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PREDICTING THE RISK OF HIGH BLOOD PRESSURE AND CARDIOVASCULAR DISEASE AMONG PAKISTANI POPULATION

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Abstract:
Background: *It has been found that aging is associated with various types of health complications. Therefore, this study was designed to evaluate plasma Paraoxonase (PON), nitric oxide (NO), total antioxidant activity (TAA), lipid peroxidation, and serum uric acid levels in blood samples of people of different age groups and to determine their relationship in predicting high blood pressure and the risk of cardiovascular disease with aging.*
Place and Duration: *In the Medicine and Biochemistry department of Services Institute of Medical Sciences and Hospital for one-year duration from July 2019 to July 2020.*
Methods: *Markers of antioxidant reserves (PON, TAA, and uric acid), lipid peroxidation and endothelial dysfunction were assessed in selected 120 healthy subjects using standard methods. Out of 120 subjects, 80 people were divided into two groups: group I (40-55 years old) and group II (≥56 years old) and statistically compared with 40 younger controls (20-30 years old).*
Results: *People from groups I and II showed a significant decrease in plasma PON and NO levels compared to healthy controls, while the levels of lipid hydroperoxide (LHP) and malondialdehyde erythrocytes (MDA) were significantly increased (P <0.05) in group I and II. themes. However, the plasma levels of TAA and uric acid changed significantly (P <0.05) only in group II. Moreover, PON levels were inversely correlated with endothelial dysfunction, lipid peroxidation and uric acid, and positively associated with TAA.*
Conclusions: *These results reflect the importance of plasma paraoxonase assessment as an excellent marker along with NO in the early prediction of the risk of hypertension and related cardiovascular complications in the elderly. Therefore, as you age, you need to strengthen your body's antioxidant defense system to avoid future complications.*
Key words: *lipid hydroperoxide, paraoxonase, uric acid, nitric oxide, total antioxidant activity*

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INTRODUCTION:

Aging is the normal, universal, and inevitable fate of any biological system, and with age, the incidence and progression of biological system disorders increases dramatically [1-2]. Among the different types of chronic age-related complications, hypertension is a major public health problem worldwide and is in fact a major cause of disease in the elderly. It was well predicted that by 2020 there would be an almost 75% increase in the global burden of cardiovascular disease, so much attention was paid to the early prediction of HT and CVD in the older population [3-4]. Among the various risk factors, oxidative stress due to increased production of reactive oxygen species (ROS) such as superoxide anion (O2 ◦-) and its metabolites, or decreased bioavailability of antioxidant defense in the elderly, predicting the bleak scenario of evolving HT and CVD complications with aging [5]. In addition, ROS can act through several mechanisms that mediate age-related complications, which include biomolecular destruction, damage to the endothelium, cartilage, membrane ion transporters, DNA strand breakage, and oxidative modification of lipoproteins [6-7]. Overall, ROS-induced lipid peroxidation is involved in development cardiovascular disease and other age-related complications. The main targets of peroxidation by ROS are polyunsaturated fatty acids (PUFA) in membrane lipids. Consequently, a wide variety of end products are produced, including reactive aldehydes (malondialdehyde, MDA) and lipid hydroperoxides (LHP). MDA and LHP levels generally indicate the degree of lipid peroxidation and serve as markers of free radical induced oxidative damage leading to cellular aging. The role of paraoxonase (PON), a glycoprotein mainly synthesized in the liver, as a HDL-bound lipo-protective enzyme transferred to apo A-I is well documented to protect lipoproteins from oxidative modification. PON also hydrolyzes organic phosphates such as pesticides, neurotoxins, and arylesters. Previous studies have found that PON levels fluctuate in a variety of age-related complications such as cardiovascular disease, musculoskeletal and neurological disorders. However, changes in PON levels as aging and determining future risk of age-related complications, including hypertension (HT), are still unclear and have been given much attention to investigate the hidden facts behind the onset of aging. In particular, nitric oxide (NO), a free radical and uncharged electron unpaired molecule, is produced in the body by isoenzyme nitric oxide synthase (NOS) using L-arginine as a substrate [8]. NO plays a versatile role in both intracellular and extracellular signaling mechanisms and maintains cell homeostasis. In addition, NO is involved in the regulation of blood pressure, regulates the tone of blood vessels and inhibits both the proliferation of smooth muscle cells and the adhesion of leukocytes and platelets. Changing the level of NO, a marker of endothelial dysfunction, has an impact on the induction of hypertension and other pathophysiological complications related to aging. It is clear that uric acid is an effective antioxidant in plasma, as it scavenges superoxide radicals, protects red blood cells from peroxide damage and free radical attack. However, emerging concepts reveal its link to circulating markers of inflammation, vascular damage and endothelial dysfunction, and encourage researchers to elucidate its role in aging [9-10]. Therefore, taking into account the role of convergence of the above-mentioned parameters at the point and thus leading to the development of various age-related complications, the aim of this study was to determine the relationship of plasma paraoxonase with endothelial dysfunction along with markers of lipid peroxidation and total antioxidant. Activity in different age groups and their role in the early prediction of HT and CVD risk with age.

METHODS:

This study was held in the Medicine and Biochemistry department of Services Institute of Medical Sciences and Hospital for one-year duration from July 2019 to July 2020. To achieve the objectives of this study, 120 healthy people were recruited and divided into 3 groups of 40 people each (depending on age), i.e. the control group (younger people) includes 40 healthy people aged 20-30, group I includes 40 healthy people (middle-aged people) aged 40-55, and group II includes 40 healthy people (elderly people) aged 56 and more. There were 20 men and 20 women in each group (1: 1 ratio). These individuals were randomly recruited after informed consent and approval of the protocol by the college ethics committee. All subjects were filled with general information or a pre-experimental questionnaire regarding demographic data, family history and limited physical examination. The height and weight of the subject were measured barefoot and lightly clothed. Body mass index (BMI) was calculated as [BMI = body weight (kg) / height (meter2)].

Subjects who gave informed consent to the study, with no medical history, and who had not been treated or taken an antioxidant supplement, were included. Patients with diabetes, hypertension, dyslipidemia, renal failure, liver disease, or receiving any medication were excluded. Pregnant and lactating women, smokers, obese people (BMI> 25), and people with hypertension (B.P.> 120 /> 80 mmHg) were excluded

from the study in accordance with 7 JNC guidelines and not following the study instructions. Blood samples (approximately 10 ml) were collected in sterile EDTA vials by arm venipuncture after an overnight fast for red blood cell 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 and group II) and compared with those of younger healthy subjects. The levels of malondialdehyde (MDA) in the erythrocytes were measured as substances reactive with thio-barbituric acid after preparation of the hemolysate. 13 As a result of the heat-induced reaction of MDA with thio-barbituric acid (TBA) in the acid solution, a trimethin-colored substance was obtained 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 H2O2 to oxidize ferrous ions in an acidic environment in the presence of xylenol orange. The resulting chromophore was measured spectrophotometrically at 560 nm. LHP levels are expressed as µmoles / ml of plasma. Plasma paroxonase activity was assessed by Gan et al. By a method using p-nitrophenyl acetate (5.5 mM / L) as substrate. The increase in p-nitrophenol absorbance formed at 412 nm was measured spectrophotometrically. PON activity was measured in Tris buffer (20 mM / L; pH 8.0) containing 1 mM CaCl2. The p-nitrophenol product produced was calculated using a molar extinction coefficient of 17,000 per mol / cm at pH 8.0 and results are expressed in units / ml. Measurement of NO in plasma is difficult because this radical is poorly soluble in water and has a short tissue half-life (10-60 s), but its half-life can be as high as 4 minutes in the presence of oxygen. For these reasons, the end products of this phenomenon, nitrates and nitrites, are preferred in clinical biochemistry. Total plasma nitrate and nitrite levels were measured using the Griess reagent as previously described. The total antioxidant activity of the plasma was determined spectrophotometrically by a method involving the reaction of a standardized EDTA iron complex solution with hydrogen peroxide, i.e., a Fenton-type reaction leading to the formation of hydroxyl radicals. This reactive form of oxygen breaks down the benzoate, releasing thiobarbituric acid reactive substances (TBARS). The antioxidants from the added plasma inhibit the production of TBARS. The reaction was measured spectrophotometrically at 532 nm. All chemicals used were analytical. evaluation and obtained from certified agencies. The data collected from the study groups was entered separately in Microsoft Excel for Windows 2019, and the values were expressed as Mean ± SD. The significance of the mean difference between the studied groups was compared using the Student's t-test. The probability distribution "t" was computed against "n" and the significance of the test was obtained. P values less than 0.05 and 0.001 were considered significant and highly significant, respectively. Additionally, an analysis of the correlation between the above-mentioned parameters was carried out using the Pearson correlation test.

RESULTS:

The demographic indicators of the mean blood pressure of the subjects observed in this study are shown in Table 1.

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

To avoid the effect of the gender difference (men are more prone to risk of hypertension and cardiovascular disease), Gender was included in a 1: 1 ratio. BMI showed a slight increase (P less than 0.1) in the elderly compared to middle and younger controls. However, the elderly showed significant differences in blood pressure (P less than 0.05) compared to younger controls, indicating that the elderly was more prone to future HT risk. Plasma PON activity, TAA, markers of lipid peroxidation and endothelial dysfunction, and uric acid levels in the study group were calculated, respectively. Plasma PON activity was significantly low in group I (23.2%; p less than and group II (34.9%; P less than 0.05) compared to younger controls. Similarly, a decrease in the level of the endothelial dysfunction (NO) marker was found consistently with age, i.e. (P less than 0.05; 22, 2% low) in group I and (P less than 0.05; 33.4% low) in group II On the other hand, it was found that the levels of MDA in red blood cells and LHP in plasma were significantly high in group I (P <0 , 05; 22.8% and 39.8%) and in group II (P <0.001; 40.4% and 64.6% high), however, serum concentrations of TAA and uric acid were significantly increased only in the elderly age, i.e. (P less than 0.1; 18.2 and 15.6%) in group I compared to younger controls.

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

Particulars	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

After the analysis of correlation coefficients, the activity of PON in the plasma was positively correlated with TAA and NO levels in the subjects. Moreover, PON activity was inversely associated with markers of lipid peroxidation and uric acid concentration in middle-aged and elderly subjects (Table 2).

DISCUSSION:

Biological aging predisposes people to various diseases through age-related disturbances of the systemic oxidative balance, i.e., uncontrolled production of ROS. Endothelial cells and vascular smooth cells produce ROS, which oxidize low-density lipoproteins and thus initiate atherosclerosis. In addition, the participation of ROS in damage to the cell membrane through lipid peroxidation and its products, such as lipid radicals (L °), lipid peroxides (LOO °), lipid hydroperoxides and highly reactive aldehydes, which play a key role in the development and progression of vascular complications with aging. Our findings were consistent with the results of recent studies conducted on hypertension and another age-related complications[10-11]. According to them, lipid peroxides are toxic to cellular components and are responsible not only for the initiation of a complex cascade promoting the formation of atherosclerotic plaques, prostacyclin synthesis, increase of cytosolic free calcium and peripheral vascular resistance, but also for the degradation of cartilage causing physical inactivity of the elderly, thus leading to the development of HT and CVD complications with age. In particular, the evaluation of the anti-atherosclerotic enzyme is another effective approach for predicting future complications of HT and CVD in the elderly. Much attention has been given to recent studies of paraoxonase in hypertension-related disease and age-related complications[12]. PON enzyme found in conjunction with HDL and contributing to its anti-atherosclerotic and antioxidant properties by regulating LDL oxidation, hydrolyzing certain oxidized phospholipids, cholesterol linoleate hydroperoxides, and neutralizing hydrogen peroxide. The alteration in PON activity may have a significant effect in inducing an increase in blood pressure with age, possibly due to the inability of the enzyme to regulate the overproduction of reactive aldehydes. The present study found that plasma PON activity decreased continuously in middle age and then in the elderly, reflecting the use of enzymes to reduce lipid peroxidation mediated by ROS derived from endothelial cells, as well as inactivation through interaction of oxidized lipids with MON. Kumar recently found consistent results in essential hypertension patients aged 40-70 years implying a reduction in PON activity with vascular pathology[13]. It now seems evident that a role for NO is involved in the regulation of various key physiological functions that deteriorate with vascular disease. with age, e.g., vasodilation, penile erection, cerebral blood flow, bactericidal and anti-tumor effects of macrophages and neutrophils. Thereby reducing an important event

in the progression of the HT risk with aging. It is convincing that plasma uric acid, a chain-breaking antioxidant that contributes to about 65% of free radical scavenging, interacts with the peroxynitrite anion to form a stable nitric oxide donor, facilitating the thus various physiological functions the human body. Moreover, as vascular cells age, they produce an excess of ROS, which overwhelms the detoxifying capacity of the body's antioxidant defense system and induces an oxidative stress effect that leads to disease development[14-15]. In the present study, plasma TAA levels decline continuously with age, which explains the effect of decreased antioxidant status as a result of increased oxidative stress that could not be compensated for by an increase in uric acid alone. Likewise, a marked reduction in TAA in the elderly, with hypertension, and other age-related complications is well documented. However, to confirm our findings, more detailed large-sample studies are needed to solve this mystery in the geriatric population.

CONCLUSION:

Our findings showed that PON activity was inversely related to oxidative stress and endothelial dysfunction, thereby making older adults more susceptible to HT and CVD events with aging. Moreover, the body's antioxidant defense system should be fortified with a diet rich in green leafy vegetables, fruits, and low-fat dairy products to prevent oxidative stress-mediated aging. Moreover, despite the biological influence of the face on conventional risk factors for HT and CVD, our findings also encourage physicians to take NO and TAA as non-traditional risk factors, with PON as an excellent marker for screening older populations for the development of HT and CVD risk.

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