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Research Article

Prediction of hypertension and cardiovascular disease risk in North Indian geriatric population: a conundrum of senescence

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ABSTRACT

Background: Aging has been found to be associated with various sorts of health complications. Therefore, the present study was designed to evaluate the plasma paraoxonase (PON), Nitric Oxide (NO), Total Antioxidant Activity (TAA), lipid peroxidation and serum uric acid levels in the blood samples of different age group subjects and to determine their relation in the prediction of hypertension and cardiovascular disease risk with senescence.
Methods: Markers of antioxidant reserves (PON, TAA, and uric acid), lipid peroxidation and endothelial dysfunction were estimated in selected 120 healthy subjects by using standard methods. Out of 120 subjects, 80 individuals were categorized into two groups: group I (40-55 years) and group II (≥56 years) and statistically compared it with that of 40 younger controls (20-30 years).
Results: Marked depletion in plasma PON and NO levels were observed in group I and II subjects as compared to healthy controls whereas plasma lipid hydroperoxide (LHP) and erythrocyte malondialdehyde levels (MDA) were increased significantly ($P < 0.05$) in group I and II subjects. However, levels of plasma TAA and uric acid were altered significantly ($P < 0.05$) only in group II subjects. In addition, PON levels were inversely correlated with endothelial dysfunction, lipid peroxidation and uric acid, and positively related with TAA.
Conclusions: These findings reflect the importance of assessment of plasma paraoxonase, as excellent marker along with NO in early prediction of hypertension risk and its related cardiovascular complications in elderly. Therefore, antioxidant defence system of body should be boosted up with advancing of age in order to avert future complications.

Keywords: Lipid hydroperoxide, Paraoxonase, uric acid, Nitric oxide, Total antioxidant activity

INTRODUCTION

Aging is a normal, universal and inevitable fate of any biological system and as age increases, the incidence and progression of biological system impairment enhances dramatically.[1] Among different types of chronic complications associated with age, hypertension represents a major public health problem worldwide and, indeed, the main cause of morbidities in older people. It has been well predicted that by the year 2020 there would be an almost 75% increase in the global cardiovascular disease burden, and thus, received much attention for early prediction of HT and CVD in older population.[2]

Among various risk factors, oxidative stress caused by increased production of reactive oxygen species (ROS) such as superoxide anion ($O_2^{\cdot-}$) and its metabolites or by reduced bioavailability of antioxidant defenses in elderly, forecasting a grim scenario for the evolving HT and CVD complications with senescence. Moreover, ROS may act through several mechanisms to mediate age related complications, which include biomolecular destruction,

damage to endothelium, cartilage, membrane ion transporters, DNA strand breakage and oxidative modification of lipoproteins.[3]

In general, ROS induced lipid peroxidation has been implicated in the development of cardiovascular disease and other age related complications.[3,4] The prime targets of peroxidation by ROS are the polyunsaturated fatty acids (PUFA) in the membrane lipids. Consequently, a variety of end products are produced, including reactive aldehydes (malondialdehyde, MDA) and lipid hyroperoxides (LHP). The levels of MDA and LHP indicate the extent of lipid peroxidation, in general, and serve as markers of oxidative damage caused by free radicals leading to cellular senescence.[5]

In order to protect lipoproteins against oxidative modification, the role of paraoxonase (PON), a glycoprotein, synthesized mainly in the liver, as HDL-associated lipo-protective enzyme carried on apo A-I, is well documented. PON also hydrolyzes organophosphates like pesticides, neurotoxins, and arylesters.[6] Previous studies have shown that PON level alters in various age related complications such as cardiovascular diseases, musculoskeletal and neurological disorders.[4,7,8] However, alteration in PON levels with aging process and in determining future risk of age related complications including hypertension (HT), is still in obscure, and has received much attention in order to explore hidden facts related to commencement of senescence.

In particular, Nitric Oxide (NO), a free radical and an uncharged molecule with an unpaired electron, is produced in the body by the isoenzyme Nitric Oxide Synthase (NOS) using L-arginine, as a substrate. NO plays versatile roles in both intracellular and extracellular signaling mechanisms and maintains homeostasis of the cell. In addition, NO takes part in blood pressure control, regulates vascular tone and, inhibits both proliferation of smooth muscle cells and adhesion of leukocytes and platelets.[9] Alteration in the levels of NO, a marker of endothelial dysfunction, exerts culprit effect in inducing hypertension and other patho-physiological complications with senescence.

Destructive events, caused by ROS, are well controlled by antioxidant defense system of the body which includes both enzymic and non-enzymic antioxidants. Apart from enzymic one, Total Antioxidant Activity (TAA) including co-operative action of widely recognized non-enzymatic antioxidants may have a significant role in the regulation of physiochemical alterations during aging and, received much attention in preventing age related complications.[10]

It is obvious that uric acid is an effective antioxidant in plasma as it scavenges superoxide radical, protects erythrocyte against peroxidative damage and free radical attack.[11] However, emerging concepts reveal its relation with circulating inflammatory markers, vascular injury and endothelium dysfunction, and attract the researchers to clarify its role in advancing of age.[12] Therefore, considering the role of aforesaid parameters confluence at a point and thereby leading to the development of various age related complications, the objectives of present study was to determine the relation of plasma paraoxonase with endothelium dysfunction along with markers of lipid peroxidation and total antioxidant activity in different age grouped North Indian subjects and their role in focusing early prediction of HT and CVD risk with advancing of age.

METHODS

To achieve the objectives of present study, 120 healthy subjects were recruited and divided into 3 groups of 40 subjects each (on the basis of age) i.e. control group (younger people) includes 40 healthy subjects of age group 20-30 years, group I includes 40 healthy subjects (middle aged people) of age group 40-55 years and group II includes 40 healthy subjects (elderly) of age group 56 years onwards. In each group, 20 male and 20 female (1:1 ratio) were included. These subjects were recruited randomly after taking their informed consent and approval of protocol by ethics committee of college. A general information or pre-experimental questionnaire regarding demographic information, family history and limited physical examination was completed from all the subjects. 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)].

Inclusion criteria

Subjects who gave informed consent for study, having no history of disease, neither under any medical treatment nor taking antioxidant supplement were included.

Exclusion criteria

Patients with diabetes mellitus, hypertension, dyslipidemia, renal insufficiency, hepatic disease or under any medicinal treatments were excluded. Pregnant and lactating women, smokers, obese (BMI >25), hypertensives (B.P. >120/>80 mmHg) as per JNC 7th guidelines and who did not follow the study instructions, were excluded from the study.

Blood samples (approximately 10 ml) were collected in sterile EDTA vials by venous arm puncture after overnight fasting for erythrocyte preparation and plasma separation. Plasma was collected by centrifugation at 1000 g for 15 min. Markers of endothelial dysfunction, lipid peroxidation, TAA and PON along with uric acid levels were estimated in middle aged and elderly subjects (Group I & group II) and compared it with that of younger healthy controls.

Erythrocyte malondialdehyde (MDA) levels were measured as thiobarbituric acid reactive substances, after preparation of hemolysate.[13] 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.

Plasma lipid hydroperoxide (LHP) was estimated by the method of Jiang et al., which was based on the ability of H_2O_2 to oxidize ferrous ion under acidic condition in the presence of xylenol orange. The resultant chromophore was measured spectrophotometrically at 560 nm. LHP levels were expressed as µmoles/ml plasma.[14]

Plasma paraoxonase activity was estimated by Gan et al. method using p-nitrophenyl acetate (5.5 mM/L) as a substrate.[15] 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 1 mM $CaCl_2$. 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.

The measurement of plasma NO is difficult because this radical is poorly soluble in water and has a short half-life in tissue (10-60 s), but its half-life may be as long as 4 minutes in the presence of oxygen. For these reasons, the end products of the phenomenon, nitrate and nitrite, are preferentially used in clinical biochemistry. Plasma total nitrate and nitrite levels were measured with the use of Griess reagent as described earlier.[16]

Plasma total antioxidant activity was estimated spectrophotometricaly by the method involving reaction of standardized solution of iron EDTA complex with hydrogen peroxide i.e. Fenton type reaction, leading to the formation of hydroxyl radicals. This reactive oxygen species degrades benzoate, resulting in the release of Thio Barbituric Acid Reactive Substances (TBARS). Antioxidants from the added plasma cause the suppression of TBARS production. The reaction was measured spectrophotometrically at 532 nm.[17]

Plasma uric acid levels were estimated by Caraway's method in which uric acid reacted with phosphotungstic acid in alkaline medium forming a blue color complex which was measured at 700 nm.[18] All the chemicals used were of analytical grade and obtained from certified agencies.

Statistical analysis

The data collected from study group subjects were entered separately in Microsoft excel sheet of windows 2007 and values were expressed as Mean ± SD. The significance of mean difference between study group subjects was compared by using Student's t test. The distribution of 't'- probability was calculated depending on 'n' and significance of test was obtained. P value <0.05 and <0.001 were considered as significant and highly significant respectively. In addition, correlation analysis between aforesaid parameters was performed by using Pearson correlation test.

RESULTS

The demographic indices including mean blood pressure of the study group subjects, as observed in present study, are depicted in Table 1. To avoid the affect of sex difference (males sex are more prone to HT and CVD risk), subjects of both the sex in 1:1 ratio were taken in account. BMI measurement revealed insignificant increase (P <0.1) in elderly as compared to middle aged and younger controls. However, elderly subjects had significant variation in blood pressure (P <0.05) with respect to younger controls indicating that elderly were more susceptible to have future HT risk.

Table 1: Demographic profile of study group subjects (n=90).

Particulars	Control group (n=40)	Group I (n=40)	Group II (n=40)
Age (years)	24.8 (2.7)	47.8 (5.0)	65.4 (4.1)
M:F ratio	1:1	1:1	1:1
Height (meter)	1.60 ± 0.02	1.59 ± 0.02	1.61 ± 0.02
Weight (kg)	58.7 ± 2.6	60.8 ± 2.7	62.4 ± 2.2
B.M.I. (kg/m^2)	22.9 ± 1.2	24.1 ± 1.1*	24.0 ± 0.7*
Systolic blood pressure (mmHg)	108.0 ± 2.17	111.8 ± 2.47	116.4 ± 2.6
Diastolic blood pressure (mmHg)	75.5 ± 1.6	75.9 ± 1.4	78.0 ± 1.50

*P <0.1: Non-significant

Plasma PON activity, TAA, markers of lipid peroxidation and endothelial dysfunction, and uric acid levels in study group subjects are depicted as Figure 1, 2, 3 and 4 respectively. Plasma PON activity was significantly low in group I (23.2 %; p<0.05) and group II subjects (34.9%; P <0.05) as compared to younger controls. Similarly, marker of endothelial dysfunction (NO) levels were found to be decreased continuously with increasing age i.e. (P <0.05; 22.2% low) in group I and (P <0.05; 33.4 % low) in group II subjects. On the other hand, erythrocyte MDA and plasma LHP levels were found to be significantly high in group I (P <0.05; 22.8% & 39.8% high) and in group II subjects (P <0.001; 40.4% & 64.6% high). However, plasma TAA and uric acid levels were increased significantly only in elderly subjects i.e. (P <0.05; 43.2 and 38.7% high) whereas insignificant change occur (P <0.1; 18.2 and 15.6%) in group I subjects as compared to younger controls. After performing correlation coefficient analysis, plasma PON activity was positively correlated with TAA and NO

levels in study group subjects. In addition, PON activity was inversely associated with markers of lipid peroxidation and uric acid levels in middle age and elderly subjects (Table 2).

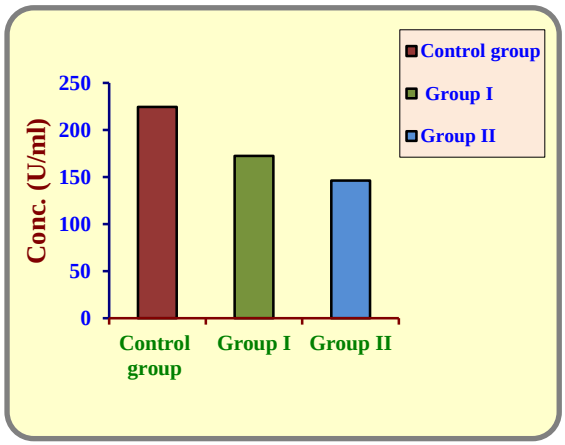

Figure 1: Plasma paraoxonase activity in study group subjects.

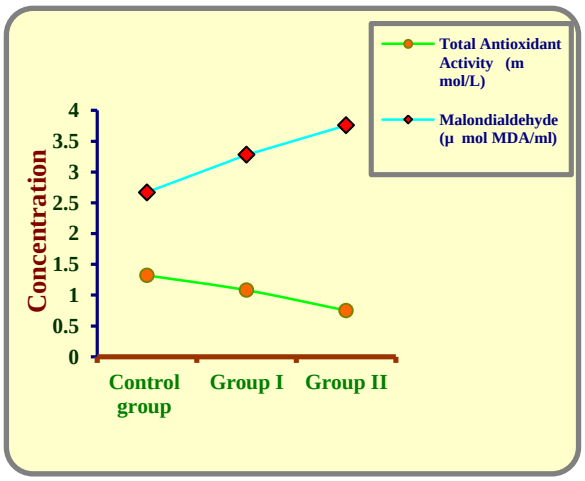

Figure 2: Plasma TAA and erythrocyte MDA levels in study group subjects.

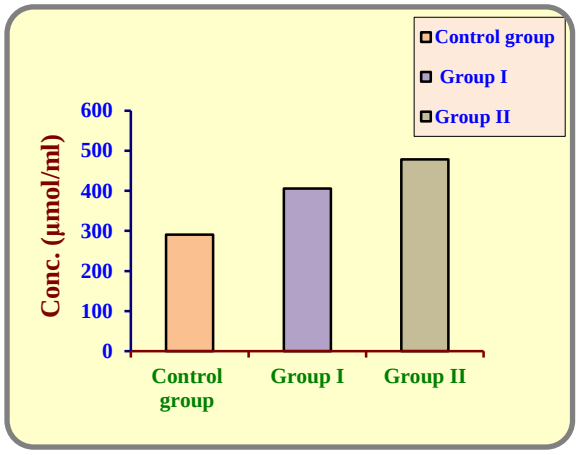

Figure 3: Plasma lipid hydroperoxide (LHP) levels in study group subjects.

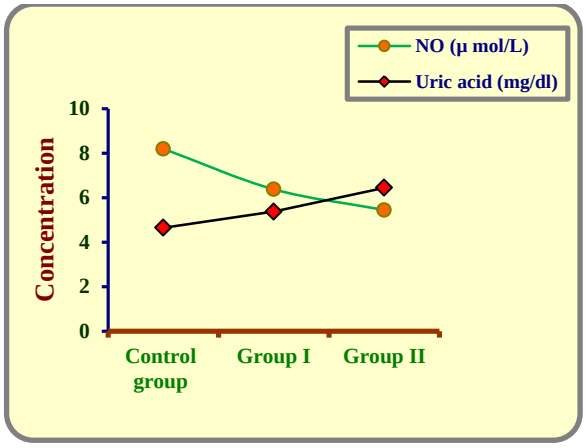

Figure 4: Plasma nitric oxide (NO) and uric acid levels in study group subjects.

Table 2: Correlation coefficient between plasma PON activity and other variables in middle age and elderly subjects.

Parti-culars	B.P.	Nitric oxide	LHP	MDA	TAA	Uric acid
PON in group I	-0.342	+0.427	-0.328	-0.451	+0.264	-0.210
PON in group II	-0.526	+0.638	-0.745	-0.762	+0.595	-0.583

DISCUSSION

Biological aging predisposes individuals to various morbidities through age related perturbation of systemic oxidative balance, i.e. uncontrolled ROS production.[19] Endothelial cells and vascular smooth cells produce ROS which oxidize low density lipoprotein and thereby initiate atherosclerosis. In addition, involvement of ROS in cell membrane damage via lipid peroxidation and its resultant products such as lipid radicals (L°), lipid peroxides (LOO°), lipid hydroperoxides and highly reactive aldehydes which play a crucial role in the development and progression of vascular complications with senescence.[5,20] In this context, marked increase in erythrocyte MDA and plasma LHP levels (i.e. marker of lipid peroxidation) were observed in group I and group II subjects ($P < 0.005$ and $P < 0.001$) as compared to younger controls and these levels were positively correlated with rise in blood pressure, which clarify the etio-pathogenic role of ROS via lipid peroxidation, in shaping elderly more susceptible to develop future incidence of HT and its related complications. Our findings were in concordance with that of recent studies carried out on hypertensives as well as other age related complications.[3,20,21] According to them, lipid peroxides are toxic to the cellular components, and responsible for not only initiation of complex cascade that promotes atherosclerotic plaque formation, prostacyclin synthesis, enhancement of cytosolic free calcium and peripheral vascular resistance, but also cartilage degradation making older people physically inactive and thereby leading to

development of HT and CVD complications with advancing age.

In particular, assessment of anti-atherogenic enzyme is another effective approach to predict future HT and CVD complications in elderly. Recent studies on paraoxonase in hypertension associated diseases and age related complications have received much attention.[4,6-8] 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.[6,22] Alteration in the PON activity may have significant effect in inducing rise in blood pressure with advancing of age, 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 continuously in middle aged followed by elderly which reflects toward the utilization of enzymes in reducing endothelial cells derived ROS mediated lipid peroxidation as well as its inactivation due to interaction of oxidized lipids with the PON free sulphydryl group. Recently, consistent findings have been reported by Kumar in patients with essential hypertensives belonged to age group 40-70 years and implicated the depletion of PON activity with vascular pathology.[23] It seems now evident that role of NO is implicated in the regulation of various crucial physiological functions which declines with progression of age e.g. vasodilation, penile erection, cerebral blood flow, microbicidal and tumoricidal activities of macrophages and neutrophils.[9] Increased production of superoxide anion with aging of vascular endothelium, reacts with NO to form toxic product peroxynitrite anion ($ONOO^-$) and thereby reduces NO bioavailability i.e. an important event in progression of HT risk with senescence.[24] Convincingly, plasma uric acid, a chain breaking antioxidant which contributes about 65% of free radical scavenging action, interacts with peroxynitrite anion to form a stable nitric oxide donor, thus facilitating various physiological functions of the human body.[9]

Marked depletion in plasma NO levels ($P < 0.05$) were observed in elderly subjects whereas it decreased insignificantly ($P < 0.1$) in middle age group subjects reflecting that older people are more prone to develop HT and its related complications due to enhanced oxidative stress mediated incidence of endothelial dysfunction. In addition, plasma uric acid levels were found to be significantly high ($P < 0.05$) merely in elderly group subjects which indicate that body is trying to protect itself from the deleterious effects of free radicals by increasing uric acid production. Consistent findings related to altered levels of NO and uric acid in elderly as well as in hypertensives, are well reported.[25-27] Furthermore, both the events i.e. depletion of NO and elevation of uric acid with senescence, could be explained by the conceptual fact of Maxwell and Bruinsma, as represented in Figure 4.[28] According to them, elevation of uric acid is a secondary event, and occurs due to removal of xanthine oxidase inhibition via reduction in vascular NO because NO is known to interact with active site of xanthine oxidase and inhibits its activity to produce uric acid. However, conversely, role of uric acid in promoting LDL oxidation and vascular injury leading to CVD complications has been well documented.[12,29]

Moreover, as vascular cells ages, they produce excess of ROS which overwhelm the detoxifying capacity of antioxidant defense system of the body and induce culprit effect of oxidative stress, leading to disease development.[24] It is well characterized by alteration in Total Antioxidant Activity (TAA) of the system and thereby shaping elderly more susceptible to HT risk which could not be compensated merely by increase in individual antioxidants. In the present study, plasma TAA levels decrease continuously with increase in age, which clarify the contributory effect of reduced antioxidant status due to augmented oxidative stress that could not be compensated merely by increase in uric acid. Similarly, marked reduction in TAA in elderly, hypertensives and other age related complications, is well documented.[30-32] However, to validate our findings, more substantial researches with large sample size are needed to solve this conundrum in geriatric population.

CONCLUSION

Our findings showed that the PON activity was inversely associated with oxidative stress and endothelial dysfunction and thereby shaping elderly more susceptible to HT and CVD events with senescence. Furthermore, antioxidant defense system of the body should be boosted up with diet rich in green leafy vegetables, fruits and low fat dairy products, in order to avert oxidative stress mediated aging process. Moreover, despite of biological face validity to the conventional HT and CVD risk factors, our findings also encourage the physicians to adopt NO and TAA as non-traditional risk factors along with PON as excellent marker in the screening of older population for HT and CVD development risk..

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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