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## Review Article

# The Metabolic Syndrome in Hispanics – The Role of Inflammation

### Abstract

We report clinical and molecular mechanisms relating the pro-inflammatory and anti-inflammatory process in the development of the components of the metabolic syndrome, emphasizing the cardiovascular problems developed in these groups of patients, especially the Hispanic population. Namely, the incidence, component characteristics and complications of the metabolic syndrome in island Puerto Ricans are described and evidence is presented supporting the fact that the metabolic syndrome may be milder in Puerto Rico than in the mainland United States because it is characterized by less aggressive coronary artery disease and a relatively normal lipid profile. Moreover, data supports the fact that increased serum cholesterol levels produce less myocardial infarctions in Puerto Rico than in mainland Hispanics and Caucasians. In addition, the incidence of ventricular tachycardia, a complication caused by remodeling and ischemia of the heart, may be lower in Puerto Rico than in the United States, although the prevalence of the metabolic syndrome is higher in the island.

## Abbreviations

MetS: Metabolic Syndrome; CHD: Cardiac Heart Disease; DNA: Deoxyribonucleic Acid; BDNF: Brain Derived Neurotrophic Factor; PR: Puerto Rico; US: United States; RAS: Renin Angiotensin System; AngI: Angiotensin I; Ang II: Angiotensin II; E1: Endothelin 1; ACE: Angiotensin Converting Enzyme; ARBs: Angiotensin Receptor Blockers; AGEs: Advanced Glycation End Products; DMT2: Diabetes Mellitus Type 2; AT1: Angiotensin receptor Type 1; AT2: Angiotensin receptor Type 2; EPA: Ecosapentaenoic Acid; OHA: Docosahexaenoic Acid; TNF:α: Tumor Necrosis Factor; IL:6: Interleukin:6; CRP: C: Reactive Protein; BMI: Body Mass Index; SCD1: Stearoyl Coenzyme A Desaturase 1; TC: Total Cholesterol; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; FBS: Fasting Blood Sugar;

## Introduction

The acknowledgment of the metabolic syndrome (MetS) as a pathological entity is one of the most important advancements in the management of cardiovascular disease in the last 2 decades. Three of 5 following risk factors establishes the diagnosis: 1) Elevated waist circumference of 102cm or more in men and 88cm or more in women, 2) triglyceride count equal or greater than 150 mg/dL, 3) high density lipoprotein (HDL) level less than 40 mg/dL in men and 50 mg/dl in women, 4) blood pressure equal or greater to 130/85 mmHg, and 5) a fasting blood glucose equal or greater than 100 mg/dL. Increasing awareness and research of this syndrome has led to a deeper understanding of how different metabolic risk factors such as inflammation, insulin resistance and vascular pathologies such as coronary heart disease (CHD) interact and aggravate one another. The existence of MetS may imply uniformity in pathology across a range of populations. However, this is not the case: the mechanisms

that underlie MetS and the cardio metabolic consequences they hold may very well vary between ethnicities. The following paper aims to encompass MetS from its most fundamental principles with a focus on inflammation and insulin resistance to the novel research pertaining to its pathophysiology and management, with an emphatic eye on the Hispanic population and inflammation.

## Metabolic syndrome in hispanics

The inner workings of MetS 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 inflammation and insulin resistance, 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 nutritional status, physical inactivity, and genetic predisposition might contribute to the disparities in the prevalence and characteristics of MetS and its components between ethnicities and the subgroups within; this subject has been studied to the extent that even the diagnostic criteria for MetS established by the AHA/NHLBI has been challenged when adapted to specific Andean population [1]. 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 Coronary Heart Disease (CHD) in other races confers a fivefold reduction in risk in African-Americans [2]. Lately, research has uncovered mutations in the Brain-derived neurotrophic factor (BDNF) gene, or *Bdnf* gene, which result in human obesity [3]. Mice having a truncated long *Bdnf* 3' UTR genetic transcript developed severe hyperphagic obesity. All these studies, whether they involve humans or mice, provide a window into a genetic basis for MetS.

Despite the obvious limits of studying a population that does not represent the entire Hispanic world, investigations exploring

cardiovascular disease and MetS in Puerto Rico (P.R.) provide invaluable information in understanding the interrelationship between genetics, environment and culture in the modification of cardiovascular health. Previous data support the fact that, given the same cardiovascular risk factors, Puerto Rico has a lower prevalence of CHD than other fully industrialized countries such as the United States [4], 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 CHD and stroke has been steadily decreasing in the United States in the past 4 decades, it has been increasing in Puerto Rico [5]. On the other hand, a recent investigation that examined the medical records of 173 patients with MetS who received treatment in the Cardiovascular Center of Puerto Rico and the Caribbean showed that these patients were devoid of aggressive CHD, meaning less ventricular tachycardia, less myocardial infarctions and less strokes, and had a relatively normal lipid profile (except for a mild elevation in serum triglycerides) [6], supporting the notion that island-based Puerto Ricans acquire a milder form of MetS than mainland populations (this notion extends to Hispanics and Caucasians living in the continental U.S.). Furthermore, several investigators have reported that the incidence of ventricular tachycardia, a complication caused by remodeling and ischemia of the heart, is lower in Puerto Rico than in the U.S.A. [7], even when adjusting for a higher prevalence of MetS in Puerto Rico [8]. Interestingly, the number of cases recorded in this study showed an increased incidence of atrial fibrillation [9]; this may be thought to be a result of differential remodeling of the left ventricle and atrial function between ethnicities. In addition, the prevalence of CHD is lower in P.R than in the U.S.A., despite a higher incidence of Diabetes Mellitus in the island than in the U.S. (16% vs. 8%)[10]. Nonetheless, the prevalence of CHD in P.R. is increasing: In the 1980s, it was 50% lower than in the United States; it is only 30% lower today [10]. This is most likely due to external factors such as the increasingly unhealthy diet and sedentary lifestyle of many of the island's inhabitants.

### Importance of the Renin-Angiotensin System (RAS)

The RAS is a complicated and essential system in the regulation of vascular homeostasis. Angiotensin II (AngII) is cleaved from angiotensin I (AngI) by angiotensin converting enzyme (ACE), which is localized on the surface of endothelial cells and in the media and adventitia of the aorta [11], a soluble form of ACE is also found in plasma. Ang I is formed from angiotensinogen, which is secreted from the liver and cleaved by renin, which in turn is found in the juxta-glomerular cells in the kidney [12]. The traditional RAS inhibitors, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), target the main RAS axis described above. However, there are additional enzymes associated with the production of AngII, such as by Cathepsin G [13], as well as other, more novel angiotensin molecules that serve as potential therapeutic targets: the ACE2/Ang-(1-9) axis is a new and important pathway to compensate for the vasoconstrictive and hyper proliferative RAS axis. A direct mechanism implicated in the production of these distinctive angiotensin molecules involves ACE2 [14], a novel component of the RAS that converts AngI to Ang-(1-9) and AngII to Ang-(1-7), a peptide with vasodilator and anti-proliferative properties. The induction of ACE2 not only holds

therapeutic promise by producing the anti-inflammatory Ang-(1-7), but also by reducing AngII levels, thereby inflammation conferring a twofold protection against cardiovascular remodeling from ongoing hypertension and inflammation.

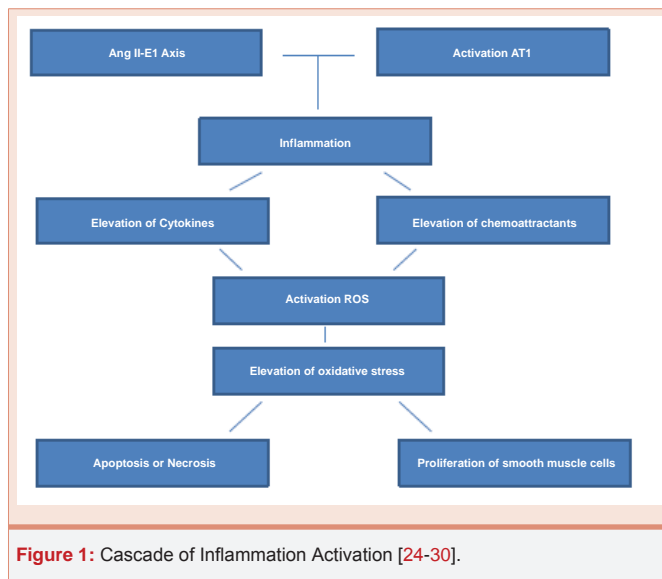
Concomitant to the progression of the RAS, hyperglycemia promotes the deposition of advanced glycation end products (AGEs) that are formed from the non-enzymatic glycation of proteins and lipids after contact with reducing sugars [15]. The accumulation of AGEs is an important factor in the development and progression of vascular injury in diabetes-associated atherosclerosis. Both hyperglycemia and induction of the main RAS axis will increase inflammation and oxidative stress increasing the rate of the atherosclerotic process that ultimately end in apoptosis and necrosis of myocytes [16,17], hence propagating the deleterious effects of inflammation, insulin resistance and endothelial dysfunction.

The inhibition of the RAS by ACE inhibitors and ARBs has been mainstay therapy to reduce the onset and/or progression of hypertension, left ventricular dysfunction, diabetic renal disease and atherosclerosis, because this effect will reduce inflammation. For example, inhibitors of the RAS seem to be more effective than other medications in halting the progression of dilated cardiomyopathy in hamsters that have an inherited mutation that predisposes to such a disease [18]. In rodents, pharmacological or genetic disruption of RAS action prevents weight-gain, promotes insulin sensitivity and relieves hypertension [19], suggesting that ACE inhibitors or ARBs may present an effective treatment for MetS in humans. In addition, when obese individuals lose weight, both adipose tissue mass and systemic RAS activity are reduced and altered [20-23].

### Inflammation- insulin resistance- new data

Systemic inflammation [24,25] is a fundamental process in the development of cardiovascular disease in patients with MetS, and this process starts with the activation of the neurohormonal system; we have data that shows elevated intra-coronary levels of AngII and endothelin I (EI) in some patients with Diabetes Mellitus Type 2 (DMT2). We measured these peptides in 5 patients with DMT2 and concomitant MetS, normal coronary arteries and sub-normal ejection fraction ( $49 \pm 5\%$ ), and discovered that the levels of AngII and EI were elevated in the coronary sinus (coronary efflux) and aorta of these patients when compared to the control group, which consisted of 5 patients with DMT2 but without MetS that were catheterized and found to have normal coronary arteries and a normal ejection fraction. [26] In the former, MetS group, AngII levels inside the coronary sinus and aorta were  $46 \pm 18$  and  $35 \pm 15$  pg/ml, respectively, while AngII levels were  $10 \pm 2$  pg/ml inside both chambers of the control group ( $P < 0.001$ ). Furthermore, in the group with MetS, the EI levels inside the coronary sinus and aorta were elevated at  $14 \pm 4$  and  $13 \pm 6$  pg/ml in both chambers, respectively, compared to  $3 \pm 1$  pg/ml inside both chambers of the control group ( $P < 0.001$ ).

This elevation of AngII and EI will activate angiotensin II receptor type 1 (AT1) (Figure 1) and produce inflammatory cytokines, increase macrophage chemo-attractants and activate reactive oxygen species that produce oxidative stress in myocytes and smooth muscle cells [27]. This will not only induce the apoptosis and necrosis of myocytes, but also promote the proliferation and migration of smooth



muscle cells, resulting in the atherosclerotic lesions that increase the incidence of myocardial infarcts [28]. Likewise, AngII, acting via angiotensin II receptor type 2 (AT2), has potent pro-inflammatory, pro-oxidant and pro-thrombotic effects [29]. Moreover, it has been shown that infusion of AngII in rats increases serum levels of AGEs. The oxidative and apoptotic effects of both hyperglycemia and AngII are most likely key in inducing diabetic cardiomyopathy [30], which explains why our patients with MetS have a subnormal ejection fraction, as opposed to the patients without MetS who have a normal ejection fraction, despite normal coronary arteries in both groups. Also, the incidence of atrial fibrillation was 16% in our MetS group. Inflammatory pathways produce electrical and structural atrial remodeling and fibrosis culminating in the development of atrial fibrillation.

Omega-3, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have also been shown to be anti-inflammatory; they are enzymatically converted to resolvins, which are very potent anti-inflammatory agents [31]. It has been shown that Omega-3 in high doses will reduce the incidence of myocardial infarction and, in some patients, revert insulin resistance. We have reported the normalization of the 2-hour postprandial levels of blood sugar with the use of Omega-3 [32]. The mean 2-hour post-prandial glucose levels in 10 patients decreased from a mean value of  $205 \pm 40$  mg/dl to  $119 \pm 13$  mg/dl ( $P < 0.003$ ). This change occurred after using 6000 mg per day of pure Omega-3 for about 6 months. The effect of Omega-3 is mediated through the insulin receptors of the cells. At present, we are studying these receptors in order to explain this increase in insulin sensibility.

Adipose tissue is a hormonally active endocrine tissue, producing cytokines, which influence other body tissues. Adiponectin is one such adipocytokine that protects cardiovascular tissue from ischemic injury and increases insulin sensitivity by stimulating fatty acid oxidation, decreasing plasma triglycerides and improving glucose metabolism [33,34]. Another adipocytokine, secreted-frizzled-related-protein-5 (Sfrp5), has been found to be increased in MetS in Hispanics – The Role

of Insulin Resistance and Inflammation has significant metabolic consequences; incorporation of Wnt signaling pathways, which classically regulate developmental processes in many organisms, in adipocytes has led to evidence that obesity induces a reduction in the Sfrp5 production along with an increase in Wnt5a expression, leading to augmented inflammatory signalling and insulin resistance [35]. Conversely, Sfrp5 acts as an anti-inflammatory molecule, restraining the chronic inflammatory state and improving insulin sensitivity. On the other hand, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) are insulin antagonizing adipocytokines [35] that are associated to augmentation of inflammation and insulin resistance. As seen, inflammation is a complicated issue in obesity that has to be stopped due to the deleterious effects produced in the cardiovascular system, such as the reduction in ejection fraction observed in our sample of patients with MetS and normal coronaries: a diabetic cardiomyopathy undoubtedly brought on by chronic inflammation and insulin resistance [36].

Insulin resistance is a fundamental mechanism underlying MetS 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 multiple-fold. Truly, there are other processes involved in the development of insulin resistance other than inflammation. Abnormalities in fat storage and mobilization have been implicated in the pathogenesis of insulin resistance [37]. Abdominal obesity in particular has been shown to be most associated with insulin resistance and MetS. However, it has been observed that general obesity is not universal in MetS and insulin resistance. In addition, many obese subjects do not have metabolic abnormalities. Systemic chronic inflammation [38], on the other hand, paints the most complete picture of insulin resistance as it is the result of all altered cytokine production and signaling pathways in the body. A more accessible marker for this inflammation can be obtained by measuring C-reactive protein (CRP); 40% of our patients with MetS had an elevated CRP. Clinically, each of the diagnostic component criteria of the metabolic syndrome has been associated with increased levels of CRP [39], elevation of which bears a negative prognostic implication in the population involved - this biomarker has been associated to the development of heart disease, although this observation is not totally clear. CRP production is located in the liver, a process induced by pro-inflammatory cytokines; this non-specific marker of inflammation has an important role in the host innate defense mechanism, but also regulates the amount of inflammatory response by activating the complement system. CRP can be used to monitor the status of the inflammatory system, and has been used to monitor the effect of statins in the inflammatory process of MetS [40]. In the Jupiter trial, rosuvastatin (20 mg/day) reduced the systemic marker of CRP.

The work of Charles Serhan [41] has generated new ideas on the molecular mechanism and mediators related to the resolution of inflammation. He has shown the importance of essential fatty acids and their metabolisms, which involves molecules called lipoxins, resolvins, protectins and maresins in the process. Lipoxins are lipids that stimulate macrophages and prevent neutrophils from entering

the damaged tissue. Resolvin reduces the exit and migration of neutrophils from the blood stream and stimulates macrophages to eat tissue debris. Maresins are produced by macrophages to stimulate tissue repair. Finally, protectins reduce the release of substances that promote inflammation. Overall, the importance of all these substances in reducing the inflammatory process in atherosclerosis, diabetes mellitus, MetS and obesity has been confirmed.

De Furia and his group have reported a new class of fatty acids synthesized by mammalian tissue that enhances glucose uptake and reduces inflammation that is present in the diabetic patient. In 2013, they published research in the Proceedings of the National Academy of Science proving that B cells promote severe inflammation in obesity and Type 2 diabetes through regulation of T cell function and an inflammatory cytokine profile and suggested that new drugs that deplete B cells may help in the treatment of diabetes mellitus Type 2 [42]. They have confirmed that the influence B cells have on T cells promotes insulin resistance.

### Circadian disorders

Common disorders of circadian behavior and sleep, such as night-shift work and jetlag, are associated with increased hunger, decreased glucose and lipid metabolism and changes in hormonal processes involved in satiety [43]. Short-duration and poor-quality sleep have been shown to predict the development of DMT2 and obesity after age, BMI and various other confounding variables are considered and taken into account. These are components of MetS which leads to inflammation and its consequences [44]. In addition, the induction of hunger may be associated to a reduction in circulating levels of leptin brought on by sleep deprivation [45]. Cardiovascular disease and hypertension are also related with sleep loss, as the risk of a fatal heart attack increases 45% in individuals who chronically sleep 5 hours per night or less [46]. Disruption of the circadian clock can lead to obesity, inflammation and insulin resistance [47].

### Diet and exercise

Lifestyle approaches to treating and preventing MetS greatly improve metabolic parameters by reducing body weight and increasing the level of physical activity. Multiple studies of obese patients with DMT2, hypertension or hypercholesterolemia have shown that weight improves the cardiovascular profile, including glycemic control, in both diabetic and nondiabetic individuals. Furthermore, lifestyle changes [48], 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 CRP, central obesity and triglyceride levels. The ATTICA [49] epidemiological study showed that adherence to the Mediterranean diet was associated with 20% lower odds of having MetS, irrespective of age, sex, physical activity, lipids and blood pressure levels. On the other hand, consumption of a high fat diet induces changes in the fat microbiota, producing inflammation that is associated with hyperphagia and an obese phenotype. In addition, data on the Hispanic and Asian diets with relation to diabetes have demonstrated that rice consumption is associated to an elevated risk of developing DMT2, presumably due to the higher glycemic index of rice when compared to whole grain

[50]. 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, lowers blood pressure and maintains immune system health, which is very important in reducing inflammation and, as a consequence, insulin resistance [51].

### Pharmacotherapy

Although intensified therapeutic lifestyle modifications may prevent the onset and progression of MetS, some patients may require drug therapy. While the individual components (e.g. glucose intolerance, hypertension, dyslipidemia) are all appropriate The Metabolic Syndrome in Hispanics – The Role of Insulin Resistance and Inflammation 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, obesity and inflammation. Orlistat, sibutramine, and rimonabant are approved for long-term treatment of obesity; however, sibutramine is known to cause secondary hypertension and thus is not the ideal choice of therapy in obese patients with MetS. As was mentioned above, statins and RAS inhibitors have proven anti-inflammatory properties that may augment insulin sensitivity. Glitazones and metformin have been used increasingly over the recent years for the management of insulin resistance.

The ongoing search for new strategies to combat the MetS has shed light on new molecules that may prove to be effective therapeutic targets in treating the syndrome; in vivo studies have established that atherosclerosis driven by the inhibition of stearoyl-coenzyme A desaturase 1 (SCD1), an enzyme involved in fatty acid metabolism, can be completely prevented by the omega-3 polyunsaturated fatty acids in dietary fish-oils [52]. Moreover, our data showing that in some patients, high doses of omega-3 polyunsaturated fatty acids will normalize the 2-hour post-prandial glucose levels in a sample from Puerto Rico is promising.

### Surgical management of obesity and MetS in hispanics: Roux-N-Y sleeve surgery

Given that lifestyle changes and pharmacology may not be sufficient to achieve durable and affective weight loss, surgery to treat obesity and MetS has become an attractive alternative. In addition to weight loss, patients may enjoy improvement in other metabolic parameters such as insulin resistance and other obesity-related comorbidities. Bariatric surgery has been shown to reverse diabetes, hypertension, sleep apnea and hyperlipidemia [53].

A recent study [54], evaluated the metabolic outcomes 12 months after bariatric surgery (Roux-N-Y) in morbidly obese Hispanic patients as well as the correlation between weight loss and the observed metabolic changes. Medical records from a 102 Hispanic obese patients who underwent bariatric surgery were analyzed. The following variables were obtained before and 12 months after surgery: Body Mass Index (BMI), body weight, total cholesterol (TC),

triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), and fasting blood sugar (FBS). Ninety-seven percent of patients underwent Roux-N-Y surgery; 79.4% were females and 44% were diabetics. We observed statistically significant reductions ( $p < 0.05$ ) 12 months after surgery in: BMI  $-14.3(\pm 6.2)$  kg/m<sup>2</sup>, weight  $-86.1(\pm 34.4)$  lbs, TC  $-17.9(\pm 32.4)$  mg/dL, triglycerides  $-28.7(\pm 40.6)$  mg/dL, LDL  $-15.4(\pm 30.6)$  mg/dL, and FBS  $-11.3(\pm 23.5)$  mg/dL. HDL increased  $+5.22(\pm 12.9)$  mg/dL ( $p < 0.0006$ ). The correlation between weight loss and changes in FBS, Cholesterol, HDL and LDL fluctuated between 0.1-0.5 ( $P > 0.05$ ). The sleeve surgery showed a lower correlation than Roux-N-Y between weight loss and FBS and no change in HDL, LDL and total cholesterol ( $P > 0.05$ ). Gastric bypass surgery of the Roux-N-Y significantly improves the lipid profile and FBS levels in obese Hispanic patients, unlike with sleeve surgery. The poor correlation factor between weight loss and these variables suggests that other mechanisms, independent from weight loss are responsible for these changes. One factor may be the reduction of inflammation after a Roux-N-Y., especially due to weight loss.

## Conclusion

In an age when millions of people are estimated to be afflicted by the MetS, new perspectives into this cluster of risk factors are imperative if we are to evolve its management: the focus on inflammation and insulin resistance is crucial in order to halt or delay the disease as soon as it is detected. Moreover, the public health of Hispanic populations throughout the world has been evidenced to pose a significant public health problem that should be addressed specifically because of the distinct metabolic characteristics this ethnicity may hold. Likewise, this approach should prompt further investigation into parallel cardio metabolic particularities in other ethnicities.

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