Metformin: is it an effective treatment for metabolic syndrome?

Matthew C. Taylor

The University of Toledo
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Dedication

This paper is dedicated to my mother, father, brother, and sister for their constant support and inspiration.
Acknowledgements

Thank you to my advisor, Dr. Patricia Hogue, for her guidance on this project.

Thank you to my family for always believing in me.
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Chapter 1
Introduction

According to the National Cholesterol Education Program’s Adult Treatment Panel III (ATP III) metabolic syndrome is a combination of multiple risk factors that increases an individual’s chances of developing Cardiovascular Disease (CVD) or Type II Diabetes (Ervin, 2009). The ATP III has named CVD the primary outcome of metabolic syndrome, however most people with metabolic syndrome have insulin resistance, which elevates the risk of developing Type II Diabetes (Ervin, 2009). The ATP III has identified six components of metabolic syndrome that are related to CVD, which are abdominal obesity, insulin resistance (with or without glucose intolerance), atherogenic dyslipidemia, high blood pressure, pro-inflammatory state, and a pro-thrombotic state (Grundy, Brewer, Cleeman, Smith, Lenfant, 2004). The Adult Treatment Panel III also issued five specific criteria in order to diagnose metabolic syndrome. An individual needs to meet at least three of the following five diagnostic criteria in any combination, to be diagnosed with metabolic syndrome: the abdominal waist circumference in men greater than 102cm (40in) and in women greater than 88cm (35in); HDL cholesterol level less than 40 mg/dL for men and less than 50 mg/dL for women; triglyceride level greater than 150 mg/dL for both men and women; blood pressure greater than or equal to 130/85 mm Hg in both males and females; finally fasting glucose should be greater 100 mg/dL (Ford, Giles, Dietz, 2002).

Metabolic syndrome affects over 47 million Americans, and 34% of Americans over the age of twenty according to Ford et al. (2002). Metabolic syndrome affects men and women at nearly equal rates. Males demonstrate a 24% prevalence rate, while women show a 23.4% prevalence rate. Prevalence rates tend to vary more considerably among different age groups and racial backgrounds Ford et al. (2002).
The prevalence of metabolic syndrome (MBS) rises directly proportional to increasing age for men and women. According to Ervin (2009), 20% of males and 16% of females under the age of 40 have metabolic syndrome. Forty one percent of males and 37% of females from the ages of 40 – 59 are diagnosed with MBS. Males who are older than sixty, are four times as likely as the youngest age group to be diagnosed with MBS. While females over sixty are six times more likely than the youngest age group to meet the diagnostic criteria for metabolic syndrome (Ervin, 2009).

Metabolic syndrome rates vary amongst racial groups and ethnicities. There is very little difference in the occurrence of MBS in females based on ethnicity; however Black and Mexican females are 1.5 times more likely to develop MBS (Ervin, 2009). Mexican Americans have the highest rates of any racial group and are about as half as likely as whites to have MBS. Thirty seven percent of Mexican males are affected, while 25% of black males are diagnosed with metabolic syndrome (Ervin, 2009).

Metabolic syndrome is also associated with many other secondary health complications such as polycystic ovary syndrome, non-alcoholic fatty liver disease, cholesterol gallstones, obstructive sleep apnea, and asthma. Hormone sensitive cancers such as prostate, breast, colorectal, and endometrial cancers have also been statistically associated as well. In addition degenerative joint disease, hyperuricemia, depression, albuminuria, and Alzheimer’s disease have also been correlated with metabolic syndrome (Grundy, 2005a).

Metformin has been used for decades as an effective glucose lowering agent in diabetes mellitus type II patients. Metformin has been used for over 40 years in Europe and since 1995 in the United States. It is an oral anti-diabetic drug that falls in the biguanide class. Metformin decreases postprandial hyperglycemia by 25% in more than 90% of patients (Howlett & Bailey,
Insulin resistance has been linked with many cardiovascular risk factors such as obesity, dyslipidemia, glucose intolerance, Type II diabetes, and hypertension. Metformin opposes insulin resistance and counteracts against many characteristics of metabolic syndrome such as preventing weight gain, reducing hyperinsulinaemia, and improving the lipid profile (Howlett & Bailey, 1999).

Metformin is multi-factorial in its mechanism of action. It has a low molecular weight, high solubility, and a physiological ionic status at a pH of 7.4. It counteracts hyperglycemia by suppressing hepatic glucose production. It also increases insulin sensitivity, promotes glucose uptake, increases glucose oxidation and storage into glycogen and fat, inhibits fatty oxidation, and increases glucose turnover in the splanchnic bed. Metformin’s precise mechanism of action is hypothesized to involve the AMP-activated protein kinase (AMPK) enzyme. AMPK is a liver enzyme that plays a critical role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. AMPK is a major regulator of lipid biosynthetic pathways due to its role in the phosphorylation and inactivation of key enzymes such as acetyl-CoA carboxylase (ACC) (Zhou, G., Myers, R., Li, Y., Chen, Y., Shen, X., Fenyk-Melody, J., et al., 2001).

Problem Statement:

Metabolic syndrome is a common disease in the United States and its prevalence increases with obesity and age. The United State’s elderly population is expected to grow considerably and with obesity showing no signs of regressing, risk factors in the development of metabolic syndrome should be reduced. It has been proven that a healthy lifestyle is the best treatment and prevention, but with most individuals unwilling to change, a prescribed medication would be useful. Metformin could be this medication, but more research and analysis of data is needed.
Purpose:

The purpose of this literature review was to determine pathophysiology, risk factors, prevalence, clinical outcomes, clarifications of metabolic syndrome, and to determine if Metformin is an effective treatment of metabolic syndrome.

Scope:

This review focused on risk factors, prevalence, ethnicity, and clinical manifestations of metabolic syndrome. This review also investigated the efficacy of Metformin and other treatment options for Metabolic Syndrome. Original research articles were the main source of information used in this review.

Literature Review:

Metabolic syndrome is a disease shown to considerably increase mortality. Recently, studies have begun to look at which factors have higher associations with mortality and how the presence of multiple factors affects mortality. In a study by Ho, J., Cannaday, J., Barlow, C., Mitchell, T., Cooper, K., and Fitzgerald, S., (2008) it was found that mortality increases with the presence of one or two MBS factors. It was also found that there is no “plateau effect”, because the presence of four or five risk factors increases mortality more so, than when only three risk factors are present. Hypertension was found to be the best indicator for cardiovascular and all-cause mortality (Ho et al., 2008).

Currently there is much controversy surrounding the question of what is the true cause of metabolic syndrome. Some think the true underlying cause is obesity and others think that it is insulin resistance. This dispute could not be more evident when one looks at the different diagnostic criteria. The WHO (World Health Organization) requires a more direct diagnosis of
insulin resistance whereas the ATP III diagnoses insulin resistance indirectly (Grundy, 2004).

The World Health Organization requires elevated glucose, hyperinsulinemia, or reduced glucose disposal under glucose-clamp conditions (Grundy, 2004).

It is also disputed whether if metabolic syndrome (MBS) is acquired or genetic. Many believe it is acquired as a result of physical inactivity that leads to obesity. Further evidence implicating obesity as the acquired cause is that MBS rates have increased as the population has become more obese. According to Grundy (2004), only one third of the obese population develops MBS, which leads one think about genetics. Genetic abnormalities that are associated with adipose tissue metabolism can be related to weight gain. Individuals can also have genetic abnormalities that affect risk factor regulation and cause insulin resistance (Grundy, 2004).

Metformin has many effects that suggest that it would be an adequate treatment approach for those individuals with metabolic syndrome. Despres (2003) points out that other anti-glycemic drugs such as glitazones or sulphonylureas have been shown to increase body weight over time with their use. However, metformin has been shown to either decrease body weight or at the very least maintain current body weight. Metformin has also been shown to decrease visceral fat (Despres, 2003).

Hundal & Inzucchi,(2003) discuss metformin’s non-hypoglycemic effects in patients. It has been found to decrease myocardial events. It has also been shown to decrease mortality and diabetic related endpoints. Type II diabetes is characterized by elevated free fatty acids, triglycerides, LDL’s, and decreased HDL’s. These factors along with elevated free fatty acids can cause increased hepatic glucose production and insulin resistance. Lipoprotein levels are also decreased with the use of metformin. Insulin resistance has been shown to cause decreased fibrinolysis which can lead to intravascular thrombosis. Metformin lessens the blood levels and
the activity of plasminogen activator inhibitor – 1 (PAI-1), Von Willenbrand factor, platelet aggregation and adhesion, and increases TPA activity. As a result of this, metformin amplifies hypercoagulability and decreases strokes. C-reactive protein is an important inflammatory indicator and is an increasingly popular nontraditional tool used to determine the risk of cardiovascular disease. Metformin has been shown to lower levels of C-reactive protein as well. Metformin also decreases Endothelin - 1, which is a potent vasoconstrictor. This action helps improve endothelial dysfunction (Hundal & Inzucchi, 2003).

**Research Question:**

Is Metformin an effective treatment for patients with Metabolic Syndrome?

**Definitions:**

Metabolic syndrome - is a combination of medical conditions that increase the risk for Cardiovascular Disease and Type II Diabetes. Adult Treatment Panel (ATP III) has listed six criteria to define metabolic syndrome and three are needed for the diagnosis; abdominal obesity, insulin resistance with or without glucose intolerance, atherogenic dyslipidemia, raised blood pressure, pro-inflammatory state, and a pro-thrombotic state (Ervin, 2009).


**Pro-inflammatory state** - recognized clinically by elevations of C-reactive protein (CRP), is commonly present in persons with metabolic syndrome (Grundy et al., 2004).
Pro-thrombotic state - characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also associates with the metabolic syndrome (Grundy et al., 2004).

Insulin Resistance – This term is used when the cells of the body have become resistant to the effects of insulin, that is, the normal response to a given amount of insulin is reduced. As a result, higher levels of insulin are needed in order for insulin to have its effects. The resistance is seen with both the body's own insulin (endogenous) and if insulin is given through injection (exogenous) (Grundy et al., 2004).

Syndrome X – This is another term for Metabolic Syndrome (Grundy et al., 2004).

MBS – Metabolic Syndrome

Methodology:

The search engines predominately used for the article were medline, pubmed, and Ohio link. The main search terms used were metabolic syndrome, metformin, Syndrome X, risk factors, prevalence, treatment, and prevention. The inclusion criteria consisted of articles related to the United States population, metabolic syndrome, and metformin. Any article requiring purchase, written in any other language besides English, or was written before 1999 was excluded.
Chapter Two

Review of Literature

This chapter investigates research literature that pertains to Metabolic Syndrome. The major sections of this review include 1) Pathophysiology of Metabolic Syndrome, 2) Risk factors for development, 3) Signs & Symptoms, 4) Diagnosis, 5) Overview of Treatment of Metabolic Syndrome, and 6) Metformin’s effectiveness as a treatment.

Pathophysiology of Metabolic Syndrome

The pathophysiology of metabolic syndrome has long been debated. Despite its high interest, the pathophysiology of metabolic syndrome still has not been identified. As of today, its pathophysiology has only been hypothesized.

Mehta and Reilly (2004) investigate the pathophysiology of metabolic syndrome. Adipose tissue plays a big role in the early stages of metabolic syndrome. Adipose tissues make different bioactive factors that regulate glucose, lipid metabolism, and innate inflammatory responses. Adipose tissue can be isolated as either subcutaneous adipose tissue or visceral adipose tissue depending on the anatomic location. Visceral fat accumulation occurs in patients with familial lipodystrophies, which gives insight into the connection between fat redistribution, visceral adiposity and the development of insulin resistance. Lipodystrophy is generally described as the loss of subcutaneous adipose tissue and the increase of visceral adipose tissue. Visceral fat is associated with insulin resistance. A mutation that results is the loss of function in the ligand binding domain of peroxisome proliferator-activated receptor gamma (PPARy), which is a nuclear hormone receptor that helps modulate adipocyte differentiation, insulin sensitivity, and carbohydrate metabolism (Mehta and Reilly, 2004).
Mehta and Reilly (2004) point out the “thrifty genotype hypothesis” which refers to the evolutionary selection of genes that promote energy storage and innate immune inflammatory responses when an individual leads a lifestyle of physical inactivity and overeating. This selection of genes is hypothesized to have been beneficial for hunters and gatherers during ancient times because they needed to fatten up as quickly as possible whenever food was plentiful due to consistent food sources being scarce. In relation to today’s population, as good diet habits and exercise decline, these same selected genes are thought to encourage central adiposity, a pro-inflammatory state, and an insulin resistant state that leads to metabolic syndrome (Mehta and Reilly, 2004).

The middle stages of metabolic syndrome are associated with increased circulating fatty acids and intra-cellular fat in the liver and skeletal muscle. The collection of cell fat is believed to cause problems in glycogen synthesis and glucose metabolism by effecting glycogen synthase and GLUT 4. According to Mehta and Reilly (2004), irregular glucose uptake in the muscle is secondary to dysregulation of intramyocellular fat metabolism. As visceral adipose tissue continues to increase, the function of adipocytes is increasingly damaged. This results in incorrect adipocyte gene expression and macrophage infiltration. The adipose tissue amplifies its secretion of bioactive substances called “adipocytokines”, which intensifies the inflammatory state and insulin resistant environment. Tumor necrosis factor alpha (TNFα), adiponectin, resistin, leptin, are all adipocytokines. These adipocytokines each separately regulate insulin sensitivity, lipid metabolism, and inflammatory responses. Together they act collectively to sustain metabolic syndrome and encourage pro-atherogenic vascular effects.

Amplified TNFα production is linked with obesity and is also known to interfere with insulin action. Patients who are obese and have insulin resistance display elevated levels of adipose
TNFα expression, whereas slimmer and healthier patients do not. It is thought that TNFα diminishes insulin mediated glucose uptake, encourages lipolysis, and changes hepatic glucose and lipid gene expression (Mehta and Reilly 2004).

According to Mehta and Reilly (2004), adiponectin is a collagen like protein that belongs to the soluble defense collagen superfamily and has structural homology with collagen VIII and X and complement factor. Mehta and Reilly (2004) point out that a relationship has been seen between hypo-adiponectinemia and insulin resistance in rodent models and humans. Adiponectin increases insulin sensitivity, lowers hepatic lipid content, and has anti-inflammatory effects on macrophages and the endothelium (Mehta & Reilly, 2004). Resistin is a 94 amino acid adipokine that is mostly devolped from inflammatory cells in humans. Higher levels of serum resistin are consistent with elevated inflammatory cytokines in both obesity and type II diabetes. Resistin blocks the anti-inflammatory effects of adiponectin on the endothelium.

Mehta and Reilly (2004) explain that during the later stages of metabolic syndrome is usually when the clinical features of metabolic syndrome are usually seen. Dyslipidemia is the hallmark of metabolic syndrome, which usually consists of increased triglycerides and lower levels of HDL’s. Typically LDL levels are normal in patients with metabolic syndrome although, an increase in small dense atherogenic LDL particles is seen (Mehta and Reilly, 2004). The enhancement in the fluctuation of free fatty acids from the periphery to the liver in the insulin resistant state fuels hepatic triglyceride synthesis. This will then encourage the manufacturing and secretion of triglycerides containing VLDL’S and helps contribute to higher triglyceride levels. Low HDL levels are thought to be caused secondarily due to increased triglycerides. This explains how the hallmark of metabolic syndrome, which is dyslipidemia arises in an
patient with central obesity and also in a insulin-resistant and pro-inflammatory state (Mehta and Reilly, 2004).

**Age**

Razzouk and Munter (2009) point out that the prevalence of metabolic syndrome increases after age 50. According to Razzouk and Munter (2009) the accumulation of excess caloric intake, dyslipidemia, a sedentary lifestyle, hormonal changes in women, the altering of the secretory functions of pancreatic B cells, and obesity are all possible environmental triggers for the genetic expression of metabolic syndrome. Estrogen levels and menopause help explain the increase of MBS in women over 50. In premenopausal women, higher estrogen levels help sustain elevated amounts of high density lipoprotein (HDL) cholesterol and lower amounts of low density lipoprotein (LDL) cholesterol. This helps explain the reason why there is a lower prevalence of metabolic syndrome in younger women compared to older women (Razzouk & Munter, 2009).

Trying to explain the increase in the prevalence of metabolic syndrome with age is more difficult with men than women according to Razzouk & Munter (2009). Unlike women, HDL levels are actually higher in older men in contrast to middle aged men. However, pancreatic B-cell function declines at a rate of 1% per year in men. Even though pancreatic B-cell function declines, insulin sensitivity remains the same as men age. This suggests an increase in glucose intolerance as the likely pathophysiologic cause of metabolic syndrome in men (Razzouk & Munter, 2009).

**Race**
Razzouk and Munter (2009) point out that between 1990 – 1994, the prevalence of metabolic syndrome based on race was 23.8%, 21.6%, and 31.9% for non-Hispanic whites, non-Hispanic blacks, and Mexican Americans respectively. For men, the prevalence rate was 24.8%, 16.8%, 28.3% among non-Hispanic whites, non-Hispanic blacks, and Mexican Americans respectively. For women, the prevalence rate was 22.8%, 25.7%, and 35.6% among non-Hispanic whites, non-Hispanic blacks, and Mexican Americans respectively.

The lower prevalence rate for African American males is believed to be caused by the population on a whole having a lower waist circumference, triglycerides, and higher HDL cholesterol levels. However, African Americans in general are more prone to hypertension and increased plasma glucose than are non-Hispanic whites (Razzouk and Munter 2009). The high prevalence rates depicted with Mexican Americans is thought to be due to their high rates of insulin resistance and diabetes mellitus. Also, Mexican Americans have higher rates of obesity, obesity caused glucose intolerance, and hyperglycemia. Not only do Mexican Americans have higher rates of obesity, but they also have high rates of hepatic steatosis. Mexican Americans display a rate of hepatic steatosis of almost twice that of non-Hispanic blacks. The prevalence rate of hepatic steatosis among non-Hispanic whites, non-Hispanic blacks, and Mexican Americans is 33%, 24%, and 45% respectively. Patients with hepatic steatosis are predisposed to eventually developing dyslipidemia (Razzouk and Munter 2009).

**Risk Factors**

Since metabolic syndrome is a cluster of problems, it also has numerous and a wide variety of risk factors. Risk factors for metabolic syndrome can be divided into three groups, which are underlying risk factors, major risk factors, and emerging risk factors.
Common underlying risk factors include obesity, inactivity, and diet. Examples of inactivity include a sedentary lifestyle, no exercise, and no physical activity. Diet is a risk factor when an individual’s diet consists of excessive caloric intake and fatty foods. Major risk factors include hypertension, tobacco use, elevated LDL’s, low HDL’s, family history of premature coronary artery disease, and aging. Emerging risk factors include elevated triglycerides, insulin resistance, glucose intolerance, a pro-inflammatory state, small LDL particles, and a prothrombotic state (Miller and Mitchell, 2006). Another possible risk factor for metabolic syndrome is gestational diabetes, which is explained by Miller and Mitchell (2006). The insulin resistance characteristic of pregnancy can result in gestational diabetes. Higher levels of fibrinogen and C-reactive protein have been recorded in women with gestational diabetes. Most notably, women with gestational diabetes have a prevalence rate of metabolic syndrome that is two to three times greater in women with a normal pregnancy. When gestational diabetes is accompanied by obesity, the risk of developing metabolic syndrome is four to tens times higher (Miller and Mitchell, 2006).

Miller and Mitchell (2006) also discuss pregnancy induced hypertension (PIH) and its relationship to metabolic syndrome. During a childbearing mother’s first pregnancy PIH enhances the risk for the mother to develop metabolic syndrome by three to five fold. Forest, Gerouard, Masse, Moutquin, Karfi, and Ness (2005), performed a controlled prospective observational study, where 168 primigravidas (first time pregnancy) with PIH were matched for age and year with primigravidas without PIH and were followed for five years. After five years had passed, it was found that those mothers with pregnancy induced hypertension were more likely to be obese and have more elevated systolic and diastolic blood pressures, lower HDL
levels, increased fasting glucose levels, and increased insulin levels than their controls. These are all components of metabolic syndrome.

Miller and Mitchell (2006) also identified that the relationship of metabolic syndrome and perinatal complications is not exclusive to child bearing women. According to Miller and Mitchell (2006) there is evidence that gestational diabetes and pregnancy induced hypertension enhances the fetus chances to developing metabolic syndrome. A large for gestational age infant has been known to be at increased risk for developing type II diabetes. Metabolic syndrome, which is also known to be a pre-diagnosis of type II diabetes has also been found to be correlated with large for gestational age infants.

Recently, small for gestational age infants have shown some correlation with metabolic syndrome. Small for gestational age infants have an elevated chance for developing coronary heart disease, hypertension, and type II diabetes as adults. All of which, are components of metabolic syndrome. With small for gestational age infants, there is an imbalance between nutrient supply and demand, which eventually causes the low birth weight. Due to the low birth weight, intra-uterine metabolic changes take place such as increased glucocorticoid secretion. The intrauterine metabolic changes benefit the fetus for a short time by reducing fetal growth and increasing glucose supply. The long term result of these metabolic changes is that they have reprogrammed the hypothalamic-pituitary adrenal axis. The reprogramming of the hypothalamic-pituitary adrenal axis as a fetus results in obesity, hyperglycemia, and hypertension as an adult (Miller and Mitchell, 2006).

**Diagnosis**

The diagnosis of metabolic syndrome can be as complicated as the many factors that make up the condition. The diagnosis of metabolic syndrome is complicated because there are various
diagnostic criteria available that have been produced by credible and respectable organizations. This creates problems because physicians have to choose which respective criteria to follow. Physicians also have to decide how strict to follow each criteria and whether or not to merge different organization’s diagnostic criteria together. The main guidelines for diagnosing metabolic syndrome have been set by The National Cholesterol Education Program’s (NCEP) Adult Treatment Panel III (ATP III), The World Health Organization (WHO), The American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF) (Grundy et al., 2004).

The most commonly used diagnostic criteria is that of the NCEP ATP III. An individual needs to meet at least three of the following five diagnostic criteria in any combination, to be diagnosed with metabolic syndrome: the abdominal waist circumference in men greater than 102cm (40in) and in women greater than 88cm (35in); HDL cholesterol level less than 40 mg/dL for men and less than 50 mg/dL for women; triglyceride level greater than 150 mg/dL for both men and women; blood pressure greater than or equal to 130/85 mm Hg in both males and females; finally fasting glucose should be greater 100 mg/dL (Ford, Giles, Dietz, 2002).

The WHO has similar guidelines for diagnosing metabolic syndrome, but there are also some differences. One difference is that the WHO requires insulin resistance to be present in order to diagnose metabolic syndrome. Insulin resistance is defined by one of the following ways: type II diabetes, impaired fasting glucose, impaired glucose tolerance; or for those with normal fasting glucose levels (<110mg/dL), it is defined as glucose uptake below the lowest quartile for the background population under investigation under hyper-insulinemic, euglycemic conditions. Once insulin resistance has been established the WHO requires for any two of the following to be present: antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥
90 mm HG diastolic); plasma triglycerides ≥ 150 mg/dL; HDL cholesterol < 35 mg/dL in men or < 39 mg/dL in women; BMI > 30 kg/m^2 and/or hip:waist ratio > .9 in men and > .85 in women; and urinary albumin excretion rate ≥ 20µg/min or albumin:creatinine ratio ≥ 30mg/g (Grundy, Brewer, Cleeman, Smith, Lenfant, 2004).

The International Diabetes Federation (IDF) has its own definition of metabolic syndrome. Liberopoulos, Mikhalidid, and Elisaf (2005) point out that the IDF’s definition is unique because it requires central obesity to be present. The IDF’s definition of metabolic syndrome is also unique because its definition is gender and ethnic group specific. The IDF has different guidelines for determining central obesity based on gender and ethnic groups. For example in Europid (aka Caucasians) men, central obesity is defined as waist circumference ≥ 94 cm (37 inches) and ≥ 80 cm (31.5 inches) for Europid (Caucasian) women. Whereas in Japanese men, central obesity is defined as a waist circumference ≥ 85 cm (33.5 inches) and ≥ 90 cm (35.4 inches) in Japanese women. Along with central obesity the IDF require that two of the following four criteria be present to diagnose metabolic syndrome: triglycerides ≥ 150 mg/dL or currently receiving treatment for dyslipidemia; HDL cholesterol level less than 40 mg/dL for men and less than 50 mg/dL for women; blood pressure greater than or equal to 130/85 mm Hg in both males and females; raised fasting plasma glucose ≥ 100 mg dL or previously diagnosed type 2 diabetes. The IDF expects that if this definition is adopted, that it will increase the prevalence of metabolic syndrome considerably (Liberopoulos et al., 2005).

Another set of clinical criteria to assess metabolic syndrome comes from The American Association of Clinical Endocrinologists (AACE). Grundy et al. (2004) feel that The AACE’s criterion is a mixture of the ATP III and WHO diagnostic guidelines. The fact that there is no defined number of risk factors required for diagnosis distinguishes The AACE’s clinical criteria
because it leaves diagnosis up to clinical judgment based on risk factors. However, it still assesses the same risk factors when making a clinical judgment. Obesity, elevated triglycerides, low HDL cholesterol, elevated blood pressure, family history of hypertension or type II diabetes, cardiovascular disease, sedentary lifestyle, polycystic ovarian syndrome, advancing age, impaired fasting glucose, and insulin resistance are all assessed when using clinical judgment to diagnose metabolic syndrome (Grundy et al., 2004).

**Abdominal Obesity**

The main concern when treating obese patients with metabolic syndrome is weight reduction. Grundy et al. (2005) suggests that weight reduction and maintaining a reduced weight is best accomplished by reducing caloric intake, increasing physical activity, and overall lifestyle modifications. Patients who are able to lose weight will lessen the severity of all or many of the metabolic risk factors. Increasing physical activity helps expedite weight loss, improve metabolic risk factors, and helps decrease the risk for atherosclerotic cardiovascular disease. Grundy et al. (2005) explain that 30 minutes or more of moderate-intensity exercise per day should be done on most or all days of the week. Longer durations of exercise produce even better results. According to Janiszewski, Saunders, and Ross (2008) 60 minutes of daily exercise over three months is associated with a 1.0 kg (roughly 30%) reduction in visceral fat and a 7.0 cm decline in waist circumference. Sixty minutes of daily exercise over three months also corresponds with an 8.0 kg weight loss in obese men and women. Approximately 20 to 25 minutes of daily exercise reduces visceral fat by only 6% to 10% and is associated with a decreased waist circumference by 1.0 to 3.0 cm. Daily exercise for 20 to 25 minutes also corresponds to 1.4 – 1.8 kg in weight reduction in overweight women and obese women with diabetes (Janiszewski et al., 2008).
Another way to address abdominal obesity and weight reduction is through diet. Grundy et al. (2005) suggests that a goal of a 7% to 10% decline from baseline total body weight over a period of 6 to 12 months should be set. In order to achieve this weight loss goal caloric intake must be lessened by 500 to 1000 calories per day. The diet should consist of a low amount of saturated fats, trans fats, cholesterol, sodium and simple sugars. The diet should also be plentiful in fruits, vegetables, whole grains, and fish (Grundy et al., 2005).

**Dyslipidemia**

The ATP III suggests that the LDL cholesterol level should always be the primary target when the LDL’s are above the therapeutic goal. The goal of therapy should be to raise HDL cholesterol and lower LDL cholesterol and triglycerides. According to Miller and Mitchell (2006) statins meet all three of these goals and should be first line treatment for dyslipidemia. Statins hinder the 3-hydroxy-3 methylglutaryl coenzyme A reductase (HMG CoA), which is a essential enzyme in cholesterol synthesis pathway in the liver. Miller and Mitchell (2006) report that statins lower triglycerides by 7% to 30%, lower HDL’s by 18% to 55%, and raise HDL cholesterol by 5% to 15%.

According to Miller and Mitchell (2006), statin therapy alone is may not be adequate to regulate cholesterol. In these cases a second anti-hyperlipidemic agent should be used. Niacin, bileacid sequestrants, fibric acid derivates, and selective intestinal cholesterol inhibitors are all possible choices to help reach therapeutic goals. Niacin is a B complex vitamin that effects all lipid levels in a positive way. An advantage of Niacin is that it is cheap, readily available in over the counter forms, and is very effective in combination with statins. A disadvantage of niacin is that it causes cutaneous flushing in almost all patients when therapy is first started. Bile acid sequestrants irreversibly attach to bile acids in the gut and prevent reabsorption, which
reduces cholesterol production in the liver. Bile acid sequestrants mainly decrease LDL cholesterol levels, and this effect is increased when used in combination with a statin. Unfortunately, the use of bile acid sequestrants is reduced because they raise triglyceride levels, which commands patients to undergo a strict and inconvenient dosing regimen. Fibric acid derivates mainly act on triglycerides and are inadequate in decreasing LDL cholesterol levels. So therefore, fibric acid derivatives are most commonly used for limited treatment of increased triglycerides affiliated with diabetes. Their long term use has not been documented (Miller and Mitchell, 2006).

A newer class of drugs called selective intestinal cholesterol inhibitors have been found to be effective in treating hyperlipidemia. According to Miller and Mitchell (2006) these drugs act at the brush border of the small intestine to inhibit absorption of cholesterol. This reduces hepatic cholesterol stores and promotes the clearance of cholesterol from the blood. When used with a statin, a collaborative effect results in the lowering of cholesterol.

**Hypertension**

In a patient with no diabetes or kidney disease, the blood pressure goal should be < 140/90, When a patient has diabetes or chronic kidney disease the blood pressure goal should be < 130/80 mm Hg. According to Grundy et al. (2005), lifestyle modifications deserve increased emphasis and should often be used first in patients with metabolic syndrome with hypertension. Small elevations in blood pressure can be adequately managed with lifestyle changes. Examples of lifestyle changes include weight loss and control, exercise, alcohol moderation, sodium restriction, and increased intake of fresh fruits, vegetables and low fat dairy products, while decreasing intake of fatty foods (Grundy et al, 2005).
When lifestyle changes are ineffective at controlling blood pressure, pharmacologic therapies must be introduced. This is necessary to prevent poor outcomes such as chronic kidney disease, myocardial infarctions, strokes, and cardiovascular disease. Most researchers including Grundy et al. (2005) and Miller and Mitchell (2006) agree that the first line anti-hypertensive drug used in patients with metabolic syndrome, and especially when either diabetes or chronic kidney disease is present, should be an Angiotensin Converting Enzyme Inhibitor (ACEI). ACEI’s work by incapacitating the production of angiotensin II, which is the enzyme that is responsible for vasoconstriction and sodium retention in the kidney. The result of this is the reduction in total peripheral resistance that decreases blood pressure. According to Scheen (2004) ACEI’s hinder the start of microvascular renal issues, such as deteriorating glomerular filtration and albuminuria, and they decrease the incidence of type II diabetes.

Another set of anti-hypertensive drugs called Angiotensin Receptor Blockers (ARBs) are used in patients when ACEI’s are ineffective. Many African Americans do not respond to ACEI and many patients do not tolerate ACEI due to a dry cough, which is a very common side effect of ACEI. ARBs have fewer side effects and lower blood pressure by relaxing smooth muscle, which encourages vasodilation. ARBs also increase sodium and water exertion, which decreases plasma volume (Miller and Mitchell, 2006).

Miller and Mitchell (2006) report that only one third of patients with hypertension are able to control their blood pressure with only one drug. McNeil, Rosamond, Girman, Golden, Schmidt, and East (2005) suggest that when mono-therapy is ineffective, a second class of drugs should be used, which is usually a diuretic. Hydrochlorothiazide (HCTZ) is a good choice because it is cheap and very effective when used in collaboration with an ACEI or an ARB.
Other anti-hypertensive agents can also be used in patients with metabolic syndrome. Beta blockers have been shown to be useful in lowering blood pressure in metabolic syndrome patients. However, beta blockers are not as capable as ARBs in preventing stroke. Because beta blockers also increase the risk for hyperglycemia and mask the signs of hypoglycemia, caution is advised when using them in patients with impaired glucose tolerance or diabetes (Miller and Mitchell, 2006).

**Insulin Resistance**

Insulin resistance is a major component of metabolic syndrome. Depending on severity, patients with an impaired fasting glucose, are usually first treated with weight loss efforts and exercise, in hopes of preventing type II diabetes. Insulin sensitizing medications are commonly used to help with insulin resistance. Pharmacologic therapies such as metformin, thiazolidinediones, and acarbose are all insulin sensitizers and are used in effort to prevent type II diabetes. According to Fonseca (2005), thiazolidinediones such as rosiglitazone and pioglitazone increase glucose transport by activating peroxisome proliferator-activated receptor gamma (PPARγ) and enhancing GLUT4 transport activity. PPARγ increases insulin-stimulated glucose uptake while simultaneously reducing hepatic glucose output. Thiazolidinediones may also lower triglycerides and raise HDL cholesterol levels. In addition to this, thiazolidinediones also enhance endothelial function (Fonseca, 2005).

**Prothrombotic State**

Grundy et al (2005) reports that many patients with metabolic syndrome are in a prothrombotic state. Patients in a prothrombotic state usually display evidence of elevated levels of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors (Grundy et al., 2005). In effort to prevent complications such as thrombotic events, anti-platelet therapy should
be used in patients with diagnosed atherosclerotic cardiovascular disease. Patients with metabolic syndrome without established ASCVD can also be treated with anti-platelet therapy such as a daily aspirin regimen to prevent complications. Aspirin prophylaxis has not been proven in clinical trials to be useful in metabolic syndrome, but it is an attractive therapy among physicians (Grundy et al., 2005).

**Pro-inflammatory State**

Many patients with metabolic syndrome have a pro-inflammatory state. One characterization of a pro-inflammatory state is the presence of elevated cytokines such as tumor necrosis factor $\alpha$ and interleukin – 6. Increased levels of C-reactive protein (CRP) and fibrinogen are another characterization of a pro-inflammatory state. Grundy et al. (2005) recommend that a CRP level $>3\text{mg/L}$ be used to classify a patient in a pro-inflammatory state. An elevated CRP measurement should first be treated by initiating life style changes followed by weight reduction. There are no drugs that specifically treat a pro-inflammatory state. However, other drugs specific for other components of metabolic syndrome indirectly treat metabolic syndrome. Statins, nicotinic acid, fibrates, ACE Inhibitors, and thiazolidinediones all indirectly lower CRP levels (Grundy et al., 2005).

**Treatment**

According to Fonseca (2005) effective management of the components of metabolic syndrome is necessary to decrease the risk of Cardiovascular Disease and the progression to diabetes. The primary goal of treatment is to reduce the risk for clinical atherosclerotic disease according to Grundy, Cleeman, Daniels, Donato, Eckel, Franklin et al. (2005b). The cornerstone of treatment is to tackle the underlying causes. Treatment options include lifestyle modifications such as increasing physical activity and reducing caloric intake. Pharmacologic therapies for
treating metabolic syndrome include lipid-modifying therapies, antihypertensive agents, insulin-sensitizing drugs, and anti-platelet drugs (Fonseca, 2005).

**Metformin**

Kraemer de Aguiar, Bahia, Villela, Laflor, Sicuro, Wiernspereer, Bottino, and Bousekela (2006) researched the vascular effects of metformin in first-degree relatives with metabolic syndrome of type 2 diabetic patients. The study consisted of 31 subjects with the average age of 38.3 years, average BMI of 36.3 kg/m², and normal glucose tolerance. The participants were randomly assigned 1:1 in a double blind manner and 15 participants received a placebo and 16 received metformin. This study examined endothelial function by studying Forearm Blood Flow (FBF) through venous occlusion plethysmography. All participants participated in the study for at least 90 days. Weight, BMI, systolic and diastolic blood pressure, waist, lipid profiles, and fasting plasma glucose were examined at baseline and after the study. The metformin group showed statistically significant decreases in the following categories; weight ($p < .05$), BMI ($p < .05$), systolic blood pressure ($p < .03$), total cholesterol ($p = .01$), and fasting plasma glucose ($p = .01$). The metformin group also showed an increase in HDL cholesterol ($p < .05$). Metformin was also associated with endothelium improvement FBF by 111% ($p = .01$). The placebo group showed no improvement in FBF, weight, BMI, blood pressure, cholesterol, or fasting plasma glucose.

Orchard, Temprosa, Goldberg, Haffner, Ratner, Marcovina, and Fowler (2005), researched the effect of intensive lifestyle interventions and metformin therapy on metabolic syndrome’s incidence and resolution. This was a randomized controlled clinical trial where 3000 people had impaired glucose tolerance according to the World Health Organization’s (WHO) criteria and were followed for an average of 3.2 years. The participants either received 850 mg of metformin
twice a day or underwent intensive lifestyle interventions that were designed to acquire and sustain a 7% weight loss and 150 minutes of exercise per week. Fifty three percent of the participants in the study were found to have metabolic syndrome at baseline. Incidence was decreased by 41% in the lifestyle intervention group ($p < .001$). The metformin group produced a 17% decrease in incidence compared to placebo ($p = .03$). Three year cumulative incidences were 51%, 45%, and 34% in the placebo, metformin, and lifestyle intervention group respectively (Orchard et al., 2005).

Andreadis, Katsanou, Georgiopoulos, Tsourous, Yfanti, Gouveri, and Diamantopoulous (2009) researched if the inclusion of metformin in the treatment of overweight and obese patients decreases the incidence of type II diabetes mellitus, metabolic syndrome, and if it improves cardiovascular disease risk factors. The study consisted of 366 adults with the mean age of 53.0 years, mean BMI 32.3 Kg/m$^2$, and no cardiovascular disease. All participants were given lifestyle recommendations, drug management of cardiovascular disease risk factors, and 95 of the participants were also given metformin. The patient’s follow up period was 12 months. At the conclusion of the study, the frequency of type II diabetes mellitus in the metformin group was 1.1% and 8.1% in the non-metformin group ($p = .012$). After one year of treatment with metformin, the proportion of patients with metabolic syndrome was reduced from 36.9% to 29.8% ($p = .01$). The decrease in the number of people with metabolic syndrome was higher in the metformin group. Prevalence decreased from 38.9% to 21.1% in the metformin group and from 36.2% to 32.8% in the non-metformin group ($p = .035$). In this study, the statistically significant decrease in the prevalence of metabolic syndrome in the metformin group was not correlated with waist circumference, triglyceride, or blood pressure levels. Instead, the metformin group showed a 2.1% decrease in patients with fasting plasma glucoses $\geq 110$ mg/dl,
whereas a 6.4% increase was seen in the non-metformin group ($p = .024$). The percentage of participants with low HDL cholesterol levels decreased by 5.6% in the metformin group and by 3.0% in the non-metformin group ($p = .046$). HDL cholesterol levels were increased by 3.1 mg/dl from baseline in the metformin group versus 1.0 mg/dl in the non-metformin group ($p = .001$). Andreadis et al (2005) concluded that metformin reduces the occurrence of type II diabetes in overweight and obese non-diabetic adults while also decreasing the rate of metabolic syndrome by improving the cardiovascular disease risk factor profile.

Vitale, Mercuro, Cornoldi, Fini, Voleterani, and Rosano (2005) investigated the effect of metformin on endothelial function and insulin resistance in patients with metabolic syndrome. Sixty five participants with metabolic syndrome, consisting of 37 men and 28 women, with an average age of 54 years old were treated with 500 mg of metformin twice daily or received a placebo. Thirty two subjects received the metformin and thirty three received the placebo. Patients had to have stable blood pressure values, lipids, and glycaemic profile over the last three months. Endothelial function was measured evaluating the flow-mediated dilation (FMD) of the brachial artery and insulin resistance was evaluated by using the homeostasis model (HOMA-IR). After three months of therapy, no significant difference were seen in blood pressure or BMI. However, a significant change in insulin resistance was seen in the metformin group. The HOMA-IR fell from 3.3.9 to 2.5 in the metformin group, whereas in the placebo group the HOMA-IR value went from 3.42 to 3.37 ($p < .001$). Also, the metformin group showed a decrease in plasma fasting glucose from $123 \pm 5$ mg/dL to $108 \pm 3$ mg/dL whereas the placebo group showed $121 \pm 6$ mg/dL to $122 \pm 7$ mg/dL ($p < .005$). The metformin group had a significant effect on endothelial function as well when compared to the placebo. The FMD improved by $12.4 \pm 1.9\%$ in the metformin group compared to just $6.9 \pm 2.7\%$ in the placebo
group \((p = .0016)\). Vitale et al. (2005) concludes that metformin improves both insulin resistance and endothelial function in patients with metabolic syndrome.

E. Meaney, Vela, Samaniego, A. Meaney, Asbun, Zempoalteca, Elisa, Emma, Guzman, Hicks, and Ceballos (2008) investigated the effect of metformin in patients with metabolic syndrome on the following variables; BMI, waist circumference, systolic and diastolic blood pressures, total cholesterol, HDL and LDL cholesterol, triglycerides, fasting glucose, nitrooxidant metabolites (free carboxyls, malondialdehye, dityrosines, and advanced oxidative protein products (AOPP)), nitric oxide, carotid vascular stiffness, carotid intima media thickness, and C-reactive protein. Sixty patients with at least three diagnostic criteria for metabolic syndrome were divided into two groups. Both groups received similar diet counseling, but only one group received metformin 850 mg once daily and was followed for one year. The groups consisted of male and females aged from 35 – 60 years old with 30 subjects in each group. Thirty nine patients finished the study; 17 subjects in the control group and 22 subjects in the metformin group. The mean patient age was 49 ± 8 years in the control group and 49 ± 10 in the metformin treated group. Waist circumference was decreased by 3.36 cm in the metformin group \((p = .001)\), and by 1.72 cm in the control group \((p = .009)\) respectively. BMI decreased minimally in both groups. Systolic blood pressure was lessened by 6 mmHG in the metformin group and 7 mmHG in the control group. Diastolic blood pressure was decreased by 5.7 mmHg in the metformin group and 4.4 mmHg in the control group. No statistical significance was found between the two groups. Triglyceride levels were decreased by 8\% (22 mg/dL) in the metformin group, but the control group was unchanged. HDL levels were increased by 17\% in the metformin group and by 10\% in the control group. A small increase in LDL cholesterol was seen in the control group and a small decrease of LDL’s was seen in the metformin group,
however both changes were not statistically significant. Intima media thickness (IMT) was measured at two sites, which were designated as site A and site B. For site A, IMT was significantly reduced by .099 mm (9%) in the metformin treated group ($p = .04$), whereas the control group only displayed a non-significant decrease of .021 mm. At site B, IMT was reduced significantly by .05 mm (4.8%) in the metformin group ($p = .05$), but was unaltered in the control group. Carotid stiffness increased by 24.5% in the metformin group and was decreased by 26.75 in the control group. Neither the carotid stiffness nor IMT intergroup or intra-group comparisons produced statically significant results. Free carbonyls were significantly diminished by 51% ($p < .01$) in the metformin group, but was insignificantly reduced by 3.76% in the control group. Dityrosine, which is a marker of intermediate nitrooxidation was significantly reduced by 34% in the metformin group ($p < .05$), whereas the control group produced only a 14% reduction. AOPP levels, which is a marker of advanced nitrooxidation was significantly reduced by 49% in those receiving metformin ($p < .001$), however no fluctuation was seen in the control group. Nitrite concentration, which is a marker of nitric oxide production did not change in the control group, but increased significantly by 65% ($p < .05$) in the metformin group. CRP, which is a non–specific marker on inflammation was unchanged in the control group, but was decreased significantly by metformin ($p < .02$). E. Meaney et al. (2008) concluded that metformin should be used in the treatment of metabolic syndrome because it prevents the development of type II diabetes mellitus and counteracts nitrooxidation, inflammation, atherogenesis, which lead to vascular complications.

Daad Akbar (2002) investigated the effect of the metformin and glibenclamide on the serum level of C-reactive protein (CRP) in well controlled type II diabetics with metabolic syndrome. The study took place at the medical outpatient clinic of King Abdulaziz University Hospital in
Saudi Arabia. Patients were divided into two groups based on the anti-hyperglycemic agents used. The study consisted of 110 patients with well-controlled blood glucose levels on metformin or glibenclamide alone without any major medical illnesses. Sixty five subject received metformin, while forty five received glibenclamide. The average use of metformin was $3.5 \pm 2.1$ years and $4.2 \pm 2.3$ years for glibenclamide. The CRP was significantly lowered in the metformin group compared to the glibenclamide group ($p = .01$). There was also a statistical significant positive correlation between CRP level and BMI ($r = 0.37$).

Chapter 3

Discussion

The pathophysiology of metabolic syndrome has not been consensually proven. Mehta and Reilly (2004) proposed a widely accepted pathophysiologic mechanism for metabolic syndrome. If their mechanism is correct I feel there is some room for research in areas that could possibly lead to health care providers being able to better manage their patients and prevent Diabetes and Cardiovascular Disease. Mehta and Reilly (2004) point out that one of the main early features of metabolic syndrome is the increase of visceral adipose tissue opposed to subcutaneous adipose tissue. The increase in visceral fat is due to the mutation that causes the loss of function in the ligand binding domain of peroxisome proliferator-activated receptor gamma (PPARy), which is a nuclear hormone receptor that helps modulate adipocyte differentiation, insulin sensitivity and carbohydrate metabolism (Mehta and Reilly, 2004). I believe that if the exact trigger or better understanding of the cause of the increase in development of visceral fat could be found then the number of patients with metabolic syndrome would decreased and earlier treatment could be
implemented. I believe a portion of the research conducted on metabolic syndrome should include an emphasis on what causes the mutation in the ligand binding domain of PPARy.

Another point of metabolic syndrome that was discussed by Mehta and Reilly (2004) was the production of adipocytokines by adipose tissue. Adipocytokines are bioactive substances produced by adipose tissue, which intensify the inflammatory state and insulin resistant environment. Tumor necrosis factor alpha (TNFα), adiponectin, resistin, leptin, are all adipocytokines. These adipocytokines each separately regulate insulin sensitivity, lipid metabolism, and inflammatory responses. They act in a collaborative manner to sustain metabolic syndrome and to encourage pro-atherogenic vascular effects. Patients who are obese and have insulin resistance display elevated levels of adipose TNFα expression, whereas slimmer and healthier patients do not. This is another area that research should focus on to continue to move forward. If the production of the adipocytokines can be regulated then the effects, risks, and incidence of metabolic syndrome can be diminished. This is also should be a potential target for future treatment in those with metabolic syndrome.

Razzouk and Munter (2009) have pointed out that metabolic syndrome increases with age. Prevalence seems to rise in women over 50 due to various reasons such as hormone changes and decline in pancreatic B cell function. Prevalence increases in older males as well due to decline in pancreatic B cell function, rise in HDL-C, and increase in glucose intolerance. Since it is well known that metabolic syndrome is more of a risk as an individual ages, it should be a priority for health care providers to begin educating their patients about the risks and effects of metabolic syndrome at an early age. Providers shouldn’t wait until a patient is on the brink of diagnosis to begin implementing education and lifestyles changes. Lifestyle changes such as diet and exercise should be emphasized earlier. However, I feel that most providers do emphasize diet
and exercise, but I feel that providers can educate their patients more effectively about the risks associated with a poor lifestyle. If patients know the risks associated with metabolic syndrome, I believe that they will be encouraged to take the steps necessary to avoid metabolic syndrome.

Miller and Mitchell (2006) provided evidence that the course of pregnancy can help predict the risk of either the child or mother developing metabolic syndrome. Gestational diabetes and Pregnancy Induced Hypertension (PIH) have been shown to be linked with higher incidences of metabolic syndrome in mothers later in life. Not only has Miller and Mitchell (2006) pointed out that gestational diabetes and PIH increased incidence among mothers, but it increases the incidence of metabolic syndrome among the child later in life as well. Also, babies who are small for gestation age or large for gestational age have been associated with an increase in incidence of metabolic syndrome as well (Miller and Mitchell, 2006). Since it is clear that perinatal history is very important and influential in the development of metabolic syndrome, it is crucial that a detailed history of the course of pregnancy be taken. Not only should a history be taken, but most importantly it should become part of the permanent medical record of the mother and child that will always follow them throughout their lifetime. This will help providers assess the risks and provide better care for their patients. This information could help dictate how aggressively to treat a patient or how aggressively to act in the effort to prevent metabolic syndrome and its complications.

It has been well documented that the diagnosis of metabolic syndrome can be accomplished in a number of ways. Providers have to pick from one of the many diagnostic guidelines that have been produced by various respectable organizations. Some providers also use their own clinical judgment and choose to use a combination of the different guidelines to diagnose their patients. The main guidelines for diagnosing metabolic syndrome have been set by The National
Cholesterol Education Program’s (NCEP) Adult Treatment Panel III (ATP III), The World Health Organization (WHO), The American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF). I feel the best diagnostic guidelines have been set forth by The American Association of Clinical Endocrinologists (AACE). According to Grundy et al. (2004), with the AACE criteria there are no defined number of risk factors required for diagnosis. This means that diagnosis is left up to clinical judgment based on risk factors. However, it still assesses the same risk factors when making a clinical judgment: obesity, elevated triglycerides, low HDL cholesterol, elevated blood pressure, family history of hypertension or type II diabetes, cardiovascular disease, sedentary lifestyle, polycystic ovarian syndrome, advancing age, impaired fasting glucose, and insulin resistance (Grundy et al., 2004).

I think that this is the best way to diagnose metabolic syndrome because it allows for more room for clinical judgment. Every patient with this disorder may not fall into preset guidelines that would lead to a diagnosis. Some patients may present in the pre-stage of the diagnosis or they may present atypically. This is why clinical judgment cannot be substituted by guidelines. I think the AACE’s criteria will increase the prevalence because it will include those individuals whose diagnosis is at the pre-stage and those who present atypically. This potential increase in prevalence will only heighten the awareness of metabolic syndrome, which could lead to more research that may result in better treatment that could result in a decrease in diabetes and cardiovascular disease.

Kramer de Aguiar et al. (2006), researched the vascular effects of metformin in first-degree relatives with metabolic syndrome of type 2 diabetic patients. The metformin group showed decreases in the following categories; weight ($p < .05$), BMI ($p < .05$), systolic blood pressure ($p < .03$), total cholesterol ($p = .01$), and fasting plasma glucose ($p = .01$). The metformin group
also showed an increase in HDL cholesterol \( (p < .05) \). Metformin was also associated with endothelium improvement FBF by 111\% \( (p = .01) \). This study showed improvement in several of the components of metabolic syndrome. The main purpose of this study was to evaluate metformin’s effect on endothelial function. Endothelial function was clearly improved, which is vital since one of the primary outcomes of metabolic syndrome is atherosclerotic cardiovascular disease. I conclude that patients with metabolic syndrome should be on metformin to slow the cardiovascular effects of metabolic syndrome. There were some weaknesses associated with this study. One major weakness was that the study consisted of a small sample size that only included 31 individuals. It is hard to make correlations to the general population with such a small sample size. Another weakness of this study was that there was a high drop out rate among the study’s participants. Thirty eight percent of the study’s participants dropped out of the study.

Orchard et al. (2005), researched the effect of intensive lifestyle interventions and metformin therapy on metabolic syndrome’s incidence and resolution. Three thousand people with impaired glucose according to WHO standards participated in this randomized controlled clinical trial and were followed for an average of 3.2 years. Fifty three \% \( (1,711 \text{ people}) \) of the participants in the study were found to have metabolic syndrome at baseline. Incidence was statistically significantly decreased by 41\% in the lifestyle intervention group \( (p < .001) \). The metformin group produced a significant 17\% decrease in incidence compared to placebo \( (p = .03) \). Three year cumulative incidences were 51\%, 45\%, and 34\% in the placebo, metformin, and lifestyle intervention group. These results show that exercise is the best way to decrease the incidence of metabolic syndrome. However, it requires effort and motivation of the patient to have the motivation to make the lifestyle change by committing to exercise. On the contrary, the
simplicity of taking a pill is more attractive to a patient who lacks self motivation or the ability and resources to exercise. It requires less time, less physical exertion, and minimal inconvenience. Even though metformin is less effective, this study does prove that metformin decreases the incidence of metabolic syndrome over time. The major limitation to this study was that it only involved volunteers with impaired glucose tolerance, which limits generalizability. The study only included those with impaired glucose tolerance and not diabetes. Volunteers with metabolic syndrome that developed diabetes as they aged were eliminated. This decreased the prevalence of metabolic syndrome in older patients, which limits generalizability of this study.

Andreadis et al., (2009) researched if the inclusion of metformin in the treatment of overweight and obese patients decreases the incidence of type 2 diabetes mellitus, metabolic syndrome, and if it improves cardiovascular disease risk factors. In this study the metformin group produced better results. At the conclusion of the study, the frequency of type 2 diabetes mellitus patients in the metformin group was 1.1% and 8.1% in the non-metformin group ($p = .012$). Lifestyle modifications are effective in treating metabolic syndrome and minimizing its potential outcomes. Metformin is also effective in doing the same. However lifestyle modifications require a great deal of self motivation and they also require even more of a commitment to sustain them. In my opinion, it is logical to combine lifestyle modifications with metformin, which I believe would limit the duration of therapy and result in less of a long term commitment if both therapies can work synergistically. A weakness in this study is that is does not include any patients over the age of 65 since the use of metformin is used with caution in elderly patients. This limits generalizability to the normal population.
Vitale et al., (2005) investigated the effect of metformin on endothelial function and insulin resistance in patients with metabolic syndrome. Sixty five participants with metabolic syndrome, consisting of 37 men and 28 women, average age of 54 years old were treated with 500 mg of metformin twice daily or received a placebo. Thirty two subjects received the metformin and thirty three received the placebo. Patients who received metformin exhibited endothelium-dependent vasodilatation and insulin resistance when compared to the placebo. Also an correlation between the improvement in insulin resistance and the in endothelial function was found. It was concluded that metformin improves endothelium function and insulin resistance in patients with metabolic syndrome. One weakness of this study was the use of the HOMA index instead of using the euglycaemic or the hyperinsulinaemic clamp to evaluate insulin resistance. The euglycaemic and the hyperinsulinaemic clamp are considered the gold standard method to measure insulin resistance. The HOMA index was used because it has been shown to be effective and it is also more economical. The finding of this study advocates the key role that insulin resistance plays in endothelial dysfunction. In my opinion the role of insulin resistance has not been investigated enough. During my clinical experience most providers when suspecting diabetes, measure fasting glucose to see if a patient has diabetes. In my opinion, if the glucose measurements do not meet the diagnostic criteria for diabetes it does not mean a patient should not be treated with metformin. This patient still may have insulin resistance. I feel that further research needs to be done on the role of insulin resistance in metabolic syndrome, ways to evaluate insulin resistance, and if ordering insulin values as a standard laboratory test should be considered.

E. Meaney, Vela, Samaniego, A. Meaney, Asbun, Zempoalteca, Elisa, Emma, Guzman, Hicks, and Ceballos investigated the effect of metformin in patients with metabolic syndrome on
the following variables; BMI, waist circumference, systolic and diastolic blood pressures, total cholesterol, HDL and LDL cholesterol, triglycerides, fasting glucose, nitrooxidant metabolites, nitric oxide, carotid vascular stiffness, carotid intima media thickness (IMT), and C-reactive protein. Sixty patients with at least three diagnostic criteria for metabolic syndrome were divided into two groups. Both groups received similar diet counseling, but only one group received metformin 850 mg once daily and were followed for one year. After one year of follow up, both groups showed a decreased in weight, waist circumference, and blood pressure. However patients on metformin also displayed decreased in triglycerides, IMT, carbonyls, dityrosines, and AOPP. The metformin group exhibited a decrease in CRP and an increase in nitro oxide which indicates better endothelial function. For the most part this was a well conducted study. One weakness is a small sample size, which limits generalizability. In my opinion this data shows the benefit of metformin. Metformin tackles so many of the underlying issues that cause metabolic syndrome, which eventually leads to diabetes and heart disease. I think by aggressively medicating those individuals in the pre-diabetic state will greatly reduce the number of individuals with diabetes and ASCVD. By aggressively treating early instead of allowing the patient the chance to change their lifestyle will save lives and increase the quality of life and the length of many people’s lives. There are too many social, behavioral, and psychological factors that come into play when a patient is asked to diet and exercise. More attention needs to be paid to the biological factors of metabolic syndrome.

Daad Akbar (2002) investigated the effect of the metformin and glibenclamide on the serum level of C-reactive protein (CRP) in well controlled type 2 diabetics with metabolic syndrome. The study consisted of 110 patients with well-controlled blood glucose levels on metformin or glibenclamide alone without any major medical illnesses. Sixty five subjects received
metformin, while forty five received glibenclamide. The CRP was significantly lowered in the metformin group compared to the glibenclamide group ($p=.01$). A statistical significant positive correlation between the CRP level and BMI ($r = 0.37$) was seen as well. A weakness to this study is that there is a small sample size. The results of this article further prove that metformin is a viable drug to treat metabolic syndrome because it does more than just tackle insulin resistance. Chronic elevated levels of CRP are a risk factor for cardiac disease. In my opinion the broad effects of metformin are invaluable because it addresses many of the factors that make up metabolic syndrome.

**Chapter 4**

**Conclusion**

The purpose of this literature review was to determine pathophysiology, risk factors, prevalence, and clinical outcomes, and clarifications of metabolic syndrome and to determine if metformin is an effective treatment of metabolic syndrome. After reviewing the literature on the subject, in my opinion metformin is an effective treatment of metabolic syndrome. This is relevant to the Physician Assistant profession because the profession was created to function in a primary care setting. Diabetes and heart disease are major issues and very common health problems encountered everyday. If there is a better way to treat those with metabolic syndrome to prevent the deadly effects of diabetes and atherosclerotic cardiovascular disease it will help Physician Assistants treat, save, and better the lives of their patients.
References


Abstract

**Objective:**

This review explored the pathophysiology, risk factors, signs and symptoms, and diagnosis of metabolic syndrome and determined if metformin is an effective treatment of metabolic syndrome.

**Method:**

The search engines predominately used for the article were medline, pubmed, and Ohio link. The main search terms used were metabolic syndrome, metformin, Syndrome X, risk factors, prevalence, treatment, and prevention.

**Result:**

Those with metabolic syndrome that go untreated or diagnosed will develop diabetes or atherosclerotic cardiovascular disease. Metformin can be implemented in the early stages of metabolic syndrome to reduce the risks of type II diabetes and heart disease.

**Conclusions:**

Metabolic syndrome is a very common disease in the United States and worldwide. Metformin can reverse the effects of metabolic syndrome due to its broad effects on many of the components of metabolic syndrome; thus preventing diabetes and heart disease.