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RESEARCH ARTICLE

STUDY OF OXIDATIVE STRESS AND SERUM PARAOXONASE 1(PON 1) IN ESSENTIAL HYPERTENSION

[1]Dr. Diptimayee Jena, *,[2]Dr. Nirupama Devi, [3]Dr. Itishri Jena, [4]Dr. Rashmita Kumari Padhy, [5]Dr. Pramila Kumari Mishra

[1]Post PG MKCG Medical College
[2]Associate Professor MKCG Medical College
[3,4]Assistant Professor IMS & SUM Hospital and MKCG Medical College
[5] Prof and HOD MKCG Medical College

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ABSTRACT

Aim and Objectives: Essential hypertension accounts for more than 90% of cases of hypertension. It is one of the most important risk factors for cardiovascular diseases and other clinical outcomes. Even though lot of research has been done for the treatment and prevention of hypertension. The present study was carried out with the objective to find out correlation between oxidative stress and paraoxonase 1 in hypertension (HTN).

Methods: The study was carried out on 90 hypertensive patients and 90 normotensive controls. Cases with diabetes mellitus, thyroid disease, chronic kidney disease, smoking, autoimmune diseases and any other chronic diseases are excluded. The study was approved by Institutional ethical committee. Informed consent was obtained from all cases. Serum PON 1 was estimated by ELISA method using commercial kit procured from Aviscera Bioscience, total oxidant load by FOX 2 assay and total antioxidant capacity by FRAP assay. Statistical analysis was done by SPSS version 20 software.

Results: serum total oxidant load (FOX 2) was increased and serum total antioxidant capacity (FRAP) and antioxidant enzyme (PON 1) was decreased in hypertension. There was a negative correlation between serum FOX2 with serum FRAP and PON1 level

Conclusion: Oxidative stress which is responsible for pathophysiology of hypertension, causes decrease in total antioxidant capacity. PON 1 is an antioxidant enzyme present on the surface of HDL also significantly decreased which is responsible for prevention of HTN and it's complications.

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INTRODUCTION

Essential hypertension accounts for more than 90% of cases of hypertension (Johnson *et al*., 2002). It is one of the most important risk factors for cardiovascular diseases and other clinical outcomes (Messerli *et al*., 2007). In addition, hypertension is associated to target-organ damage such as left ventricular hypertrophy (Devereux *et al*., 1987), microalbuminuria (Palatini, 2003) and subclinical vascular impairment as endothelial dysfunction (Perticone *et al*., 2001) an early marker of atherosclerosis. Numerous mechanisms or causes of HTN have been well characterized over the years. Increased vascular oxidative stress could be involved in the pathogenesis of HTN (Miyajima *et al*., 2007), a major risk factor for cardiovascular disease mortality. Arterial hypertension in adults is defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg. Isolated systolic hypertension is systolic blood pressure >140 mmHg and diastolic blood pressure <90 mmHg. Oxidative stress occurs when there is an imbalance between the generation of reactive oxygen species (ROS) and the insufficient antioxidant defence mechanisms, healing and remodelling, which latter become overwhelmed (Rodrigo Ramón *et al*., 2007). Metabolism of oxygen by cells generates potentially deleterious reactive oxygen species, including superoxide anions radicals, hydrogen peroxide, and hydroxyl radicals. Overproduction of oxidants that overwhelm the cellular antioxidant capacity results in pathogenic oxidative stress (Grossman Ehud, 2008). PON1 endows HDL with its antioxidant properties and is probably responsible for the principal mechanism inhibiting the oxidation of both low-density lipoproteins (LDLs) and HDL itself, a process that is directly involved in the initial phases of arteriosclerosis (Berliner *et al*., 1995) In vitro, PON1 neutralizes hydrogen peroxide and peroxidized lipids that are either free or present in atherosclerotic lesions or in minimally oxidized LDL (Aviram *et al*., 2000). HDL-associated PON was able to hydrolyze long-chain oxidized phospholipids isolated from oxidized LDL or

Corresponding author: **Dr. Nirupama Devi**
Associate professor MKCG Medical College

serve as a target for peroxides, through interactions between the enzyme-free sulfhydryl group and oxidized lipids. H_2O_2 is a major ROS produced by arterial wall cells during atherogenesis, and it is converted under oxidative stress into more potent hydroxyl radical leading to LDL oxidation. PON1 was found to use efficiently not only lipoprotein-associated peroxides (including cholesteryl linoleate hydroperoxides), but also hydrogen peroxide (H_2O_2). PON1 inhibits the accumulation of peroxynitrite-generated oxidized phospholipids by its ability to hydrolyze phosphatidylcholine core aldehydes and PC isoprostanes to yield lysophosphatidylcholine. Because of reducing hydroxide and cholesteryl linoleate hydoperoxide in LDL, it is considered that PON1 has an activity like peroxidase. Thus HDL-PON may play an important role in the prevention of atherosclerosis in prolonged hypertensive patients.

MATERIALS AND METHODS

The study was carried out on 90 hypertensive patients and 90 normotensive controls who attended the outpatient department of medicine of M.K.C.G. Medical College and Hospital Berhampur, Odisha, India. Cases with diabetes mellitus, thyroid disease, chronic kidney disease, smoking, autoimmune diseases and any other chronic diseases are excluded. The study was approved by Institutional ethical committee. Informed consent was obtained from all cases. Serum PON 1 was estimated by ELISA method using commercial kit procured from Aviscera Bioscience, total oxidant load by FOX 2 assay (Costa *et al*., 2006) and total antioxidant capacity by FRAP assay (Benzie
and Strain, 1996).

RESULTS

The demographic and clinical data of cases and controls were shown in Table 1. The mean age of cases was 51.74±10.13. Mean systolic and diastolic B.P were 147.98±2.445 and 96.78±3.765 in cases. It was statistically significant when compared to controls (P<0.01).

Table 1. Demographic and clinical data

Parameter	Cases (N=90) Mean±SD	Controls (N=90) Mean±SD	P Value
AGE (years)	51.74±10.13	52.60±9.94	0.563
Systolic BP In mm of Hg	147.98±2.445	115.44±3.672	<0.01
Diastolic BP in mm of Hg	96.78±3.765	78.62±3.996	<0.01

Table 2. Comparison of biochemical parameters

Parameter	Cases (N=90) Mean ± SD	Control (N=90) Mean ± SD	t	p
PON1 (ng/ml)	25.62±2.0628	41.06±2.47	45.52	<0.001
FRAP (µmol/l)	154.67±35.24	334.52±56.90	25.4	<0.001
FOX2 (µmol/l)	4.61 ± 1.52	1.16±0.32	21.006	<0.001

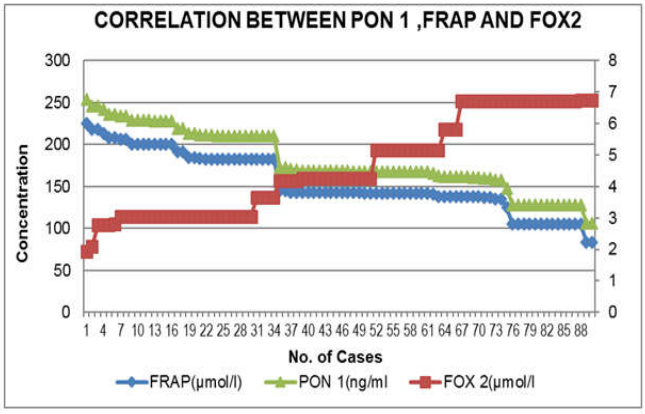
The mean serum values for PON1 were compared in cases and controls. A statistical significant difference was found with a P value of <0.001. Similarly, the Mean ± SD of serum FOX-2 as a measure of Total Oxidant Stress equivalent of H_2O_2 in µmol/L was analysed and found statistically significant (P<0.001). While the Mean ± SD of plasma FRAP as a measure of total plasma antioxidant capacity equivalent of ferrous sulphate in µmol/L was compared with controls and found highly significant (P<0.001).

Table 3. Correlation of PON 1 with oxidative stress

Parameter	PON 1	
	R	P
FRAP (µmol/l)	0.842	0.000
FOX 2 (µmol/l)	-0.745	0.000

This table shows that serum PON 1 level has positive correlation with serum FRAP level (r = 0.842) and negative correlation with serum FOX 2 level (r = -0.745).

Correlation Graph between oxidant and antioxidant



Graph shows there is a negative correlation of PON 1 with FOX 2 (total oxidant load) positive correlation of PON 1 with FRAP (total antioxidant capacity). As total oxidant load (FOX 2) increases both PON 1 and total antioxidant capacity (FRAP) decreases.

DISCUSSION

High blood pressure is ranked as the third most important risk factor for attributable burden of disease in south Asia (2010) (Lim *et al*., 2010). Hypertension exerts a substantial public health burden on cardiovascular health status and healthcare systems in India (Srinath Reddy *et al*., 2005).

Age and Sex Distribution of Cases and Controls

In both cases and controls the age group ranged from 32 to 67 and maximum cases and controls are within the range of 50 - 60 years. Male to female ratio is 2:1 showing that males are more prone to suffer from hypertension (Table 1). Uzun *et al*, (2004) studied oxidative stress and paraoxonase in white coat hypertension consisting of total 86 subjects, 30 with white coat hypertension aged 49±11 yrs, 30 with sustained hypertension aged 47±11 yrs and 26 normotensive controls aged 48±10 yrs. (Uzun *et al*., 2004) Ramon *et al*. (2007) studied the relationship between oxidative stress and essential hypertension taking male subjects between the age group of 35 to 60 years. (Ramon Rodrigo *et al*., 2007) Dildar Konukoglu *et al*. (2009) studied the relationship among plasma secretory phospholipase A2, oxidized low density lipoprotein and paraoxonaase activities in hypertensive subjects treated with angiotensin converting enzyme inhibitors taking cases having mean age 48.1±7.7 yrs and controls having mean age 42.8±9.5 yrs. (Dildar *et al*., 2009) Tripti Saxena *et al*. (2013) studied hsCRP in 100

prehypertensive subjects in the age group of 30-75 years with mean age of 65±14.63 years in controls and 63.16±14.10 years in nondiabetic prehypertensive cases. (Tripti *et al*., 2013) Arun Kumar (2014) studied the correlation of serum paraoxonase activities in known cases of 130 elderly hypertensive south Asian aged 56-64 years. (Arun Kumar, 2014)

Oxidative Stress in Hypertension

This study shows that increase FOX 2 as a measure of total oxidant load and decrease plasma FRAP as measure of total antioxidant capacity in hypertension (Table 2). Russo *et al*, (1998) showed that essential HTN is associated with greater than normal lipoperoxidation and an imbalance in antioxidant status suggesting that oxidative stress is important in the pathogenesis of essential hypertension. (Russo *et al*., 1998) Minuz *et al*. (2002) demonstrated that oxidant stress is markedly increased in hypertensive patients with renovascular disease compared with healthy normotensive subjects. (Minuz *et al*., 2002) Lip *et al*. (2002) al also showed all hypertensive subjects had higher lipid hydroperoxide production, as measured by the ferrous oxidation –xylenol orange (FOX2) assay, compared with control subjects. (Lip *et al*., 2002) Uddin (2003) reported that oxidants like hydrogen peroxide increased while antioxidants decrease in hypertensive rats (Uddin *et al*., 2003). Ramon Rodrigo *et al*, (2007) showed that lipid peroxidation is a risk factor for blood pressure elevation. Additionally the low plasma FRAP levels in hypertensives and their strong negative correlation with SBP and DBP. (Ramon Rodrigo *et al*., 2007) Kumar (2014) showed an increase of lipid peroxides with a decrease in that of antioxidants such as catalase and superoxide dismutase. (Arun Kumar, 2014)

Oxidative stress may contribute to the pathophysiology of hypertension via a number of possible mechanisms, as outlined below.

- Quenching of the vasodilator nitric oxide
- Generation of vasoconstrictor lipid peroxidation products
- Depletion of tetrahydrobiopterin (BH_4)
- Damage to endothelial cells
- Damage to vascular smooth muscle cells
- Increase in intracellular free calcium concentration
- Increased endothelial permeability
- Stimulation of inflammation
- Stimulation of growth signalling event

Paraoxonase 1 in Hypertension

Paraoxonases are a family of three enzymes called PON 1, PON 2 and PON 3. They have multifactorial roles in various biochemical pathways such as protection against oxidative damage and lipid peroxidation. Uzun *et al*. (2004) reported that the PON 1 levels were dependent on the difference in the blood pressure levels (Uzun *et al*., 2004). Saruhan *et al*, (2007) suggested the serum PON1 levels remained unchanged with age and gender in Turkish population (Saruhan *et al*., 2007). Dildar Konukoglu *et al*, (2009) also showed decrease in PON1 activities in hypertensive cases as compared to normotensive controls (Dildar *et al*., 2009). Arun Kumar (2014) showed in his study that oxidative modifications due to HTN causes changes in serum PON 1 activity there by accelerating the atherogenic process. The analysis demonstrated that enzyme activities and concentrations were significantly lowered in hypertensive patients (Arun Kumar, 2014).

Possible mechanisms by which serum PON1 activity was decreased in hypertension are due to:

1. Oxidative stress in hypertension causes decrease in total antioxidant capacity which reflects serum PON1 activity. Antioxidants and free radicals could conceivably protect PON1 through augmentation of the overall antioxidant capacity.
2. Hypertension are also associated with lower serum levels of HDL concentrations hence could explain alterations in PON1 activities.

Conclusion

Oxidative stress is increased in hypertension. The total antioxidant capacity and serum PON 1, which is an antioxidant enzyme present on surface of HDL is also decreased in hypertension. Serum PON 1 level negatively correlates with total oxidant load. This suggests a therapeutic role of antioxidants in hypertension. Yoga, pranayama, stress management and life style modifications may be advised to raise HDL cholesterol and it's associated PON 1 level in hypertensive patients. Diet rich in antioxidant, antioxidant therapy and antilipid drugs may also helpful to raise PON 1 level thereby reducing morbidity and mortality in hypertensive patients.

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