METABOLIC SYNDROME-A LITERATURE REVIEW

by

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ABSTRACT

Metabolic Syndrome is an aggregate of conditions that together increases the risk of developing cardiovascular disease and Type 2 diabetes. The commonly accepted underlying risk factors for Metabolic Syndrome include insulin resistance and abdominal obesity. Poorly understood biological mechanisms link insulin resistance with the other metabolic risk factors.

Confusion about Metabolic Syndrome exists in part due to the lack of a consensus definition and the lack of a consensus treatment protocol. It is estimated that approximately 25% of the world's population has Metabolic Syndrome. In the U.S., Metabolic Syndrome is more common in males than females, more common in Hispanics and increases with age.

Individuals that are genetically predisposed to insulin resistance combined with physical inactivity and obesity can elicit insulin resistance and the progression to Metabolic Syndrome

Treatment of Metabolic Syndrome begins first with therapeutic lifestyle changes and then pharmacological treatment of the individual components of the syndrome.

INTRODUCTION

Metabolic Syndrome is an aggregation of conditions that together increases the risk of cardiovascular disease in individuals that would not otherwise be recognized to be at risk. Additionally, Metabolic Syndrome increases the risk of developing diabetes mellitus and chronic kidney disease and is associated with a number of other disorders. It is a common, affecting approximately 24% of the adult U.S. population (Grundy, 2004, from http://www.medscape.com/viewarticle/484166_print accessed October 29, 2006), and dangerous, yet treatable risk factor for a variety of diseases, yet confusion about and rejection of the syndrome still exists. The lack of a consensus definition of Metabolic Syndrome, debate about its etiology and pathogenesis and lack of a consensus document for its treatment contribute to this confusion.

The dominant underlying risk factors for Metabolic Syndrome appear to be abdominal obesity and insulin resistance, a generalized metabolic disorder in which the body is unable to use insulin efficiently. Metabolic Syndrome is also sometimes called Insulin Resistance Syndrome. Some individuals are genetically predisposed to insulin resistance and physical inactivity and obesity can elicit insulin resistance in these individuals. However, most people with insulin resistance have abdominal obesity. Poorly understood complex biological mechanisms at the cellular level appear to link insulin resistance with other metabolic risk factors (AHA, n.d., from http://www.americanheart.org/presenter.jhtm?identifier=4756, accessed October 29, 2006)

The historical progression, current definitions, epidemiological significance, pathophysiology and clinical significance of Metabolic Syndrome are the focus of this literature review. This literature review was limited to original and review articles from the year 2000 to the present and limited to the adult population.

BACKGROUND

The history of Metabolic Syndrome reflects the recognition of the concept of insulin resistance and its consequences as well as the recognition of adipose tissue as a physiologically active organ (Leslie, 2005, p. 264). First to use the phrase "metabolic syndrome" was Hanefield and Leonhardt. In 1981, Hanefield and Leonhardt used the phrase to describe the joint incidence of hyperlipoproteinemia, diabetes, hypertension, gout and obesity in combination with an increased incidence of cardiovascular disease, fatty liver and cholelithiasis (Leslie, p. 266).

In 1985, Modan and his associates proposed a syndrome of insulin resistance or hyperinsulinemia as a common pathophysiological feature for obesity, hypertension and glucose intolerance, which could possibly explain their common association (Leslie, 2005, p. 266).

Syndrome X was the name proposed by Reaven in a 1988 lecture to the American Diabetes Association. According to Reaven, Syndrome X was a group of associated conditions that were important in the development of coronary artery disease and included hyperinsulinemia, glucose intolerance, hyperglycemia, elevated low density lipoprotein cholesterol and hypertension all resulting from resistance to insulin mediated glucose uptake. Syndrome X has also been called Reaven's Syndrome (Leslie, 2005, p. 266).

Kaplan coined the term "deadly quartet" for the association of upper body obesity, hypertension, hypertriglyceridemia and glucose intolerance in which hyperinsulinemia played the key pathogenic role. Defronzo and Ferrannini developed the term "insulin

resistance syndrome" to define a syndrome of non-insulin dependent diabetes, hypertension, dyslipidemia, atherosclerotic cardiovascular disease and obesity. Zimmet developed "syndrome X plus" which included the elements of syndrome X as defined by Reaven, but also included upper body obesity, hyperuricemia, physical inactivity and aging (Leslie, 2005, p. 266).

Lastly, Hjerrman proposed renaming syndrome X "metabolic cardiovascular syndrome" or "atherothrombogenic syndrome". In addition to the components of syndrome X he noted the presence of atherogenic, small, dense low-density lipoprotein cholesterol that accompanied low high-density lipoprotein cholesterol in the presence of a raised level of very low-density lipoprotein triglyceride, even in the absence of hypercholesterolemia. He also noted an increased tendency for thrombosis from elevated levels of fibrinogen, factor VIIc and elevated plasminogen activator inhibitor-1 (Leslie, 2005, p. 266).

In 2001, the Centers for Disease Control and Prevention approved the request by the American Association of Clinical Endocrinologists (AACE) for a new diagnostic code, ICD-9-CM 277.7 for "Dysmetabolic Syndrome X" and thus, created a new disease. Although the AACE website lists 12 criteria for the dysmetabolic syndrome X, the CDC does not require that a given number of components be present to use the ICD code. The code may be used if the physician determines based on their professional opinion that the dysmetabolic syndrome X is present (Leslie, 2005, p. 266).

TABLE 1. Synonyms for Metabolic Syndrome

Android obesity syndrome	Insulin resistance/hyperinsulinemia
Syndrome of Affluence	syndrome
Plurimetabolic syndrome	Atherothrombogenic syndrome
GHO (Glucose intolerance/	Metabolic cardiovascular syndrome
Hypertension/Obesity syndrome	Syndrome X plus
Syndrome X	Deadly quartet
Metabolic syndrome X	Cardiovascular and metabolic syndrome
Reaven syndrome	Dysmetabolic syndrome X
Insulin resistance syndrome	MetSyn
CHOAS (Australia)	Wohlstandssyndrome (Germany)

DEFINITIONS OF METABOLIC SYNDROME

Just as there are numerous synonyms for Metabolic Syndrome that have evolved over time, there are also several definitions of Metabolic Syndrome beginning with the World Health Organization's (WHO) attempt in 1988 to standardize the criteria. The WHO viewed insulin resistance as a required component for diagnosis which was defined as one of the following: Type 2 diabetes, impaired fasting glucose, impaired glucose tolerance and for those with normal fasting glucose (<110 mg/dl) glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic-euglycemic conditions. In addition, two other risk factors must be present to meet the WHO definition of Metabolic Syndrome. These other risk factors include antihypertensive medication and or high blood pressure (>/= 140 mmHg systolic or >/= 90 mmHg diastolic), plasma triglycerides >/= 150 mg/dl, HDL cholesterol <35 mg/dl in men or <39 mg/dl in women, BMI > 30 kg/m2 and or waist: hip ratio > 0.9 in men and > 0.85 in women (waist circumference at the umbilicus, hip circumference at their widest point) or urinary albumin excretion rate >/= 20 mcg/min or albumin:creatinine ratio >/= 30 mg/g. One disadvantage of the WHO criteria is that special testing of glucose beyond the routine clinical assessment may be necessary to diagnose Metabolic Syndrome (Grundy, Brewer, Cleeman, Smith & Lenfant, 2004, p. 435).

In a comment by Balkau and Charles (1999) for the European Group for the Study of Insulin Resistance (EGIR) on the WHO criteria for defining Metabolic Syndrome, the EGIR proposed their own definition of Metabolic Syndrome, but only for non-diabetic

individuals. The EGIR stated that there was no simple way at that time to measure insulin resistance in diabetic individuals but that fasting insulin values were a reliable means of determining insulin resistance in non-diabetic persons. The EGIR recommended that Metabolic Syndrome include insulin resistance as defined as the top 25% of fasting insulin values among non-diabetic individuals plus two or more of the following: hyperglycemia (fasting plasma glucose >/= 6.1 mmol/L [110 mg/dl] but non-diabetic), central obesity (waist circumference >/= 94 cm in males, >/= 80 cm in females), dyslipidemia (triglycerides >/= 2.0 mmol/L [180 mg/dl], and or HDL cholesterol < 1.0 mmol/L [40 mg/dl]) or treatment for dyslipidemia and hypertension (>/= 140/90) or treatment for hypertension).

In 2001, the National Cholesterol Education Program (NCEP) introduced the concept of Metabolic Syndrome into its guidelines to reduce cardiovascular risk. The NCEP Adult Treatment Panel (ATP) III criteria somewhat overlaps the WHO criteria and a diagnosis is based on having at least three out of five of the following: waist circumference > 40 inches in men or >35 inches in women, triglycerides >/= 150 mg/dl, HDL cholesterol <50 mg/dl in women and <40 mg/dl in men, blood pressure >/= 135/85 mmHg and fasting serum glucose of >/= 110 mg/dl (NCEP ATP III, from http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf accessed October 29, 2006). The intent was to include a group of risk factors accompanying type 2 diabetes. (Reisin & Martin, 2005, p. 270). The placement of abdominal obesity as the first risk factor reflects its priority as a contributor to the pathogenesis of Metabolic Syndrome, in particular, the development of insulin resistance. According to the ATP III criteria, insulin resistance

does not need to be demonstrated in order to diagnose Metabolic Syndrome, increased fasting glucose suffices (Grundy, 2004, from http://www.medscape.com/viewarticle/484166_print accessed October 29, 2006). Even though the Metabolic Syndrome does not encompass all cardiovascular risk factors, it provides a picture of a predominantly increasing risk for a growing portion of the population. The ATP III guidelines were intended to be more user friendly and provided both clinicians and epidemiologists with simple measures that were applicable in both clinical and research settings (Zimmet & Alberti, 2005, from www.medscape.com accessed October 29, 2006).

In 2005, the International Diabetes Federation (IDF) proposed their own definition of Metabolic Syndrome intended for global application in clinical practice and represents modifications to the WHO definition and ATP III criteria. The IDF places more emphasis on abdominal obesity as the core feature of the syndrome as it is independently associated with each of the other metabolic syndrome factors including insulin resistance. The IDF took an additional step to develop ethnic specific values for waist circumference cut off points based on various sources of epidemiologic data. The IDF cautions that these cut off points are only pragmatic and more data would be needed to link them to specific risk. According to the IDF definition, an individual is diagnosed as having Metabolic Syndrome if they have central obesity (waist circumference of >/= 94 cm for Europid men and >/= 80 cm for Europid women with ethnicity specific values for other groups) and any two of the following factors: elevated triglycerides (>/= 150 mg/dL) or treatment for elevated triglycerides, decreased HDL cholesterol (< 40 mg/dL

in males and < 50 mg/dL in females), hypertension (systolic >/= 130 mmHg or diastolic >/= 85 mmHg) or treatment for hypertension and raised fasting plasma glucose (>/= 100mg/dL) or previously diagnosed with diabetes (IDF, 2005, p. 1 from http://www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf accessed October 29, 2006).

Although the four definitions of Metabolic Syndrome that were reviewed all recognize a clinical entity with multiple risk factors for cardiovascular disease, a careful examination indicates many similarities and important disparities. The WHO definition includes those persons with high risk of developing diabetes as well as individuals diagnosed with Type 2 diabetes. The obesity component can be measured by waist to hip ratio or BMI and includes microalbuminuria, which links the syndrome with risk for developing chronic kidney disease. The WHO definition has been criticized for including Type 2 diabetics in the definition and not reserving the diagnosis of Metabolic Syndrome for those who are at risk for developing diabetes. Additionally, the WHO definition includes impaired glucose tolerance measured by oral glucose tolerance test (OGTT) or 2-hour post glucose challenge as part of its criteria, tests considered by some to be less practical and an added cost with a small added value of predicting cardiovascular risk (Grundy, Brewer, Cleeman, Smith & Lenfant, 2004, p. 436).

The EGIR excludes diabetics, includes central obesity - long recognized as a risk factor for cardiovascular disease, and dyslipidemia and hypertension as well as individuals treated for these two disorders. However, the determination of those with insulin resistance as being in the top 25% of insulin values for non-diabetics would be cumbersome and not practical in clinical practice.

The NCEP ATP III definition is easy to use and each component is justified by its prevalence in the U.S. population, however, this definition does not exclude diabetics and is criticized for the same reasons as the WHO definition (Grundy, Brewer, Cleeman, Smith & Lenfant, 2004, p. 436). Also, it fails to consider treated hypertension or dyslipidemia when defining its criteria.

The IDF definition emphasizes the presence of abdominal obesity as a core factor in Metabolic Syndrome and also provides pragmatic waist circumference criteria for various ethnic groups. IDF also recognizes dyslipidemia or treatment for dyslipidemia, and hypertension or previous diagnosis for hypertension as risk factors. However, IDF does not exclude diabetics from the definition.

Resin and Alpert (2005) have proposed a definition for Metabolic Syndrome that attempts to bridge the differences among current definitions and unify the risk factors. They propose that abdominal obesity be the leading component based on its strong association with Metabolic Syndrome and the increasing recognition of its biological activity (Hutley & Prins, 2005, p. 280). They also incorporate the IDF determined cut-off-points for various ethnic groups as part of their definition. Resin and Alpert also recognize the risks associated with previous diagnoses of hypertension and dyslipidemia in addition to numerical cut-off values for these two conditions. Additionally, they recommend using the American Diabetes Association cut point for prediabetes as fasting glucose greater than 100 mg/dL since Metabolic Syndrome is a condition that may predict the development of Type 2 diabetes. Resin and Alpert also recommend the

inclusion of the WHO microalbuminuria criteria in recognition that it is a component that links Metabolic Syndrome with the risk of development of chronic kidney disease.

The Resin and Alpert definition of Metabolic Syndrome is as follows: Central obesity to be determined by ethnic cut-off-points established by IDF, triglyceride > 150 mg/dl or specific treatment, HDL cholesterol < 50 mg/dl for women, < 40 mg/dl for men or specific treatment, blood pressure >/= 130/85 mmHg or specific treatment, fasting plasma glucose >/= 100 mg/dl and albuminuria mg/g albumin to creatinine ratio >/= 30.

OPPOSING VIEWS

Kahn, Buse, Ferrannini and Stern (2005) authored a joint statement issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes in which they appeared to have second thoughts about the validity of Metabolic Syndrome. They raised concerns about the lack of precision in the definition of Metabolic Syndrome, whether or not it is a valid indicator of cardiovascular risk, the lack of understanding about the pathogenesis of the syndrome, which criteria is best to use in clinical practice and if treatment of Metabolic Syndrome differs from treatment of the individual components.

Kahn, et al. point out that other established cardiovascular risk factors, such as, family history, gender, smoking and age are not included in the ATP III and WHO definitions, but hypertension is. Also, risk factors for insulin resistance such as pro-inflammatory and pro-thrombic markers and physical inactivity are not included, but obesity, elevated triglycerides and glucose intolerance are included in the ATP III and WHO definitions. The authors believe that additional research is needed in order to establish whether or not the inclusion of other well-known risk factors would improve the predictive value of Metabolic Syndrome for cardiovascular disease and Type 2 diabetes.

Kahn, et al. also state that a syndrome is usually defined as a group of specific signs and symptoms that are usually caused by a unifying underlying pathophysiology and that the collected risk is greater than the sum of its parts. The authors admit that most researchers believe that insulin resistance is the hallmark of metabolic syndrome, but insulin resistance or hyperinsulinemia need not be present in an individual to be

diagnosed with Metabolic Syndrome. In addition, the WHO and ATP III definitions include risk factors that are only weakly associated with insulin resistance, e.g., hypertension, but exclude risk factors that are more closely related, i.e., pro-inflammatory and pro-thrombic markers.

With respect to treatment of Metabolic Syndrome, Kahn, et al., point out that the current WHO and ATP III definitions include those with active disease, including diabetes, hypertension and diagnosed cardiovascular disease as well as those that have normal values or milder conditions that meet the criteria for Metabolic Syndrome, but do not require specific treatment. They believe further research is needed to determine the value of treating particular combinations of defining criteria.

UTILITY OF THE DEFINITIONS

Several researchers have studied the utility of the various definitions of Metabolic Syndrome in the identification of various traits of the syndrome and comparing the prevalence of Metabolic Syndrome using different definitions. For example, Ford and Giles (2003) compared the prevalence of Metabolic Syndrome using the ATP III definition and the WHO definition in a nationally representative sample from the Third National Health and Nutrition Examination Survey (1988-1994). In this study, the age adjusted prevalence for the sample of 8608 individuals 20 years old or older was 23.9% using the ATP III guidelines and 25.1% using the WHO definition. This study also found substantial differences in prevalence within specific ethnic groups. For example, the prevalence using the WHO definition in African American men was 24.9% compared to 16.5% using the ATP III definition.

In a research study that compared three different definitions of Metabolic Syndrome conducted by the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study Group (2005), disparities were also found in the prevalence of the syndrome depending on the definition used. The study consisted of 4190 men and 4950 women non-diabetics from seven DECODE study centers with cross-sectional data on fasting serum insulin and the other variables needed for the definition of Metabolic Syndrome. The prevalence of the syndrome using the WHO, ATP III and the EGIR criteria ranged from 16.5-24.7% in men and 15.2-20.9% in women aged 30-77 years, the lowest was using the EGIR definition. Subjects that met all three definitions were 31% of the men and 34% of the women who had Metabolic Syndrome by any one

of the criteria compared to 37% of these men and 39% of these women met only one of the definitions.

Many researchers believe that insulin resistance is the pathological process that underlies the Metabolic Syndrome and the associated cardiovascular risk factors and that identifying Metabolic Syndrome is a reliable way to also identify persons with insulin resistance. The ATP III guidelines use impaired fasting glucose (>/=110 mg/dL) as the criteria for identifying individuals with Metabolic Syndrome. However, several studies have brought into question the ability of the ATP III criteria to identify insulin resistant individuals. In a study by Cheal, Abbasi, Lamendola, McLaughlin, Reaven and Ford (2004) they determined that the ATP III criteria does not provide a sensitive approach to identifying individuals who are insulin resistant. In this study, 443 healthy volunteers were used and their BMI, HDL, triglycerides, blood pressure and fasting plasma glucose were measured as well as steady state plasma glucose to determine insulin resistance. Insulin resistance was defined as being in the top tertile of steady state plasma glucose. The results of the study indicated that 20% of the sample met the ATP III criteria for Metabolic Syndrome, and insulin resistance and the presence of Metabolic Syndrome were significantly associated ($P < 0.001$). However, only 69 out of 149 individuals with insulin resistance met the criteria for Metabolic Syndrome (sensitivity of 45%) and 69 out of 91 persons identified with Metabolic Syndrome were also identified with insulin resistance (positive predictive value of 76%) indicating that the ATP III criteria do not provide the most sensitive approach to identifying insulin resistant individuals. Cheal, et al., also found that obesity and elevated lipids, both HDL and triglycerides, were better

indicators of insulin resistance. Sierra-Johnson, Johnson, Allison, Bailey, Schwartz and Turner (2006) achieved similar results in their study of 256 white subjects. In this study, the usual ATP III criteria were measured as well as multiple glucose tolerance tests and insulin resistance was defined as insulin sensitivity below the lowest quartile for non-diabetic subjects. The results showed that Metabolic Syndrome had a low sensitivity in identifying insulin resistance (46% in men and 39% in women) but high specificity (93% in men and 95% in women). They also found that waist circumference provided greater accuracy for identifying insulin resistance rather than the diagnosis of Metabolic Syndrome.

Liao, et al. (2004), also found that the ATP III criteria for Metabolic Syndrome have a low sensitivity for predicting insulin resistance. This study used 74 non-diabetic individuals and calculated the glucose disposal rate using hyperinsulinemic-euglycemic clamp to determine insulin resistance. The sensitivity of the ATP III criteria was compared to various glucose disposal rate cut-off points and was maximized at 50% when a cut-off of glucose disposal rate of 9.5-10 mg/kg/min. The specificity remained at about 90% for all cut-off points. The poor sensitivity of the ATP III criteria to identify insulin resistance means that there are a number of people that are insulin resistant but do not meet the criteria for Metabolic Syndrome. In the Liao et al., study approximately one-third of the subjects who did not meet the ATP III criteria were insulin resistant, many of who had adverse cardiovascular risk profiles including dyslipidemia. Since it is desirable for screening tools to have a high sensitivity the value of the ATP III criteria as

a screening method for those individuals at risk for cardiovascular disease and diabetes is questionable.

Unpublished, preliminary data from Liao et al., suggests that ATP III criteria exhibit an even lower sensitivity for identifying insulin resistance in African Americans. This may indicate that the cluster of traits identified as Metabolic Syndrome may be compositionally different in African Americans. This is supported by a small pilot study conducted by Appel, et al. (2005). This study compared the agreement between using ATP III criteria alone and the ATP III criteria with an additional measure of insulin resistance (acanthosis nigricans, hyperinsulinemia or Homeostatic Model Assessment Insulin Resistance) to diagnose Metabolic Syndrome in a sample of 33 African American women. Using ATP III criteria alone, six of the 33 women were identified. But when one of the markers for insulin resistance was added, 15 to 19 women were identified with Metabolic Syndrome.

In a study to assess the capacity of Metabolic Syndrome to identify impaired glucose tolerance, Meigs et al. (2004) found that Metabolic Syndrome specifically defined as impaired fasting glucose, large waist size and elevated triglycerides was an efficient way to identify those with impaired glucose tolerance by oral glucose tolerance test. The purpose of the study was to determine if Metabolic Syndrome could be used to screen for individuals likely to fail an oral glucose tolerance test and thus be eligible for Type 2 diabetes prevention strategies. Using over 9000 subjects from four different epidemiological studies Meigs et al. found that 61 to 93% with the three Metabolic

Syndrome traits of impaired fasting glucose, large waist size and elevated triglycerides failed an oral glucose tolerance test.

SIGNIFICANCE OF THE PROBLEM

Several researchers have used the National Health and Nutrition Examination Survey (NHANES III) 1988-1994 data to determine the prevalence of Metabolic Syndrome in the U.S. (Ford, Giles & Dietz, 2002; Park, Zhu, Palaniappan, Heska, Carnethon & Heymsfield, 2003; Reynolds & He, 2005). In addition, Ford, Giles and Mokdad (2004) used data from NHANES 1999-2000 to determine the change in prevalence of Metabolic Syndrome in the U.S. population. Also, Reynolds and He (2005) used international health survey data, for example, the Kuopio Ischaemic Heart Disease Risk Factor study conducted in Finland and InterASIA conducted in China to provide a global picture of the Metabolic Syndrome. Eckel, Grundy and Zimmet (2005) also compiled international data from various studies, and in spite of differing in design, precise definition of Metabolic Syndrome used, age and sex structure, draw inferences about prevalence between sexes, ethnic groups and age groups worldwide.

From Eckel, Grundy and Zimmet (2005), prevalence among men varies from 8% in India to 24% in the U.S. and varies in women from 7% in France to 43% in Iran. The InterASIA study in China reported that the prevalence among women was higher than men at every age group (Reynolds & He, 2005, p. 275). There is a steep increase in the prevalence after 30 years of age in both men and women in the U.S., peaking for men between 50 and 70 years and for women-60 to 80 years. Similar trends have been found in European and Chinese populations (Reynolds & He p. 275). In general, the International Diabetes Federation estimates that one-quarter of the world's adult

population has Metabolic Syndrome (IDF, 2005, p. 2, from http://www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf accessed October 29, 2006).

In general, for the U.S. population, Metabolic Syndrome is more common in men than women, more common in persons of Hispanic origin and the prevalence increases with age. From the NHANES III data for the U.S. population, the age-adjusted prevalence for Metabolic Syndrome is 22.8% in men and 22.6% in women over 20 years old (Park, et al., 2003, p. 427). The prevalence varies substantially by ethnic group. Again using the NHANES III data, the age-adjusted prevalence in whites was 24.8% in men and 22.8% in women (total 23.8%), in African American men, 16.4% and African American women, 25.7% (total 21.6%). The age-adjusted prevalence in Hispanic men was 28.3% and 35.6% in Hispanic women (31.9% total). The age-adjusted prevalence in persons identified as "other" ethnicity, 20.9% in men and 19.9% in women (total 20.3%). Among American Indians in the Strong Heart Study, the prevalence of the syndrome was 55.2% in persons aged 45 to 74 (Reynolds & He, 2005, p. 275). The prevalence in the U.S. population increased from 6.7% in 20 to 29 year olds, to 43.5% aged 60 to 69 years and 42% for those older than 70 years (Ford, Giles & Dietz, 2002, p. 356).

Analyzing data from the more recent NHANES 1999-2000 Ford, Giles and Mokdad (2004) found that the prevalence of Metabolic Syndrome has significantly increased among U.S. adults older than 20 years, especially in women. The age adjusted prevalence increased from 24.1% in NHANES III (1988-1994) to 27.0% (P=0.088) in the NHANES 1999-2000. The age adjusted prevalence increased in women by 23.5 % (P=0.021) with the greatest increase in the 20-39 year age group. Increases in high blood

pressure, waist circumference and elevated triglycerides accounted for most of the increase, especially in women. Ford, Giles and Mokdad (2004) also noted that the increase in the prevalence of obesity between the NHANES III 1988-1994 and NHANES 1999-2000 was 22.9 to 30.5%, respectively. Their analysis showed that this increase in obesity accounted for much of the corresponding increase in Metabolic Syndrome.

PATHOPHYSIOLOGY

Insulin Resistance and Glucose Intolerance

Insulin is the most potent anabolic hormone in the body, exerting a plethora of effects on lipid and protein metabolism, ion an amino acid transport, cell cycle proliferation, cell differentiation and nitric oxide synthesis (Wang, Goalstone & Drazin, 2004, 2735). The majority of persons with Metabolic Syndrome also have insulin resistance. Insulin resistance and/or associated hyperinsulinemia are believed to be the direct cause of other Metabolic Syndrome risk factors (Grundy, Brewer, Cleeman, Smith & Lenfant, 2004, p. 434). Insulin resistance is accepted as the most unifying pathophysiologic mechanism underlying the cluster of characteristics of Metabolic Syndrome and is usually caused by a defect in insulin action within target organs and tissues that results in compensatory hyperinsulinemia (Eckel, Grundy & Zimmet, 2005, p. 1418). Although hyperinsulinemia may compensate for insulin resistance to some biological actions of insulin, i.e., maintenance of normoglycemia, in some tissues, it may cause over expression of insulin activity in normally sensitive tissues. This accentuation of some insulin actions coupled with resistance to other actions of insulin results in the clinical manifestations of Metabolic Syndrome (Gill, Mugo, Whaley-Connell, Stump & Sowers, 2005, p. 291).

Several possible mechanisms of insulin resistance have been proposed: pre-receptor, receptor and post-receptor mechanism. The most studied pathway that appears to be absolutely necessary for mediating metabolic effects of insulin involves the phosphorylation of the insulin receptor substrate (IRS) 1 and 2 and activation of

phosphatidylinosital (PI) 3-kinase. This pathway also contributes to the mitogenic aspects of insulin activity. Under normal conditions in endothelial cells, insulin is antiatherogenic and stimulates NO (a potent vasodilator) production and decreases the expression of adhesion molecules thereby protecting cells from excessive interaction with circulating monocytes. In the insulin resistant state, the PI 3-kinase pathway is impaired and insulin is no longer antiatherogenic (Wang, Goalstone & Drazin, 2004, 2736).

A second pathway involves the phosphorylation of the She and activation of Ras, Raf, MEK and mitogen activated protein (MAP) kinases (Erk 1 and 2). This second pathway contributes solely to the nuclear and mitogenic effects of insulin and does not convey the metabolic action of insulin. This pathway is unimpaired in insulin resistance and is more strongly activated by compensatory hyperinsulinemia leading to increased activity of growth promoting agents. Over stimulation of this pathway is perhaps the source of the proatherogenic mechanism (Wang, Goalstone & Drazin, 2004, p. 2737).

Insulin resistance is enhanced by excess adipose tissue, in particular abdominal adiposity. Excess adipose tissue releases non-esterfied fatty acids (NEFA). A high NEFA level overloads muscle and liver with lipid and enhances insulin resistance. Free fatty acids are also produced through the lipolysis of lipoproteins by the action of lipoprotein lipase, the stimulation of which is influenced by insulin. Insulin also inhibits lipolysis in adipose tissue. When insulin resistance develops, increased lipolysis in adipose tissue produces more fatty acids, further inhibiting the antilipolytic effect of insulin and creates additional lipolysis (Eckel, Grundy & Zimmet, 2005, p. 1418). Over production of toxic metabolites that contribute to defective insulin signaling and insulin resistance can result

from intracellular accumulation of free fatty acids (Gill, Mugo, Whaley-Connell, Stump & Sowers, 2005, p. 291).

High plasma levels of free fatty acids accompanied by fatty acid overloaded muscle cells contributes to the development of fatty liver as excess free fatty acids are directed to the liver. Hyperinsulinemia may increase the production of very low-density lipoprotein triglycerides and thus raise triglycerides. Insulin resistance can raise blood pressure (Grundy, 2004, p. 2597).

Insulin resistance generally rises with body fat content, but a broad range of insulin resistance exists at any given body fat level (Grundy, Brewer, Cleeman, Smith & Lenfant, 2004, p. 434). Visceral or omental fat appears to be the most detrimental and contributes most to the development of lipotoxicity in peripheral tissues by the secretion of adipocytokines. Several of these adipocytokines: adiponectin, resistin, leptin, tumor necrosis factor-alpha and interlukin-6 are implicated in insulin resistance. For example, circulating levels of adiponectin seem to correlate with hyperinsulinemia and insulin resistance, but the relative contribution of each of the adipocytokines requires further study (Gill, Mugo, Whaley-Connell, Stump & Sowers, 2005, p. 291).

Adiponectin is an anti-inflammatory cytokine that is produced by adipocytes. Adiponectin not only enhances insulin sensitivity, but also inhibits several steps in the inflammatory process. It also inhibits hepatic gluconeogenic enzymes and the rate of endogenous glucose production in the liver. It increases glucose transport in muscle and enhances fatty acid oxidation (Eckel, Grundy & Zimmet, 2005, p. 1421)

In a study by Salmenniemi, et al., 119 subjects were evaluated for Metabolic Syndrome, insulin sensitivity by way of the euglycemic hyperinsulinemic clamp, cytokines, as well as adhesion molecules. Their findings indicate that Metabolic Syndrome is associated with a high amount of intra-abdominal fat, low adiponectin levels, and elevated levels of cytokines (interleukin 1RA and interleukin 1beta). Tumor necrosis factor-alpha and interleukin-6 did not differ and may not be the best markers for the syndrome according to the authors. The authors also found that adhesion molecules P-selectin and ICAM-1 were associated with Metabolic Syndrome. Adiponectin inhibits the expression of adhesion molecules and has anti-inflammatory properties, so in the reduced adiponectin environment of insulin resistance, adhesion molecules are more expressed and can be responsible for endothelial damage and low-grade chronic inflammation.

Stuhlinger, et al., studied the association between insulin resistance and asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, in an attempt to further study the relationship between insulin resistance and endothelial dysfunction. ADMA is known to be elevated in syndromes associated with vascular diseases. Also, ADMA is known to correlate with NO mediated vasodilation and with adherence of monocytes to the endothelium. Measurements of ADMA and insulin sensitivity via the insulin suppression test indicate that ADMA concentrations are elevated in insulin sensitive individuals, both normo and hypertensive. This relationship was further validated when pharmacological intervention with rosiglitazone enhanced insulin sensitivity and reduced ADMA concentrations. ADMA may be yet another

metabolic contributor to endothelial damage and increased risk for cardiovascular disease in insulin resistance.

In another study of post-menopausal women with Metabolic Syndrome, leptin and resistin were elevated where as adiponectin was decreased. In addition, BMI correlated strongly with markers of insulin resistance and adipocytokine levels (Chu, Cosper, Orio, Carmina & Lobo, 2006, p. 100).

The relation between impaired fasting glucose or impaired glucose tolerance and insulin resistance is well supported. To compensate for defects in insulin activity, insulin secretion or clearance needs to be modified to sustain normal glucose levels. Hyperglycemia is the end result if these mechanisms fail (Eckel. Grundy & Zimmet, 2005, p. 1419). Hyperglycemic induced endothelium damage takes place by five major molecular mechanisms all of which result in overproduction of superoxide by the mitochondrial electron transport chain. The formation of these reactive oxygen species can lead to endothelial dysfunction and decreased NO and prostacyclin production. Also, reactive oxygen species can increase the formation of vasoconstrictor prostanoids and endothelin and promote atherosclerotic plague formation. Increased vascular permeability is also a consequence of hyperglycemia induced reactive oxygen species formation and is responsible for the expression of endothelial mitogen vascular endothelial growth factor, which promotes diabetic microangiopathy (Moreno & Fuster, 2004, p. 2294).

Since insulin resistance increases a person's risk for developing cardiovascular disease and Type 2 diabetes, several researchers have proposed measures of insulin

resistance in obese individuals with and without Metabolic Syndrome. Mclaughlin, Abbasi, Cheal, Chu, Lamendola & Reaven (2003) found that plasma triglyceride concentration, the ratio of triglyceride to HDL cholesterol and insulin concentrations were the most useful metabolic markers for determining insulin resistance in a study of 258 non-diabetic, normotensive obese volunteers. Reilly, Wolfe, Rhodes, Girman, Mehta & Rader (2006) found that the addition of measures of insulin resistance (HOMA index: plasma glucose in mol/l multiplied by plasma insulin in mU/l divided by 22.5) in association with Metabolic Syndrome significantly improved the association of coronary artery calcification even after adjusting for age, non-Metabolic Syndrome risk factors and C-reactive protein. Reilly, et al., believe that insulin assays or alternative biomarkers of insulin resistance may facilitate cardiovascular risk prediction in individuals with Metabolic Syndrome.

Schianca, Sainaghi, Castello, Rapetti, Limonicini & Bartoli (2006) found that ISI-gly (insulin sensitivity index), which includes post load glucose and insulin concentrations, provides a more accurate whole-body measure of insulin sensitivity. According to Schianca, et al., fasting glucose concentrations are largely reflective of basal hepatic glucose production and impaired peripheral insulin resistance can affect a significant number of individuals with normal hepatic insulin sensitivity.

Two other studies used only waist circumference to determine insulin resistance. Wahrenberg, Hertel, Leijonhufvud, Persson, Toft & Arner (2005) used a sample of 2746 healthy adults and measured waist circumference and BMI and compared these measurements to the HOMA index. The cut-off point was HOMA index of 3.99. Using

multivariate regression models to assess the predictive power of the variable, waist circumference was the strongest regressor of the covariates. Using receiver operating characteristics curve analysis to select an appropriate cut-off, Wharenberg, et al., found that the optimal cut-off for predicting insulin resistance was a waist size of 100 cm in both men and women. Sensitivities and specificities were between 94 and 98% and 61to 63%, respectively, in both sexes.

Steele, Shields, Knight & Pearson (2005) collected anthropometric and biochemical data on-600 adult men without diabetes. Insulin resistance (HOMA-S) was strongly associated with waist, subscapular skin fold and BMI measurements. In a linear regression analysis with BMI included as a covariate to waist circumference, BMI did not improve the correlation with insulin resistance, suggesting that BMI does not provide additional useful information on top of waist circumference in predicting insulin resistance. Steele, et al, recommend that waist circumference be routinely measured to assess individuals for increased risk for insulin resistance related cardiovascular disease, Metabolic Syndrome and Type 2 diabetes and to target individuals for health promotion interventions.

Obesity and Abnormal Body Fat Distribution

Pladevall, et al. (2006), used confirmatory factor analysis to conclude that there is a single underlying factor that influences the expression of the traits of Metabolic Syndrome and that the individual components of the syndrome occur together with a frequency greater than that expected by chance. Even though insulin resistance is considered to be the unifying process, the worldwide obesity epidemic has been the most

important driving force behind the increase in the prevalence of Metabolic Syndrome (Ford, Giles and Mokdad, 2004, p. 2447). Recently, studies have suggested that central adiposity precedes the development of the other components of Metabolic Syndrome and that weight reduction at that point could be the best way to prevent it (Pladevall, et al., 2006, p. 220).

Furthermore, Carr et al., (2004) evaluated the differential effects of insulin resistance and central body fat in determining Metabolic Syndrome based on the ATP III criteria using 218 healthy men and women with a wide age range. Multivariate models using insulin sensitivity index, intra-abdominal fat and subcutaneous fat found that only intra-abdominal fat was independently associated with all five of the Metabolic Syndrome criteria.

Adipose tissue, once only considered to be a storage depot for triglycerides, is now recognized as a complex and active endocrine tissue that secretes many factors that regulate metabolic and vascular biology. These factors, collectively called adipokines, include adiponectin, leptin, tumor necrosis factor-alpha, resistin, angiotensinogen, interleukin-6 plasminogen activator inhibitor-1 and C-reactive protein. Disregulation of these adipokines may participate in the pathogenesis of Metabolic Syndrome (Hutley & Prins, 2005, p. 281).

There are considerable differences in the various adipose tissue depots, with visceral adipose tissue being associated with multiple medical morbidities, as well as Metabolic Syndrome. Secretions from the visceral adipose depot are directly circulated to the portal system, have direct access to the liver and have a relatively greater affect on

hepatic metabolic function. Also, visceral adipose tissue secretes greater amounts of interleukin-6 and plasminogen activator inhibitor-1 (Kershaw & Flier, 2004, p. 2554). Direct measurement of visceral fat by ultrasound by Kim & Kim, et al. (2004) was found to be a simple way to identify diabetic patients at increased risk for cardiovascular disease. Kim & Kim, et al., found that men in the middle and high visceral fat tertiles had higher odds ratio of coronary artery disease and Metabolic Syndrome.

Altered expression or activity of adiponectin may be a factor in the development of Metabolic Syndrome. Adiponectin is expressed and secreted at high levels in adipocytes and has roles in glucose and lipid homeostasis and whole body metabolism. Adiponectin has been strongly correlated with cardiovascular health and decreased concentrations are associated with manifestations of the Metabolic Syndrome, including C reactive protein, fibrinogen, hypertension and endothelial function. Decreased levels of adiponectin are associated with higher BMI, insulin resistance, unfavorable plasma lipid profiles and the development of cardiovascular disease (Hutley & Prins, 2005, p. 281). Lara-Castro, Luo, Wallace, Klein and Garvey (2006) found that it is the high molecular weight multimer form of adiponectin that is primarily associated with BMI, insulin resistance and unfavorable plasma lipid profiles. However, Ruige, Ballaus, Funahashi, Mertens, Matsuzawa and Van Gall (2005) found that high levels of adiponectin were associated with a low resting metabolic rate. This result led Ruige, et al., to hypothesize that persons with low resting metabolic rates who are theoretically predisposed to obesity disorders, may be protected by elevated adiponectin levels.

Adiponectin levels have also been shown to predict future insulin resistance. In a two-year follow up study of 590 male Japanese, baseline adiponectin levels were negatively correlated with subsequent changes in insulin and insulin resistance determined in the two-year follow up (Yamamoto, Hirose, Saito, Nishikai & Saruta, 2004, p. 89)

Further, adiponectin and adiponectin receptors have been proposed as therapeutic targets to combat obesity-linked diseases (Kadowaki, Yamauchi, Kubola, Hara, Ueki & Tobe, 2006, p. 1784).

Leptin is secreted by adipocytes and secretion is regulated by the size of fat stores. Leptin receptors are located mostly in the hypothalamus and the brain stem and signals through these receptors controls satiety, energy expenditure and neuroendocrine function. Most overweight and obese individuals have elevated levels of leptin that do not suppress appetite, or in other words, leptin resistance. Leptin resistance is thought to be a fundamental pathology in obesity (Hutley & Prins, 2005, p. 282).

Tumor necrosis factor-alpha has also been implicated in the development of obesity and insulin resistance. Elevated levels of tumor necrosis factor-alpha are positively correlated with insulin resistance and chronic exposure of tumor necrosis factor-alpha induces insulin resistance (Kershaw & Flier, 2004, p. 2550). Tumor necrosis factor-alpha may also impair insulin receptor tyrosine kinase activity and lead to impaired downstream insulin signaling (Abate, 2000, p. 161). Tumor necrosis factor-alpha also impairs insulin signaling by increasing serum non-esterfied fatty acids, which can induce insulin resistance in many tissues (Kershaw & Flier, p. 2550).

Interleukin-6 is also associated with insulin resistance and obesity and its expression and concentration are positively correlated with obesity, impaired glucose tolerance and insulin resistance. In addition, plasma concentrations of interleukin-6 predict the development of type 2 diabetes. Interleukin-6 decreases insulin signaling in peripheral tissues by decreasing the expression of insulin receptor signaling components (Kershaw & Flier, 2004, p. 2550). Interleukin-6 has recently been revealed to be an important factor in the chronic inflammatory state and hepatic insulin resistance in obesity (Hutley & Prins, 2005, p. 284).

Plasminogen activator inhibitor-1 is a regulator protein in the coagulation cascade and elevated levels in obese states are a known risk factor for thrombosis, as it decreases the generation of plasmin and thus decreases fibrinolysis. High levels of plasminogen activator inhibitor-1 along with obesity-induced increases in clotting factors and platelet activation create a hypercoagulable state, atherogenesis and increase cardiovascular risk. Plasminogen activator inhibitor-1 has also been implicated in the accumulation of visceral fat (Hutley & Prins, 2005, p. 284).

Resistin (resistance to insulin) expression is 15-fold greater in visceral as compared to subcutaneous fat in rodents and is potentially linked to obesity with insulin resistance. However, numerous epidemiological studies in humans have failed to link resistin expression in adipose tissue or circulating resistin levels with adiposity or insulin resistance (Kershaw & Flier, 2004, p. 2552).

Hypertension

The cause of hypertension in Metabolic Syndrome is multifactorial and likely includes all the elements of the syndrome, including obesity, insulin resistance, and dyslipidemia. Obesity may be the most important factor, however, the other elements of the syndrome also play a role in creating and mediating the changes that ultimately result in hypertension (Morse, Zhang, Thakur & Reisin, 2005, 303).

Epidemiological evidence and the Framingham Heart Study indicate that most essential hypertension may be due to excess body weight. Risk estimates from the Framingham Heart Study estimate that excess weight was the cause of hypertension in 78% of men and 65% of women (Morse, Zhang, Thakur & Reisin, 2005, 303).

Increased renal sodium retention in obesity has been hypothesized to be associated with SNS activity increases and renin-angiotensin system activity as well as insulin resistance and hyperinsulinemia (Morse, Zhang, Thakur & Reisin, 2005, p. 304). Increased sodium retention causes a compensatory increase in fluid volume and initiates the rise in blood pressure.

The Insulin Resistance Atherosclerosis Study, a large prospective study, set out to determine the association between insulin sensitivity and risk factors for cardiovascular disease. Using the data from this study, Goff, Zaccaro, Hafner & Saad (2003) determined that there is an 11% lower risk of developing incident hypertension with every one unit greater of insulin sensitivity measured by the frequently sampled intravenous glucose tolerance test (FSIGT). The association between in insulin resistance and hypertension relates to several different mechanisms. Insulin is a vasodilator when given IV to persons

of normal weight and also increases renal sodium reabsorption (Eckel, Grundy & Zimmet, 2005, p. 1420). The cellular mechanisms of vascular smooth muscle contraction may be altered in insulin resistance. Normally, insulin has been shown to reduce intracellular calcium ions by inhibiting the voltage operated channel and by activating Ca ATPase resulting in the efflux of Ca ions from the cell, thus decreasing cytosolic Ca ions and decreasing vascular resistance. In the environment of insulin resistance, this vasodilatory effect is lost whereas the sodium reabsorption is preserved. In addition, angiotensinogen, angiotensin converting enzyme and angiotensin type 1 receptors are present within human adipose tissue. Studies suggest that the regulation of the adipose renin-angiotensin system is correlated with the degree of obesity and that angiotensin II may modulate adipose tissue blood flow, growth and metabolism. Thus, an up regulated adipose renin-angiotensin system may contribute to insulin resistance and hypertension in obese individuals (Prasad & Quyyumi, 2004, p.1509).

Several studies suggest that angiotensin II may modulate the actions of insulin. Insulin and the renin-angiotensin system share the P13 kinase and MAP kinase signaling pathways and tyrosine phosphorylation of the insulin receptor substrate 1 (IRS1) and substrate 2 (IRS2). Insulin receptor mediated activation of IRS1 and IRS2 activates the P13 kinase pathways where the angiotensin II mediated activation inhibits the P13 kinase pathway. When activated, the renin-angiotensin system may inhibit the metabolic actions of insulin but promote the mitogenic actions of the MAP kinase pathway. Further, both hyperglycemia and insulin activate the renin-angiotensin system by increasing the expression of angiotensinogen, angiotensin II and the angiotensin I receptor which may

contribute to the development of hypertension in patients with insulin resistance (Prasad & Quyyumi, 2004, p. 1509).

There is also evidence that insulin resistance and hyperinsulinemia lead to SNS activation, which may contribute to the pathogenesis of hypertension. As a result of sympathetic activation, the kidneys increase sodium reabsorption, the heart increases cardiac output, and the arteries respond with vasoconstriction resulting in hypertension (Morse, Zhang, Thakur & Reisin, 2005, p. 306).

Dyslipidemia

Elevated triglycerides and low levels of HDL cholesterol characterize dyslipidemia in Metabolic Syndrome. Increased triglycerides in the presence of insulin resistance and hyperinsulinemia results from increased circulating free fatty acids. As insulin resistance increases, the lipolysis inhibitory mechanisms of insulin on adipose tissue diminishes and more free fatty acids are produced. Also, with more insulin circulating in the periphery, lipoprotein lipase is stimulated and increases the release of triglycerides. Hypertriglyceridemia is associated with alterations, both in structure and metabolism of HDL and LDL (Menuet, Lavie & Milani, 2005, p. 297).

Obesity in itself reduces HDL levels and obese individuals with Metabolic Syndrome and dyslipidemia almost always have low HDL levels (Grundy, 2004, p. 2597). The presence of low HDL cholesterol in Metabolic Syndrome is partially due to high triglycerides. As triglycerides increase, the cholesterol esters of HDL are exchanged for triglycerides through the action of cholesteryl ester protein, causing the HDL particle to become smaller and less dense. Through mechanisms not well understood, the smaller

HDL particle is metabolized and cleared at an abnormally high rate, resulting in low HDL levels. This shift to smaller particles makes them less antiatherogenic since the larger and more buoyant they are the more free cholesterol they can remove from cells and atherosclerotic plaque. (Menuet, Lavie & Milani, 2005, p. 297).

HDL levels in individuals may be low even in the presence of normal fasting triglyceride levels suggesting that some other mechanism may also be responsible. One possibility is that even persons with normal fasting triglycerides may have impaired post-prandial responses to dietary fat and that the exchange of cholesterol esters of HDL for triglycerides takes place post-prandial (Reilly & Rader, 2003, p. 1548).

LDL cholesterol levels are often normal, but a common finding is that LDL particles are smaller and denser than normal, which is associated with increased cardiovascular risk (Reilly & Rader, 20003, p. 1548). Smaller LDLs also increases the ability to penetrate the vascular endothelium and a greater affinity for intimal glycans. The retention in the intima allows for enhanced oxidative transformation, endovascular injury and the accumulation of foam cells (Menuet, Lavie & Milani, 2005, p. 297). Most researchers agree that the larger the number of smaller, denser LDL particles, the greater the cardiovascular risk (Grundy, 2004, p. 2597). In addition to increased numbers of smaller and denser LDL cholesterol particles, there is a corresponding increase in apolipoprotein B. In fact, it appears that once apolipoprotein B concentrations are elevated, cardiovascular risk can be considered high (Sattar, Williams, Sniderman, D'Agotsino and Haffner, 2004, p. 2692).

Inflammation

Chronic, sub-clinical inflammation and its association with Metabolic Syndrome is a well documented (Eckel, Grundy, Zimmet, 2005, p. 1421). Inflammatory mediators have been recognized as factors that increase the risk of cardiovascular disease, but also are one cause of insulin resistance (see discussion under Obesity and Abnormal Body Fat Distribution). Further, obesity has been associated with inflammation and more data is accumulating that obesity is a pro-inflammatory state. Increased concentrations of inflammatory mediators, such as, C-reactive protein, tumor necrosis factor-alpha, interleukin-6 and others have been found in the obese. Adipose tissue has been found to express most of these inflammatory markers (Dandona, Aljada, Chaudhuri, Mohanty & Garg, 2005, p. 1451). Florez, et al. (2006) studied the relationship of C-reactive protein levels and Metabolic Syndrome as well as the individual features of Metabolic Syndrome. In this study, the most important feature associated with elevated C-reactive protein was abdominal obesity (> 3mg/dl)(OR=3.1, 95% C.I.:1.4-10.1). Other researchers, Ridker, Wilson and Grundy (2004) believe it is time to incorporate C-reactive protein measurements into the criteria for diagnosing Metabolic Syndrome. Recasens, Lopez-Bermejo, Ricart, Vendrell, Casamitjana and Fernandez-Real (2005) devised an inflammation score composed of WBC count, ESR, C-reactive protein, soluble fraction of tumor necrosis factor-alpha receptors 1 and 2. Each of the 81 healthy subjects in their study underwent a frequently sampled IV glucose tolerance test, an oral glucose tolerance test and insulin resistance indexes were calculated. Recasens, et al.,

found that for every increase in the inflammation score, there was an associated increase in insulin resistance.

It has also been shown that macrophages residing in the adipose tissue may also be a source of pro-inflammatory markers and may modulate the secretory activity of adipocytes (Dandona, Aljada, Chaudhuri, Mohanty & Garg, 2005, p. 1451). It is generally thought that adipocytes initiate the process and macrophages amplify it (Shoelson, Lee & Goldfine, 2006, p. 1797). Macrophages in the obese have also been shown to have increased binding of NF-KB, the key pro-inflammaory transcription factor, and increased intranuclear expression of P65, the major protein component of NF-KB, and decreased amounts of the inhibitor of NF-KB.

If obesity is a pro-inflammatory state and inflammatory mechanisms and mediators interfere with insulin signaling, what is the underlying source of the inflammation? Recent studies suggest that macronutrient intake may produce oxidative stress and initiate the inflammatory process. A 75-gram glucose challenge has been shown to increase superoxide generation by leukocytes by 140% over basal levels and increase amounts of a subunit of NADPH oxidase, the enzyme that converts molecular oxygen to superoxide. Superoxide is an activator of at least two pro-inflammatory transcription factors and one of them NF-KB regulates at least 125 genes, most of which are pro-inflammatory. The same phenomenon is observed with equal calories of fat. Glucose ingestion also results in increases in inflammatory transcription factors or their binding, and decreases in transcription factor inhibitors. It should be noted that all genes that are stimulated by acute nutrient ingestion are also activated in the basal state of obese

individuals. The reduction of both oxidative stress and inflammatory mediators by reducing caloric intake in obese subjects (1000kcal/d for 4 weeks) supports this notion.

Pro-thrombic State

The current definitions of Metabolic Syndrome do not include a measure of fibrinolytic and thrombic markers in spite of the significant associations of between these markers and insulin resistance, adipose tissue, inflammation and dyslipidemia (Godsland, Crook, Proudler & Stevenson, 2005, p. 191). People with metabolic syndrome have high plasma concentrations of plasma plasminogen activator inhibitor 1 and endogenous tissue-type plasminogen activator (in response to high levels of plasma plasminogen activator inhibitor 1) and are reflective of a state of dysfunctional fibrolytic activity (Anand, et al., 2003, p. 420). Metabolic syndrome is also characterized by elevated fibrinogen (Grundy, Brewer, Cleeman, Smith & Lenfant, 2004, p. 434).

Most of the understanding of the association between hemostatic markers and Metabolic Syndrome comes from the study of plasminogen activator inhibitor-1. Other researchers have investigated other hemostatic markers. Marques-Vidal, et al., (2002) conducted a cross sectional study of 597 men and 556 women who were assessed for BMI, waist-hip-ratio, blood pressure, total cholesterol, HDL, triglycerides, glucose, plasma insulin level, WBC count, fibrinogen level, factor VII levels, as well as other parameters to assess inflammation. This study found increased WBC count, factor VII levels and coagulating factor VII levels in subjects with insulin resistance, but found no significant difference in fibrinogen levels between subjects with and without insulin

resistance. Stepwise multiple regressions showed that age, BMI, waist-hip-ratio, triglycerides, HDL cholesterol was most frequently related to the hemostatic markers.

In another study, Godsland, Crook, Poudler & Stevenson (2005) investigated the relationships between insulin resistance, hemostatic factors and Metabolic Syndrome components. In this study, 106 men were measured for plasma levels of fibrinogen, factors VII and X, proteins C and S, antithrombin III, plasminogen, tissue plasminogen activator, plasminogen activator inhibitor-1, fibrinopeptide A, plasma glucose and insulin, serum total cholesterol, triglycerides, HDL, LDL, CBC, LFT, WBC, and ESR. As with other studies, Godsland, et al., found that plasminogen activator inhibitor-1 was found to be strongly, negatively associated with insulin sensitivity and in factor analysis, was found to be a prominent component of the factor that included the classic Metabolic Syndrome features (low insulin sensitivity, increased abdominal obesity, high triglycerides and low HDL). Additionally, elevated levels of factors VII, X, and anticoagulant proteins C and S are features of the Metabolic Syndrome.

Aso et al. (2005) investigated the association between a newly identified inhibitor of fibrinolysis. Thrombin-activatable fibrinolysis inhibitor (TAFI) in patients with Type 2 diabetes was associated with the components of Metabolic Syndrome, including C-reactive protein, plasminogen activator inhibitor 1 and LDL cholesterol. This study used 136 subjects with Type 2 diabetes and used the ATP III diagnostic criteria. Their results indicated that there was a positive correlation between TAFI and total and LDL cholesterol. However, no significant associations were found between TAFI and other components of Metabolic Syndrome, including BMI, triglyceride and HDL cholesterol in

Type 2 diabetics. This study also confirmed the findings of previous studies of the positive correlation between plasminogen activator inhibitor 1 and Metabolic Syndrome. Measures of plasmin alpha 2- antiplasmin complex (a measure of on-going fibrinolysis) was lowest in diabetic patients with both Metabolic Syndrome and high cholesterol and this group demonstrated the most impaired fibrinolysis. However, no significant correlation was found between TAFI and plasmin alpha 2-antiplasmin complex. Plasminogen activator inhibitor-1 seems to be the more important determinant of fibrinolytic activity rather than TAFI.

ROLE OF GENETICS

The "thrifty gene" hypothesis implicates an evolutionary selection for metabolic genes for the development of Metabolic Syndrome in the current environment of over-nutrition and sedentary lifestyle. Family studies suggest complex, yet significant genetic basis for the individual components of the Metabolic Syndrome (Reilly, Daniel & Rader, 2003, p. 1550). One family study, the National Heart, Lung and Blood Institute, Family Heart Study used 1940 individuals from 445 families and estimated genetic correlations between the Metabolic Syndrome features using a variance components procedure. Using this study, Tang, et al, (2006) found significant genetic correlations among BMI, waist circumference, HDL, triglycerides, insulin, and plasminogen activator inhibitor 1 antigen and uric acid was correlated with all of the above parameters, except insulin. C-reactive protein and WBC count were genetically correlated with each other and waist circumference and insulin. Fasting glucose was not genetically correlated with any of the other Metabolic Syndrome traits.

In the Insulin Resistance Atherosclerosis Study (IRAS) Family Study, Rich, et al. (2005) conducted a genome scan in 42 African American and 60 Hispanic extended families to identify regions that may contain genes for fasting insulin and glucose (total of 1604 subjects). There was significant evidence to link the short arm of chromosome 17 and fasting insulin as well as strong evidence for linking this location to fasting glucose.

Langefeld, et al. (2004) again in the IRAS Family Study used extended Hispanic family volunteers recruited from San Antonio, Texas and San Luis Valley, Colorado.

Thirty-five of these families had at least two individuals with Metabolic Syndrome. The prevalence of Metabolic Syndrome and its components were 35% Metabolic Syndrome, 43% increased waist circumference, 31% high triglycerides, 69% low HDL, 31% hypertension and 25% either elevated fasting glucose or diabetes. Nonparametric linkage analysis provided evidence for linkage of Metabolic Syndrome to chromosome 1q23-q31. These results provide additional evidence that chromosome 1q contains at least one locus Metabolic Syndrome.

Bowden et al. (2006) conducted a genome scan of the subjects in the Diabetes Heart Study. A total of 977 Caucasian subjects from 358 families with at least two individuals with Type 2 diabetes were analyzed in an attempt to genetically relate cardiovascular disease and Type 2 diabetes. The researchers found evidence for coincident linkage of Type 2 diabetes, Metabolic Syndrome and measures of cardiovascular disease into four chromosomal loci. When traits are mapped as a combined super phenotype, significant evidence is observed for linkage on chromosome 3p.

Kent, et al. (2004) used 428 adults from 20 extended Mexican-American families from the San Antonio Family Heard Study to analyze the genetic and environmental correlations between circulating ICM-1 and 17 phenotypes associated with Metabolic Syndrome. Bivariate quantitative genetic analyses were performed. Results indicate that circulating ICAM-1 concentration is heritable (h2=0.56). ICAM-1 concentrations showed significant positive genetic correlations with fasting insulin, insulin 2 hours after oral glucose challenge, insulin resistance, BMI, waist circumference and leptin

concentration, but not with systolic or diastolic pressure and fasting or 2 hour serum glucose.

Goodarzi, et al. (2004) conducted a study to directly test whether or not lipoprotein lipase is an insulin resistance gene. The study population was 485 individuals from 80 families Mexican American population who were genotyped at six polymorphisms in the lipoprotein lipase gene that define the most common haplotypes in the population. Lipoprotein lipase haplotypes showed linkage to the glucose infusion rate, a direct physiologic measure of insulin sensitivity. Significant associations were also found between glucose infusion rate and the most common and fourth most common haplotypes. Haplotype 1 was associated with insulin sensitivity and haplotype 4 was associated with insulin resistance.

Ng et al. (2004) conducted autosomal genome scans to map loci for Metabolic Syndrome and associated components in the Hong Kong Family Diabetes Study. Two study populations were selected. The first consisted of 55 families with 137 affected members for nonparametric linkage analysis for Metabolic Syndrome and the second was composed of 179 families with 897 members for variance component based linkage analysis on seven Metabolic Syndrome traits. Their analysis revealed three regions that showed suggestive linkages for Metabolic Syndrome and suggestive linkages for Metabolic Syndrome and overlapping signals for metabolic traits. Location of a susceptibility locus on chromosome 1q21-q25 was found to be involved in the pathogenesis of multiple metabolic abnormalities.

Li, et al. (2006) again used the Hong Kong Family Diabetes Study to investigate the clustering of Type 2 diabetes and Metabolic Syndrome in families with young onset Type 2 diabetes. The study sample consisted of a total of 913 subjects from 179 families. BMI, waist circumference, blood pressure, plasma insulin, triglyceride, HDL, insulin resistance and beta cell function had high estimates of inheritability (0.45-0.63). Bivariate quantitative analysis indicated a differential contribution of genetic and environmental factors to the phenotypic correlation between metabolic trait pairs. Obesity indices showed the strongest correlation with other traits and were significantly influenced by genetic factors (genetic correlation=0.29-0.60).

Gertow, et al. (2004) concluded from a study of fatty acid transport protein-4 in-608 healthy, middle-aged men that alterations in Gly209Ser genotype may be the cause of variations seen in fatty acid transport protein-4. This alteration was also significantly associated with several features of Metabolic Syndrome.

Cardona, Morcill, Gonzalo-Marin and Tinahones (2004) studied polymorphisms of apolipoprotein E gene, alterations of which are known to be associated with increased fasting and post-prandial levels of triglycerides. Sixty-six patients with Metabolic Syndrome, but without diabetes were studied to test the hypothesis that variations apolipoprotein E genotype have impaired triglyceride rich lipoprotein metabolism. Results indicated that those with non E3/3 genotype had and odds ratio of post-prandial hypertriglyceridemia of 6.2 and an odds ratio of hyperuricemia compared with the E3/3 positive patients of 7.5. The authors suggest that apolipoprotein E genotyping may be

clinically useful to rule out the future presence of post-prandial hypertriglyceridemia in patients with Metabolic Syndrome.

Wang, Zhang, et al. (2004) examined whether variations in the adiponectin 1 receptor gene may contribute to the risk of developing Metabolic Syndrome and Type 2 diabetes. Variations in the adiponectin gene have been shown to be associated with obesity, insulin resistance and Type 2 diabetes. Wang, Zhang, et al. hypothesized that variations in the adiponectin receptor would likewise induce insulin resistance. They identified two alleles of a single nucleotide polymorphism in the 3 prime untranslated region that were expressed unequally and adiponectin 1 receptor and mRNA levels were 45% lower among transformed lymphocytes in African American individuals than control cell lines. This altered gene might suggest a role for adiponectin 1 receptor gene in the Metabolic Syndrome among African Americans.

Sanchez-Corona, et al. (2004) researched whether or not polymorphisms of the insulin gene, insulin receptor gene and the insulin receptor substrate-1 gene were genetic determinants for Metabolic Syndrome. Their study population consisted of 163 individuals from the Yucatan in Mexico. Among the eight polymorphisms of the genes, the *Pst*1 polymorphism in the insulin gene was significantly associated with hypertriglyceridemia and with the presence of at least one abnormality of Metabolic Syndrome. The *Mae*III polymorphism in the insulin gene was associated with fasting hyperinsulinemia. When analyzing both polymorphisms, significant associations were seen with hypertriglyceridemia, hypercholesterolemia and with the presence of at least one metabolic abnormality. None of the polymorphisms of the insulin receptor gene or

the insulin receptor substrate 1 gene were associated with any of these traits indicating that the insulin gene may be an important determinant in Metabolic Syndrome, especially dyslipidemia, in this population.

In a study to determine if a common variant in mitochondrial DNA at bp 16189 (T/C transition), that has been associated with small birth size, adulthood hyperglycemia and insulin resistance in Caucasians, was associated with Metabolic Syndrome in Chinese adults, Weng, et al. (2005) recruited 615 adult Chinese over 40 years old. The prevalence of the study variant was 44% in subjects with Metabolic Syndrome. The prevalence of fasting plasma glucose, Type 2 diabetes and hypertriglyceridemia were all significantly higher in the group with the study variant. However, hypertension, BMI and LDL did not reach statistical significance.

METABOLIC SYNDROME AS A RISK CONDITION

Cardiovascular Disease

Cardiovascular disease in the U.S. is a continuing crisis of epidemic proportions. In 2000, 38.5% of all deaths in the United States were due to cardiovascular disease (Govindarajan, Whaley-Connell, Mugo, Stump & Sowers, 2005, p. 311). The growing incidence of cardiovascular disease among younger individuals can be attributed to the increasing incidence of obesity.

Dekker, et al. (2005) using data from The Hoorn Study compared the 10 year risk of fatal and non-fatal cardiovascular disease with different definitions of Metabolic Syndrome, i.e., ATP III, WHO, EGIR, and American College of Endocrinology. The ATP III definition was associated with a two-fold increase in age-adjusted risk of fatal cardiovascular disease in men and nonfatal cardiovascular disease in women. Hazard ratios were slightly lower for the other definitions.

Wannamethee, Shaper, Lennon and Morris (2006) set out to compare the Metabolic Syndrome with the Framingham Heart Score as predictors of coronary heart disease, stroke and Type 2 diabetes. The study population included 5128 men aged 40 to 59 without a previous history of cardiovascular disease. For those with Metabolic Syndrome, 26% showed significantly higher relative risk than men without the syndrome for developing coronary heart disease, stroke and Type 2 diabetes. The probability for developing cardiovascular disease or Type 2 diabetes over 20 years increased to 31.2% for those with 3 abnormalities, to 40.8% for those with 4 or 5 abnormalities. However,

the Framingham Heart Score was a better predictor of coronary heart disease and stoke, but not of Type 2 diabetes.

Rutter, Meigs, Sullivan, D'Agostino and Wilson (2004) assessed C-reactive protein and the Metabolic Syndrome to predict new cardiovascular events in the Framingham Offspring Study. The results of the study indicate that both C-reactive protein and Metabolic Syndrome are independent risk factors for cardiovascular disease and have similar discriminatory ability with respect to subsequent cardiovascular risk, but combining them offers little to overall risk prediction.

Marroquin et al. (2004) studied the interrelationships between Metabolic Syndrome angiographic coronary artery disease and incident cardiovascular events in 755 women (25% had Metabolic Syndrome) from the Women's Ischemia Syndrome Evaluation. Women with Metabolic Syndrome had a significantly lower 4-year survival rate and event-free survival from major adverse cardiovascular events.

Saley, et al. (2005) conducted a study to determine to what extent insulin resistance contributed to the increased the risk of cardiovascular events associated with Metabolic Syndrome. The impact of Metabolic Syndrome and insulin resistance was evaluated in a prospective cohort study of 750 male and female, diabetic and non-diabetic patients undergoing coronary angiography. Saley et al. were able to conclude that Metabolic Syndrome and insulin resistance were mutually independent predictors of vascular risk among angiographed patients, even after adjusting for diabetes status. Further, insulin resistance does not account for the total amount of risk associated by the

Metabolic Syndrome and that cardiovascular risk increases with the number of Metabolic Syndrome components.

In a similar study, Rutter, Meigs, Sullivan, D'Agostino and Wilson (2006) conducted a study to determine if Metabolic Syndrome predicts cardiovascular disease independent of insulin resistance. Their study sample included 2898 people without diabetes or cardiovascular disease at baseline. Using two different measures of insulin resistance, the HOMA-IR and the Insulin Sensitivity Index, the association between baseline Metabolic Syndrome and insulin resistance and seven year cardiovascular risk was determined with sex-adjusted proportional hazards regression models. The authors concluded that Metabolic Syndrome and the Insulin Sensitivity Index, but not HOMA-IR independently predicted the incident of cardiovascular disease and that Metabolic Syndrome may not capture all of the cardiovascular risks associated with insulin resistance.

In a study to compare variations in BMI with the effect of cumulative features of insulin resistance syndrome on the risk of ischemic heart disease, St.-Pierre, et al. (2005) followed a group of 1824 non-diabetic men for a period of 13 years. During this 13-year period, 284 first ischemic heart disease events were recorded. Although men with a BMI >/= 30 were most likely to accumulate features of the insulin resistance syndrome, the risk of ischemic heart disease was not significantly higher in this group compared with the normal BMI group. However, obese men that accumulated more than four features of the insulin resistance syndrome were at increased risk of ischemic heart disease. Conversely, normal-weight men with four or more features of the insulin resistance

syndrome had a three-fold increase in the risk of ischemic heart disease. The researchers concluded that BMI alone poorly reflects the risk of ischemic heart disease associated with the features of insulin resistance syndrome.

Other cardiovascular abnormalities and their association with Metabolic Syndrome have also been studied. Katz, et al. (2006) investigated the prevalence of aortic valve calcification in relation to Metabolic Syndrome in a group of 6780 participants from the Multi-Ethnic Study of Atherosclerosis (MESA). The prevalence of aortic valve calcification for those with Metabolic Syndrome was 12% for women and 22% for men, compared to 8% for women and 14% for men without Metabolic Syndrome or diabetes. The relative risks for the presence of aortic valve calcification were 1.45 for women and 1.70 for men with Metabolic Syndrome. The data also indicated that there was a graded, linear relationship between aortic valve calcification prevalence and the number of Metabolic Syndrome components.

Burchfiel, et al. (2005) examined the relationship of Metabolic Syndrome with echocardiographic left ventricular mass in Blacks. The study group consisted of 1572 black men and women, aged 49 to 75 years old from the Atherosclerosis Risk in Communities Study. Echocardiography was performed and the left ventricle dimensions were assessed. Data analysis indicated that the left ventricular chamber size was not significantly and independently associated in general with the number of Metabolic Syndrome disorders, but the posterior wall and interventricular septal thickness were. Relative wall thickness was also associated with the number of components of the syndrome.

With respect to cardiovascular disease morbidity and mortality and the Metabolic Syndrome, it is not surprising that several studies have indicated an increase in cardiovascular mortality and morbidity in those with Metabolic Syndrome. Lakka, et al. (2002) compared the ATP III and the WHO definitions and cardiovascular and all-cause mortality in middle aged men from the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based, prospective cohort study of 1209 Finnish men 42 to 60 years old. Men with Metabolic Syndrome defined by ATP III were 2.9-4.2 times more likely to die of coronary heart disease. Men with Metabolic Syndrome defined by WHO criteria were 2.9-3.3 times more likely to die from coronary heart disease, 2.6 to 3.0 times more likely to die from cardiovascular disease and 1.9 to 2.1 times higher all-cause mortality.

In a study that yielded similar results, Malik, et al. (2004) compared the impact of Metabolic Syndrome on coronary heart disease, cardiovascular disease and overall mortality in U.S. adults. Data from 6255 subjects, 30 to 75 years odd from the Second National Health and Nutrition Examination Survey were examined. Analysis indicated that the adjusted hazard ratios for coronary heart disease mortality were 2.02 and 1.82 for cardiovascular mortality for those with Metabolic Syndrome. For over all mortality, hazard ratios for those with Metabolic Syndrome were 1.40. Those with even one or two Metabolic Syndrome components were at increased risk for morality for coronary heart disease and cardiovascular disease and Metabolic Syndrome more strongly predicts coronary heart disease, cardiovascular disease and total mortality than its individual components.

Finally, in a study that used only the WHO definition of Metabolic Syndrome, Isomaa, et al. (2001) estimated the prevalence and cardiovascular risk associated with the Metabolic Syndrome using 4483 subjects, 35 to 70 years old from the Botnia Study. The risk for coronary heart disease and stroke was increased three-fold in subjects with the syndrome and cardiovascular mortality was markedly increased (12.0 vs. 2.2%) in subjects with the Metabolic Syndrome.

Type 2 Diabetes

Wilson, D'Agostino, Parise, Sullivan and Meigs (2005) conducted a study to determine the risk of Type 2 diabetes (and cardiovascular risk) according to Metabolic Syndrome traits. The study followed a sample of 3323 middle-aged adults for the development of new Type 2 diabetes over an 8-year period. There were 178 new cases of Type 2 diabetes. In men with Metabolic Syndrome, the age adjusted relative risk for Type 2 diabetes was 6.92 and 6.90 for women. Population attributable risk estimates associated with Metabolic Syndrome and Type 2 diabetes were 62% in men and 47% in women, accounting for approximately half of the new Type 2 diabetes over eight years.

Hanson, Imperatore, Bennett and Knowler (2002) used factor analysis to determine the association of components of Metabolic Syndrome and the incidence of Type 2 diabetes. Following a study group of 1918 Pima Indians for approximately four years, 144 of the original 890 non-diabetic subjects developed Type 2 diabetes. Factor analysis identified four factors: insulinemia, body size, blood pressure and lipid metabolism. The insulinemia factor was strongly associated with Type 2 diabetes and

body size and lipid metabolism factors strongly predicted diabetes. However, the blood pressure factor did not predict diabetes.

Also using factor analysis, Hanley, Festa, et al. (2004) investigated the clustering of metabolic and inflammation variables, which included non-traditional cardiovascular risk factors, such as C-reactive protein and plasminogen activator inhibitor-1 and the prediction of diabetes. The subjects were 1087 non-diabetic participants in the Insulin Resistance Atherosclerosis Study (IRAS) and were followed for a period of 5.2 years. Factor analysis identified three factors: a metabolic factor, an inflammation factor and a blood pressure factor. In prospective analysis, each of the factors was a significant predictor of diabetes and predicted diabetes in multivariate analysis.

Hanley, Karter, et al. (2005) again used the Insulin Resistance Atherosclerosis Study (IRAS) participants to determine the predictability of Type 2 diabetes of alternative definitions for the Metabolic Syndrome. Using 822 subjects who were non-diabetic at baseline, 148 out of the original group had developed Type 2 diabetes after 5.2 years. Impaired glucose tolerance, Metabolic Syndrome definitions and insulin resistance markers all significantly predicted diabetes (OR 3.4 to 5.4). Modifying or requiring obesity, glucose, inflammation variables or insulin resistance components in the ATP III definition did not significantly alter its predictive ability. To summarize, they found that the International Diabetes Federation and ATP III guidelines predicted diabetes at least as well as the WHO definition. Modifications or additions to the ATP III definition had limited impact on the prediction ability of Type 2 diabetes. Lorenzo, Okoloise, Williams Stern and Haffner (2003) found similar results when they compared the ATP III

definition, a modified WHO definition, and impaired glucose tolerance to predict Type 2 diabetes.

OTHER DISEASES AND CONDITIONS ASSOCIATED WITH METABOLIC SYNDROME

Intracranial Atherosclerosis/Cognitive Decline

Ovbiagele, Saver, Lynn and Chimowitz (2006) examined the impact of Metabolic Syndrome and the prognosis of symptomatic intracranial atherosclerosis. Using 476 patients enrolled in the Warfarin Aspirin Symptomatic Intracranial Disease Trial the baseline characteristics and outcomes were compared between patients with and without the Metabolic Syndrome. Metabolic Syndrome accounted for approximately half of the individuals with symptomatic intracranial atherosclerotic disease. During the 1.8 year follow-up, the time to the first ischemic stroke, myocardial infarction or vascular death was shorter for those with Metabolic Syndrome and the time to the first ischemic stroke alone was shorter.

Yaffe, et al. (2004) evaluated a total of 2632 black and white elders to determine if Metabolic Syndrome is a factor for cognitive decline and if the association is modified by inflammation. Their data showed that elders with the Metabolic Syndrome had a high risk for developing cognitive impairment, particularly those with high levels of serum markers for inflammation. In the group with high inflammation, the number of components of Metabolic Syndrome did not affect the risk of cognitive decline.

In a study of obesity in middle age as a risk for dementia later in life, Whitmer, Gundreson, Barrett-Conner, Quesenberry and Yaffe (2005) followed 10,276 men and women for 27 years and found that people who were obese in mid-life were 74% more likely to have dementia, while overweight people were 35% more likely to have dementia

compared to normal weight individuals. The authors discuss the connection between obesity, Metabolic Syndrome and inflammation as a possible cause for their findings.

Liver Disorders

The liver is frequently an unrecognized site of injury in persons with insulin resistance. Non-alcoholic fatty liver disease is an umbrella diagnosis that describes excess fat in the liver. Non-alcoholic-steatohepatitis is a subset of patients who in addition to having excess fat in the liver have hepatocellular injury and necroinflammatory changes. Patients with non-alcoholic steatohepatitis are at increased risk for developing cirrhosis. As insulin resistance and Metabolic Syndrome have become increasingly more prevalent, insulin resistance is now considered the most common underlying risk factor for the development of non-alcoholic steatohepatitis. Central adiposity has also been recognized as a risk factor for non-alcoholic fatty liver disease, including non-alcoholic steatohepatitis (Neuschwander-Tetri, 2005, p. 326)

The risk of having non-alcoholic steatohepatitis increases with the presence of components of Metabolic Syndrome (Neuschwander-Tetri, 2005, p. 330). Liver markers have been shown to be associated with Metabolic Syndrome and predict Type 2 diabetes. In a study by Hanley, Williams, Festa, Wagenknecht, D'Agostino and Hafner (2005) 633 subjects from the Insulin Resistance Atherosclerosis Study (IRAS) who were free of Metabolic Syndrome were followed for 5.2 years. They were assessed for AST, ALT, other liver markers and C-reactive protein to determine if liver markers could predict the development of Metabolic Syndrome. After 5.2 years, 127 people developed Metabolic

Syndrome. Subjects in the upper quartiles of ALT, ALD and C-reactive protein were at significantly increased risk of Metabolic Syndrome.

Liangpunsakul and Chilasani (2005) examined the prevalence and predictors of unexplained elevated ALT levels in adults participating in the National Health and Nutrition Examination Survey III. The study group consisted of 4376 adults with Metabolic Syndrome, ALT levels were obtained from previous data, and the prevalence of microalbuminuria was compared between 710 individuals with unexplained elevated ALT levels and 1780 controls. Their analysis showed that individuals with the Metabolic Syndrome have a significantly higher prevalence of unexplained elevations in ALT levels, however, there was no relationship between elevated ALT levels and microalbuminuria.

Wannamethee, Shaper, Lennon and Whincup (2005) investigated the potential utility of hepatic enzyme measurements in determining the risk of Type 2 diabetes. In a prospective study of 3500 non-diabetic men, 60-79 years old followed for approximately 5 years, ALT and GGT were strongly associated with obesity, insulin resistance and Metabolic Syndrome using cross sectional analysis. Prospectively, the risk of Type 2 diabetes significantly increased with increasing levels of ALT and GGT. Among high-risk subjects (obese men or those with Metabolic Syndrome) elevated GGT and ALT enhanced the prediction of diabetes risk.

Kidney Disorders

Evidence suggests that the hyperhemodynamic status of obesity, impaired pressure natriuresis, excess excretory load, insulin resistance, increase free fatty acids,

chronic inflammatory and prothrombic states, and impaired endothelial function all initiate renal injury in the Metabolic Syndrome (Zhang, Liao, Morse, Donelon & Reisin, 2005, p. 323). In a study by Chen et al. (2004) examining the correlation between chronic kidney disease and Metabolic Syndrome, their analysis indicated that not only was each component of Metabolic Syndrome associated with increased prevalence of chronic kidney disease, but the more components that were present, the greater the prevalence of both chronic kidney disease and microalbuminuria. Waist circumference was also significantly correlated with reduced glomerular filtration rates.

Cosmo, et al. (2006) investigated the role of insulin resistance and the cluster of Metabolic Syndrome related characteristics on kidney function in patients with Type 2 diabetes. In a sample of 731 Type 2 diabetics, both men and women, age of 61 +/- 10 years and length of diabetes duration 10.8 years +/- 9 years were evaluated. When singularly considered, hypertension, dyslipidemia and waist circumference were significantly associated with estimated glomerular filtration rates and estimated glomerular filtration rate progressively and significantly decreased with increasing number of Metabolic Syndrome characteristics. The association between number of Metabolic Syndrome characteristics and glomerular filtration rate was still significant after adjusting for cofounders.

Cancer

Ness, Oakes, Punyko, Baker and Gurney (2005) estimated the prevalence of Metabolic Syndrome in persons with a history of cancer. Emerging evidence suggests that Metabolic Syndrome may be an important treatment related adverse late effect of

cancer in both adults and children. Using the data from the Third National Health and Nutrition Examination Survey, Ness et al. analyzed the prevalence and prevalence differences of the Metabolic Syndrome and persons with and without reported cancer history. Metabolic Syndrome was found to be more prevalent in persons with a self reported cancer history than those without. Also, a lower prevalence of Metabolic Syndrome and lung, prostate and colon cancer and higher prevalence of the syndrome and breast cancer were found.

Hypogonadism and Low Testosterone Levels in Men

Several studies have demonstrated an association between hypogonadism and or low testosterone levels and Metabolic Syndrome in men. This suggests that testosterone may be protective against the development of Metabolic Syndrome. Laaksonen, et al. (2004) followed 702 middle-aged Finish men for 11 years. After the 11-year follow-up, 147 men had developed Metabolic Syndrome. Men with total testosterone, calculated free testosterone and SHBG levels in the lower quartile had a several fold increase in the risk of developing Metabolic Syndrome. Pitteloud, et al. (2005) conducted a study to determine the relationships between testosterone, insulin sensitivity and mitochondrial function in men. The sample included a total of 60 men with a mean age of 60.5 years. Their analysis found that subjects with hypogonadal testosterone levels had a BMI greater than 25 and a three fold higher prevalence of the Metabolic Syndrome.

Similarly, Muller, et al. (2005) studied the association between age related sex hormone changes in men and the association with insulin sensitivity and the Metabolic Syndrome. Their sample consisted of 400 men between 40 and 80 years old. Their

analysis found that higher testosterone and SHBG levels in aging men are independently associated with a higher insulin sensitivity and a reduced risk of Metabolic Syndrome independent of insulin levels and body composition.

Makhsida, Shah, Yan, Fisch and Shabsigh (2005) also found that Metabolic Syndrome was strongly associated with hypogonadism in men and that testosterone treatment may have a high potential for not only treating hypogonadism, but also slowing the progression of the Metabolic Syndrome to Type 2 diabetes. Their recommendation is that all men with hypogonadism be assessed for Metabolic Syndrome and visa versa.

Gestational Diabetes and Polycystic Ovary Syndrome

Using three different definitions of Metabolic Syndrome: ATP III, WHO and the European Group for the Study of Insulin Resistance, Lauenborg, et al. determined the prevalence of Metabolic Syndrome among a group of women with previous gestational diabetes. Independent of the definition used, the prevalence of Metabolic Syndrome was three times high in the women with previous gestational diabetes compared to the control group.

Metabolic Syndrome and Polycystic Ovary Syndrome share the common characteristic of insulin resistance. It has been suggested that Polycystic ovary syndrome may be a female-specific manifestation of the Metabolic Syndrome (Sartor & Dickey, 2005, p. 337).

Apridonidze, Essah, Iuorno and Nestler (2004) conducted a study to determine the prevalence of Metabolic Syndrome in women with Polycystic Ovary Syndrome. They conducted a retrospective chart review over a three-year period. Forty-six women had

Metabolic Syndrome and Polycystic Ovary Syndrome and 50 women only had Polycystic Ovary Syndrome. Prevalence of Metabolic Syndrome was 43%, a two-fold higher increase than the general population. Women with both Metabolic Syndrome and Polycystic Ovary Syndrome had significantly higher levels of serum free testosterone, lower levels of serum SHBG and higher prevalence of acanthosis nigricans than women with only Polycystic Ovary Oyndrome. These results suggest that women with both conditions may be even more insulin resistant.

In another study to determine the prevalence of Metabolic Syndrome in women with Polycystic Ovary Syndrome, Dokras, et al. (2005) used a sample of 129 women with Polycystic Ovary Syndrome and compared them to a control group of 177. The age-adjusted prevalence of Metabolic Syndrome was 47.3% in women with Polycystic Ovary Syndrome and 4.3% in the control group. The risk for Metabolic Syndrome in women with Polycystic Ovary Syndrome was higher for all age groups and all markers for insulin resistance were abnormal for this group.

Stress

There are indications that neurohormonal activity may be involved in the development of the Metabolic Syndrome. Stress activates the sympathoadrenal system and the hypothalamic-pituitary-adrenocortical axis. The stress response includes catecholamine release, cortisol secretion and activation of the renin-angiotensin system. When the stress becomes chronic, coping becomes inadequate or if ability to turn off the stress response is deficient, the stress response can become maladaptive (Hjemdahl, 2002, p. 2634).

Brunner, et al. (2002) conducted a nested case controlled study of working aged men 45 to 63 from the Whitehall II cohort. Thirty participants with Metabolic Syndrome were compared to 153 health controls. The authors set out to examine the associations between Metabolic Syndrome and measures of hypothalamic-pituitary-adrenocortical, sympathoadrenal and cardiac autonomic activity (from heart rate variability recordings). Also, inflammatory and hemostatic markers as well as adrenal androgen output were examined. Major results of this study included elevated urine cortisol and normetanephrine (a marker for sympathetic activity), lower heart rate variability and elevated levels of interleukin-6 and C-reactive protein in cases of Metabolic Syndrome compared to the controls. Psychosocial factors (employment grade, assets and job strain) were found to account for 5% to 37% of the link between Metabolic Syndrome and normetanephrine output and 7% to 19% for cardiac autonomic activity. Health related behaviors (diet, physical activity, smoking and alcohol intake) accounted for 5% to 18% of the neuroendocrine differences. The results of this study indicate that chronic stress may be a cause of Metabolic Syndrome.

Chandola, Brunner and Marmot (2006) also used the Whitehall cohort and investigated the association between stress at work and the Metabolic Syndrome using a prospective cohort study design. Participants included 10,308 men and women, 35 to 55 years old who were employed as civil servants. Work stress was based on the iso-strain model, measured on four occasions. The results of the study indicated that the greater the exposure to job stress over the 14 year study period, the greater the risk of Metabolic

Syndrome. In addition, men and women in the lowest employment grades had more than double the odd of having Metabolic Syndrome.

Nutritional factors

Magnesium, serum ferritin and serum Vitamin D have all been associated with Metabolic Syndrome. He, et al. (2006) examined the association of magnesium intake and the incidence of Metabolic Syndrome. The NCEP ATP III criteria were used to define the syndrome and magnesium intake was assessed using the nutrient database from the Minnestoa Nutrition Coordinating Center and an interviewer-administered questionnaire. The subjects were 4637 Americans, aged 18 to 30 years who did not have Metabolic Syndrome or Diabetes at baseline. During the 15 years of follow-up, 608 cases of Metabolic Syndrome were identified. Magnesium intake was inversely associated with the incidence of Metabolic Syndrome, after adjusting for lifestyle and dietary variables and the baseline status of each component of the syndrome.

Jehn, Clark and Guallar (2004) found that Metabolic Syndrome was more common in those with the highest levels of serum ferritin, after excluding those with hemochromotosis. Their study consisted of 6044 adults over 20 years old from the Third National Health and Nutrition Examination Survey (NHANES III). Insulin resistance also increased across quartiles of serum ferritin and persisted after adjustment for age, race/ethnicity, C reactive protein, smoking, alcohol intake and BMI.

Ford, Ajani, McGuire and Liu (2004) examined the association between serum Vitamin D concentrations and the Metabolic Syndrome to determine if Vitamin D deficiency may be a risk factor for the Metabolic Syndrome. The authors used

participants of the Third National Health and Nutrition Examination Survey (NHANES III) and the Metabolic Syndrome was diagnosed using the NCEP ATP III guidelines. Using 8,421 participants, the mean concentration of 25-hydroxy-vitamin D was 67.1 nmol/l among those with Metabolic Syndrome and 75.9 nmol/l among those without the syndrome ($P<0.001$). In addition, the odds of having the Metabolic Syndrome decreased progressively with increasing concentration of 25-hydroxy-vitamin D. Additionally, Chiu, Chu, Go and Saad (2004) not only found that subjects with low levels of 25-hyrdoxy-vitamin D had a higher prevalence of the components of Metabolic Syndrome, but that the 25-hydroxy-vitamin D concentration was positively and independently correlated with the insulin sensitivity index (ISI) after univariate and multiple regression analysis.

PREVENTION AND TREATMENT

Nearly one in four Americans fulfill the criteria for Metabolic Syndrome, it is commonly encountered in clinical practice and risk factors should be considered when conducting every clinical assessment. The National Cholesterol Education Program has identified Metabolic Syndrome as an independent risk factor for cardiovascular disease. Clinical identification and management of patients with the Metabolic Syndrome is important to begin efforts to adequately implement treatments to reduce their risk of subsequent disease (Wong, 2005, p. 47). Effective treatments include lifestyle changes, primarily weight loss, diet and exercise and the appropriate use of pharmacological agents to reduce specific risk factors (Deen, 2004, p. 2875).

Educational strategies should be patient-centered and focused on assessing the patient's understanding of the impact of exercise and diet on their over-all health and stressing the importance of exercise and diet to improving Metabolic Syndrome. Providers should help patients to identify short-term and long-term goals and barriers to change. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with lifestyle changes (Deen, 2004, p. 2880).

Weight Loss and Exercise

Several authors (Grundy, Hansen, Smith, Cleeman and Kahn, 2004; Eckel, Grundy & Zimmet, 2005; Grundy, Cleeman, Daniels, Donato, Eckel, Franklin, Gordon, Krauss, Savage, Smith, Spertus and Costa, 2005) recommend a weight loss goal of 10% reduction in body weight the first six months to a year and continued weight loss there

after until BMI is less than 25. Recommendations for calorie reduction in general include reduction of 500-1000 calories per day.

Pharmacological approaches to weight loss include two main classes: appetite suppressants and inhibitors of nutrient absorption. Appetite suppressants include phentermine dierivatives and sibutramine. These agents are usually taken in the late morning and reduce appetite in the late afternoon and evening. Orlistat is the only nutrient absorption inhibitor currently available. It prevents absorption of up to 30% of the fat consumed and must be taken at the time of consumption. A single agent is generally recommended and average weight loss ranges greatly from 5% to 10% of initial weight (Wilson and Grundy, 2003, p. 1423). To date, weight reduction medications have not been particularly useful in treating obesity (Eckel, Grundy and Zimmet, 2005, p. 1423).

Bariatric surgery in the U.S. is increasingly being used to treat morbid obesity. Surgery is recommended for individuals with a BMI greater than 40 or between 35 and 40 with comorbid conditions, which are typical elements of the Metabolic Syndrome (Wilson and Grundy, 2003, p. 1424). Many of the components of Metabolic Syndrome improve with the weight loss after surgery, including lipids and fasting glucose, with 95% of patients being free of the syndrome one year after surgery (Eckel, Grundy and Zimmet, 2005, p. 1423).

Continued weight loss and weight loss maintenance is generally successful when regular, moderate exercise is added a weight loss program and regular exercise improves all risk factors associated with the Metabolic Syndrome (Eckel, Grundy and Zimmet,

2005, p. 1423). For example, Aronson, Sella, Sheikh-Ahmad, Kerner, Avizohar, Rispler Bartha Markiewicz, Levy and Brook (2004) assessed the level of physical fitness of 1640 subjects and the relationship between C-reactive protein levels and fitness levels in subjects with Metabolic Syndrome. A strong inverse relationship was found between increasing levels of fitness and decreasing C-reactive protein levels. This relationship was found in subjects without Metabolic Syndrome, those with one or two metabolic abnormalities and was particularly striking in subjects with Metabolic Syndrome (all p </= 0.001). This study suggests that increasing physical activity should be effective in reducing the pro-inflammatory state associated with the Metabolic Syndrome.

In addition, physical activity may be an important prevention strategy for Metabolic Syndrome. A study by LaMonte, Barlow, Jurca, Kampert, Church and Blair (2005) found that cardiorespiratory fitness is a strong and independent predictor of incident Metabolic Syndrome in men and women. The author prospectively studied 9007 men and 1491 women with an age of 44 =/- 9 years free of Metabolic Syndrome and measures of waist circumference, blood pressure, lipids and fasting glucose where documented at baseline and at follow-up exams. Cardiorespiratory fitness was measured by maximal treadmill test duration. During the average follow up of 5.7 years, 1346 men and 56 women developed Metabolic Syndrome. Significant patterns of inverse associations between fitness and Metabolic Syndrome incidence were found, suggesting that greater cardiorespiratory fitness levels may be beneficial in the primary prevention of Metabolic Syndrome. In addition, Eklund, Brage, Franks, Hennings, Emms and Wareham (2005) examined the associations between physical activity energy expenditure

(PAEE), aerobic fitness (VO2 max) obesity and the progression towards Metabolic Syndrome. In a prospective study over 5.6 years of 605 middle aged men and women, the PAEE and VO2max were determined and a Metabolic Syndrome score was calculated by summing the standardized values for obesity, hypertension, hyperglycemia, insulin resistance, hypertriglyceridemia and inverse level of HDL. Results of this study indicated that PAEE predicted the progression to Metabolic Syndrome independent of baseline Metabolic Syndrome, body fat and VO2max. VO2max was not an independent predictor of Metabolic Syndrome, suggesting that physical activity in itself is an important strategy for prevention of Metabolic Syndrome even in the absence of aerobic fitness.

The standard exercise regimen recommended by most authors (Grundy, Hansen, Smith, Cleeman and Kahn, 2004; Eckel, Grundy & Zimmet, 2005; Grundy, Cleeman, Daniels, Donato, Eckel, Franklin, Gordon, Krauss, Savage, Smith, Spertus and Costa, 2005) is moderate intensity aerobic activity (brisk walking) for at least 30 minutes, but preferably 60 minutes, at least five days a week, preferably daily.

Dietary Modifications

A consensus exists among most authors about dietary modifications that will improve the dyslipidemia associated with Metabolic Syndrome (Grundy, Hansen, Smith, Cleeman and Kahn, 2004; Fletcher and Lamendola, 2004, Eckel, Grundy and Zimmet, 2005; Grundy, Cleeman, Daniels, Donato, Eckel, Franklin, Gordon, Krauss, Savage, Smith, Spertus and Costa, 2005). These recommendations include reducing the intake of saturated fat, trans-fat and cholesterol. Saturated fat should comprise less than 7% of

total calories, dietary cholesterol should be less than 200 mg/day and total fat should be 25% to 35% of total calories. In addition, reduction of intake of trans-fats is recommended as well as intake of simple sugars, and most fat consumed should be unsaturated. Eckel, Grundy and Zimmet discuss the controversy around the various amounts of fats and carbohydrates. Some recommend lower fat diets where others favor higher fat diets. Lower fat diets promote weight reduction, where higher monounsaturated fat diets diminish postprandial glycemia, reduce serum triglycerides and raise HDL cholesterol. Additionally very high carbohydrate diets may increase atherogenic dyslipidemia and lower carbohydrate diets have been found to decrease insulin levels and lower triglycerides (Fletcher and Lamendola, 2004, p. 342).

Several studies looked at the association between whole-grain intake and its effect on insulin resistance and prevalence of Metabolic Syndrome. McKeown, Meigs, Liu, Saltzman, Wilson and Jacques (2004) used the Framingham offspring cohort to examine the relationships between carbohydrate related dietary factors, insulin resistance and the prevalence of Metabolic Syndrome. Using 2834 subjects, the authors found that the prevalence of Metabolic Syndrome was significantly lower in those in the highest quartile of cereal fiber and whole grain intakes and significantly higher among those in the highest quartile relative to the lowest quartile of insulin resistance. In a similar study of older adults, Sahyoun, Jacques, Ahang, Juan and KcKeown (2006) 535 health subjects aged 60 to 98 years were assessed for nutritional status using a three- day food diary. In addition, metabolic risk factors were determined and Metabolic Syndrome was defined using the NCEP-ATP III guidelines. A significant inverse trend was found between

whole-grain intake and the Metabolic Syndrome (p=0.005). There were also similar trends between whole-grain intake and mortality from cardiovascular disease (p=0.04).

Poppitt, Keogh, Prentice, Williams, Sonnemans, Valk, Robinson and Wareham (2002) investigated the effect of replacing one quarter of daily fat intake with complex carbohydrates or simple carbohydrates on body weight and intermediary metabolism. Using 46 subjects with three or more factors of Metabolic Syndrome, Poppitt, et al. randomly assigned each subject to receive a low-fat, complex carbohydrate diet or a low-fat, simple carbohydrate diet for six months. Weight loss was greatest in the complex carbohydrate group and total cholesterol decreased the greatest in the complex carbohydrate group whereas triglycerides increased the greatest in the simple carbohydrate group. However, LDL cholesterol did not significantly change and HDL cholesterol decreased among the complex and simple carbohydrate groups as well as the controls. The authors concluded that a diet with high complex carbohydrates promotes weight loss and somewhat improves the serum cholesterol. Also, increasing simple carbohydrates did not promote weight loss and increases triglyceride levels.

Other researchers looked at specific diets and their relationship to the Metabolic Syndrome. Valachovicova, Krajcovicova-Kudlackova, Blazick and Babiska (2006) studied the relationship between insulin resistance in a group of vegetarians compared to non-vegetarians. The vegetarians consisted of 95 ovo-lacto-vegetarians, averaging 10.2 =/- years being vegetarian and the 107 non-vegetarians were from the general population on had a traditional Western diet. Glucose and insulin resistance (HOMA-IR) values were significantly lower in vegetarians, independent of age. The vegetarians had a

significantly higher consumption of whole grain products, pulses and products from oats and barley. The researchers conclude that long-term vegetarian diets are beneficial in prevention of Metabolic Syndrome.

In another study by Williams, Prevost, Whichelow, Cox, Day and Wareham (2000) 802 subjects, aged between 40 and 65 years, were randomly selected from a population and underwent a 75 g oral glucose tolerance test. Principle component analysis of dietary patterns identified four dietary patterns that were found to explain 31.7% of the dietary variation in the study group. The component that was characterized by a health balanced diet with frequent intake of raw vegetables, fruits in summer and winter, fish, rice, pasta and low intake of fried foods, sausages, fried fish and potatoes was negatively correlated with central obesity, fasting plasma glucose, 120 min non-esterified fatty acid and triacylglycerol and positively correlated with HDL. These results support the hypothesis that dietary patterns are associated with glucose intolerance and other features of the Metabolic Syndrome.

In an examination of the popular low-carbohydrate, high-fat diets, i.e., Atkins Diet, Zone Diet and the South Beach Diet, Lara-Castro and Garvey (2004) emphasize that the benefits of any diet plan must not only promote weight loss, but reduce insulin resistance. Improving insulin sensitivity is more related to decreasing omental fat rather that total body weight loss and these popular diets must be examined in light of their metabolic effects. For example, diets high in saturated fats can induce insulin resistance whereas diets high in fiber and low calorie dense carbohydrates can reduce insulin resistance. Lara-Castro and Garvey caution that long term safety and efficacy of these

diets has not been determined and these diets should not be embraced as an alternative to challenging lifestyle changes and calorie reduction.

Pharmacological Treatment

If lifestyle changes including weight loss, exercise and dietary changes prove to be insufficient to reduce risk factors associated with Metabolic Syndrome, many pharmacological options are available to reduce the individual risk factors.

For dyslipidemia associated with Metabolic Syndrome, the ATP III treatment recommendations emphasize the treatment of elevated LDL as the primary target of lipid-lowering therapy. The statin family inhibits that rate-determining step in cholesterol biosynthesis. Several statins are on the market and all work by similar mechanisms and have various advantages. For example, lovastatin the least expensive and available as a generic, fluvastatin is less potent than many other agents, but has a minimum of drug interactions and rosuvastatin is the most potent of the statins (Tuomilehto, 2005, p. S28), but since it is new, it does not yet have clinical event data (Menuet, Lavie and Milani, 2005, p. 299).

Once the serum LDL target has been reached, blood lipids should be measured again to determine whether lipid abnormalities still remain. Statins rarely raise serum HDL levels by more than 5% to 10% or lower serum triglyceride levels by more than 10%, so other therapeutic interventions may be required. With elevated triglyceride levels, fibrates have proven to be very effective at lowing triglyceride levels in addition to raising HDL levels and are generally the drugs of choice (Hafidh, Senkottaiyan, Villarreal and Alpert, 2005, p. 346). The two fibrates currently used clinically are

gemfibrozil and fenofibrate, both of which can lower triglycerides by 25% to 30% and generally increases HDL by 10% (Menuet, Lavie and Milani, 2005, p. 300). The advantage of gemfibrozil is that it is lower in cost, but fenofibrate has fewer drug interactions, especially when prescribed along with a statin. Several studies have reported isolated severe myopathy occurring from the combination of a statin with gemfibrozil (Grundy, Hansen, Smith, Cleeman and Kahn, 2004. p. 554).

Niacin is also cable of lowering serum triglycerides, increasing HDL and lowering LDL at levels equal to the fibrates. However, the concern with niacin is that it may worsen glycemic control in insulin resistance and therefore doses should be kept to a minimum (Grundy, Hansen, Smith, Cleeman and Kahn, 2004; (Hafidh, Senkottaiyan, Villarreal and Alpert, 2005; Menuet, Lavie and Milani, 2005).

The issue of the most effective medication for elevated blood pressure in the Metabolic Syndrome has not been resolved (Eckel, Grundy and Zimmet, 2005, p. 1424). The use of diureteics has been associated with reduced glycemic control and the development of Type 2 diabetes. Beta-blockers have been shown to increase body weight and may be related to Type 2 diabetes (Wilson and Grundy, 2003, p. 1538), but are not contraindicated for patients with Type 2 diabetes (Grundy, Hansen, Smith, Cleeman and Kahn, 2004. p. 554). Both Hafidh, Senkottaiyan, Villarreal and Alpert (2005) and Grundy, Hansen, Smith, Cleeman and Kahn (2004) recommend the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as the first line therapies for elevated blood pressure in patients with the Metabolic Syndrome.

Angiotensin receptor blockers have also been shown to improve endothelial function and markers of inflammation in the Metabolic Syndrome. Sola, et al. (2005) randomized 58 subjects with Metabolic Syndrome using double-blinded methods and administered one group of 14 with irbesartan, one group of 15 with lipoic acid, one group of 15 with both lipoic acid and irbesartan and a group with a placebo for four weeks. Endothelium dependent flow mediated vasodilation of the brachial artery was measured prior to the study and after four weeks. Endothelium dependent flow medicated vasodilation was increased by 67% in the irbesartan group, 44% in the liproic acid group and 75% in the irbesartan and lipoic acid groups. In addition, treatment with irbesartan and or lipoic acid significantly reduced plasma levels of interleukin-6 and plasminogen activator-1. However, no significant changes in blood pressure were noted in any of the study groups.

There is growing interest in the possibility that medications that can improve insulin resistance will delay the onset of Type 2 diabetes. The Diabetes Prevention Program showed that treatment with metformin in patients with prediabetes will prevent or delay the onset of diabetes. In this study, 3,324 obese subjects with impaired glucose tolerance were treated for an average of 2.8 years with either lifestyle changes, metformin or a placebo. Lifestyle changes included weight loss of 7% and 150 minutes of weekly exercise. There was a 58% decrease in the incidence of Type 2 diabetes in the lifestyle group compared to the controls (an incidence of 4.8 cases per 100 patient years verses 11.0 cases per 100 patient years in the controls). There was also a reduced incidence in the group receiving metformin (incidence of 7.8 cases per 100 patient years) compared to

the control group, but less than the lifestyle modification group (Hafidh, Senkottaiyan, Villarreal and Alpert, 2005. p. 345).

The pro-thrombic state in individuals with Metabolic Syndrome is characterized by increased levels of fibrinogen and plasminogen activator inhibitor-1. Most authors (Grundy, Hansen, Smith, Cleeman and Kahn, 2004; Grundy, Cleeman, Daniels, Donato, Eckel, Franklin, Gordon, Krauss, Savage, Smith, Spertus and Costa, 2005; Eckel, Grundy and Zimmet, 2005: Shoelson, Lee and Goldfine, 2006) recommend low-dose aspirin therapy.

At present, there is no specific medication therapy recommended for the treatment of the pro-inflammatory state characterized by elevated C-reactive protein, tumor necrosis factor-alpha and interleukin-6.

SIGNIFICANCE TO NURSING

Nearly one in four Americans meets the criteria for Metabolic Syndrome, it is commonly encountered in clinical practice and risk factors should be considered when conducting every clinical assessment. Since the underlying pathophysiological process of Metabolic Syndrome appears to be insulin resistance, it is imperative that insulin resistant individuals be identified as early as possible to ensure that the risk of progression to cardiovascular disease and Type 2 diabetes be minimized.

The ATP III definition has been shown to have a low sensitivity for predicting insulin resistance. Additionally, insulin resistant individuals that do not meet the ATP III criteria are at increased risk for future cardiovascular disease and Type 2 diabetes. Some studies suggest that the sensitivity and specificity of the ATP III criteria are optimized by using two or more abnormal risk factors instead of three factors to diagnose Metabolic Syndrome. Research has also shown that the Metabolic Syndrome traits may vary with race and ethnicity and the ATP III criteria under diagnoses Metabolic Syndrome in African Americans.

In light of the low sensitivity of the ATP III criteria and the possible racial and ethnic variation of the syndrome, it is important that the practitioner keep a low threshold for identifying individuals with Metabolic Syndrome. It would be prudent for the practitioner to single out individuals with any of the five risk factors for further evaluation. Practitioners can have a significant impact on the prevention and treatment of the Metabolic Syndrome by routine screening of patients with risk factors and early intervention.

Future research will likely provide a better understanding of the underlying mechanisms and treatment options for Metabolic Syndrome, particularly in the promotion of healthy lifestyle choices, such as diet and exercise and compliance with treatment. Practitioners can play an active role in addressing these research issues and can have a major impact in helping reduce this significant health issue.

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