• REVIEW ARTICLE •

Metabolic Syndrome among Puerto Ricans and other Hispanic Populations

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Metabolic syndrome is a cluster of risk factors for cardiovascular disease that affects an estimated 50 million Americans. The present article reviews this syndrome with respect to its definition, epidemiology, pathophysiology, and management. A primary focus in research has been to elucidate the processes that have been determined to cause insulin resistance, the fundamental mechanism underlying metabolic syndrome; these processes are reviewed here along with the interplay of the syndrome with the renin-angiotensin system, circadian rhythm, and atherosclerosis. Lifestyle changes promoting exercise and a healthy diet can reduce the incidence and prevent the progression of metabolic syndrome; however, refractory cases may warrant drug therapy. Recent emphasis has been placed on targeting obesity and insulin resistance as new therapeutic modalities are developed. In this manuscript, the incidence, component characteristics, and complications of metabolic syndrome in island-living Puerto Ricans and other Hispanic populations are described. The fact that island patients suffering from the syndrome tend to have less aggressive coronary disease and relatively normal lipid profile compared to their stateside counterparts is also discussed. ***[P R Health Sci J 2011;30:145-151]***

Key words: Metabolic Syndrome, Obesity, Cardiovascular Diseases

The recognition of metabolic syndrome as a pathological entity is one of the most important advancements in the management of cardiovascular disease in the last 2 decades. The increasing awareness of and research into this syndrome has led to a deeper understanding of how different metabolic risk factors such as insulin resistance and vascular pathologies such as coronary heart disease (CHD) interact and aggravate one another. In an age when approximately 50 million Americans are estimated to be afflicted by metabolic syndrome, it is imperative to comprehend this cluster of risk factors to its fullest extent for the sake of the public health of the United States and of Puerto Rico.

The National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) identified 6 components of metabolic syndrome that relate to cardiovascular disease (CVD): abdominal obesity, atherogenic dyslipidemia, increased blood pressure, insulin resistance, the proinflammatory state, and the prothrombic state. Framingham data analysis demonstrated that the presence of metabolic syndrome alone predicted approximately 25% of all new-onset CVD but that in the absence of diabetes, it did not raise the 10-year risk for CHD to above 20%, which is the threshold for a CHD risk equivalent, according to the ATP. Metabolic syndrome without diabetes raises the 10-year risk for CHD to between 10 and 20%.

The Components of the Syndrome

There has been controversy in the past few years about the definition of metabolic syndrome. Recently, the need for a global definition has brought about the initiative of the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), joined by the World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity, to develop one unified definition of metabolic syndrome. Furthermore, it has been agreed that abdominal obesity should not be considered to be a prerequisite for diagnosis but instead 1 of the 5 criteria (1). The presence in a single individual of any 3 of the following 5 risk factors can be used to establish a diagnosis of metabolic syndrome: 1) Elevated waist circumference (cut-points based on population and country-specific definitions; until more data are available, it is recommended that the IDF cut-points, 94cm or more in

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men and 80 cm or more in women, be used for non-Europeans and that either the IDF or the AHA/NHLBI cut-points, 102 cm or more in men and 88 cm or more in women, be used for people of European origin), 2) a triglyceride count equal to or greater than 150 mg/dL, 3) a high density lipoprotein (HDL) level of less than 40 mg/dL in men and 50 mg/dl in women, 4) blood pressure equal to or greater than 130/85 mmHg, and 5) a fasting blood glucose equal to or greater than 100 mg/dL. Certain combinations of metabolic syndrome components confer greater risks of developing CVD and dying. A 10-year study evaluating the progression of metabolic syndrome and its components determined that participants who acquired the syndrome having a combination of abdominal obesity, high blood pressure, and hyperglycemia had a 2.36-fold increase in the incidence of CVD and a 3-fold increase in mortality (2). This study determined 2 risk-factor combinations that confer a greater risk of cardiovascular morbidity and mortality compared with the others: 1) high blood pressure coupled with either central obesity and hyperglycemia, or 2) high blood pressure along with dyslipidemia.

Pathophysiology

Insulin Resistance

Insulin resistance is a fundamental mechanism underlying metabolic syndrome and its components. Insulin is an anabolic hormone that exerts its effects primarily by promoting glycogen synthesis in the liver and muscle, increasing triglyceride synthesis in adipose tissue, and augmenting protein synthesis and inhibiting proteolysis. Therefore, the consequences of insulin resistance are multifold. Magnetic resonance spectroscopy studies have determined that insulin resistance in skeletal muscle manifests specifically as a reduction of insulin-stimulated glucose transport into the cell via the glucose transporter-4 (GLUT-4) (3). This reduced transport is caused by lipid overload in the form of the accumulation of long-chain acyl-CoA (LCCoA) and diacylglycerol (DAG) inside the skeletal muscle cell. This lipid overload stimulates the serine/threonine kinase cascade and the phosphorylation of critical insulin-receptor sites (IRS-1), thus inhibiting IRS-1 binding and activation and in turn leading to reduced glucose transport and subsequent hyperglycemia (4). Tissue resistance to insulin causes the pancreas to increase insulin secretion, resulting in systemic hyperinsulinemia

There have been a number of processes determined to cause insulin resistance, but they can be categorized in 2 general mechanisms: lipid overload and cytokine-induced inflammation. Lipid overload (occurring in skeletal muscle, the liver, and other tissues) is brought on by increased fatty acid uptake, increased synthesis within the tissue involved, and diminished fatty acid oxidation and disposal. Insulin resistance in adipocytes leads to increased lipolysis, with subsequent elevations in free fatty acids and accumulation in the ectopic sites mentioned above. Increased fatty acid concentrations are typical of most insulin-resistant states, such as type 2 diabetes and obesity. Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor-gamma (PPARγ) agonists, have been shown to increase insulin sensitivity by lowering plasma free fatty acid levels and ectopic accumulation. These insulin sensitizers have also been shown to shift the distribution of fatty acids away from abdominal and intramuscular deposits and into subcutaneous fat (5). Abdominal obesity in particular has been shown to be most associated with insulin resistance and metabolic syndrome. It has been observed that general obesity is not universal in metabolic syndrome or in insulin resistance. In addition, many obese subjects do not have metabolic abnormalities.

In addition to the above, insulin resistance is associated with a systemic chronic inflammatory response characterized by altered cytokine production and the activation of inflammatory signalling pathways. Activation of signalling intermediates may be directly involved in serine phosphorylation and the inhibition of the binding and activation of IRS-1. In addition, inflammatory cell/cytokine infiltration of adipose tissue may alter adipocyte lipid metabolism. In mice, fat-derived cytokines activate the nuclear factor-κB signalling pathway in hepatocytes and generate systemic insulin resistance, most likely through the generation and actions of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (6). TNF-α expression, which has been associated with insulin resistance for more than a decade, is increased in adipose tissue in obese rodents and humans (7), and the infusion of TNF-α antibodies reduces insulin resistance in rodents but not in humans (7, 8). It has also been found that obesity increases the macrophage content of adipose tissue (9). Moreover, subcutaneous adipose tissue express significantly more leptin and less TNF-α than do abdominal tissue (10). Clinically, each of the components of metabolic syndrome has been associated with increased levels of C-reactive protein (CRP), a non-specific sign of inflammation (11).

Adipose tissue is a hormonally active tissue, producing cytokines, such as TNF-α and IL-6, that influence other body tissues. Adiponectin is one such adipocytokine that increases insulin sensitivity by stimulating fatty acid oxidation, decreasing plasma triglycerides, and improving glucose metabolism. Serum levels of adiponectin are reduced in individuals with visceral obesity and states of insulin resistance. On the other hand, weight loss induces adiponectin synthesis (12), as do thiazolidinediones (through their activation of PPARγ). Furthermore, a reduced plasma level of adiponectin has been found in people who have a history of cigarette smoking (13) as well as in hypertensive patients (14). The role of adiponectin has not been definitely established, but it

may be a factor in explaining the association between insulin resistance, hypertension, and CVD. Another adipocytokine, leptin, has been shown to improve glucose homeostasis in lipodystrophic mice and humans but has failed to correct hyperglycemia in patients with obesity, supporting the concept of leptin resistance and its association with insulin-resistance states (15).

Renin-Angiotensin System (RAS)

Activation of the renin-angiotensin system (RAS) occurs in many cardiovascular disorders. The inhibition of this system by angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARB) has been a mainstay therapy for reducing the onset and/or progression of hypertension, left ventricular dysfunction, diabetic renal disease, and atherosclerosis. It has been theorized that increased levels of angiotensin II (AII) inhibit pre-adipocyte differentiation into mature adipocytes, thus impairing the ability of fat cells to store fat, which in turn shunts fatty acids into visceral organs and worsens insulin resistance (16). Moreover, angiotensin II, which acts largely through the AT1 receptor (present in various tissues such as the heart, blood vessels, kidney, and adipocytes), is a strong stimulus for the increased oxidative stress that is fundamental in exacerbating endothelial dysfunction, inflammation, and plaque formation through additional vessel macrophage and T-lymphocyte recruitment. ACE inhibitors and ARB not only promote adipocyte differentiation, but they also have peripheral vasodilatory effects that lead to improved skeletal muscle perfusion and glucose uptake, thereby improving insulin sensitivity. Furthermore, it has been shown that long- and short-term inhibition of RAS can reverse or halt the progression of endothelial dysfunction through increased nitric oxide (NO) bio-availability, reduced oxidative stress, and the anti-inflammatory modulation of cell surface and circulating adhesion molecules (17).

Insulin Resistance and Atherosclerosis

Insulin resistance, inflammation, and atherosclerosis seem to be linked via metabolic syndrome, but it still has not been completely elucidated whether the nature of this association is due either to a common molecular pathology related to insulin receptor signalling (IRS binding and activation) or to the vascular consequences of insulin resistance. There are 2 potential mechanisms: the deregulated production of inflammatory cytokines and the elevated levels of systemic oxidative stress (18). Thus, obesity-derived pro-inflammatory cytokines (i.e., IL-6, TNF-α) and reactive oxygen species can generate peripheral insulin resistance but can also have a direct impact on the endothelium, causing endothelial dysfunction and initiating the atherosclerotic cascade. The inflammatory nature of atherosclerosis has been further substantiated by the demonstration of a correlation between high-sensitivity CRP (hsCRP) levels and a greater risk of cardiovascular events, confirming hsCRP to be a strong and independent predictor of future myocardial infarction and ischemic stroke (19). Making routine plasma CRP level readings has been suggested as a strategy for monitoring statin therapy, which therapy has been proven to have anti-inflammatory in addition to lipid-lowering effects (20).

The process of atherosclerosis is characterized by an increased pro-thrombotic milieu, disordered lipid accumulation, and endothelial dysfunction. In experimental models that mimic insulin resistance, vasodilation is impaired partly because of insulin's inability to stimulate the activity of NO synthase, the enzyme responsible for NO synthesis. It is now established that the vascular endothelium must be intact and that NO plays a critical role in mediating the hemodynamic actions of insulin. In addition, insulin resistance and metabolic syndrome often accompany elevated levels of fibrinogen and plasminogen activator inhibitor 1 (PAI-1), the main inhibitor of the fibrinolytic system (21). The more severe the metabolic syndrome, the higher the plasma level of PAI-1 (22). Increased PAI-1 levels may predispose patients to the formation of atherosclerotic plaques that are prone to rupture and that have a high lipid-to-vascular smooth muscle cell ratio as a result of decreased cell migration (23).

Circadian Rhythm and Metabolic Syndrome

There have been numerous studies that have shed light upon the relationship between the circadian rhythm and the body's cardiovascular and metabolic health. Common disorders of circadian behaviour and sleep, such as night-shift sleep disorder and jet lag, are associated with increased hunger, decreased glucose and lipid metabolism, and changes in the hormonal processes involved in satiety (24). Short-duration and poor-quality sleep have been shown to predict the development of type 2 diabetes and obesity after age, BMI, and various other confounding variables are considered (25). In addition, the induction of hunger may be associated with a reduction in circulating levels of leptin brought on by sleep deprivation (26). Cardiovascular disease and hypertension are also related to sleep loss, as the risk of a fatal heart attack increases 45% in individuals who chronically sleep 5 hours per night or less (27).

Management

Diet and Exercise

Lifestyle approaches to treating and preventing metabolic syndrome greatly improve metabolic parameters by reducing body weight and increasing the level of physical activity. Multiple studies of obese patients with type 2 diabetes, hypertension, or hypercholesterolemia have shown that having a lower weight improves the cardiovascular profile of a given patient, including glycemic control, in both diabetic and non-diabetic individuals. Furthermore, lifestyle changes comprising reduced

total/saturated fat intake and increased polyunsaturated fat/fiber intake have been shown to significantly reduce multiple metabolic and inflammatory parameters such as hsCRP, central obesity, and triglyceride levels (28).

The Mediterranean diet has received much attention in the last few years as an ideal diet to follow for the metabolic and cardioprotective benefits it may confer. The ATTICA epidemiological study showed that adherence to the Mediterranean diet was associated with 20% lower odds of having metabolic syndrome, irrespective of age, sex, physical activity, and lipid and blood pressure levels (29). The diet is low in saturated fat, high in monounsaturated fat (mainly from olive oil), high in complex carbohydrates from legumes, and high in fiber (mostly from vegetables and fruits). Moreover, the Mediterranean diet has been associated with improvements in the blood lipid profile, in particular HDL cholesterol and oxidized LDL, a decreased risk of thrombosis, improvements in endothelial function, lowering insulin resistance, and a decrease in body fat.

Physical activity is a cornerstone in weight balance. However, only part of the beneficial effect of physical activity on the metabolic and cardiovascular profile is mediated through body-weight changes. Physical activity improves insulin sensitivity, increases HDL levels, and lowers blood pressure. The ATTICA study, which also evaluated the association between physical activity and the prevalence of metabolic syndrome, showed that even light-to-moderate leisure time physical activity (<7 kcal/min expended) was associated with a considerable reduction in the prevalence of metabolic syndrome, while regular, intense exercise was associated with a much greater decrease (29). The level of physical activity needed for a beneficial impact on coronary risk remains controversial. The Center for Disease Control and Prevention and the American College of Sports Medicine recommend the accumulation of at least 30 minutes of moderate-intensity physical activity (equivalent to brisk walking at 3-4 mph) on most days of the week.

Pharmacotherapy

Intense therapeutic lifestyle modifications may prevent the onset and progression of metabolic syndrome, but some patients may require drug therapy. While the individual components (e.g., glucose intolerance, hypertension, dyslipidemia) are all appropriate targets for treatment, newer therapies that manage the syndrome centrally may benefit from such a collective approach and thus prove more effective. Although traditional approaches to the separate risk factors have proven effective, increasing attention is now being directed at the management of insulin resistance and obesity.

One of the main obstacles patients with metabolic syndrome face is achieving and sustaining weight loss, and many times pharmaceutical treatments are required. Recently published guidelines recommend that adjunctive drug treatment for obesity should be considered in patients with a body mass index (BMI) equal to or greater than 30 or a BMI of 27 to 29.9 concomitant with medically complicated obesity (30). Orlistat, a gastrointestinal lipase inhibitor, sibutramine, a centrally acting monoamine reuptake inhibitor, and rimonabant, an endocannabinoid receptor antagonist, are all approved for long-term treatment of obesity; but all anti-obesity drug trials have been limited by their high attrition rates and lack of long-term cardiovascular morbidity and mortality data.

TZDs, the mechanism of which was explained above, have been used increasingly over the recent years for the management of diabetes and have greatly broadened the understanding of the pathophysiology of insulin resistance. These peroxisome proliferator activator receptor agonists act at a nuclear level to improve glycemia, decrease insulin resistance, and variably decrease plasma triglyceride levels and increase HDL cholesterol levels (31). Specifically, pioglitazone reduced triglycerides and increased HDL levels to the same degree of either statins or fibrates in a large observational study (32). Metformin, another anti-diabetic drug, has also been shown to decrease insulin resistance, hepatic glucose production, triglycerides, and cholesterol (33).

The ongoing search for new strategies to combat metabolic syndrome has shed light on new molecules that may prove to be effective therapeutic targets in treating the syndrome; researchers working with stearoyl-coenzyme A desaturase 1 (SCD1) are in the vanguard of this search (34). By catalyzing the conversion of long-chain saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs), SCD1 promotes multiple aspects of metabolic syndrome. However, it was subsequently established that an anti-inflammatory function exists for SCD1, as its inhibition or deletion in mice accelerates atherosclerosis (35). SCD1 may indirectly suppress inflammation by preventing SFA-induced toll-like receptor 4 (TLR4) inflammatory signalling and SFA enrichment of membranes (35). Fortunately, recent in vivo studies have established that SCD1 inhibition-driven atherosclerosis can be completely prevented by the omega-3 polyunsaturated fatty acids in dietary fish-oils (36), thus providing a novel and synergistic approach to treating metabolic syndrome and atherosclerosis.

Hispanics and Metabolic Syndrome

Presently, 45.5 million Hispanics live in the United States, comprising 15% of the total population. The majority of Hispanics in the U.S. are of Mexican origin (64%); other significant populations are Puerto Ricans (9%), Cubans (3.4%), and Dominicans (2.8%) (37). Hispanics are nearly twice as likely to have diabetes as are age-matched whites. The high prevalence of diabetes in this ethnic population has been attributed to higher rates of obesity (38), highly atherogenic diets, and genetic susceptibility (39) Moreover, a genetic link

between being Hispanic and having an increased susceptibility to insulin resistance has been reported (40).

The distinct metabolic characteristics that members of the Puerto Rican population (be they located on the island, in the U.S., or elsewhere) may possess could pose a significant threat to those individuals and, thereby, to public health; with regard to this population, then, the specifics of metabolic syndrome warrant special attention. In Puerto Rico, the prevalence of diabetes is more than 12.7%, while in the U.S., it is 8.2%. The death rate per 100,000 people related to diabetes has increased from 10.6% to 66% in the last 4 decades (41), and heart disease continues to be the leading cause of death on the Caribbean island. A recent cross-sectional study (42) performed in the capital city of San Juan, Puerto Rico, showed that the age-standardized prevalence of metabolic syndrome was 38.1%, slightly higher than the 34% prevalence found in the general United States population (individuals 20 years of age or older). In addition, this study demonstrated that the prevalence of metabolic syndrome significantly rose with age, increasing from 12.8% among participants aged 21 to 29 years to 58.2% for participants aged 70 to 79 years. Elevated glucose (49.8%) and abdominal obesity (49.0%) were the most common components of metabolic syndrome present in the sample studied, followed by elevated blood pressure (46.1%), reduced high-density lipoprotein cholesterol (46.0%), and elevated triglycerides (31.3%). Noteworthy is the fact that, in the study sample, 36.7% of the participants were overweight and 40.8% were obese, a higher prevalence than the self-reported estimates for the U.S. population (39.4% overweight and 24.7% obese) provided by the 2006 Behavioral Risk Factor Surveillance System (BRFSS) report compiled by the Centers for Disease Control and Prevention (43).

The inner workings of the metabolic syndrome have yet to be fully elucidated; thus it remains difficult to evaluate how they differ between specific ethnic populations. Nevertheless, it remains a possibility that the processes involved in the syndrome, such as insulin resistance and endothelial dysfunction, differ in degree and function with relation to Hispanic compared to non-Hispanic populations. It has been a recurring theme that the interactions between poor nutrition, physical inactivity, and genetic predisposition might contribute to the disparities seen in the prevalence and characteristics of metabolic syndrome and its components between ethnicities and the subgroups within; this subject has been studied to the extent that even the diagnostic criteria for metabolic syndrome established by the AHA/NHLBI were challenged when these criteria were being adapted to a specific Andean population (44). Moreover, researchers have found that a single DNA variation in the form of a guanine base pair on a gene already linked to a higher risk of (CHD) in other races confers a 5-fold reduction in risk in African-Americans (45).

Previous data support the fact that increased serum cholesterol levels result in fewer myocardial infarctions in Puerto Rico than occur on the mainland (46); however, the validity of these data may not be as strong today as when published nearly 3 decades ago: recent epidemiologic data show that although mortality from coronary disease and stroke has been steadily decreasing in the United States in the past 4 decades, it had been increasing in Puerto Rico (47). On the other hand, a recent study that examined the medical records of 173 patients with metabolic syndrome who received treatment in the Cardiovascular Center of Puerto Rico and the Caribbean found these patients to be devoid of aggressive coronary artery disease meaning less ventricular tachycardia, less myocardial infarctions and less strokes (48) and having a relatively normal lipid profile (except for a mild elevation of serum triglycerides), supporting the notion that island-based Puerto Ricans acquire a milder form of metabolic syndrome than do mainland populations (which notion extends to Hispanic and Caucasian populations living in the continental U.S.) (49). Furthermore, several investigators have reported that the incidence of ventricular tachycardia, a complication caused by remodelling and ischemia of the heart, is lower in Puerto Rico than it is in the United States (50), even when adjusting for a higher prevalence of metabolic syndrome in Puerto Rico. In addition, the prevalence of CHD is lower in Puerto Rico than in the United States. Nonetheless, the prevalence of CHD in Puerto Rico is increasing: In the 1980s, it was 50% lower in Puerto Rico than in the United States; it is only 20% lower today (51) This is most likely due to external factors, such as the increasingly unhealthy diet and sedentary lifestyle of many of the island's inhabitants.

Situational factors have also been reported to be related to the incidence of metabolic syndrome in Hispanic populations. A cross-sectional analysis that examined associations between television viewing and metabolic syndrome among a representative sample of Puerto Rican and Dominican seniors living in Massachusetts showed a high prevalence of metabolic syndrome that was associated with prolonged television viewing, independent of physical activity and energy intake (52). Furthermore, a study that evaluated the frequency of metabolic syndrome and its relationship with socioeconomic position and education in women of largely Caribbean Hispanic origin showed an alarming rate of the syndrome in less educated Caribbean Hispanic women and was independently associated with lower education level (53). Although no generalizations can be made from these studies, they highlight both the complexity of metabolic syndrome and the human body's connection to the psychological stress caused by the outside world.

Despite the obvious limitations of studying a population that does not represent the entire Hispanic world, further investigations exploring cardiovascular disease in Puerto Ricans are of utmost importance if we are to further our understanding

of the roles played by genetics, environment, and culture in the modification of cardiovascular health. Ultimately, the ongoing message continues to be that stronger efforts to control cardiovascular risk factors and to improve the management of diabetes, hypertension, and the other components of metabolic syndrome need to be made and are essential for the citizens of the United States and of Puerto Rico.

Resumen

El síndrome metabólico es una agrupación de factores de riesgo para enfermedad cardiovascular que afecta un estimado de 50 millones de americanos. Este artículo repasa el síndrome metabólico con respecto a su definición, epidemiología, patofisiología y manejo terapéutico. Un enfoque investigativo primario ha sido elucidar los procesos que determinan la resistencia a la insulina, el mecanismo fundamental que causa el síndrome metabólico; estos procesos son descritos, junto a la interacción entre el síndrome metabólico con el sistema de renina-angiotensina, el ritmo circadiano y la arteriosclerosis. La incidencia y progresión del síndrome metabólico pueden ser prevenidas en la mayoría de sus casos modificando el estilo de vida a favor de una dieta saludable y mayor actividad física; sin embargo, hay casos que necesitan farmacoterapia. Recientemente, se ha puesto mayor énfasis en las modalidades terapéuticas que modulan los mecanismos que causan la obesidad y la resistencia a la insulina. En este manuscrito se describen la incidencia, características de los componentes y las complicaciones del síndrome metabólico en la isla de Puerto Rico y en otras poblaciones hispanas. Finalmente, se discute el hecho que los pacientes con el síndrome en Puerto Rico tienden a tener una enfermedad coronariana menos agresiva y un perfil de lípidos relativamente normal que sus contrapartes en Norteamérica.

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