

A Comprehensive Review on Diabetes, Hypertension and Metabolic Syndrome

¹T.Mohana Lakshmi*, ²B.S.Ravi Kiran, ³R.Srikumar ⁴E.Prabhakar Reddy

ABSTRACT

MetS is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and all cause mortality. DM is a crucial factor in MS and is highly predictive of Cardiovascular Disease (CVD) risk. Nutrition is a very complex research topic and it is not clear whether an individual component of the diet or a combination of nutrients and dietary habits may be responsible for any cardioprotective effects. Furthermore, the dose of the antioxidant should be chosen based on dose-finding studies relying on the same biomarker. Further, the majority of patients who need an antihypertensive therapy will likely need more than one agent for the proper blood pressure control with beta blockers/Thiazides as the first and second line agents, respectively. Increased oxidative stress and inflammatory stress are recognized as playing an important role in the initiation and progression of atherosclerotic vascular disease. Future studies are needed to elucidate the mechanisms responsible for the pro-oxidative and pro-inflammatory phenotype in this at risk and largely clinically untreated population. Patients with high levels of oxidative stress or depletion of natural antioxidant defense systems may be the most likely to benefit from antioxidant therapy.

KEY WORDS : Diabetes Mellitus, Metabolic syndrome, Hypertension, Nutrition, Oxidative Stress, Inflammation, Beta blockers

Introduction

Diabetes mellitus and hypertension are two of the most common diseases in Westernized, industrialized civilizations, and the frequency of both diseases increases with increasing age [1-9]. An estimated 2.5 to 3 million Americans

have both diabetes and hypertension [10]. Although diabetes mellitus is associated with a considerably increased cardiovascular risk [9-10], the presence of hypertension in the diabetic individual markedly increases morbidity and mortality [10].

Metabolic syndrome is characterized by insulin resistance and the presence of risk factors for cardiovascular diseases and diabetes mellitus type 2 [11]. During the 1980s, Reaven [12] observed that dyslipidemia, arterial hypertension and hyperglycemia were very often found in combination in a single patient and that they indicated increased cardiovascular risk a condition he named Syndrome X. Since then, many different definitions of metabolic

¹Assistant Professor, Department of Microbiology, ²Tutor,

⁴Associate Professor of Biochemistry,

³Research Associate, Centre for Research,

Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry.

*Corresponding Author

Mrs.T.Mohana Lakshmi,

Assistant Professor of Microbiology,

Sri Lashmi Narayana Institute of Medical Sciences,

Osudu, Puducherry, India,

Email id: peby_mythri@yahoo.com

Telephone No : +919849616163

syndrome have emerged. Consensus has not yet been reached on the diagnostic criteria for metabolic syndrome and to diagnose the metabolic syndrome, other metabolic abnormalities, such as increased fibrinogen and plasminogen activity factor, hyperuricemia, increased C-reactive protein, hyper homocysteinemia, increased TNF- α expression and reduced adiponectin levels, are frequently present[1].

There is no definition of the metabolic syndrome in childhood that is accepted by the entire scientific community[11]. Cook et al.[13] adapted the NCEP criteria and proposed a definition of pediatric metabolic syndrome based on the presence of three out of the following criteria: waist circumference greater than or equal to the 90 percentile, fasting glycemia greater than or equal to 110 mg/dL, triglycerides greater than or equal to 110 mg/dL, HDL-cholesterol less than 40 mg/dL and arterial blood pressure greater than or equal to the 90 percentile. Furthermore, measurement of waist circumference in children is not standardized. Some authors have standardized measurements by age and define measurements above the 90 percentile as elevated[14].

The metabolic syndrome (MetS) is a major and escalating public-health and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity and sedentary life habits. MetS is considered as a first order risk factor for atherothrombotic complications. Its presence or absence should therefore be considered an indicator of long-term risk.

Definition

MetS is defined by a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic

cardiovascular disease (ASCVD), T2DM, and all cause mortality [15-16]. This collection of unhealthy body measurements and abnormal laboratory test results include atherogenic dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and a prothrombotic state. There have been several definitions of MetS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO) [17].

Epidemiology

Worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used [18, 19]. In general, the IDF estimates that one-quarter of the world's adult population has the MetS [20]. Higher socioeconomic status, sedentary lifestyle, and high body mass index (BMI) were significantly associated with MetS. Cameron et al. have concluded that the differences in genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education all influence the prevalence MetS is a complex disorder described as a cluster of risk factors for cardiovascular diseases and T2DM including visceral obesity, glucose intolerance, high blood pressure, high triglyceride levels and low high-density lipoprotein cholesterol levels. Irrespective of MetS definition, MetS prevalence is increasing worldwide, and it has become a common clinical condition and a major public health problem with high socioeconomic costs in countries with high incidence of obesity and Western dietary patterns[21].

Increased oxidative stress and inflammatory stress are recognized as playing an important role in the initiation and progression of atherosclerotic vascular disease[22, 23]. For example, oxidized low-density lipoprotein

(ox-LDL)[22], a marker of oxidative stress, is elevated in subjects with established coronary heart disease (CHD) [22] and is a prognostic marker for the progression of subclinical atherosclerosis [24]. Furthermore, elevated pro-inflammatory cytokines, including tumor necrosis factor (TNF) [25], interleukin (IL)-6 [26] and IL-18 [27], as well as C-reactive protein (CRP) [28], are markers of systemic inflammation and strong determinants of future atherosclerotic events.

The purpose of this review is to discuss Oxidative stress and Antioxidant status in Diabetes, Hypertension and Metabolic syndrome.

Discussion

Oxidative Stress

Oxidative stress is a consequence of the imbalance between ROS production and antioxidant capacity. This can occur as a result of either heightened ROS generation, impaired antioxidant system, or a combination of both. In the presence of oxidative stress, uncontained ROS attack, modify, and denature functional and structural molecules leading to tissue injury and dysfunction. I wish to point out that while excessive production of ROS causes injury and dysfunction, normal rate of ROS production is essential for life. This is because ROS serve many biologically important roles in signal transduction, regulation of cell growth and apoptosis, fetal development, and innate immunity, among other functions.

Evidence for Causal Role of Oxidative Stress in Hypertension

Increasing evidence has emerged that point to a causal link between oxidative stress, HTN, and inflammation[29, 30]. This proposition is based on the following observations: First, a consistent association has been found between HTN and oxidative stress in the kidney,

blood vessels, and brain in nearly all forms of acquired and hereditary HTN in experimental animals. For instance, oxidative stress has been shown to be present in animals with HTN caused by chronic lead exposure, chronic kidney disease, deoxycorticosterone acetate-salt administration, aorta coarctation, diabetes mellitus, metabolic syndrome, nitric oxide synthase (NOS) inhibition, high salt intake, and angiotensin II[31-52]. Second, alleviation of oxidative stress with pharmacological doses of several antioxidants has been shown to reduce blood pressure in hypertensive animals, but not in the normotensive animals[31,32], [34-39], [43-52].

And third, the observations cited above represent indirect evidence for the role of oxidative stress in the pathogenesis of HTN. Direct evidence for the causal role of oxidative stress comes from the following observations: (a) induction of oxidative stress has been shown to cause HTN in genetically normal, otherwise intact, animals[53, 54]; (b) mice with manganese SOD deficiency exhibit salt-sensitive HTN[55]; and (c) binding of angiotensin II to the angiotensin I (AT1) receptor results in production of ROS via activation of NADPH oxidase in the kidney and vasculature. Activation of NADPH oxidase involves assembly of the enzyme's cytoplasmic (P47phox and P67phox) and membrane-associated (p22phox and gp91phox or its tissue-specific isoforms, NOX-1, NOX-4, etc) subunits. The ROS production and hypertensive response to angiotensin II infusion is attenuated by pharmacological inhibition of NADPH oxidase and by suppression of its p22phox subunit expression[56, 57]. These observations illustrate the role of ROS as a major mediator of the pressor action of angiotensin II.

Evidence for the Role of Hypertension as a Cause of Oxidative Stress

The observations cited above provide irrefutable evidence that oxidative stress in the kidney, blood vessels, and brain causes HTN. Conversely, HTN, per se, has been shown to cause oxidative stress. This assertion is based on investigations that revealed presence of oxidative stress in the vascular tree residing proximal to (hypertensive zone), but not distal to the abdominal aorta coarctation in rats with abdominal aorta banding [58-60]. Since both of the arterial segments are supplied by the same blood in this model, these experiments clearly illustrate the role of high blood pressure and shear stress as opposed to those of circulating hormones and other humoral factors as a cause of oxidative stress. Taken together, these observations suggest that oxidative stress can cause HTN, and HTN can cause oxidative stress; hence, the two conditions are involved in a self-perpetuating cycle.

Antioxidants

Antioxidant Vitamins

Animal studies have shown that an adequate supply of dietary antioxidants may prevent or delay diabetes complications including renal and neural dysfunction by providing protection against oxidative stress [31]. However, clear evidence in humans is lacking. Vitamin C (ascorbic acid) is a chain-breaking antioxidant, scavenging ROS directly, and preventing the propagation of chain reactions that would otherwise lead to a reduction in protein glycation. In animals, vitamin C also reduces diabetes-induced sorbitol accumulation and lipid peroxides in erythrocytes [48]. Vitamin C (800 mg/day) partially replenishes vitamin C levels in patients with type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance.

Vitamin E (α -tocopherol) a component of the total peroxyl radical-trapping antioxidant system, reacts directly with peroxyl and

superoxide radicals and singlet oxygen and protects membranes from lipid peroxidation. A deficiency in vitamin E is associated with increased peroxides and aldehydes in many tissues. There have been conflicting reports about vitamin E levels in diabetic subjects .

To assess the reversibility of lipid peroxidation and platelet activation in type 2 diabetes, Previous studies examined the effects of short-term vitamin E supplementation (600 mg daily for 2 weeks) on the urinary excretion of 8-iso-PGF₂ α and 11-dehydro-TXB₂ [49]. Vitamin E supplementation was associated with detectable changes in plasma vitamin E levels and caused virtually complete normalization of 8-iso-PGF₂ α excretion. Moreover, changes in F₂-isoprostane formation were accompanied by similar reductions in thromboxane metabolite excretion [13], consistently with a cause-and-effect relation between enhanced lipid peroxidation and persistent platelet activation in this setting [48].

Observational, prospective cohort previous studies [61] suggest that higher dietary intake or supplementation of antioxidants (vitamins A, C, E, folic acid, niacin, β -carotene, selenium, zinc) is associated with a lower risk of cardiovascular disease and mortality [61]. In view of these findings, the American Heart Association recommended the consumption of a balanced diet with emphasis on antioxidant-rich fruits, vegetables, and whole grains [61]. However, the results of randomized, controlled clinical trials have failed to demonstrate a consistent protective effect of any single antioxidant or combination of antioxidants (vitamins C, E, and β -carotene) in the primary or secondary prevention of cardiovascular events [53,54].

Moreover, in some clinical trials the supplementation of vitamins C, E, and/or β -carotene was associated with an increased risk of all-cause mortality [48, 49]. Vitamin

B supplementation was also associated with a more rapid decrease in glomerular filtration rate and an increase in vascular events as compared to placebo in patients with diabetic nephropathy [53]. Recently, vitamin E proved effective over placebo for the treatment of nonalcoholic steatohepatitis, a disease closely associated with insulin resistance, in non diabetic adults.

Studies in healthy subjects [43,44] helped identifying the basal rate of lipid peroxidation as a major determinant of the response to vitamin E supplementation. The evidence that the same dose of vitamin E may have variable antioxidant effects in different patient populations characterized by variable rates of lipid peroxidation is consistent with this concept.

Hypertension & Metabolic Syndrome

The role of cardiovascular disease Hypertension (HTN), loosely defined as a blood pressure equal to or greater than 140/90 mm Hg, is the most significant CVD risk factor involved in MS prognosis. HTN is directly caused by increased circulating blood volume, decreased arteriolar elasticity, and endothelial dysfunction which triggers a decrease in production of vasodilators such as nitric oxide (NO) and promotes the circulation of inflammatory cytokines [61]. Persistent hypertension is a primary risk factor for stroke, heart attack, heart failure, aneurysm, and end-organ damage. 11β -HSD1 enzyme catalyse the interconversion from inactive cortisone to the active cortisone. Upon induction of 11β -HSD1 enzyme, Excessive glucocorticosteroids generated from Inactive cortisone. Glucocorticoids induce the expression of angiotensin- converting enzyme within vascular smooth muscle and significantly decreased the expression level of endothelial nitric oxide synthase (eNOS)

in human endothelial cells. It enhance the production of endothelin leads to enhance vasoreactivity of blood vessels as well as inhibition of cofactor tetrahydrobiopterin required the synthesis of nitric oxide and impair baroreceptor sensitivity. From above contributing factor leads to endothelium dysfunction arise and introduce various cardiovascular problems. Glucocorticoids play a very important role for the pathogenesis of hypertension by excessive generation of aldosterone with the help of rate limiting enzyme 11β -HSD1 [62]. So it indicate that 11β -HSD1 play a very important role in regulation of blood pressure by controlling the level of cortisol level.

Diabetes Mellitus & Metabolic Syndrome

Diabetes Mellitus (DM) is a disorder characterized by persistent hyperglycemia due to insulin resistance. Insulin is a pleiotropic hormone which signals a number of cellular processes such as glucoregulation, lipid metabolism, and protein synthesis in multiple tissues. In patients with DM, these actions of insulin are reduced. Consequently, there is an increase in free fatty acids which promote oxidative stress, endothelial dysfunction, vascular damage, and atheroma formation. The clinical results are high BP, HDL suppression, and high triglycerides (TAG) additionally, DM is associated with macrovascular (myocardial infarction, stroke) and microvascular (retinopathy, neuropathy, renal disease) problems which interfere with blood and nutrient delivery to multiple tissues throughout the body. DM is a crucial factor in MS and is highly predictive of Cardiovascular Disease (CVD) risk. In 1999 the San Antonia Heart Study found that insulinresistant patients had a greater incidence of hypertension and dyslipidemia than non-insulin-resistant patients[63]. Other epidemiological studies have established a similar relationship between

hyperglycemia and CVD which implicates the importance of DM as a risk factor for cardiovascular mortality. MS has been documented across all racial groups in the U.S. [64] and in the rest of the world. However, MS prevalence is greatest amongst Hispanics and blacks, particular in women. The most prevalent combination of risk factors in blacks is obesity/HTN, while in other ethnic groups (White, Hispanics and Asians) it is obesity/DM. The racial disparity is largely attributed to environmental, lifestyle and social factors which influence the incidence of obesity, CVD and DM[65]. Glucocorticoids increase hepatic gluconeogenesis which decreases glucose utilization by cells and leads to elevated circulating levels of glucose and insulin resistance. Glucocorticoids (GCs) have been shown to destroy β cells in the islets of diabetic rats, and 11β -HSD1 expression and activity are increased in the islets of diabetic fatty rats with β cell destruction. It may conclude that 11β -HSD1 plays a very important role in development of diabetes and associated vascular complication.

The coexistence of these two diseases likely contributes substantially to overall mortality in industrialized societies. Despite the critical importance of the coexistence of these two diseases, much information regarding their interaction remains unclear and controversial. Nevertheless, much information of theoretical and practical relevance is available, and there is considerable ongoing research exploring the relation between carbohydrate intolerance and hypertension. The subject of diabetes mellitus as a comorbid disease that frequently confounds hypertension, adding significantly to its overall morbidity and mortality[66, 67], will be updated in the present review.

Amongst middle-aged and older adults, the rising prevalence of T2DM, hypertension, and other conditions that comprise the metabolic

syndrome is a global health epidemic, attributed largely to sedentary lifestyles, poor diet, and lack of exercise. Atherosclerosis is a chronic disease that develops over a lifetime, with clinical manifestations that occur after decades of silent progression. atherosclerotic disease is still the leading cause of mortality in developed countries. atherosclerosis-related diseases represent an enormous socio-economic burden increasing healthcare expenditures and are an important source of human suffering. Lifestyle modifications such as poor dietary patterns and physical inactivity are recent events in the human evolution and are responsible for the development of obesity.

Immunity and atherosclerosis

The immune system evolved to ensure a protection against 'non-self', allowing a defense line against the infectious threat. For years it was taught that the immune system functions as sensor that allows recognition of 'self' from 'non-self', and to mount a specific response against 'non-self' by the use of adaptive immune responses. However, this immunological paradigm has been challenged in the 1990s with the danger model of immunity in which the immune system responds to damaged cells rather than to foreign[68]. This model of immunity has allowed the expansion of the scope of immunological implication in diseases with an inflammatory component that might be detrimental to the host. The discovery at the end of the 20th century of the Toll-like receptors (TLRs) in mammalian innate immune cells such as macrophages and dendritic cells has reinforced the view that innate immune system plays a key role in inflammatory response[68]. Furthermore, the discovery that, beside bacterial products, endogenous substances such as oxidized LDL (ox-LDL) and heat shock proteins(HSPs) mediate activation of TLRs has reinforced the view that innate immune system play a key role in the genesis of atherosclerosis [68].

Therefore, immune cells are the gate keepers that detect cellular damage and initiate a response allowing our body to defend against 'offending' insults. Endogenous danger signals are from intracellular or secreted extracellular products. Some are constitutive whereas others are inducible and require either neosynthesis or modifications before they can activate the innate immune system. Atherosclerosis is characterized by a chronic inflammatory state in which interplay between metabolic factors and cytokines leads to stimulation of the innate immune system when these signals are detected as danger. Therefore, signals from different sources including: modified lipid products, endogenous inducible factors, and cytokines are implicated in a complex inflammatory response that relies on tissue damage as the primary stimulating event leading to immune activation. Metabolic syndrome and ox-LDL In light of the numerous pro-inflammatory activities of ox-LDL, clinical studies have highlighted its role as a proatherogenic particle[69]. Indeed, ox-LDL plasma level is increased in patients with CHD, and several components of the metabolic syndrome independently predicted high levels of ox-LDL [68]. It is often observed that patients with the metabolic syndrome have a LDL-C within normal range [70]. In previous studies[70] there is a poor correlation between visceral obesity and plasma LDL-C, suggesting that other factors might influence LDL phenotype toward a more atherogenic particle. Elevated triglycerides (TGs) and increased release of free fatty acids (FFAs) in patients with the metabolic syndrome lead to assembly and secretion of very LDL (VLDL). Through exchange of cholesteryl esters and TGs between VLDL and LDL, production of TGs-enriched LDL particles occurs. TGs-enriched LDL particles then undergo lipolysis and become smaller and denser [69-70].

Therefore, patients with the metabolic syndrome have a higher proportion of small and dense LDL particles, which are highly atherogenic. Small LDL particles penetrate the arterial wall with more facility than their buoyant counterpart, and are more susceptible to oxidative transformation, explaining at least in part their proatherogenic activities [69-70]. In the Québec Cardiovascular Study, small LDL size independently predicted the rate of CHD. Furthermore, when associated with hyperinsulinemia and elevated apo B concentration, small LDL size was found to increase CHD risk remarkably[68]. Accordingly, although LDL-C level is an accepted predictor of CHD, other factors that influence LDL phenotype such as particle size and oxidative transformation, have a profound effect on their atherogenicity.

While metabolic syndrome is associated with LDL particle modifications, it also affects HDL-C level and phenotype. HDLs are a group of heterogeneous particles with anti-atherosclerotic properties. Indeed, the association between low levels of HDL-C and CHD is well established through clinical and epidemiological studies

Therapy

Effects of Treatment on Perfusion Hypertension It has been confirmed recently in hypertensive patients that effective antihypertensive therapy can reverse both functional and structural rarefaction of skin capillaries[70]. Several years ago, literature reviews concluded that antihypertensive agents that act mainly by vasodilation are effective in improving microvascular structure, whereas agents that act mainly by reducing cardiac output are not effective[71,72]. Recent work has confirmed this view and highlighted the antioxidative and antiinflammatory actions of some agents.

Blockers

Blockers act primarily by reducing cardiac output and are not effective in improving microvascular structure and function in SHR (Spontaneously Hypertensive Rats) or in hypertensive or hypertensive and diabetic patients[72, 73]. It would be expected that blocker therapy might improve coronary flow reserve by lowering basal myocardial blood flow owing to reduced cardiac work; however, 1st year of treatment with atenolol had no net effect on coronary flow reserve owing to reductions in both basal and maximal myocardial blood flow[74]. Interestingly, nebivolol, a β_1 blocker with β_2 adrenoceptor agonist effect and vasodilatory properties, improved coronary flow reserve and maximal coronary blood flow in hypertensive patients[69].

Metabolic Syndrome

Clinical identification and management of patients with the MetS are important to begin efforts to adequately implement the treatments to reduce their risk of subsequent diseases. Effective preventive approaches include lifestyle changes, primarily weight loss, diet, and exercise, and the treatment comprises the appropriate use of pharmacological agents to reduce the specific risk factors. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with the preventive measures and lifestyle changes. The clinical management of MetS is difficult because there is no recognized method to prevent or improve the whole syndrome, the background of which is essentially insulin resistance. Thus, most physicians treat each component of MetS separately, laying a particular emphasis on those components that are easily amenable to the drug treatment. In fact, it is easier to prescribe a drug to lower blood pressure, blood glucose, or triglycerides

rather than initiating a long-term strategy to change people's lifestyle (exercise more and eat better) in the hope that they will ultimately lose weight and tend to have a lower blood pressure, blood glucose, and triglycerides.

Conclusion

In clinical practice are known to modulate one or more pathogenic mechanisms underlying the development of diabetes mellitus, metabolic syndrome, Hypertension and their complications thus providing the target and outcome measures to test their efficacy and safety. Nutrition is a very complex research topic and it is not clear whether an individual component of the diet or a combination of nutrients and dietary habits may be responsible for any cardioprotective effects. Patients with high levels of oxidant stress or depletion of natural antioxidant defense systems may be the most likely to benefit from antioxidant therapy

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