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PARAOXONASE 1, HDL-CHOLESTEROL AND TOTAL CHOLESTEROL IN ESSENTIAL HYPERTENSION

MULANI MANZURA R., GANU JAYASHREE V.

Assistant Professors in St. John College of Pharmacy, Pharmaceutics.

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Abstract: Background: - Essential hypertension (EHT) a major health problem for the world population and is universally regarded as among the strongest prognostic markers of cardiovascular disease (CVD). CVD is three times more frequent in hypertensive than in normotensive individuals and clinical manifestations are dyslipidemia. The antioxidant activity of high density lipoprotein (HDL) is a largely due to the paraoxonase 1 (PON1) located on it and PON-1 protect against atherogenesis. The present study was planned to measure the serum level of PON1 activity, high density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) in essential hypertensive patients and to compare with healthy controls. **Material and methods:** - In this study total 90 subjects were included above 40-65 years of age. These patients were newly diagnosed by clinicians and blood sample were collected before starting antihypertensive treatment and 30 subjects were recruited as controls. PON 1, HDL-C & TC level were measured by the spectrophotometric method, Auto Pure T HDL-C 3rd generation homogeneous assay and Wybenga & Pileggi method respectively. Data were analyzed using 'F' test for their level of significance. **Results:** - The mean PON 1 and HDL-C level were significantly lower in EHT patients as compared to the control subjects. The significant correlation was observed between the levels of PON 1 and HDL-C in essential hypertensive patients. The mean TC levels were significantly higher in patients when compared with controls. **Conclusions:** - Reduced serum PON 1 activity, HDL-C and elevated TC level might contribute to the increased susceptibility for the development of CVD in essential hypertension.

Keywords: Essential hypertensive patients, PON 1, HDL-C and TC.



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Corresponding Author: MS. MULANI MANZURA R

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INTRODUCTION

HTN generally defined as persistent increase of systematic arterial pressure. ^[1] is clearly a quantitative phenomenon in which the definition of abnormalities is arbitrary. It reflects a complex interaction between genetic and environmental factors. ^[2] HTN is an iceberg disease because unknown morbidity for exceeds the known morbidity. ^[3]

In considerable proportion of cases HTN tends to be asymptomatic for prolonged time, hence also labeled as "Silent Killer." ^[4]

HTN has also been reported as the 4th contributor to premature death in developed countries and 7th in developing centuries. Thus it is clear that, HTN is an enormous health problem and is one of the biggest health challenges of the 21st century. ^[5] A meta- analysis of HTN prevalence rates in India, India will have the largest number of people with HTN in the world, with the potential of becoming the "HTN capital of world." ^[6]

Subject with HTN possess two fold times risk of developing coronary artery disease (CAD), four times higher risk of congestive heart failure and seven times higher risk of cerebrovascular disease compared to normotensive subjects. ^[7]

The "Global Burden of Disease Study' projected CAD and cerebrovascular disease as the leading causes for death worldwide in the year 2020. ^[8]

The World Hypertensive League (WHL) an umbrella organization of 85 national HTN societies and leagues recognized that more than 50% of the hypertensive population worldwide are unaware of their condition. ^[9] To address this problem, the WHL initiated a global awareness campaign on HTN in 2005 and dedicated May 17 each year as world Hypertension Day (WHD). ^[10]

Therefore, we were interested to determine certain biochemical parameters relevant to risk of CVD.

Hyperlipidemia is well established risk factor for atherosclerosis and CVD. ^[11] The coexistence of EHT and vascular disease and coronary artery disease in patients. ^[12] Hence we planned to determined total cholesterol in EHT.

HDL-C considered as an anti-risk factor for CHD. ^[13] Increased vascular oxidative stress could be involved in the pathogenesis of HTN, a major risk factor for CVD mortality. ^[14]

With this view we planned to estimate HDL-C, PON1 activity in essential hypertensive patients. PON1 is an HDL associated antioxidant esterase enzyme. ^[15]

MATERIAL AND METHODS: -

The present study was carried out in the Department of Biochemistry, Government Medical College, Miraj and study protocol was approved by institutional ethics committee, Study group included 90 patients 40-65 years of age. These patients were newly diagnosed by clinicians on the basis of clinical examination and persistent high blood pressure confirmed by 3 separate sphygmomanometer measurements of blood pressure.

The newly diagnosed EHT patients were classified into 3 categories of HTN according to JNC VI [16] as follows.

JNCVI Category of HTN	SBP mmHg	DBP mmHg
Stage I	140-159	90-99
Stage II	160-179	100-109
Stage III	>180	>110

Control group included 30 subjects without hypertension (SBP 120-129 mmHg, DBP 80-84 mmHg) and matching in age and sex patients.

EXCLUSION CRITERIA: -

The subjects having diseases like tuberculosis, diabetes mellitus, malignancy, stroke, autoimmune disease, hepatic and renal diseases were excluded from the study.

Biochemical parameters were determined before starting antihypertensive treatment. For this blood samples were collected taking all aseptic precautions. After separation of sera PON1 was determined on fresh sample and stored sera (0-4^{0C}) were used for estimation of HDL-C and TC. Estimation of PON1 was carried by spectrophotometric assay of Thery FD et al in which phenyl acetate was used as a substrate [17], HDL-C was estimated by Auto Pure T HDL-C 3rd generation direct homogeneous assay [18] and total cholesterol were determined by Wybenga and Pileggi method. [19].

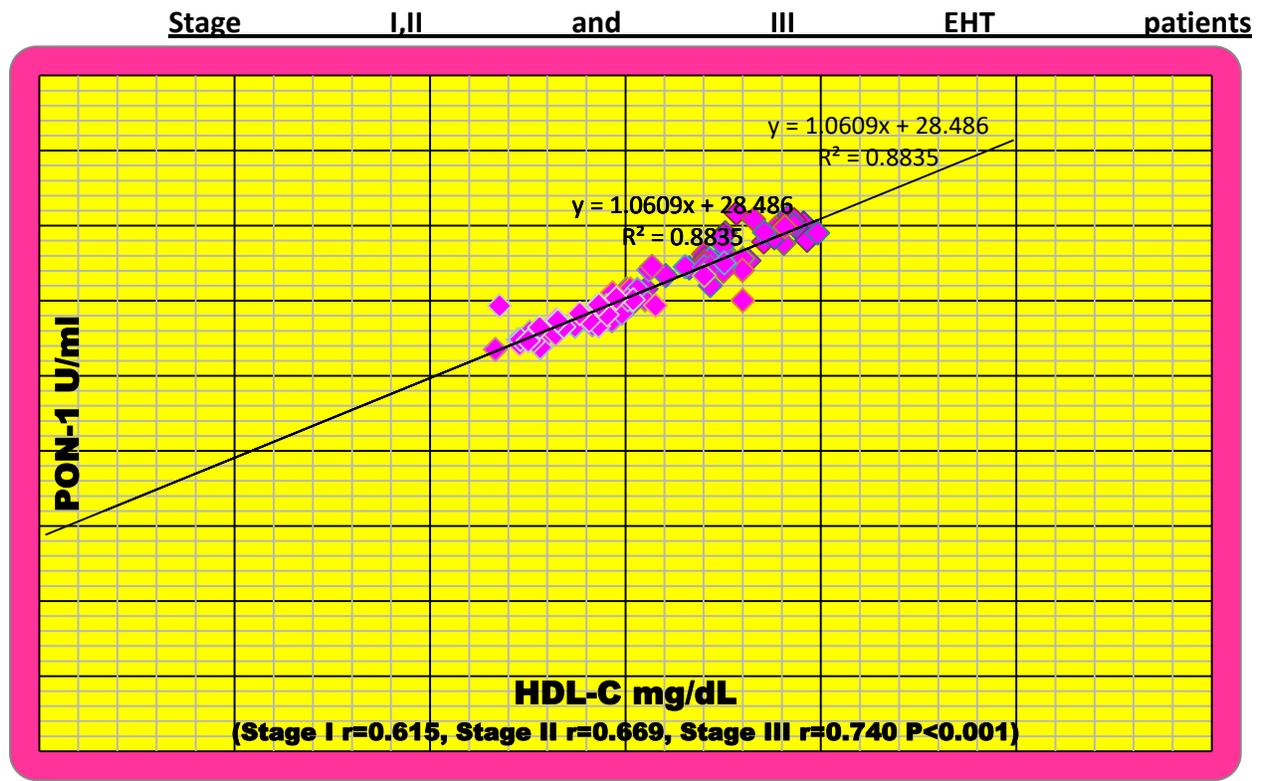
Statistical analysis: - The statistical analysis was performed using Minitab software. The data of patients and controls was analyzed by 'F' test. P values <0.001 were considered significant.

Table No. 1: Serum PON1 activity, serum HDL cholesterol and total cholesterol levels in essential hypertensive patients and controls.

Subjects	PON 1 U/ml Mean±SD	HDL-C mg/dL Mean±SD	Total cholesterol mg/dL Mean±SD
Stage I essential hypertensive patients (n=22)	68.04± 2.21*	36.78±1.72*	162.30±5.05*
Stage II essential hypertensive patients (n=36)	62.62±2.13*	32.43±2.07*	179.62±6.04*
Stage III essential hypertensive patients (n=32)	56.88 ±1.95*	27.01±2.01*	241.25±22.24*
Controls (n=30)	82.72±3.21	43.66±3.01	161.17±8.94

n= Number of Patients *P < 0.001 highly significant.

Graph No.1:- Correlation between HDL-C and PON-1 in



RESULT AND DISCUSSION: -

We observed a significant decrease in the PON-1 activity in all the stages of EHT patients, when compared to that of healthy controls. We found a significant reduction in the activity of PON1 among the EHT patients as the disease progresses from stage I to stage II and then to stage III. (Table No. 1, $P<0.001$)

PON1 is a HDL associated antioxidant enzyme with paraoxonase, arylesterase and dyazoxonase activities. PON1 prevents LDL and HDL oxidation and stimulates cholesterol efflux, the 1st step in cholesterol transport. It is also responsible for the antioxidant efflux of HDL. [20]

While planning this study the rationale was that, if PON1 was of relevance, lower levels could be observed in more severe cases of hypertensive patients. Our results show negative correlation of PON1 with severity of EHT clearly showing that, oxidative stress may be a key process involved in pathogenesis of EHT. PON1 plays a role in preventing lipid oxidation not only of low density lipoprotein (LDL) but also of HDL itself. [21]

In future, PON1 can be included to the battery of routine analysis in clinical biochemistry laboratories and reduce the risk of CVD in EHT.

We observed a significant decrease in the HDL-C activity in all the stages of EHT patients, when compared to that of healthy controls. We found a significant reduction in the activity of HDL-C among the EHT patients as the disease progress from stage I to stage II and then to stage III. (Table No. 1, $P < 0.001$)

The function of HDL-C is the capacity to promote cellular cholesterol efflux from peripheral cells and deliver cholesterol to the liver for excretion i.e. reverse cholesterol transport. [22] The other atheroprotective function of HDL-C is anti-inflammatory, antioxidant and vasodilator properties. But the decreased plasma concentration HDL-C in EHT may accelerate development of atherosclerosis, which is considered to be one of the major processes in pathogenesis of EHT and leading to CVD. [23]

An increase in 1% in the HDL-C level is associated with 2-3% reduction in the risk of CHD. [13]

We observed a significant stage wise increase in the mean total cholesterol levels, when compared to that of healthy controls. (Table No.1 $P < 0.001$)

HTN which is characterized by multiple alterations in the structure and function of the cell membrane may be associated with important metabolic abnormalities including lipid metabolism. [24] Hence, determination of HDL-C and TC at regular intervals will definitely help the clinician in the treatment and management of EHT and prevention and CVD complications.

Correlation between HDL-C and PON-1 levels:-

A positive and highly significant correlation we observed between levels of HDL-C and PON-1 in all three stages of EHT patients. (Graph No.1)

HDL and HDL-PON1 both are antirisk factors of CVD and both possess antioxidant properties. We observed a negative association between severity of blood pressure and concentration of HDL-PON1 and HDL-C. This may be because the chronic oxidative stress of EHT consumes the reserves and impair antioxidant enzyme activity.

This finding indicates increased risk of CAD as EHT progress and this is linked to diminished protective capacity of HDL- PON1 and HDL-C.

We examined all these biochemical parameters like, antioxidant PON-1, HDL-C levels are one of the hallmarks of atherosclerotic inflammatory disorder, total cholesterol concentration accompanied by structural changes of the arteries, appearance of fatty streaks and later of the atheroma may help the clinicians for selecting antihypertensive drugs. In patients with high risk of EHT and dyslipidemia the combined multi targeted management approach to treat both in a plausible method for CVD risk reduction.

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