Paraoxonase 1 Activities and Lipid Parameters in Hypertension and Their Association with Chronic Alcoholism

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Abstract

Objective: To determine lipid profile, antioxidant vitamin (E and C), and malondialdehyde (MDA) levels, as well as superoxide dismutase (SOD) levels and paraoxonase 1 (PON 1) activities in alcoholic hypertensive patients.

Methods: Five hundred subjects were selected for this study consisting of 250 normal healthy individuals and 250 alcoholic hypertensive subjects. Total cholesterol, triglyceride, and HDL levels were measured using the enzymatic method while the LDL and VLDL levels were calculated by Friedwald equation. The MDA level were measured using thiobarbiturate (TBA) and the Vitamin E and C were measured using the enzymatic method. The SOD and PON 1 activities were measured using phenyl acetate as the substrate.

Results: Total cholesterol, triglycerides, LDL, VLDL, and MDA levels were found to be significantly high while the HDL and Vitamin E and C levels decreased among the alcoholic hypertensive subjects when compared to the control. Furthermore, significant decreases in SOD and PON 1 activities were also found among the alcoholic hypertensive subjects as compared to control.

Conclusion: Alterations in lipid parameters, antioxidant vitamin levels, MDA level, SOD activities, and PON 1 activities are associated with hypertension that may be enhanced by alcohol intake, which may lead to the development cardiovascular disease.

Keywords: Alcoholism, hypertension, MDA, lipid parameter, antioxidants vitamins (E and C)

Introduction

Alcohol abuse leads to the buildup of fat in the liver. In alcoholics, significant amounts of alcohol disrupt many metabolic processes in the liver, resulting in the formation of reactive oxygen species (ROS). Under mammalian tissue, free radicals are produced in both healthy and pathological situations. In chronic alcoholism, free radicals have an impact and there is oxidative damage, which is a shift in the oxidant-antioxidant balance.[1]

Chronic liver disease is the tenth leading cause of mortality in adults, with alcoholic cirrhosis accounting for over 40% of cirrhosis-related deaths. Three enzymes, Alcohol Dehydrogenase (ADH), Cytochrome P-4502E1 (CYP2E1), and mitochondrial catalase, metabolise alcohol in the liver. Heavy drinkers have steatosis in 90 percent to 100 percent

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of cases, alcoholic hepatitis in 10% to 35% of cases, and alcoholic cirrhosis in 8% to 20% of cases. Alcoholic fatty liver eventually leads to alcoholic hepatitis, cirrhosis, and liver failure.[2]

The enzyme paraoxonase (PON) has both paraoxonase and aryl esterase activity. Aromatic carboxylic acid esters and certain organophosphorus insecticides, particularly paraoxon and nerve gas, are hydrolyzed. PON1, PON2, and PON3 are members of the PON gene family, which are found on chromosome 7q21.3–22.1. PON1 is primarily produced in the liver and is firmly linked to HDL, protecting both LDL and HDL against lipid peroxidation (LPO).[3]

Paraoxonase 1 (PON1) activity varies up to 40-fold between individuals4, and it is regulated by genetic, developmental, environmental, and pathologic factors.5,6 Low PON1 and Arylesterase (AE) activity has been linked to a number of health problems.7 Due to the liver damage produced by high alcohol use, it has been hypothesised that excessive alcohol consumption would result in a decrease in serum PON1 and AE activity, which has been seen in a few studies.[8]

Excess synthesis of peroxides and free radicals causes oxidative stress, which is described as an imbalance between oxidants and reductants within the body. Oxidative stress is linked to an increase in the generation of oxidizing species or a considerable reduction in the efficiency of antioxidants and antioxidant enzymes chemically. LPO is a free radical-related process that can be damaging if it goes unchecked; the self-enhancing process disrupts membranes, lipids, and other cell components.[9] As a result, the presence of LPO in the blood can help determine the prognosis of non-alcoholic fatty liver disease (NAFLD) patients. The study on PON 1 activity in hypertension and its association with chronic alcoholism is limited hence the objective of this study was to evaluate the effect of chronic alcohol intake on lipid parameters, oxidative stress and paraoxonase 1 activity in hypertensive subjects.

Methods

The present cross-sectional study was carried out in the Department of Biochemistry Santosh Medical College and Hospital Ghaziabad, Department of Biochemistry, Muzaffarnagar Medical College and Hospital, Muzaffarnagar. This study was approved by Institutional Ethical Committee and informed consent was taken from the subjects, prior to study. The minimum sample size has been calculated using the appropriate sample size formula:

$n=z^2pq/d^2$
Where z=1.96 at 95 % confidence interval,
p=0.20 and q=1-p=0.80,
d=absolute error 5%
$n= (1.96)^2\times0.20\times0.80/(0.05)^2$
$=245.86\approx246$

In this study, 500 subjects were included out of which, 250 were already diagnosed hypertensive subjects with alcoholism and 250 were normal and healthy controls. All the subjects were male with 30-60 years of age.

Patients with Type 2 diabetes mellitus, hepatic disease, cardiovascular disease, renal disease, Pulmonary tuberculosis, Acute or chronic inflammatory illness, Gout and arthritis, Prolonged illness, Subjects not willing to give consent in the study, Patients receiving medicines known to alter glucose and lipid metabolism were excluded from the study.

The subjects were requested individually for overnight fasting. Blood samples were drawn with the help of disposable syringe and collected in clean vials. The serum was separated and lipid profile was done on fresh serum and remaining serum sample was kept in small fractions at -200C. Total cholesterol and HDL cholesterol were measured by CHOD-PAP method, triglyceride by GPO-PAP method and the level of LDL-c and VLDL-c were calculated by Friedwald Equation. MDA was measured by chemical method by using thiobarbituric acid (TBA). SOD was measured by modified Marklund and Marklund method by using pyrogallol. Vitamin E & C were determined by chemical method. The activity of PON 1 was measured by chemical method by using phenyl acetate as a substrate. Statistical analysis between controls & study subjects were performed by the student's t-test using SPSS package for windows. The data were expressed as mean ± SD. $p<0.05$ was considered as highly significant.

Result

The difference between alcoholic hypertensive subjects and control subjects were statistically significant. Alcoholic hypertensive patients were showed significant increase in CHO, TG, LDL and VLDL ($p<0.001$) and significantly decrease in HDL ($p<0.0001$) as compared to healthy control. The level of antioxidant vitamins (E&C) were found significantly

Table 1 Demographical Parameters in Studied Subjects

Variables	Controls	Hypertensive with Alcoholics	p-Value
Age (Years)	42.93 ± 6.32	42.99 ± 6.53	>0.05 NS
SBP (mm of Hg)	113.86 ± 4.99	160.15 ± 6.47	<0.001 S
DBP (mm of Hg)	81.42 ± 3.82	100.15 ± 3.66	<0.001 S
BMI* (kg/m^2)	24.92 ± 3.29	27.71 ± 3.17	<0.001 S
WHR**	0.80 ± .058	1.08 ± 0.11	<0.001 S

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: basic metabolic index; WHR: waist to height ratio; S: statistically significant; NS: statistically non-significant

lower (p<0.001) and MDA (p<0.001) was found significantly higher in alcoholic hypertensive subjects as compared to normal healthy Individuals. Superoxide dismutase and paraoxonase 1 activity were found to be reduced in alcoholic hypertensive subjects as compared to normal healthy controls (Table 2). Upon Correlation analysis, a significant and negative correlation of MDA with SOD & PON 1 and a significant positive correlation of SOD and PON 1 were observed (Table 3).

Discussion

Multiple metabolic abnormalities often accompany essential hypertension. Essential hypertension is associated with increased production of ROS predisposing to increase in lipid peroxidation which is a marker for cellular damage. MDA can exacerbate the actions of superoxide ions by impairing endothelium-dependent relaxation and propagation of lipid peroxidation by a chain reaction in membranes.

In this study, increased BMI and Waist/Hip Ratio (WHR) were observed in hypertensive subjects with alcoholics as compared to controls. As BMI and WHR being the markers of general obesity and central obesity, increased BMI and WHR in hypertensive subjects with alcoholics predispose these subjects to an increased risk for CVD.

Table 2 Biochemical Parameters in Studied Subjects

Variables	Controls	Hypertensive with Alcoholics	p-Value
Total Cholesterol (mg/dL)	197.75 ± 23.21	280.52 ± 31.64	<0.001
Triglycerides (mg/dL)	125.93 ± 18.72	239.18 ± 46.16	<0.001
HDL- Cholesterol (mg/dL)	48.82 ± 7.68	32.24 ± 4.62	<0.001
LDL-Cholesterol (mg/dL)	123.75 ± 21.18	200.45 ± 30.18	<0.001
VLDL-Cholesterol (mg/dL)	25.19 ± 3.74	47.84 ± 9.23	<0.001
MDA (nmol/mL)	2.92 ± 0.45	5.05 ± 1.41	<0.001
PON 1 (U/mL)	67.61 ± 7.45	47.21 ± 13.45	<0.001
SOD (U/mL)	10.88 ± 1.87	7.63 ± 1.65	<0.001
Vitamin-E (mg/dL)	1.76 ± 0.25	1.30 ± 0.12	<0.001
Vitamin-C (mg/dL)	1.57 ± 0.18	1.19 ± 0.092	<0.001

MDA: malondialdehyde; PON 1: paraoxonase 1; SOD: superoxide dismutase

Table 3 Correlation Coefficient Among Parameters in Hypertensive Subjects with Alcoholism

Variable	PON1	SOD	Vitamin E	Vitamin C
MDA	r=-0.740 p<0.001	r=-0.620 p<0.001	r=-0.244 p<0.01	r=-0.512 p<0.001

In this study, significantly increase in CHO, TG, LDL-c, VLDL-c and significantly decrease in HDL-cholesterol were observed in alcoholic hypertensive subjects as compared to normal healthy individuals. A study by Paneri *et al.*[10] concluded that there is rise in MDA level in alcoholic hypertensive individuals as compared to normal controls. Decrease in the serum HDL and TAC is also observed in alcoholic individuals when compared to normal controls. Serum total cholesterol, TG, LDL, VLDL were also found to be elevated in the study group when compared to the normal controls. Chen *et al.*[11] found significant increase in total cholesterol, triglycerides, LDL-c and VLDL-c in heavy alcohol consuming individuals. Consumption greater than 50 g/ day significantly reduced the risk of developing low levels of HDL-c, but elevated the risks of developing high levels of cholesterol.

Increased plasma total cholesterol levels which are known to be associated with decreased LDL receptor gene expression and protein abundance in the liver, may be a factor for the change. Chronic alcohol exposure may activates down-regulating the activation of a signaling enzyme that is known to be associated with decreased LDL receptor expression in hepatocytes, suggesting that multiple mechanisms are involved in alcohol-induced down-regulation of LDL receptor.

This study revealed that there was significantly increase in MDA levels associated with high alcohol consumption as compared to control. Our results are in consistent with Deshpande *et al*.[12] who concluded that increase in MDA levels are related to the alcohol consumption and that may be associated with pathogenesis and progression of liver disease. A study by Tan *et al.*[13] reported the same results. An increased MDA level inactivates the antioxidant enzyme (SOD) in untreated hypertension 14 causing damage to various proteins that may also the cause for reduced enzymatic activity of SOD.[15]

The body produces its own antioxidants as a protective mechanism against oxidative stress. Vitamin-like beta carotene, ascorbic acid, Vitamin E, antioxidants enzyme like glutathione peroxidase, catalase and superoxide dismutase are natural antioxidants, which maintain the balance between oxidants and antioxidants.

As discussed earlier, antioxidant vitamin (E & C) decrease the superoxide anion level in the presence of superoxide dismutase in a healthy individual. In case of hypertension, it was found in the present study that there was a direct correlation between the activity of superoxide dismutase (SOD) and the levels of Vitamin E and ascorbic acid.

The significant rise in the levels of reactive oxygen species and decrease antioxidant enzyme may be explained as the combat mechanism showing a relationship between oxidant and antioxidant that has been further raised in alcoholic with hypertensive subjects.

This study observed a significant decrease in PON 1 activity in hypertensive with alcoholic patients as compared to control. A positive correlation was also observed between antioxidant vitamin (E & C) and PON 1. Individuals carrying low PON 1 activity may have a higher risk for CVD. A case-control study has shown that the reduced PON 1 activity is very common in CHD patients.[16]

Previous studies, including ours, have suggested that the PON1 provides the protection for LDL and HDL oxidation and PON1 confers antioxidant activity on HDL. While the susceptibility of HDL to lipid peroxidation and the antioxidant effect of HDL were not measured in our population, the increased risk of CVD in subjects carrying low PON 1 activity could be attributed to the acceleration of atherosclerotic process in these subjects, i.e., an increased susceptibility of LDL to oxidation, a reduction in the antioxidant effect of HDL, and an alteration of their functionality.[17]

Serum PON 1 levels decline in various types of liver diseases. PON1 in association with HDL in the circulation protects LDL from peroxidation. The lowering of PON 1 may be due to peroxidative changes that occur in the hepatocytes. A fall in serum PON 1 could be taken as a manifestation of the different liver function tests i.e., synthesis, detoxication, and secretion.

Correlation studies have found that MDA was positively and significantly correlated with TC where as it was significantly negatively correlated with HDL, PON1, SOD, Vit E and Vit C. However, PON1 was significantly and negatively correlated with TC and MDA where as it was positively correlated with HDL, SOD, Vit E and C.

Furthermore, SOD was significantly and negatively correlated with TC and MDA. However, it was positively correlated with HDL, PON1, Vit E and C in hypertensive subjects with alcoholism. Moreover, Vitamin E was significantly and negatively correlated with TC and MDA and positively correlated with HDL, PON1, SOD and Vit C. Similarly, Vitamin C was significantly and negatively correlated with TC

and MDA and positively correlated with HDL, PON1, SOD and Vit E in hypertensive subjects with alcoholism.

This study showed a negative correlation between MDA & vitamin C, vitamin-E, SOD, PON1 and positive correlation between PON1 & antioxidants (SOD, Vitamin-E & C). Results of present study demonstrate that serum PON1 activity measurement may add a significant contribution to cardiac marker. Thus the present study concluded that the decreased activity of PON1 and HDL-c levels may be contributed to the risk of atherosclerosis via alteration in oxidized-LDL and oxidative stress.

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