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PON 1 ACTIVITY IN NEWLY DETECTED TYPE 2 DIABETES MELLITUS PATIENTS WITH & WITHOUT HYPERTENSION

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ABSTRACT

The prevalence of diabetes mellitus & hypertension has been increasing worldwide. Diabetes mellitus is an independent risk factor for coronary artery disease & risk is markedly increased when hypertension is present. Paraoxonase (PON1) is an HDL – associated esterase / lactonase & its activity is inversely related to the risk of cardiovascular disease. Antiatherogenic properties of PON1 include protection of LDL, HDL & macrophages against oxidation. Therefore we studied PON1 activity in newly detected type 2 diabetes mellitus with & without hypertension. We estimated the serum PON1 activity, total cholesterol, triacylglycerides, HDL-C & LDL-C in 100 newly detected type 2 diabetes mellitus with & without hypertension & 50 healthy controls. The result showed that PON1 & HDL-C were decreased & total cholesterol, triacylglycerides & LDL-C were increased in patients as compared to healthy controls. We suggest that PON1 activity decreased may be due to glycation of HDL as well as conformational changes in composition of HDL leading to detachment of PON1 itself from HDL in type 2 diabetes mellitus, resulting in inactivation of PON1. This indicates that PON1 may be very good predictor of coronary heart disease in type 2 diabetes mellitus.

KEYWORDS: PON1 activity, Diabetes mellitus, hypertension

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INTRODUCTION

There has been an increase in the prevalence of diabetes mellitus over past 40 yrs. worldwide. The worldwide prevalence of diabetes in 2000 was approximately 2.8% & is estimated to grow to 4.4% by 2030. This translates to a projected rise of diabetes from 171 million in 2000 to well over 350 million in 2030. There is considerable evidence for an increased prevalence of hypertension in type 2 diabetic person. Both hypertension & diabetes predisposes to the development of cardiovascular disease & renal disease. Subjects with diabetes are at about 60% increased risk of early mortality (2). Insulin resistance and diabetes can precipitate hypertension by stimulating sympathetic nervous system and rennin angiotensin system there by promoting sodium retention. Diabetes is also associated with increased proliferation of vascular smooth muscle cells. High blood glucose and elevated blood pressure can impair vascular endothelial cells, leading to increased oxidative stress (2). Paraoxonase 1 (PON1) is an HDL- associated esterase / lactonase and its activity is inversely related to the risk of cardiovascular disease. PON1 is synthesized in liver. PON 1 antiatherogenic properties include protection of LDL, HDL & macrophages against oxidation. The serum HDL concentration is inversely correlated with atherosclerosis risk. HDL protects against oxidative modification of LDL which is believed to be central in the initiation and progression of atherosclerosis (3, 4, 5, 6). The PON1 activity in type 2 diabetes mellitus and hypertension has been addressed in many studies but results are still complicated and controversial. Therefore we studied PON 1 activity in newly detected type 2 Diabetes Mellitus with & without Hypertensive patients.

MATERIALS AND METHODS

The present study was carried out in the department of biochemistry Bharati Vidyapeeth deemed university medical college and hospital (BVDUMCH) Sangli. The study protocol was approved by ethics committee of BVDUMCH Sangli. Present study included 150 subjects, out of which 50 were controls and 100 were patients. Out of 100 patients, 50 were newly detected type 2 diabetes mellitus with normotensive subjects and 50 were newly detected type 2 diabetes mellitus with hypertensive subjects. The subjects were selected above the age of 40 years. They were diagnosed clinically in the department of medicine and investigated in clinical biochemistry BVDUMCH Sangli. The patients of type 1 diabetes mellitus, other cardiovascular disease patients, liver disorders patients, renal failure patients, endocrinal disorders patients were excluded from the study. The venous blood samples were collected from patients in fasting condition. Serum lipid profile was assayed by standard enzymatic methods (7-10). Serum Paraoxonase1 (PON1) activity was measured with phenylacetate as substrate. The results are expressed as U / ml. (11). Plasma sugar was assayed by GOD-POD (Biolab diagnostics). Blood samples were collected from 50 healthy volunteers who served as healthy controls. All values were expressed as mean ± S.D. statistical significance was analyzed by student‘t’ test. The level of significance was set at $p< 0.05$ for all tests.

Table 1
PON activity & lipid profile in newly detected type 2 diabetes mellitus with normotensive patients & healthy controls.

Parameters	Controls n = 50	Type 2 Diabetes Mellitus with Normotensive n = 50
PON U/ml Mean ±SD	92 ± 0.5	82 ± 15*
Total cholesterol mg/dl Mean ±SD	170 ± 20.1	192 ± 28*
Triglycerides mg/dl Mean ±SD	105 ± 6.4	130 ± 13*
HDL-C mg/dl Mean ±SD	50 ± 3.7	42 ± 6.5*
LDL-C mg/dl Mean ±SD	114 ± 11.2	124 ± 18*

**** P value < 0.001***

Table 2
PON activity & lipid profile in newly detected type 2 diabetes mellitus with hypertensive patients & healthy controls.

Parameters n = 50	Controls n = 50	Type 2 Diabetes Mellitus with hypertension
PON U/ml Mean ±SD	92 ± 0.5	70 ± 14*
Total cholesterol mg/dl Mean ±SD	170 ± 20.1	198 ± 22*
Triglycerides mg/dl Mean ±SD	105 ± 6.4	145 ± 10.5 *
HDL-C mg/dl Mean ±SD	50 ± 3.7	38 ± 5*
LDL-C mg/dl Mean ±SD	114 ± 11.2	131± 16*

****P value < 0.001***

Table 3
Comparison between PON activity & lipid profile in newly detected type 2 diabetes mellitus with normotensive patients and type 2 diabetes mellitus with hypertensive patients

Parameters	Controls n = 50	Type 2 Diabetes Mellitus with Normotensive	Type 2 Diabetes Mellitus with hypertension n = 100
PON U/ml Mean ±SD	92 ± 0.5	82 ± 15*	70 ± 14*
Total cholesterol mg/dl Mean ±SD	170 ± 20.1	192 ± 28*	198 ± 22*
Triglycerides mg/dl Mean ±SD	105 ± 6.4	130 ± 13*	145 ± 10.5 *
HDL-C mg/dl Mean ±SD	50 ± 3.7	42 ± 6.5*	38 ± 5*
LDL-C mg/dl Mean ±SD	114 ± 11.2	124 ± 18*	131± 16*

**** P value < 0.001***

RESULTS

All newly detected diabetic normotensive patients showed significantly lower activity of PON 1 as compared to healthy controls ($P < 0.001$). Serum total cholesterol ($P < 0.001$), serum triglycerides ($P < 0.001$) & serum LDL-C ($P < 0.001$) were significantly increased in type 2 diabetes mellitus with normotensive patients as compared to healthy controls while serum HDL-C ($P < 0.001$) significantly decreased in patients as compared to healthy controls. (Table -1) All newly detected diabetic hypertensive patients showed significantly lower activity of PON 1 as compared to healthy controls ($P < 0.001$). Serum total cholesterol ($P < 0.001$), serum triglycerides ($P < 0.001$) & serum LDL-C ($P < 0.001$) were significantly increased in type 2 diabetes mellitus with hypertensive patients as compared to healthy controls while serum HDL-C ($P < 0.001$) significantly decreased in patients as compared to healthy controls. (Table -2) All newly detected diabetic hypertensive patients showed significantly lower activity of PON 1 as compared to diabetic normotensive patients ($P < 0.001$). Serum total cholesterol ($P < 0.001$), serum triglycerides ($P < 0.001$) & serum LDL-C ($P < 0.001$) were significantly increased in type 2 diabetes mellitus with hypertensive patients as compared to type 2 diabetes mellitus with

normotensive patients while serum HDL-C ($P < 0.001$) significantly decreased in type 2 diabetes mellitus with hypertensive patients as compared to type 2 diabetes mellitus with normotensive patients. (Table -3)

DISCUSSION

Cardiovascular diseases including coronary artery disease occur more frequently in individuals with type 2 diabetes mellitus. Several studies were revealed markedly increase in peripheral arterial disease, congestive heart failure, coronary artery disease, myocardial infarction and sudden death in type 2 diabetes mellitus. Risk factors for macrovascular disease in diabetic individuals are dyslipidemia, hypertension, obesity, reduced physical activity and cigarette smoking (12). In the present study we observed PON1 & HDL were significantly decreased in newly detected type 2 diabetes mellitus with normotensive patients as well as in newly detected type 2 diabetes mellitus with hypertensive patients; as compared to healthy controls. This probably is due to a process in type 2 diabetes mellitus which may cause increase glycation of HDL & reduction in efficiency of cholesterol transport. This leads to accumulation of unesterified cholesterol in the HDL particle which may release PON1 from cells & also may cause alteration in conformation of HDL. Additionally this may lead to change in binding properties of apolipoprotein A-I to the lipoprotein particle. In diabetes HDL has less ability to bind PON1 & has a poor capability for stabilizing its activity. In summation these changes may cause inactivation of PON1 activity in type 2 diabetes mellitus & may step up the atherosclerosis process.

Serum cholesterol, serum triacylglycerides and LDL cholesterol were significantly increased in newly detected type 2 diabetes mellitus with normotensive patients as well as in newly detected type 2 diabetes mellitus with hypertensive patients as compared to healthy controls. The oxidation of LDL may result from increased oxidative stress. The enzyme PON1 has been suggested to constitute an essential part in the defense system against oxidative burden of lipoprotein. Subsequently, decreased circulating levels of PON1 may increase oxidative modification of lipoproteins. Considering the proposed antiatherogenic role of PON1, it was followed that decreased PON1 activity may promote micro & macroangiopathy in diabetes mellitus. But all markers except PON1 were not increased above the pathological range in type 2 diabetes mellitus with normotensive as well as hypertensive patients. PON1 independently increased in these conditions. Glycation of HDL & insulin resistance is associated with impaired PON1 activity. When PON1 activity becomes impaired, its ability to impede LDL oxidation is reduced, leading to acceleration of atherosclerosis. The observations of present study, suggest that loss of antiatherogenic properties PON1, may be due to its inactivation in type 2 diabetes mellitus with hypertensive patients. Deranged HDL may cause formation of foam cell & reduced cholesterol transport (13, 14, 15). Thus PON1 activity may serve as significant predictor of cardiovascular diseases in newly detected type 2 diabetes mellitus with hypertension. Monitoring PON1 activity as a parameter of vascular risk could improve the prognosis of complex vascular disease in type 2 diabetes mellitus.

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