically obese, normal-weight persons, presumably with increased abdominal fat mass, have been identified (Lemieux et al. 2000).

Approximately 22% (47 million) of the US adult population have the metabolic syndrome, as defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (ATP III) (Ruderman et al. 1998). This diagnosis was made by having 3 or more of the following: 1) abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women), 2) hypertriglyceridemia (≥ 1.69 mmol/L), 3) low HDL cholesterol (< 1.04 mmol/L in men; < 1.29 mmol/L in women), 4) high blood pressure (≥ 130/86 mm Hg), and 5) high fasting glucose (6.1 mmol/L).

Recently, the metabolic syndrome was formally recognized as a distinct medical condition, and the ICD-9-CM code 277.7 for Dysmetabolic Syndrome X was approved by the Centers for Disease Control. This syndrome denotes the presence of a constellation of metabolic abnormalities, such as those listed in this figure, but does not require that a predetermined number of components be present.

In 2001, the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP Treatment Panel III, or ATP III) released updated guidelines for cholesterol testing and management that included a definition and treatment recommendations for the metabolic syndrome. According to ATP III, the metabolic syndrome consists of a constellation of risk factors that place patients at risk for both the development of type 2 diabetes and atherosclerotic disease. The hallmarks of the syndrome are: abdominal obesity, atherogenic dyslipidemia – characterized by elevated triglycerides, small LDL particles, and low HDL, elevated blood pressure, insulin resistance with or without glucose intolerance, a prothrombotic state and a proinflammatory state.

These "lipid and non-lipid risk factors of metabolic origin" not only increase the risk of type 2 diabetes, but also enhance the risk for coronary heart disease "at any given cholesterol level" (Expert Panel, 2001).

Although it has been widely assumed that the metabolic syndrome is associated with an increased risk of cardiovascular disease, relatively little research has been done on the prevalence of cardiovascular morbidity and mortality in patients with the syndrome. Following the introduction of the WHO definition, Isomaa et al (2001) assessed cardiovascular morbidity and mortality in a cohort of subjects (N = 3,928; age, 35 to 70 years) being followed in a longitudinal study in Finland and Sweden (the Botnia study). Median follow-up was 6.9 years. Subjects meeting the WHO definition of metabolic syndrome were significantly more likely to have a history of coronary heart disease, myocardial infarction, and stroke than those without the syndrome. The presence of metabolic syndrome was associated with significantly increased risk of coronary heart disease (relative risk, 2.96, $P < 0.001$), myocardial infarction (RR 2.63, $P < 0.001$), and stroke (RR 2.27, $P < 0.001$). Overall, the prevalence of coronary heart disease, MI, and stroke were approximately 3-fold higher in the group with metabolic syndrome.

In an epidemiologic study of female nurses (The Nurses Health Study; age, 35-55 y) after 2.2 million person-years of follow-up, the relative risk of cardiovascular disease was significantly elevated prior to diagnosis of diabetes. During 20 years of follow-up, 110,227 women remained free of diabetes and 5894 were diagnosed with type 2 diabetes. 1556 new cases of myocardial infarction, 1405 strokes, 815 cases of fatal coronary heart disease, and 300 fatal strokes were documented. Among the nurses who developed diabetes, the age-adjusted relative risk of myocardial infarctions or stroke was 2.82 for the period before diagnosis and 3.71 for the period after diagnosis compared with women who did not develop diabetes during the same period. The relative risk of a myocardial infarction in subjects with a diagnosis of diabetes at baseline was 5.02. These results suggest that aggressive management of cardiovascular risk is warranted in individuals at increased risk for type 2 diabetes. This study provides strong evidence for adopting a strategy for diabetes prevention rather than just a policy screening frequently for type 2 diabetes in high-risk subjects. The latter strategy could not prevent cases of CVD that develop prior to the onset of clinical diabetes (Hu et al. 2002).

In a prospective cohort study among female registered nurses in the U.S., 44,702 women (age, 40-65 y) who were free of prior coronary heart disease, stroke, or cancer, provided waist and hip circumferences. After an 8-year follow-up, after adjusting for BMI, age (continuous), age2, smoking, parental history of myocardial infarction, alcohol consumption, physical activity, menopausal status, hormone replacement therapy, aspirin intake, saturated fat, and antioxidant score, waist circumference significantly correlated to an increased risk in coronary heart

disease ($P < 0.001$ for trend). Waist circumference and waist-to-hip ratio (WHR) were independently strongly associated with increased risk also among women with a BMI ≥25. After adjusting for reported hypertension, diabetes, and high cholesterol, a waist circumference of ≥30" or a WHR of ≥0.76 was associated with a 2-fold higher risk of coronary heart disease. (Rexrode et al. 1998).

Abdominal fat distribution increases the risk for coronary heart disease (CHD) among lean, overweight, and obese persons. The risk of CHD begins to increase at a normal BMI, which is 23 kg/m2 for men and 22 kg/m2 for women [Stamler et al, 1986]. Data from both the Iowa Women's Health Study [Folsom et al. 2000] and the Nurses' Health Study [Rexrode et al. 1998] found that women in the lowest BMI but highest waist-to-hip circumference ratio tertiles (a measure of abdominal adiposity) had a greater risk of fatal and nonfatal myocardial infarctions than women in the highest BMI but lowest waist-to-hip circumference ratio tertiles.

An increase in weight since young adulthood (18–20 years of age) in men and women is associated with increased risk of developing type 2 diabetes. A weight gain of 10 kg, which is the average amount of weight gained by US adults from 20 to 50 years of age, is associated with a two- to threefold increase in the risk of diabetes. Weight gain during adulthood is also associated with an increased risk of coronary heart disease, hypertension, and cholelithiasis compared with those who maintain their weight after 18 to 20 years of age (Willet et al. 1999).

It is estimated that obesity accounts for 6% of the total healthcare expenses in the US, with $51.6 billion/year in direct costs and over $100 billion/year in both direct and indirect costs. Direct costs include the costs of personal health care, hospital care, physician services, allied health services, and medications. Indirect costs include the value of lost productivity from illness or premature mortality. The estimated direct cost of obesity is comparable to that of other prevalent, chronic diseases, such as type 2 diabetes and coronary heart disease, and is more costly than both hypertension and stroke. Moreover, obesity contributes to the development of other chronic diseases; it is estimated that 61% of the direct cost of type 2 diabetes, 17% of the direct cost of coronary heart disease, and 17% of the direct cost of hypertension are attributable to obesity (Wolf and Colditz, 1998, Hodgson and Cohen, 1999).

Increases in body mass index (BMI) are associated with considerable increases in total expected lifetime medical care costs for treatment of coronary heart disease, type 2 diabetes mellitus, hypertension, hypercholesterolemia, and stroke [Thompson et al., 1999]. For example, in men aged 45 to 54 years, total costs increase from $19,600 among lean men (BMI 22.5 kg/m2) to $36,500 in obese men (BMI 37.5 kg/m2). The cost difference between lean and obese persons also increases with age. Compared with lean persons, overweight (BMI 27.5 kg/m2) raises lifetime healthcare costs for these five diseases by 20%, class I obesity (BMI 32.5 kg/m2) raises them by 50%, and class II obesity (BMI 37.5 kg/m2) raises them by nearly 100%. These findings obtained in men are similar to those obtained in women.

Obesity is associated with increased outpatient and inpatient medical costs. There is a relative increase in the cost of healthcare services required by obese compared with lean members of a health maintenance organization (HMO) in northern California. These healthcare services can be divided into three categories: 1) outpatient healthcare visits, outpatient pharmacy services, outpatient laboratory services, 2) total outpatient services, total inpatient services, and 3) total cost of health care. Among the 17,118 members of this HMO, there was a 25% increase in

total healthcare costs in those with class I obesity (body mass index [BMI] 30.0-34.9 kg/m2) and a 44% increase in total healthcare costs in those with class II or III obesity (BMI 35 kg/m2 or greater), compared with lean patients (BMI 20.0-24.9 kg/m2). The increased healthcare costs for obese patients were largely a result of costs related to coronary heart disease, hypertension, and diabetes (Quenesberry et al. 1988).

Regular physical activity is an important component of any weight loss program because it is associated with long-term weight maintenance and has beneficial health effects, such as decreasing coronary heart disease and diabetes that are independent of weight loss itself. The important physiological and clinical issues regarding the use of physical activity as part of obesity therapy will be reviewed in this section.

The relation of plasma triglyceride to LDL particle size and subclass pattern reflects the existence of differing forms of VLDL that give rise to larger and smaller LDL particles. Lower plasma triglyceride levels reflect VLDLs that are secreted with lower triglyceride content and are efficiently lipolyzed to larger LDL particles by the action of lipoprotein lipase (LPL). These LDLs have high affinity for LDL receptors (LDL-R). A higher level of plasma triglyceride is associated with larger VLDL particles that are lipolyzed less efficiently by LPL, giving rise to remnant particles. The properties of these remnants, including increased content of the apoprotein CIII, further slow lipolysis and also lead to reduced receptor-mediated plasma clearance. The remnants are further lipolyzed by the combined action of LPL and hepatic lipase (HL), and also undergo exchange of triglyceride for cholesterol derived from LDL and HDL, a process mediated by cholesterol ester transfer protein (CETP). The resulting triglyceride is, in addition delipidated and remodeled to form smaller, lipid-depleted LDL. These particles have lower affinity for LDL-R. Moreover, higher levels of remnant particles lead to increased exchange of triglyceride for cholesterol in both LDL and HDL, a process mediated by cholesterol ester transfer protein. Triglyceride-rich LDLs and HDLs are degraded further by HL, leading to yet smaller LDLs and to smaller and less stable HDLs that are more rapidly catabolized, resulting in reduced HDL cholesterol (Figure 4.1.)

Thus, pattern B LDL is associated with a cluster of interrelated metabolic abnormalities associated with increased risk for cardiovascular disease that has been designated atherogenic dyslipidemia. Factors leading to this dyslipidemia include abdominal adiposity, high dietary carbohydrate (especially simple sugars), insulin resistance, and genetic predisposition.

In the San Antonio Heart Study (Hanley et al. 2002), the higher the HOMA-IR quintile, the higher the insulin resistance and the greater the risk of cardiovascular disease even when adjusted for age, sex, and ethnicity. This association remained significant when adjusted for all other relevant variables.

The National Cholesterol Education Program (NCEP) has traditionally focused on high low-density lipoprotein cholesterol (LDL-C) as a risk factor for coronary heart disease (CHD). In the NCEP Adult Treatment Panel III (ATP III) recommendations published in JAMA in 2001, the NCEP suggested that the metabolic syndrome might independently predict the development of both type 2 diabetes and CHD. Note that in most definitions of the metabolic syndrome whether NCEP, WHO or AACE, diabetic subjects are included among those subjects who now have the metabolic syndrome.

Figure 4.1. *Model for Origins of AtherogenicDyslipidemia of Obesity and Metabolic Syndrome*

Most papers examining the relationship of the metabolic syndrome to cardiovascular disease have excluded diabetic subjects with the metabolic syndrome since diabetic subjects are at high risk of cardiovascular disease whether they have the metabolic syndrome or not. Note also that the arrow pointing from the metabolic syndrome to type 2 diabetes refers to non-diabetic metabolic syndrome patients.

The prevalence of coronary heart disease was studies in subjects in the Botnia Study in Western Finland. This study showed that the prevalence of the metabolic syndrome increases as glucose tolerance worsens from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to diabetes (DM). Note that this paper use the 1998 WHO definition, which is a slightly older version of the WHO definition discussed in this slide talk. Remember that IGT and diabetes are one of the components of the WHO definition (Isomaa et al, 2001). In the case of high-density lipoprotein (HDL), numerous studies, such as this early analysis from the Framingham Heart Study, have shown that is has an inverse relationship with coronary heart disease risk. This risk is independent of total and low-density lipoprotein (LDL) cholesterol, such that the risks due to lower HDL and higher LDL levels are additive (Gordon et al. 1977).

The ratio of total/high-density lipoprotein cholesterol is a good index of the relative contribution of atherogenic vs. antiatherogenic lipoproteins to coronary heart disease risk. As shown here in data from the Physician's Health Study, the risk associated with high levels of this ratio is further increased in the setting of increased plasma triglyceride. These results are also consistent with data from other studies indicating that the impact of elevated triglyceride on cardiovascular risk is related to the levels of other lipoproteins (Stampfer et al. 1996). The presence of pattern B low-density lipoprotein (LDL), with smaller LDL particles, underestimates the risk for coronary heart disease as assessed by elevated LDL cholesterol. In this example, for LDL cholesterol of 130 mg/dL, subjects with pattern B can have a substantially larger number of cholesterol-depleted LDL particles. There is one molecule of apolipoprotein B (Apo B) per LDL particle; hence, for subjects with pattern B, Apo B provides a better index of atherogenic particle number than does LDL cholesterol (Berneis and Krauss, 2002).

While lifestyle measures (diet, weight loss, physical activity) should be the primary approach to improving the atherogenic dyslipidemia of obesity, those subjects at high risk for coronary heart disease (CHD), including those with existing vascular disease, require more aggressive intervention to meet current CHD prevention guidelines. In the subgroup of hypercholesterolemic CHD subjects in the 4S trial who had concomitant elevations of triglyceride and reductions in high-density lipoprotein (left panel), statin treatment was found to achieve a significant reduction in the CHD event rate, whereas there was no significant benefit to subjects with an isolated low-density lipoprotein (LDL) increase (right panel). Hence, statins may be of particular benefit in the treatment of patients with atherogenic dyslipidemia who are at high risk of CHD, and statins should be considered to be first-line treatment if non-pharmacologic measures are not successful in achieving LDL target levels (Ballantyne et al. 2001). This study also determined that non-Hispanic whites and individuals with normal glucose tolerance, hypertension, dyslipidemia and a low waist circumference have a lower risk for cardiovascular events. Furthermore, the interaction statistics are all non-significant, suggesting that the relationship of insulin resistance to CVDs does not differ among ethnic groups or gender (Hanley et al. 2002).

Recommended literature:

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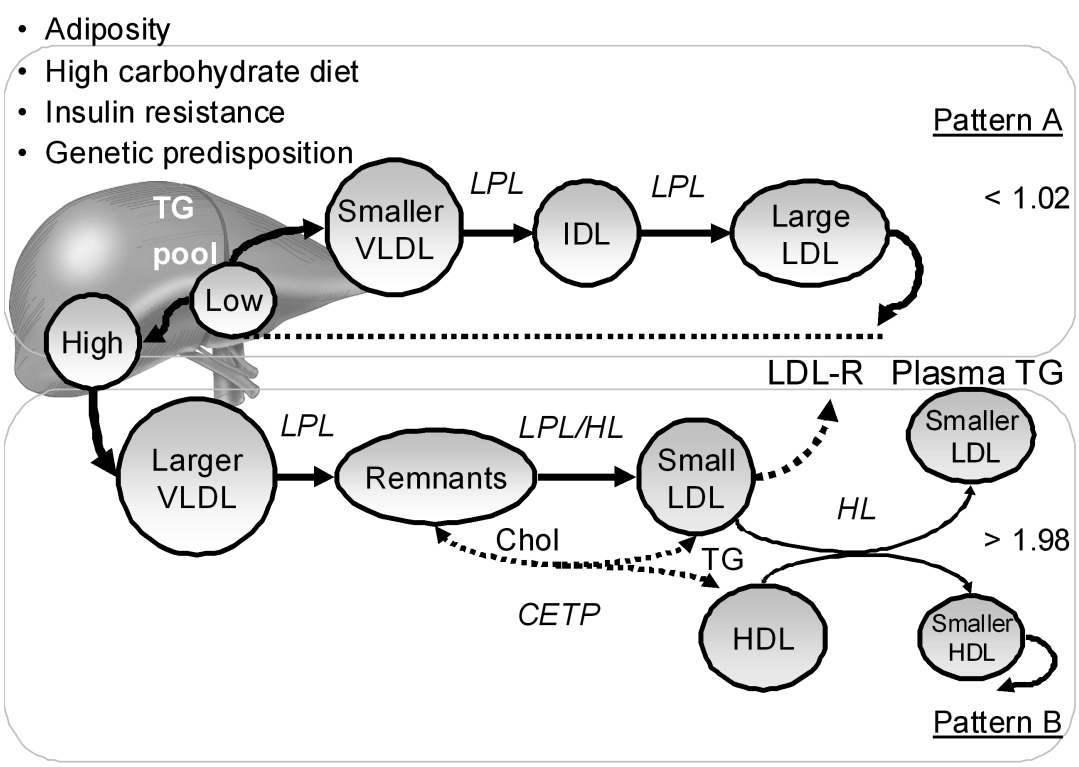
Figure 4.1. *Model for Origins of AtherogenicDyslipidemia of Obesity and Metabolic Syndrome*
CETP, cholesteryl ester transfer protein; Chol, cholesterol; HDL, high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipopritein; LDL, low density lipoprotein; LDL-R, LDL receptor; MetS, metabolic syndrome; TG, triglycerides; VLDL, very-low-density lipoprotein.


• Adiposity
• High carbohydrate diet
• Insulin resistance
• Genetic predisposition
Pattern A
TG pool
Low
High
Smaller VLDL
LPL
IDL
LPL
Large LDL
< 1.02
LDL-R
Plasma TG
Larger VLDL
LPL
Remnants
LPL/HL
Small LDL
Smaller LDL
HL
Chol
TG
> 1.98
CETP
HDL
Smaller HDL
Pattern B