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Oxidative Stress, Lipid Parameters and Paraoxonase1 Activity in Normoglycemic Hypertensive Patients

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ABSTRACT

Hypertension is a common disease and is an important cause of morbidity and mortality worldwide. Occurrence of oxidation and peroxidation is one of the unfavorable consequences of hypertension on molecular systems. Large epidemiologic studies have demonstrated that subjects with hypertension have a marked increase in the prevalence of hypercholesterolemia, diabetes, hypomagnesemia, hypertriglyceridemia. Paraoxonase1(PON1),an HDL bounded enzyme, protects LDL from oxidative stress by destroying biologically active phospholipids . Human serum PON1 activity was shown to be inversely related to the risk of cardiovascular diseases, and low PON1 activities were observed in atherosclerotic, hypercholesterolemic and hypertensive patients .

Keywords: Hypertension, Oxidative Stress, Paraoxonase 1, LDL

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INTRODUCTION

Hypertension is a common disease. It is an important cause of morbidity and mortality worldwide. Elevated systolic blood pressure is a major risk factor for cardiovascular diseases. Hypertension has been associated with an increased risk of certain cancers. It is also a major cause of cerebrovascular and coronary artery diseases, congestive heart failure, renal failure, peripheral vascular disease and premature death[1, 2]. A better understanding of the pathophysiology of hypertension is indispensable to give optimal care to the 1.5 billion hypertensive patients who are estimated to exist by the year 2025[1]. Hypertension is classified based on its severity in The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) classification[3]. Regarding its etiology, hypertension is classified as primary or secondary hypertension. Primary hypertension, also known as essential or idiopathic hypertension, accounts for as many as 95% of all cases of hypertension.[4] Hypertension, known as "silent killer", is a disorder that can damage many organs especially heart and brain. Occurrence of oxidation and peroxidation is one of the unfavorable consequences of hypertension on molecular systems. In these oxidation processes, peroxides and free radicals are produced, which cause injuries and erosions in the wall of vessels. There are two kinds of antioxidants; enzymatic, and non-enzymatic (glutathione, vitamin E, vitamin C, vitamin A, etc). The most important enzyme is superoxide dismutase (SOD)[5]. Hypertension is one of the most important risk factors for cardiovascular diseases and clinical outcomes[6]. In addition, hypertension is associated to target-organ damage such as left ventricular hypertrophy[7], microalbuminuria [8,9], or subclinical vascular impairment as endothelial dysfunction[10,11], an early marker of atherosclerosis. Numerous mechanisms or causes of hypertension have been well characterized over the years. Several vasoconstrictive mechanisms, the sympathetic nervous system, the endothelin system, the vasopressin system and more recently the reactive oxygen species have all been implicated in the development of experimental or human hypertension. Increased vascular oxidative stress could be involved in the pathogenesis of hypertension[12, 13], a major risk factor for cardiovascular disease mortality. Oxidative stress occurs when there is an imbalance between the generation of reactive oxygen species and the antioxidant defense systems so that the latter become overwhelmed [14, 15]. The association between blood pressure and the risks of stroke and CHD are well established. Similarly, there are also strong associations between serum cholesterol and risks of CHD. Large epidemiologic studies have demonstrated that subjects with hypertension have a marked increase in the prevalence of

hypercholesterolemia, diabetes, hypomagnesemia, hypertriglyceridemia etc[16]. It is widely accepted that CVD is associated with hypertension and increased blood levels of low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG). In contrast, a low level of high density lipoprotein (HDL) is a risk factor for mortality from CVD[17]. PON1 belongs to the family of serum paraoxonases, consisting of PON1, PON2 and PON3. The genes coding for these enzymes are all located next to each other on the long arm of chromosome 7 (7q21.3-q22.1)[18]. PON1 and PON3 are expressed in the liver and excreted in the blood where they are associated with the high-density lipoprotein (HDL) particle.[19, 20] PON2 is not present in blood, but is expressed widely in a number of tissues, including the liver, lungs, brain and heart. Of the paraoxonase family, PON1 is the most investigated and best understood member. Paraoxonase (PON1) is an enzyme with three activities, which are paraoxonase, arylesterase and diazoxonase. PON1 is a calcium-dependent esterase consisted of 354 amino acids with a molecular mass of approximately 45 kDa, and it is found exclusively associated with high density lipoprotein (HDL) in serum. It protects LDL from oxidative stress by destroying biologically active phospholipids [21]. Human serum PON1 activity was shown to be inversely related to the risk of cardiovascular diseases [22], and low PON1 activities were observed in atherosclerotic, hypercholesterolemic and hypertensive patients [23,24]. Various underlying mechanisms have been put forward over the years in the causation of hypertension. It could be vasoconstrictive mechanisms among them, the sympathetic nervous system, the endothelial system, the vasopressin system and more recently the reactive oxygen species which is suggestive in the development of experimental or human hypertension [25].

REVIEW OF LITERATURE

The presence of oxidative stress and its role in elevation of arterial pressure has been shown in various other forms of hypertension including that seen with lead exposure[26], chronic renal insufficiency[27], salt sensitivity[28], angiotensin infusion[29], pre-eclampsia[30], renal artery stenosis[31], and coarctation of the aorta[32]. Some researchers such as Raij *et al*[5], Hafidi and Baños[33], Pierdomenico *et al*[34], Vaziri *et al*[35], Lerman *et al*[36], and Donmez *et al*[37] also investigated oxidation and peroxidation. They indicated that hypertension caused increased oxidation processes, which emphasized on importance and usefulness of antioxidants. Because SOD is the first enzymatic antioxidant defense, its low level in hypertensive patients may be due to excess of oxidative stress. The results of Piranfar *et al*[38],are similar to the results obtained by Raij et al.[5], Pierdomenico et al[34]., Tokkia et al[39]., Quinines- Galvan et al.[40], and Brockes,[41] and indicate that

oxidative processes increase in hypertension and cause increasing level of serum Ox-LDL. Gongura *et al*[42] concluded that angiotensin II induced hypertension increased the vascular ecSOD. They proposed that this was a compensatory mechanism that blunted the hypertensive response. To test this hypothesis, they studied ecSOD-deficient mice and found that hypertension caused by angiotensin II was greater in ecSOD compared with wild type mice (168 versus 147 mmHg, respectively, $P<0.01$). Ferroni *et al*[43] found that superoxide anion was a major determinant of nitric oxide (NO) biosynthesis and also acted as a vasoconstrictor. Increased level of biomarkers of lipid peroxidation and oxidative stress had been found in patients with hypertension. Maharjan *et al*[44] concluded that lipid profile is unfavorably altered in hypertension and oxidative stress is significantly raised. Dyslipedemia and raised oxidative stress are the established risk factors for the atheroscelerosis. Therefore, this study indicates that monitoring of the lipid level and maintaining of the oxidative balance in hypertensive patients would be helpful in preventing the cardiovascular diseases and other diseases associated with hypertension. It has been shown to be elevated in animal models of experimentally induced hypertension, suggesting that it is a consequence rather than a cause of hypertension. This suggests that active lipid peroxidation is occurring in essential hypertension, and this may be related to the development of atherosclerosis. A study by Dildar *et al*[45] concluded that oxidative modification of LDL levels and elevation in hypertensive stage were reversed by ACE inhibitors. They also found that the PON1 activities of the hypertensive patients were lower than the normotensives. In this study sPLA2 levels were positively correlated with ox LDL and negatively correlated with PON1 in hypertensive group. This finding may be attributed to the loss of PON1 activity from sPLA2-modified HDL. PON1 prevents LDL oxidation and also renders HDL resistant to oxidation, thereby maintaining the capacity of HDL to induce reverse cholesterol transport[46]. Increase in HDL-cholesterol is suggested to be associated with decreased risk of coronary artery diseases[47]. It has been reported that sPLA2 liberates polyunsaturated fatty acids from not only LDL but also HDL and sPLA2 –modified HDL loses its protective properties against LDL oxidation [48]. Uzun *et al*[22] suggested that reduced paraoxonase activity might be a basis of increased oxidative stress in patients with hypertension. A Study of Aymelek are in agreement with mentioned reports. In this study, PON1 activity was decreased in essential hypertensive patients compared with healthy controls. Reduced PON1 activity could be related to the increased oxidative stress in serum from these patients.They found lower activity of PON1 in non-dipper hypertensive patients than dipper hypertensive patients. Thus, in non-dipper hypertensives, more qualitative changes occur to LDL which render them more susceptible to oxidation;coupled to a reduction in the potential

antioxidant activity of HDL. This is suggestive of non-dipper hypertensives as high-risk group for atherosclerosis compared to dipper hypertensives[49]. Yildiz et al. were found PON1 activity was decreased in non-dipper patients compared with dipper patients and healthy controls[50]. A study done by Kumar *et al* to test ,the study of lipid profile, serum magnesium and blood glucose in hypertension. The systolic blood pressure was more significant than the diastolic blood pressure with increasing age groups. Elevated levels of cholesterol, LDL, VLDL, triglycerides are observed and no significance in HDL and magnesium is seen. Fasting blood glucose is statically significant in hypertensive cases when compared to controls but the significance may be due to the presence of 12% diabetic cases among the hypertensive patients. They concluded that dyslipidemia is associated with hypertension. This may due to the genetic predisposition, secondary life styles, fatty food consumption, saturated fat, cholesterol in the food increase the blood cholesterol and saturated fat is the main culprit, smoking and increased alcohol intake[16]. A study by Shekhanawar *et al* [51]reported that HDL associated PON1 can exert a protective effect on HDL functions. This effect is due to PON's peroxidase like activity and it contributes to HDL's antiatherogenic properties. Hence, evaluating the effects of PON1 for CAD patients may be promising in the treatment and prognosis of CAD. PON1 would thus seem worthy of further studies as an aetiologic factor in the development of CAD and perhaps other diseases. Saxena *et al*[52] concluded that Prehypertension is associated with decreased Paraoxonase activity with increased oxidative Stress .The fall in PON1 and SOD levels were observed in smokers as well as obese prehypertensives, where as MDA levels were found to be increased in both subgroups. This study confirms that there is elevated oxidative stress and reduced antioxidant capacity of PON1 in pre-hypertensive patients compared to controls emphasizes the importance of these parameters in assessing these markers for early diagnosis and therapeutic interventions. In previous studies, Fukai *et al*[53] showed that angiotensin II and hypertension increased the vascular oxidant stress. They examined how these might affect expression of the extracellular superoxide dismutase (ecSOD), a major form of SOD. On the other hand, the effects of oxLDL in the development of atherosclerotic process have been shown to be inhibited by paraoxonase (PON1), an HDL- associated esterase[54]. PON1 deficiency is associated with increased macrophage – oxidative stress, where an effect on LDL oxidation was observed[55]. PON1 plays a role in preventing lipid peroxidation not only of LDL but also of HDL[56]. Only small increases in HDL concentrations have been shown to greatly reduce atherogenecity and this effect has been confirmed to be related to increased PON1 activities[54]. However, the mechanism by which PON1 protects against oxidative damage and consequently development of atherosclerosis is not

entirely clear. A study by Kumawat et al[57] observed a significant decrease in reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), and superoxide dismutase (SOD) as compared to the control subjects. However catalase (CAT) and malondialdehyde (MDA) levels were found significantly increased in hypertensive patients as compared to normal healthy individual. In their study, essential hypertensive subjects showed an impairment of the antioxidant defense system as assessed by a diminution of plasma and erythrocyte antioxidant status and their study was in agreement with Simic et al[58], Laffer et al[59] and Moreno et al[60]. A study was performed by Bhale et al[61] to investigate the oxidative stress in patients with hypertension, demonstrated that increased MDA level in hypertensive patients. Their result were in consistent with Gönenç et al[62] and Ahmad *et al* [63]. Ahmad A *et al*., observed that MDA level was significantly increased in hypertensive group when compared with normotensive group but there was no significant difference in MDA level between prehypertensive and normotensive group. MDA level was significantly increased in hypertensive group as compared to prehypertensive group. A Study by Kumar [64] concluded that the results of their study were agreeable with the hypothesis oxidative modifications due to hypertension causes changes in serum PON activity there by accelerating the atherogenic process. Hypertension are also associated with lower serum levels of HDL concentrations hence could explain alterations in PON activities. Antioxidants and free radicals could conceivably protect PON through augmentation of the overall antioxidant capacity, therefore the result of their study showed significant differences among hypertensive patients when compared to normotensive controls. More important, perhaps, he demonstrated that differences in PON concentrations in their study can influence the ability of HDL to protect LDL from oxidation. Thus, incremental increases in HDL PON are associated with incremental decreases in the level of LDL hydroperoxides generated under oxidization conditions. He also concluded that the association between blood pressure, a prooxidant phenomenon with a demonstrated inhibitory effect on PON, and serum PON activities and concentrations and its concentrations remain unaltered in normotensive controls. His data also indicate that lower serum PON levels are associated with increased severity of hypertension and reduced capacity to protect LDL from oxidation. He is consistent with the hypothesis that hypertension modifies serum PON such that there is an increased risk of coronary artery disease, which may be due to a diminished capacity to protect lipoproteins from oxidative stress.

CONCLUSION

Oxidative Stress results when their is imbalance between oxidants and antioxidants. Oxidative stress plays an important role in the pathogenesis of hypertension. From the our study, we concluded that the alteration occurs in paraoxonase activity, oxidative stress and lipid profile in patients with hypertension. So there is need to evaluate paraoxonase activity, oxidative stress and lipid parameters in patients of hypertension.

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