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Plasma Paraoxonase Activity and Its Relation with the Malondialdehyde in Stage I Essential Hypertension Patients

Dr. Muppirala Venkatramana[1], Dr. Nitin Faldessai[2*], Dr. Rahul Saxena[3]
[1]Professor Department of Biochemistry, Mahavir Institute of Medical Sciences, Vikarabad Rangareddy, Telangana India
[2]Associate Professor, Department of Biochemistry, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda Telangana India
[3]Assistant Professor, Department of Biochemistry, School of Allied Health Sciences, Sharda University, Greater Noida, U.P, India

Original Research Article

***Corresponding author**
Dr. Nitin Faldessai

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Abstract: Paraoxonase 1 (PON1) is an esterase, synthesized and secreted by liver and found to be protective for both HDL and LDL against peroxidation, which suggests a possible involvement of PON1 in the anti-atherogenic properties of HDL. The present study was carried out to estimate the plasma parapxonase activity and erythrocyte malondialdehyde (marker of lipid peroxidation) in Stage I essential hypertensive subjects (HT) recruited as per JNC 7th norms and to determine their relation with each other in Stage I essential hypertensive patients. In the present study, plasma PON1 activity and malondialdehyde levels were measured in 50 Stage I essential hypertensive subjects (30-60 years) and statistically compared it with that of 50 healthy individual, served as control. Correlation analysis between aforesaid parameters was performed by using Pearson correlation test. Plasma PON1 activity was found to be significantly low in patient group as compared to control ($P < 0.001$) whereas erythrocyte malondialdehyde levels were increased significantly in patient group as compared to control ($P < 0.001$). Plasma PON1 activity was also inversely correlated with MDA in stage I essential hypertension patients. Thus, free radical mediated biomolecular destruction is the common pathway for vascular ageing and a variety of cardio vascular complications and body has a defense system of antioxidants which are involved in the prevention of free radical mediated cellular damage. From our study, it was concluded that increased lipid peroxidation and reduced plasma PON1 along with increase in blood pressure can be used as a marker for future cardiac complication in essential hypertension patients.

Keywords: Paraoxonase1, lipid peroxidation, antioxidant enzyme, oxidative stress, free radical.

INTRODUCTION

Essential hypertension (also called primary hypertension or idiopathic hypertension) is the most common type of hypertension, affecting 95% of hypertensive patients, it tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors[1]. Although precise etiology of this disease is poorly understood, probability of HT patients to develop future cardiovascular disease (CVD) risk appears to be more due to involvement of some common risk factors such as aging, high body mass index, dyslipidemia and sedentary lifestyle[2]. In addition, the increased prevalence and manifestation of CVD in HT patients has renewed the interest of researchers to identify various other unidentified risk factors. The unidentified risk factors such as oxidative stress has been implicated in the increased burden of HT and its related disorders[3]. Oxidative stress can be defined as an imbalance between oxidant agents, such as superoxide anion, and antioxidant molecules, and leads to a decrease in nitric oxide bioavailability, which is the main factor responsible for maintaining the vascular tone. In addition, reactive oxygen species (ROS) confer their toxic effects through cascade of deleterious events including oxidation of LDL, i.e. lipid peroxidation, which eventually lead to development of HT associated various vascular complications[4,5]. Amongst various products of lipid peroxidation, malondialdehyde (MDA) is the most abundant and plays a crucial role in vascular pathology.

Antioxidant defense system plays a crucial role by incorporating antioxidant enzymes and antioxidants to provide protection against harmful effects of ROS. In this context, the role of paraoxonase (PON) against oxidative modification of lipoproteins has received

much attention. PON is a glycoprotein, synthesized mainly in the liver, as HDL-associated lipo-protective enzyme carried on apo A-I and protects the lipoproteins from ROS mediated oxidative damage. PON also hydrolyzes organophosphates like pesticides, neurotoxins, and arylesters[6]. Previous studies have shown that PON level alters in various HT related complications such as cardiovascular diseases, hypertension and obesity[7,8].

Suneja *et al*. also measured the activity of PON1 as enzymic antioxidants in patients with pre-eclampsia[9]. Reduced activity of antioxidant enzymes have also been described in patients with myocardial infarction, obesity, smokers and other vascular disorders [10-12]. Previous studies have documented the incidence of oxidative stress in HT patients, however, studies related to association of PON1 activity and lipid peroxidation in different stages of HT patients are scanty. Therefore, the aim of present study was to evaluate the plasma PON1 activity in stage I essential hypertension and to determine the association of (PON1) with the marker of lipid peroxidation.

MATERIALS & METHODS

In the present study, 50 subjects of Stage I essential hypertension [Stage I HT (SBP 140-159 & DBP 90-99 mm Hg)] of either sex (29 males and 21 females) belonged to age group 40-55 years were recruited in the patient group as per "Seventh Report of Joint National Committee on High Blood Pressure (JNC 7th report)" and 50 age matched healthy individuals were recruited in control group (40-55 years) after taking their informed consent form and approval of the study from Ethical committee of the college. Fasting venous blood sample was collected into EDTA (5ml) vials from the study group subjects after taking the demographic information, history and limited physical examination such as age, sex, height, weight, blood pressure and confirmation of healthy state. For the estimation of study group parameters, plasma was separated from the collected blood sample by centrifugation at 1000 g for 15 min at room temperature and stored at -80^{0}C until use. Height and weight were measured with subject barefoot and light dressed. The body mass index (BMI) was calculated as BMI = *weight (Kg) / Height (metre^2)*. Obese (B.M.I > 30) and smokers were also excluded from the study.

Plasma paraoxonase activity was estimated by Gan et al method using p-nitrophenyl acetate (5.5 mM/L) as a substrate[13]. The increase in absorbance of p-nitrophenol formed at 412 nm was measured spectrophtometrically. The activity of PON was measured in Tris buffer (20 mM/L; pH 8.0) containing 1mM $CaCl_2$. The generated product p-nitrophenol was calculated by using molar extinction coefficient of 17000 per mole/cm at pH 8.0 and results were expressed as Units/ml.

Erythrocyte malondialdehyde (MDA) levels were measured as thiobarbituric acid reactive substances, after preparation of hemolysate. The heat induced reaction of MDA with thio barbituric acid (TBA) in the acid solution formed a trimethine coloured substance, which was measured spectrophotometrically at 532 nm[14].

STATISTICAL ANALYSIS

The data collected from patients and control subjects and values were expressed as Mean ± SD. The significance of mean difference between groups was compared by using Student's't'-test. Linear regression analysis and Pearson correlation test were performed to determine the association between above said indexes or parameters.

RESULTS

In the present study, 50 patients of stage I essential hypertension and 50 healthy individuals, served as controls were included. The mean plasma paraoxonase (PON1) activity and lipid peroxide level (i.e. malondialdehyde) of the patient and control group are depicted in Table.1.0. The mean plasma paraoxonase (PON1) activity in hypertensive subjects were decreased significantly (P<0.001) as compared to controls (29.84% low). On the other hand, erythrocyte malondialdehyde levels were found to be increased significantly (P<0.001) i.e. 48.10% high in stage I HT patients as compared to healthy controls. In addition, we observed a significant correlation between plasma PON1 activity and the marker of lipid peroxidation (MDA) in HT patients, as shown in Fig 1. PON1 activity was negatively correlated with MDA and blood pressure (p < 0.001) in HT patients. These results clarify the association of increased blood pressure with oxidative stress in enhancing the CVD risk in HT patients.

Table-1.0: Plasma paraoxonase activity and erythrocyte malondialdehyde level (µmol MDA/ml) in patients and control group. (Mean±SD)

S.No.	Particulars	Control Group	Patient Group
1.	No. of Samples	50	50
2.	Age (years)	35 – 55	35 – 55
3.	Systolic Blood Pressure (mm Hg)	117 ± 2.6	153 ±4.5
4.	Diastolic Blood Pressure (mm Hg)	77 ± 1.42	98 ± 1.34

5.	Malondialdehyde (µmol MDA/ml)	1.58± 0.14	2.34 ±0.18**
6.	Paraoxonase (IU/gm Hb)	220.38 ± 31.20	154.6 ± 27.52*

Where: * P < 0.05: Significant; ** P < 0.001: Significant

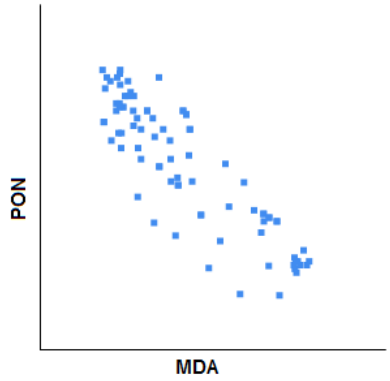

Fig 1: Correlation of PON activity with MDA levels in Stage 1 HT patients

DISCUSSION

Essential hypertension is a highly prevalent pathological condition that is considered as one of the most relevant cardiovascular risk factors and is an important cause of morbidity and mortality around the world [3]. In spite of its high health impact, primary prevention of HT is partly hampered because of a limited knowledge of HT risk factors. Several prospective cohort studies have shown that oxidative stress is associated with an increased risk of acute cardiovascular events and cardiovascular mortality [15]. Involvement of free radicals in membrane damage via lipid peroxidation and its resultant products such as lipid radicals (L◦), lipid peroxides (LOO◦), lipid hydroperoxides (LOOH) and highly reactive aldehydes plays a crucial role in the development and progression of disease. In the present study, a highly significant increased levels of malondialdehyde (i.e. marker of lipid peroxidation) were observed in each patient group (P<0.001) as compared to healthy control which rises continuously with increase in blood pressure and clarify the etiopathogenic role of free radicals via lipid peroxidation in HT patients. Our findings were in concordance with the findings of Bhattacharya *et al*. [16] According to them, lipid peroxides are toxic to the cellular components and lipid peroxidation may be responsible for vascular disorder in HT.

Interestingly, assessment of anti-atherogenic enzyme is another effective approach to predict CVD complications in HT patients. Recent studies on antioxidant enzymes in HT related disorders such as cardiovascular disease, diabetes and in obese patients have received much attention [8,17]. PON enzyme found in association with HDL and contributing it to anti-atherogenic and antioxidant capability by regulating oxidation of LDL, by hydrolyzing specific oxidized phospholipids, cholesterol linoleate hydroperoxides, and by neutralizing hydrogen peroxide [6,7,9]. Alteration in the PON activity may have significant effect in inducing CVD complications in HT patients, possibly due to inability of enzyme to regulate the overproduction of reactive aldehydes. In the present study, plasma PON activity was found to be decreased significantly in HT patients which reflects toward the utilization of enzymes in reducing ROS mediated biomolecular deterioration as well as its inactivation due to interaction of oxidized lipids with the PON free sulphydryl group. Consistent findings have been reported by Saxena and Mehrotra in North Indian geriatric population and implicated the role of depleted PON activity with hypertension and CVD complications [18].

Similarly, low PON activity in individuals with significantly high blood pressure and its association with increased oxidative stress were observed by Senti *et al*. in metabolic syndrome patients [19]. In addition, Suneja *et al*. and Das *et al*. also observed decreased PON1 activity in patients with high blood pressure [9]. According to them, decrease in PON activity is associated with high blood pressure, as observed in our study, and thereby reinforcing the establishment of association of lipid peroxidation with pro-oxidant condition mediated PON deficiency in HT patients. Thus, the enhanced oxidative stress and its association with decreased antioxidant enzyme activity in HT appear to be a major cause of cardiac complications.

CONCLUSION

In conclusion, excessive production of free radicals characterized by lipid peroxidation followed by depletion of plasma PON1 activity along with increased blood pressure could be a potential risk factor in the development of future cardiovascular complications. Moreover, as the blood pressure increases, plasma PON1 activity decreases not only due to its free radical scavenging action but also in maintaining body's antioxidant reserve and in limiting the lipid peroxidation. Therefore, adoption of healthy life style by incorporating antioxidant rich diet including fruits, vegetables and grains along with regular physical exercise should be recommended to HT patients. Furthermore, combined measurement of PON activity and lipid peroxidation may be an efficient marker in early prediction of CVD incident in HT patients.

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