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The Potentials of Antioxidant Micronutrients in the Management of Metabolic Syndrome

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Abstract

There is increasing evidence of the prevalence manifestations of metabolic syndrome worldwide. Metabolic syndrome is a cluster of abnormalities characterized by hypertension, central obesity, insulin resistance, endothelial dysfunction, dyslipidemia and oxidative stress. All these alterations predispose individuals to type 2 diabetes and cardiovascular disease that are major contributing factors to earlier mortality among people. The investigation of food nutrients that could reverse the features of metabolic syndrome is an important aspect for dietary-based therapies that may ameliorate the burden of the disorder. Antioxidant micronutrients are of great interest due to the recent described association between obesity, cardiovascular alterations and oxidative stress. These antioxidant nutrients are also being considered in the management of metabolic syndrome due to their potential benefits on hypertension, insulin resistance and hypertriglyceridemia since growing evidence has emerged that point to a causal link between oxidative stress and metabolic syndrome. Thus, dietary antioxidant supplements could have favourable effect on the attenuation and prevention of the manifestations of metabolic syndrome traits. Therefore, the present review focuses on the importance of antioxidant micronutrients in the treatment and management of metabolic syndrome.

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Introduction

Metabolic syndrome has emerged as an important clinical entity over the last two decades. It is a cluster of risk factors for cardiovascular morbidity and mortality [1]. Metabolic syndrome is a constellation of clinically specific risk features including central obesity, insulin resistance, dyslipidemia (elevated triglycerides and low density lipoprotein cholesterol and decreased high density lipoprotein cholesterol), hypertension, and diabetes [2, 3]. The disorder is rising worldwide as a consequence of continued obesity epidemic [4, 5]. In addition to genetic predisposition, physical inactivity as well as high-density energy food availability are among the main determinants of obesity and cardiovascular diseases [6] and metabolic syndrome important causes of mortality [7]. Increased cardiovascular risk in the metabolic syndrome is due to complex interaction of the individual risk factors. Although, central obesity is a key risk factor of metabolic syndrome, a study by Amloy *et al.* [8] of the middle aged men with metabolic syndrome indicated that cardiovascular risk is also increased independently of body mass index with metabolic syndrome. There is also a link between endothelial dysfunction and metabolic syndrome. A study found that metabolic syndrome subjects who also exhibit endothelial dysfunction are at increased risk for cardiovascular disease than either group alone [9]. Consequently, metabolic syndrome increases the chances of cardiovascular disease to an extent greater than the likelihood conferred by any of its individual components.

Increased oxidative stress has come to light as playing a critical role in metabolic syndrome and its component pathologies, and may be a unifying factor in the advancement of this disorder. Reactive oxygen species such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2) are highly reactive derivatives that are produced significantly in the course of oxygen metabolism. Under normal conditions, reactive oxygen species are maintained at optimal level due to a balance between their production and elimination by antioxidants. However, in a disease state such as the metabolic syndrome, the oxidative or antioxidative balance shift towards the oxidative status due to increase in reactive oxygen species with diminished antioxidant capacity which creates an unbalanced environment that results in oxidative stress. Reactive oxygen species have been shown to play essential role in the pathogenesis of cardiovascular disease [10, 11]. Moreover, oxidative stress has been identified as a major mechanism of complications in metabolic syndrome [12, 13].

Evidence from clinical studies suggested that metabolic syndrome also increases the risk of proteinuria and chronic kidney disease [14]. Insulin resistance is considered one of the key factors to the development of metabolic syndrome of which visceral obesity plays a critical role in the development of insulin resistance. Infact, adipokines such as tumor necrosis factor α (TNF-

α) and non- esterified fatty acid (NEFA), which are produced by visceral obesity, might contribute to the development of insulin resistance in the muscles and adipose tissue [15]. Metabolic syndrome is increasingly recognized as an independent predictor of cardiovascular disease in hypertension [16]. Since there are emerging evidences of the role of oxidative stress in the pathogenesis of a wide range of cardiovascular diseases, including hypertension, hyperglycemia, dyslipidemia, and insulin resistance and these diseases are component of metabolic syndrome, strategies to reduce oxidative stress has provided a rationale for potential therapeutic interventions using antioxidant micronutrients.

Antioxidants Defense System and Metabolic Syndrome

The antioxidant defense system is a highly complex biochemical organization that consists of several enzymes and a large number of scavenger molecules. Each of these enzymes and antioxidant molecules participate in highly specific reactions in counteracting the effect of oxidant radicals. Interaction of antioxidant molecules with reactive oxygen species protects the functional and structural molecules from oxidative injury. The common antioxidants include the vitamins A, C, and E, glutathione, and the enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Other antioxidants include lipoic acid, mixed carotenoids, coenzyme Q10, and many bioflavonoids, antioxidant minerals (copper, manganese, selenium, and zinc). The antioxidants work in synergy with each other and against different types of free radicals [17]. Vitamin E suppresses the propagation of lipid peroxidation; vitamin C, with vitamin E, inhibits hydroperoxide formation; metal complexing agents, bind transition metals involved in some reactions in lipid peroxidation and inhibit Fenton and Haber- Weiss-type reactions; while vitamins A and E scavenge free radicals [18, 19]. Decreased levels of antioxidant and elevated levels of thiobarbituric acid reactive substances are consistently observed in hypertension [20, 21, 22], diabetes [23, 24], and other cardiovascular related diseases. Antioxidants are of immense interest because of their positive effects against oxidative stress, which is a process closely related to obesity, cardiovascular alterations, some degenerative diseases and certain types of cancer [25].

Oxidative Stress and Obesity

There have been accumulating evidences of obesity-induced oxidative stress in humans and experimental animals. Obesity is a core component in the development of metabolic syndrome and plays a critical role in exacerbating oxidative stress. Obesity in children, without any other metabolic syndrome components, has been repeatedly correlated with increased oxidative stress and endothelial dysfunction [26]. Weight loss by moderate diet restriction and moderate-intensity aerobic exercise in metabolic syndrome patients has been shown

to improve markers of oxidative stress [27]. On the other hand, result from an intensive 21-day residential diet and exercise program in obese patients revealed a decrease in oxidative stress and improvement in other markers of cardiovascular risk associated with metabolic syndrome [28]. This effect could have been attributed to reduction in oxidative stress through improvement in endothelial function due to availability of nitric oxide or up regulation of antioxidant defense system.

Several studies indicated higher basal levels of malondialdehyde, marker of oxidative stress in lipoprotein samples of obese than non-obese individuals [29, 30]. It has been observed that the authors concluded that malondialdehyde is involved in systemic oxidative stress and impairments of normal glucose metabolism in obese patients [29, 30]. Stojilkovic *et al.* [31] reported high level of F_2 isoprotanes values in the plasma of obese, hypertensive patients compared with non obese individuals when infused intralipid/heparin was used to increase non esterified fatty acids in their blood. There was positive correlation between F_2 isoprotanes and non esterified fatty acids, an indication that free fatty acids contributed to oxidative stress in obesity. Animal study provides evidence regarding training and reduction of oxidative stress. The effects of an eight-week treadmill running program in obese Zucker rats were examined [32]. Following the intervention, obese trained rats had body weights similar to those of sedentary obese rats and higher than the non obese rats but the trained obese rats had fasting blood glucose concentrations lower than the sedentary obese animals. In obese trained rats, exercise training preserved liver glutathione, glutathione peroxidase and superoxide dismutase activities at levels similar to the controls. Sedentary obese animals had substantially lower glutathione, glutathione peroxidase and superoxide dismutase activities than in the trained obese and non obese controls. In other animal model, reactive oxygen species production in adipose tissue of obese mice was reduced by treatment with the NADPH oxidase inhibitor, apocynin resulting in improvement in glucose and lipid metabolism independent of body weight [33]. Thus, there is full agreement that lifestyle changes focused primarily on weight reduction are the first line approach to patients with metabolic syndrome.

Oxidative Stress and Hypertension

Hypertension is another component of the metabolic syndrome which is independently associated with increased cardiovascular risk. Oxidative stress in essential hypertension involves enhanced NADPH oxidase activity and uncoupling of endothelial nitric oxide synthase (Figure 1). Vascular oxidative stress has also been demonstrated in experimentally-induced hypertension, such as salt- induced hypertension, Angiotensin II– mediated hypertension, obesity-associated hypertension, mineralocorticoid hypertension, and aldosterone-provoked hypertension [34, 35, 22]. A few clinical studies also showed increased generation of reactive oxygen species in patients with essential

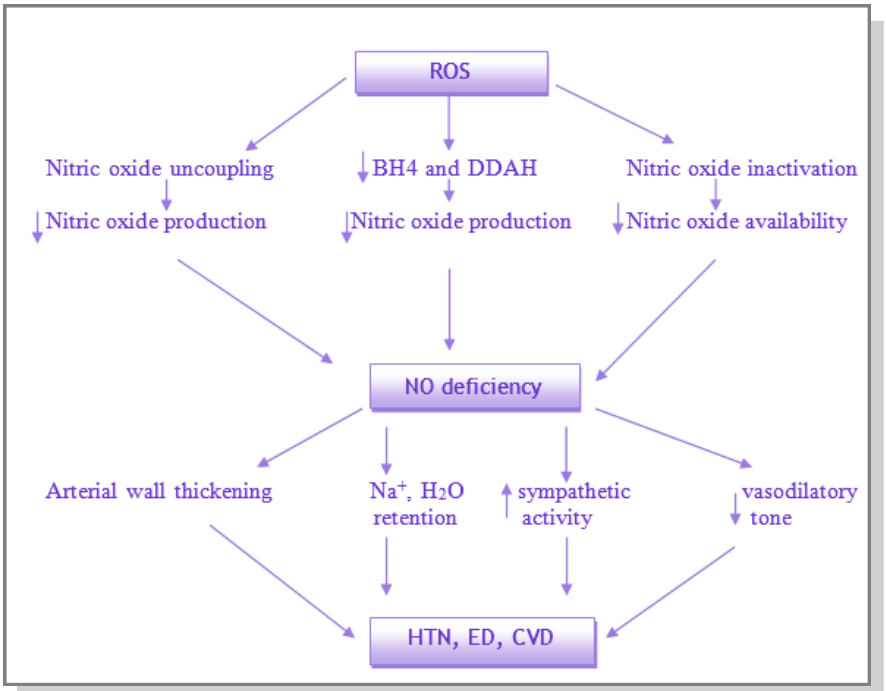

Figure 1: Effects of Oxidative Stress on Nitric Oxide Metabolism and Action

ROS- reactive oxygen species, NO- nitric oxide, BH4- tetrahydrobiopterin, DDAH- dimethyl arginine dimethyl aminohydrolase, HTN- hypertension, ED- endothelial dysfunction, and CVD- cardiovascular disease.

Taken from Vaziri,[116]

hypertension, and pre-eclampsia [36, 37, 38, 39, 40]. These findings are generally based on increased levels of plasma thiobarbituric acid-reactive substances and 8-isoprostanes, biomarkers of lipid peroxidation and oxidative stress [41, 42]. It has been demonstrated that the development of hypertension in spontaneously hypertensive rats and salt- induced hypertensive rats was prevented by treatment with antioxidants [43, 19]. Accordingly, Ulker *et al*. [44] demonstrated that vitamins C and E can exert a down- regulation on NADPH oxidase activity and thus could contribute to attenuate the elevation of blood pressure associated with metabolic syndrome. A study in metabolic syndrome patients showed that hypertension alone was responsible for elevated oxidative stress whereas other metabolic syndrome components had minimal contribution to increased oxidative stress in these patients [45]. In the study, there exists paucity evidence of how the effects of hypertension were separated from the effects of the other risk factors in the established pathology of the metabolic syndrome.

Oxidative Stress and Dyslipidemia

Dyslipidemia is also a component of metabolic syndrome. It is characterized by elevated low-density lipoprotein cholesterol and triglycerides and decreased high-density lipoprotein cholesterol. Studies have shown positive correlation between elevated low-density lipoprotein cholesterol and triglycerides and low high-density lipoprotein cholesterol and oxidative stress in human studies and animal models. Low -density lipoprotein receptor-deficient mice fed a cholesterol-enriched diet developed elevated LDL levels and consequently oxidative stress [46]. High plasma oxidative stress markers positively correlated with elevated plasma triglycerides and inversely correlated with low HDL [47] in a group of metabolic syndrome patients. It is important to note that low level of high density lipoprotein cholesterol is a surrogate marker for atherogenic metabolic situation in the metabolic syndrome, which also comprises the components obesity, hypertension, insulin resistance, and hypertriglyceridemia. Lipid peroxidation, a marker of oxidative stress, correlated with low high-density lipoprotein levels, irrespective of age, gender, and presence of the other metabolic syndrome components [48].

Oxidative Stress and Endothelial Dysfunction

The control of vascular tone and maintenance of blood circulation, fluidity, coagulation, and inflammatory responses is influenced by vascular endothelium which is an active and dynamic tissue. The endothelium controls vascular tone via the release of vasodilating and vasoconstricting substances. Nitric oxide is one of the most essential vasodilating substances. Nitric oxide also has vascular protective effect and can inhibit inflammation, oxidation and vascular smooth muscle cell proliferation, and migration. Endothelium appears to play a key role in the vascular damages induced by insulin resistance associated with metabolic syndrome [49]. Injure to the endothelium may result in endothelial dysfunction which will in turn impaired the release of nitric oxide and loss of its antiatherogenic protection [50]. The primary defect that connects endothelial dysfunction and insulin resistance is associated with deficiency of endothelial-derived nitric oxide. Nitric oxide deficiency is caused by decreased synthesis and/or release, in combination with too much consumption in tissues by either high levels of reactive oxygen species (Figure 1) or reactive nitrogen species, which are formed by cellular disturbances in glucose and lipid metabolism. Endothelial dysfunction impaired insulin action due to alteration in the transcapillary passage of insulin to the target tissue [51].

Cardiovascular risk factors have an effect on many of the normal functions of the endothelium. Particularly, oxidized low-density lipoprotein cholesterol starts a series of events that begin with cell activation, endothelial dysfunction, local inflammation, and a procoagulant vascular surface. These events results in plaque formation with a consequential plaque rupture

and cardiovascular events [52]. Patients with metabolic syndrome or type 2 diabetes mellitus exhibit impaired endothelium-dependent vasodilation [53]. Oxidative stress has been suggested to contribute to insulin resistance [54, 13], and play a crucial role in the pathogenesis of endothelial dysfunction [55, 56]. The most important effect of increased oxidative stress on vascular endothelial function is the decrease in nitric oxide bioavailability resulting from both nitric oxide inactivations by superoxide anions and nitric oxide synthase uncoupling (57)

Oxidative Stress in Cardiovascular Disease and Metabolic Syndrome

Oxidative stress plays a central role in the development of atherosclerosis. NADPH oxidases are the primary source of reactive oxygen species in the vasculature. Activation of the renin-angiotensin system has been proposed as a mediator of NADPH oxidase activation and reactive oxygen species production [58, 59, 60, 61, 62, 63]. Increased expression and activity of the phagocytic NADPH oxidases with a parallel decrease of high density lipoprotein cholesterol and increase of oxidized low density lipoprotein cholesterol and nitrotyrosine levels accompanied by thickened intima to media ratio in the carotid arteries, indicative of early clinical manifestation of atherosclerosis, have been demonstrated in metabolic syndrome patients [64]. Increased oxidative stress associated with increased production of reactive oxygen species is strengthened by decreased expression of antioxidant enzymes [22]. Studies in a diet-induced rat model of metabolic syndrome found increased oxidative stress and endothelial dysfunction [65, 66]. The study by Robert *et al.* further demonstrates increased reactive oxygen species production capacity by the NADPH oxidase along with down regulation of key superoxide dismutase isoforms indicating a disrupted antioxidant defense system in metabolic syndrome [65]. The principle sources of reactive oxygen species in the vaculature include NADPH oxidase and xanthine oxidase, so developing strategies that could target the inhibition of these enzymes could play significant role in the management of metabolic syndrome since excess reactive oxygen species contributes greatly to the development of features of metabolic syndrome. Reports from the Third National Health and Nutrition Examination Survey indicate decreased levels of the antioxidants vitamins C and E and several carotenoids, even after adjusting for lower fruit and vegetable consumption in participants with metabolic syndrome [67]. Hence, it is clear that the human metabolic syndrome is characterized by oxidative stress precipitated by excess production of reactive oxygen system and diminished antioxidant defense system.

The novel concept for the use of antioxidant micronutrients as a therapeutic tool against metabolic syndrome should be pursued vigorously because of the multiple benefits of these micronutrients.

Hypertension in Relation to Insulin Resistance

Hypertension is another component of the metabolic syndrome which is independently associated with increased cardiovascular risk. Evidence has emerged that essential hypertension is frequently associated with insulin resistance. The association between essential hypertension and insulin resistance is a clearly established fact but the impact of insulin resistance on blood pressure homeostasis is still a topic of debate. The relationship between hypertension and insulin resistance is more significant in obese subjects. Obese subjects who lose reasonable amounts of weight had significant decreases in blood pressure which correlated closely with the decline in fasting plasma insulin concentrations [68]. A number of possible mechanisms have been suggested to explain how insulin resistance may cause hypertension [69]. Increased prevalence of hypertension in the metabolic syndrome could only moderately be attributed to insulin resistance when analysed by concentrations of fasting insulin, or the Homeostasis Model Assessment- Insulin Resistance HOMA-IR [70]. Hyperinsulinaemia stimulates hypertension via increased renal tubular reabsorption of sodium and water, increased sympathetic nervous system activity, proliferation of vascular smooth muscle cells, and modifications of transmembrane cation transport. Decreases in urinary sodium excretion by insulin at physiological concentrations mediated by binding to specific high-affinity receptors [71]. Obviously, hypertension is itself a complex disorder with many causes of the disease and not all subjects with essential hypertension are insulin resistant [72].

Insulin Resistance and Diabetic Mellitus in Metabolic Syndrome

Obesity and dyslipidemia independently contributed significantly to oxidative stress and visceral obesity is the core risk factor for the development of insulin resistance (Figure 2), with dyslipidemia now emerging as a possible contributing factor. Insulin resistance is a major factor to developing the component of metabolic syndrome [73]. Hypertensive subjects often exhibit high degree of hyperinsulinemia as compared with normotensive [74]. This is attributed to higher visceral fat area in hypertensive subject than normal individual. According to Banerji *et al.* [75], visceral fat area correlated negatively with the insulin sensitivity as measured by insulin-induced glucose uptake.

A positive correlation between percentage weight increase and insulin resistance in albino rats as measured by HOMA-IR, an indication that obesity is a key contributing factor to the development of metabolic syndrome has been reported [66]. A growing body of evidence indicated that adipocytes produce several cytokines, the so-called adipokines, such as leptin, non-esterified fatty acids, tumor necrosis factor α, resistin, and angiotensiongen can influence insulin sensitivity [76]. Visceral fat contributed to insulin resistance in mice fed with a high fat diet by up regulation of the angiotensinogen gene expression [15]. In obese

individual, the levels of the circulating components of the renin angiotensin system are elevated; however, reactive oxygen species (ROS), especially the superoxide anion ($O_2^{\cdot}$), or from reduced antioxidant reserve.

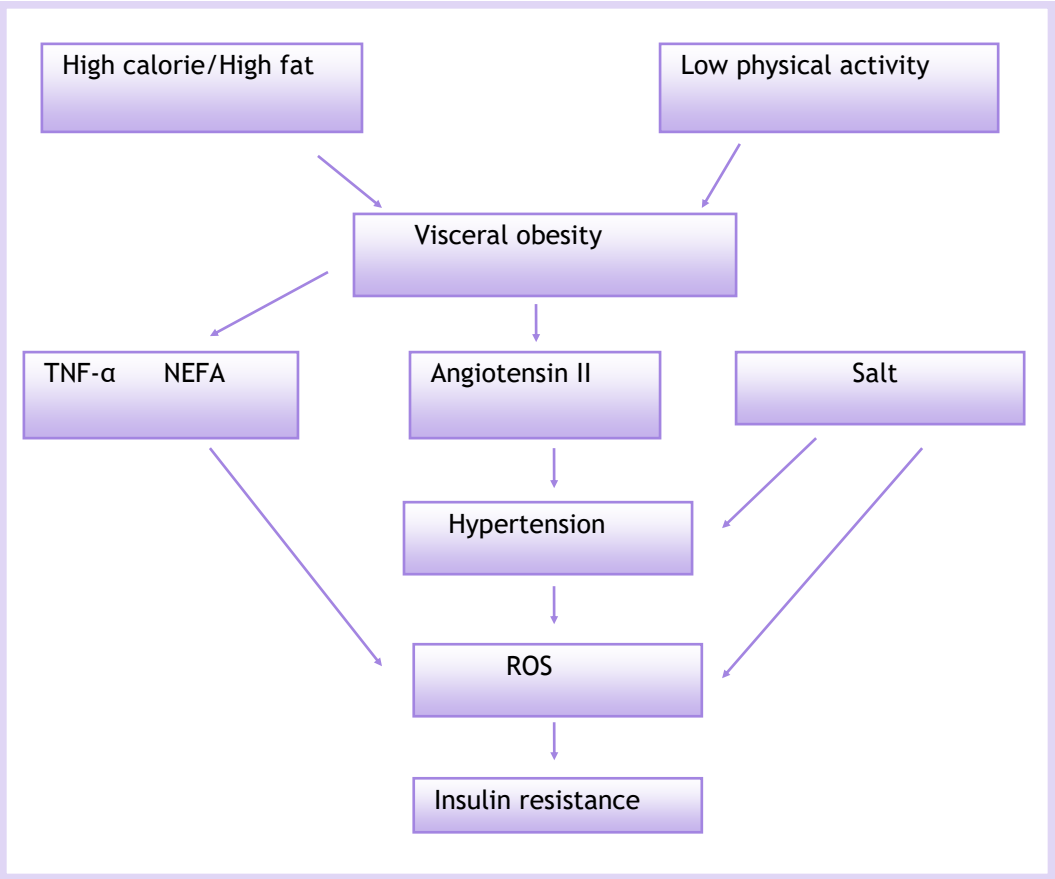

Figure 2: Mechanism for Insulin Resistance in Metabolic Syndrome
TNF-α- tumor necrosis factor α, NEFA- non-esterified fatty acids
Adopted from Toshiro, [76]

weight reduction is associated with a decrease in the levels of these components of the renin angiotensin system [77]. The adipocytes-related renin angiotensin system, therefore, play a significant role in the development of metabolic syndrome.

Diabetes mellitus is recognized as an important cardiovascular risk factor. Several hypotheses were suggested to explain the enhanced risks associated to diabetes; among these, one of the most plausible is an increase in oxidative stress [78, 79, 80, 81]. Oxidative stress may result from either excessive production of

Oxidative stress is a regular characteristic of diabetic complications when the action of antioxidant systems is overwhelmed by excess production of reactive oxygen species [82]. Obesity increases the risk of cardiovascular disease in adults and has been strongly associated with insulin resistance in normal persons and in individuals with type 2 diabetes [83]. Studies have shown that insulin resistance, a hallmark of the metabolic syndrome [84], is a predisposing factor of ischemic heart disease in the population at large [85] and in patients with type II diabetes [86]. According to WHO [87], people with a

family history of type II diabetes, who had the metabolic syndrome had a higher mortality [88]. However, patients with the metabolic syndrome had a higher prevalence of cardiovascular disease and diabetes. Thus, metabolic syndrome represents a cycle whereby insulin resistance leads to compensatory hyperinsulinemia which maintain normal plasma glucose and may exacerbate insulin resistance.

Antioxidants Therapy in the Prevention of Metabolic Syndrome

Antioxidant therapy of metabolic syndrome is based on the paradigm that obesity and excess production of reactive oxygen species contributes to hypertension, endothelial dysfunction, insulin resistance, glucose intolerance, and dyslipidemia which accounts for the clinical manifestation of metabolic syndrome. Data from epidemiological studies suggest that intake of antioxidant vitamins, such as vitamins C and E, beta carotene are associated with reduced risk of cardiovascular morbidity and mortality [89]. Several animal studies support this hypothesis [90, 91, 92], as do a number of relatively short-term functional studies in human, although many of these studies employed supra -physiological concentration of vitamins. Vitamin E [93, 94, 95] and vitamins A, C and E [66] have been shown to decrease LDL oxidation and improved endothelial function in metabolic syndrome.

Despite strong evidence demonstrating antioxidant effects of vitamins E and C in animal, and human studies, prospect randomized clinical trials have produced conflicting results. The Heart Outcomes Prevention Evaluation (HOPE) study evaluated long-term vitamin E therapy in patients at least 55 years old who had either vascular disease or diabetes mellitus [96] failed to show any improvement in cardiovascular outcomes. The Alpha Tocopherol Beta Carotene Cancer Prevention (ATBC) study, which evaluated beta-carotene (20 mg/day) supplementation in 1,862 male smokers with a previous myocardial infarction (MI), did not show any significant effect on cardiac-related mortality [97]. Study by Schroder [98] also supports this hypothesis. In contrast, some experimental and epidemiological studies seem to indicate beneficial effects of antioxidants vitamin supplementation on the development of the atherosclerotic plaques, resulting in reduction of cardiovascular events.

The first National Health and Nutrition Examination Survey epidemiological follow-up study reported that individual who received a high dose of vitamin C (>50mg/day) had lower overall total mortality rate after 10 year, and in particular lower mortality from cardiovascular disease [99]. Joshipura *et al.* [100], conducted a prospective cohort study in which consumption of fruits and vegeatables, particularly green leafy vegetables and vitamin C- rich fruits and vegetables, appeared to have protective effects against coronary heart disease. Kushi *et al.* [101] in the Nurses' Health Study epidemiological study found no relationship between vitamin C intake and major coronary events but

found vitamin E supplements of 100- 250IU/day to have reduced the incidence of major coronary events by 35-40%. Antioxidant supplementation in Atherosclerosis Prevention Study [102] also report positive result. Animal studies also showed beneficiary role of antioxidant supplementation in hypertension [103, 21, 22] and metabolic syndrome [66].

Nutritional studies have obtained positive results on metabolic syndrome features using botanical or pharmaceutical antioxidant supplements [104, 105], however, the most healthy compounds are those coming from the most popular antioxidant rich foods such as fruits, vegetables, legumes, olive oil, red wine, green tea and nuts [106, 107, 108, 109]. Several explanations have been proposed for the lack of observed benefit in most randomized trials. They include oxidant stress status of the participants, dose, and combination of vitamins administered. Vitamin C is water soluble while vitamin E is fat soluble and these vitamins reside in different cellular compartments, supporting the concept of combined antioxidant therapy. Moreover, vitamin E may be oxidized to tocopheroxyl radical. This radical can enhance lipid peroxidation and needs to be converted back into the reduced form by other antioxidants [110]. Since the role of the antioxidant vitamins in the prevention of cardiovascular disease remains controversial, we hypothesize that a 'healthy diet' that may contains several antioxidant vitamins and minerals or combination therapy of antioxidant micronutrients could act in synergy in the prevention and management of metabolic syndrome.

Possible Mechanisms of Antioxidant Micronutrients in Metabolic Syndrome

Antioxidants are of great interest by their positive effects against oxidative stress. We hypothesize the possible mechanisms of the beneficial effect of antioxidants in metabolic syndrome as being attributed to their crucial effects in inhibiting NADPH oxidase activity, scavenging free radical and stimulating the activity of nitric oxide synthase thereby reducing the blood pressure, decrease plasma triglycerides and low-density lipoprotein, increase high-density lipoprotein, and improvement of endothelial function and insulin sensitivity. The exact molecular mechanisms underlying the beneficial effects of antioxidants are not fully understood, but some studies have elucidated potential pathways. Ulker *et al.* [44] reported that 24 hr exposure to vitamin C (10-100μM) or vitamin E (100 100μM) enhanced nitric oxide synthase activity and attenuated NAPH oxidase activity in rat aorta. It has been suggested that vitamins C and E [111) and vitamin C [112, 113] can stimulate the activity of endothelial nitric oxide synthase by increasing the intracellular availability of the endothelial nitric oxide synthase (eNOS) cofactor tetrahydrobiopterin (BH_4), which could further increase nitric oxide (NO) synthesis. Consistent with this proposition, long term treatment of apolipoprotein-E-deficient mice with vitamin C resulted in a decrease levels of 7,8-dihydrobiopterin (BH_2), an

oxidized form of BH_4 and an improvement in the ratio of BH_4/ BH_2 [114]. The mechanism whereby vitamins C and E may cause down-regulation of NADPH oxidase and up regulation of eNOS could be at the transcriptional or post-transcriptional levels [115].

Conclusion

Metabolic syndrome, a disorder increasingly recognized as an independent predictor of cardiovascular disease in hypertension is associated with increased oxidative stress. It appears that some component pathologies of the metabolic syndrome contribute to a higher percentage of total oxidative stress than others; however, additional studies are needed to determine the exact contribution of individual components to total oxidative stress. The antioxidant defense system would be expected to uncouple the deleterious effect of oxidative stress, however, the expression of the main antioxidant enzymes and other antioxidant systems were reported decreased in metabolic syndrome, with concomitant increase in lipid peroxidation products. Accordingly, the fact that radical-scavenging antioxidants are consumed by increased free radical activities in metabolic syndrome has provided a rationale for potential therapeutic interventions based on the early administration of antioxidants micronutrients to metabolic syndrome patients. Studies of the role of antioxidant micronutrients in the prevention and management of metabolic syndrome should not focused only on the antioxidant properties because their biological effects surpass their ability as antioxidant molecules. Thus, vitamins C and E also prevent the impairment of endothelial cell function, among other non -antioxidant mechanism. It has been demonstrated that apart from reactive oxygen species scavenging properties of vitamins C and E, they also act as enzyme modulators, thus avoiding superoxide anion formation and increasing the bioavailability of nitric oxide. However, it is important to note at this point that, antioxidant micronutrients therapeutic intervention is a potential candidate to dwindle the morbidity and mortality associated with metabolic syndrome.

Finally, we are of the opinion that despite the reported controversy on the success of large antioxidant clinical trials, we believe that antioxidant micronutrients might be useful for the prevention and treatment of cardiovascular disease in metabolic syndrome patients. Several lines of evidence support this opinion. First, the drugs currently used to successfully impede the progression of cardiovascular and renal disease in patients with the metabolic syndrome all have strong direct antioxidant effects. Second, in carefully designed studies the effect of antioxidants on cardiovascular indicators was significant in metabolic syndrome patients and this is evidenced in reduction of oxidative stress. We suggest that the needs to conduct well-designed large-clinical trials with antioxidant micronutrients which would involve selected populations of metabolic syndrome patients so as to draw more definite conclusion. Thus, antioxidant micronutrients supplement may be designed

as a therapeutic prospect that would combat metabolic syndrome.

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