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Assessment of abnormalities in lipoprotein components in hyperlipidemic, diabetic and non-diabetic patients

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Abstract: Hyperlipoproteinaemia is a metabolic abnormality and mainly modulated by apolipoproteins. Furthermore, lipoprotein abnormalities contribute significantly to the risk of development of cardiovascular disease and diabetes mellitus. Additionally, abnormal glycemic state, lipid and lipoprotein abnormalities have been shown to be important contributors to early atherosclerosis. Present study evaluates the status of low density lipoprotein, high density lipoprotein, apolipo-protein A and B in hyperlipidemic, diabeteic and non-diabetic patients. Total 69 patients of both gender, sub-grouped as 39 non-diabetic hyperlipidemic (NDHL) and 30 diabetic hyperlipidemic (DHL) patients were included in the study. Total cholesterol and Apo B was noted to be significantly higher in DHL than NDHL patients. Moreover, levels of Apo B was higher than Apo A in both DHL and NDHL groups when compared with healthy group. Elevated levels of both triglyceride and total cholesterol in both DHL and NDHL groups depicts a strong hyperlipidemic state. It is concluded that diabetes and hyperlipidemia are important risk factors for the onset of cardiac abnormalities. Additionally higher levels of Apo B and A and that of higher Apo B than Apo A are indicative of dyslipidemic state and thus significant parameters for assessing the prevailing conditions and extent of risk for developing coronary heart disease (CHD) and atherosclerosis.

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INTRODUCTION

Hyperlipoproteinaemia is known to be a metabolic abnormality and largely modulated by apolipoproteins[1,2.] It has been reported that hyperlipoproteinaemia may result from an abnormality of plasma lipoprotein metabolism due to some factors such as diabetes mellitus or perhaps a defect in the function of plasma apolipoprotein or in lipoprotein receptor especially in LDL receptor[3,4]. It is important to note that apolipoproteins levels such as that of Apo B and Apo A1, are better indicators of abnormalities in subjects and controls than cholesterol and lipoproteins[5,6,7]. Main apolipoproteins in the plasma lipoproteins are Apo A (major protein of the high density lipoprotein or HDL) and Apo B (major protein in the low density lipoprotein or LDL). Apo B is also the major protein in the intermediate density lipoprotein (IDL) and very low density lipoprotein (VLDL) fractions[3]. It is reported that a correlation exist between increased levels of glucose, cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and a decreased high density lipoprotein cholesterol (HDL-C) and diabetes mellitus[8,9-12.]. In this respect, the investigation of the patients related suffering from diabetes and comparing with non-diabetic patients has gained importance for assessment of early changes pertaining to carbohydrate and lipid metabolism (lipoprotein abnormalities) and possible measures to evaluating some of the subsequent complications such as cardiovascular disease (CVD). It is well documented that lipoprotein abnormalities contribute significantly to the risk of development of CVD and diabetes[1,13,16]. Furthermore lipid and lipoprotein abnormalities have been shown to be important contributors to early atherosclerosis[1,13-16]. A recent study for the SEARCH for Diabetic youth reported higher prevalence of having two or more traditional CVD risk factors among youth with type 1 diabetes, compared with national estimates for youth without diabetes[17].

The present study was undertaken to evaluate status of any abnormalities in apolipoproteins concentration in diabetic and non-diabetic hyperlipidemic patients.

MATERIALS AND METHODS

The study includes 69 patients of both gender, sub-grouped as 39 non-diabetic hyperlipidemic (NDHL) and 30 diabetic hyperlipidemic (DHL) patients. 10 healthy control subjects with no known family history of diabetes mellitus/hyperlipidemea, were included as control. Patients were selected from general medicine and endocrinology OPD and wards, Liaquat National Hospital during the period of March 2006-June 2008. Both control and diabetic related subjects were in the age group of 29-55 years from middle socio-economic group. Among control group, there were 7 males and 3 females while in the

NDHL group, 20 males, 19 females, and DHL group, 17 males and 13 females. Fasting blood samples of both control and NDHL/DHL persons were drawn. Measurements of plasma glucose, cholesterol (TC), triacylglycerol (TAG), HDL cholesterol, low density lipoprotein (LDL), Apo A, Apo B, uric acid were performed on a Hitachi 912 autoanalyzer (Roche Diagnostics, Basel).

Protocols of Akanji *et al.*[16] was followed for management of research design regarding anthropometric and chemical analysis. The average of two weight measurements (electronic scale) and two height measurements (stadiometer) were used to calculate body mass index (BMI; kilograms per square meter). Percentiles for BMI were determined to be specific to sex and month of age using the algorithms of the Centers for Disease Control and Prevention (based on the 2000 Centers for Disease Control and Prevention growth charts) and used to classify study participants. Three blood pressure measurements were obtained after the patient had been sitting for at least 5 min using a portable mercury manometer, and cuffs of five different sizes were used, depending on the size of the arm of the participants. High blood pressure was defined for analyses as systolic blood pressure greater than 120 mm Hg and/or diastolic blood pressure greater than 80 mm Hg. Statistical significance of the results were maintained at $P < 0.05$ and was evaluated by SPSS version 13.

RESULTS

The present study evaluated sixty nine hyperlipidemic patients including 37 males and 32 females. The patients were divide according to their clinical and diagnostic evaluations into NDHL (mean age=46.20 yrs; n=39) and DHL (mean age=47.90 yrs; n=30) groups. Twenty five healthy subjects both males (n=17) and females (n=8) were included as control group. Body mass index (BMI) and waist/hip ratio were noted to be similar in both NDHL and DHL groups and comparatively nearer to the results obtained in healthy group. Furthermore, uric acid is another parameter which showed comparable results in all three groups. Other biochemical parameters such as total cholesterol, TAG, LDL, VLDL, Apo A and B, glucose and HbA1c were compared between the groups of DHL vs healthy and DHL vs NDHL. Significant elevation in all parameters was noted in former comparative group than the later one. Elevated levels of total cholesterol and TAG in both DHL and NDHL groups also confirms their generalized hyperlipidemic. Exceptionally, it was also observed that total cholesterol and Apo B levels in DHL group were higher as compared to NDHL group ($P<0.05$). Similarly it was also ascertained during present study that Apo B levels is higher in DHL when compared with healthy subjects and NDHL group. However the level of significance of elevated Apo B was much higher DHL vs healthy group ($P<0.001$) than DHL vs NDHL groups. Furthermore, Apo B level was also comparatively higher than its counterpart Apo A, in both DHL and NDHL groups (Table 1).

Table 1: Anthropometric indices and biochemical parameters in non-diabetic (n=39) and diabetic (n=30) hyper-lipidemic patients

Parameters	NDHL (n=39)	DHL (n=30)	H (n=25)
Age (years)	41.5±4.1	44.2±3.1	38.6±3.1
BMI (Kg/m^2)	30.1±2.2	31.4±3.2	26±3.4
WHR	0.92±0.05	0.98±0.06	0.8±0.06
TC (mg/dl)	239±40.4	268±30.8[a]	144±15.32**
TAG (mg/dl)	272±38.1	301±33.5	109±9.5*
HDL (mg/dl)	46.4±4.52	41.6±3.3	66.3±4.9
LDL (mg/dl)	161±10.2***	172±13.42	103±7.21*
VLDL (mg/dl)	42.2±5.62	59.1±7.3	12.1±2.1*
Apo A-1 (mg/dl)	132±9.46	141±11.09	109±6.4*
Apo B (mg/dl)	168±14.24	189±15.21[a]	88.4±3.1*
Glucose (mg/dl)	99.2±3.7	161±11.45*	80.5±3.5**
Uric acid (mg/dl)	4.6±0.71	5.2±0.42	3.25±0.1
HbA1c (%)	5.84±1.1	7.9±0.89	5.3±0.65**

*Significantly different from other members of group ($p<0.01$), **Significantly different from DHL group ($p<0.01$), ***Significantly different from Healthy group ($p<0.01$), [a]Significantly differ from NDHL group ($P<0.05$) and DHL ($P<0.001$), BMI=Body mass index; WHR=waist/hip ratio; NDHL=non-diabetic, hyperlipidaemic; DHL=diabetic hyperlipidaemic;H=healthy non-diabetic non-hyperlipidaemic; TC=total cholesterol; TAG=triacylglycerol; LDL=low-density lipoproteins; VLDL=very low density lipoproteins; HDL = high-density lipoproteins.

DISCUSSION

Hyperlipoproteinemia is regarded as one of the most important risk factors for the development of artheriosclerotic diseases especially when co-founded with diabetes [12, 16, 18,19]. Studies indicate that in addition to the routine determinations of triacylglycerol and cholesterol, quantitative determination of the corresponding apolipoproteins

is also important. One of such specific component is the Apo B, which is a carrier protein for low density lipoprotein (LDL b-lipoprotein). Apo B determination noted to be is useful in the differential diagnosis of hyperlipoproteinemia. When evaluated in normal population, the Apo B determination usually detects only b-lipoprotein or LDL. However, in hyperlipemic subjects, the result is also affected by the Apo B content of the pre-b-lipoproteins or VLDL[16]. It was observed that another component Lp(a) and its role in diabetes is debated by several researchers and still needed to be thoroughly investigated[20]. Only few reports are available on the association between Lp(a) levels and the severity of coronary artery disease (CAD) in diabetic patients. In spite of the hurdles, analysis in a large group of type 2 diabetic patients has been carried out for the association of the degree of coronary atherosclerosis with Lp(a) levels and apo(a) polymorphism [21]. The data suggest that Lp(a) levels and apo(a) polymorphism may be reliable predictors of CAD severity in type 2 diabetic patients[21].

It has been stated that these lipid abnormalities are often present before the clinical onset of diabetes and are known to become worse with the development of diabetic long-term complications such as nephropathy[16] . A study carried out earlier in Kuwaiti population, agrees with our study, that the commonest lipid abnormalities seen diabetic patients are hypertriacylglycerolidaemia with low HDL levels and variable LDL levels. Interestingly non diabetic but hyperlipidemic group (NDHL) also demonstrated similar pattern, but in a lower range as compared to DHL. It has also been observed that there were significant variation in the statistical relationships between LDL and HDL and its respective apolipoproteins, apo B and apo A-1, in diabetic, non-diabetic and healthy subjects[22]. Similar pattern was reported in selected diabetic and non-diabetic Kuwaiti population[16,22]. It is documented that low-density lipoprotein cholesterol (LDL-C) is an important risk factor for atherosclerosis[23]. However, recent research reported that serum levels of apolipoprotein B (Apo B) and Apo B to apolipoprotein A-1 (Apo A-1) ratio were better predictors of atherosclerotic vascular disease as compared to LDL-C[23]. In a recent study, it was reported that the combination of Apo B and HOMA-R is a superior marker of carotid atherosclerosis as compared to LDL-C alone in patients with type 2 diabetes[23].

Previous studies carried out with a new found class of apolipoprotein, apoL-I, showed that there were significant associations between apoL-I and VLDL-TAG and hyperlipidemia. Associations of apoL-I with total plasma TAGs in normolipidemic individuals, and in those with dyslipidemias that include hypertriacyglycerolidemia, have been reported previously [24]. The investigations were further extended to patients with low HDL-C and CAD and later provided evidence that VLDL-TAG is the specific TAG component associated with apoL-I. It was postulated that a small fraction of total plasma apoL-I has been found on the VLDL particle and therefore it is possible that the independent relationship exhibited with VLDL-TAG is directly related to changes in VLDL particle number or composition, or to another highly correlated variable[24, 25, 26]. The association of apoL-I with hyperglycemia has not been previously reported and manifested a new dimension adding another lipid variable to the list of abnormalities seen in the dyslipidemia of diabetes and the metabolic syndrome[26, 27, 28]. It was also noted that the association between apoL-I and hyerglycemia was stronger than that with fasting glucose, and there is a possibility that the relationship between apoL-I and the hyperglycemic state is not directly related to glucose level itself but to some other metabolic abnormality, such as hypertriacylglycerolidemia associated with, or contributing to, the hyperglycemic phenotype[24].

A comparative analysis carried out among four groups of subjects with hyperlipidemia on the hypothesis that a relationship exists between apoL and total cholesterol and triacylglycerol in normolipidemic patients. Interestingly, endogenous hypertriacylglycerolidemia, primary hypercholesterolemia, and combined hyperlipidemia populations, except hypoalphalipoproteinemia population, showed to possess higher levels of apoL in plasma [29,30].

This also again confirms result of our study and other similar data available that apolipoprotein showed a tendency to elevate in hyperlipidemic subjects. Moreover, similar to the finding such as ours and those reported earlier, that apoL was significantly correlated with plasma triacylglycerol in all lipoprotein disorders studied. Therefore it was suggested that the levels of apoL in these phenotypes is not a reflection of the dyslipoproteinema per se, but a result of the increase of triacylglycerol levels in plasma[29-32]. Researchers also analyzed apoL mass in the plasma of subjects with type II diabetes[29] and found significant increase in plasma apoL levels correlating with increased levels of total cholesterol and triacylglycerol[29]. They postulated that the

significant increase in apoL in these patients is related to the dyslipidemia[29, 30].

In a recent study it was reported that in youths with type 2 diabetes, elevated apoB and dense LDL were shown to be common lipoprotein abnormalities[33]. A previous study carried out in diabetic and non-diabetic patients showed the ratio of apoB/LDL cholesterol ratio was significantly higher ($P<0.002$) among diabetic compared to nondiabetic subjects. Furthermore, it was also observed that the diabetic subjects with ischaemic heart disease (IHD) had significantly higher ($P<0.003$) apoB/non-HDL cholesterol ratio compared to those without IHD. These findings suggest that the ratios of apoB/LDL cholesterol and apoB/non-HDL cholesterol may have a role in the risk stratification of diabetic patients with dyslipidaemia[34].

In agreement with our study, a group of hypertriacylglycerolidemic subjects had shown increased apoB.[35] Furthermore, as seen in our study, decreased Apo AI appears to be a main component of the dyslipidaemic serum profile observed in diabetic patients as well as those with atherosclerotic occlusive disease of the lower extremities[36].

Perceptively increased Lp(a) levels is an independent risk factor and decreased HDL-cholesterol is also involved in the dyslipidaemic profile[36]. Similar with our outcome, a study reported earlier that dyslipidemic profile was characterized by increased triglyceride level, decreased apolipoprotein A1 level and small dense LDL associated with both NIDDM and non-diabetic subjects [37] .

CONCLUSION

It is concluded that diabetes and hyperlipidemia are important risk factors for developing CAD. Furthermore higher levels of Apo B and A and that of higher Apo B than Apo A are indicators of dyslipidemic state. Thus it is suggested that lipoprotein B and A are significant parameters for assessing the prevailing conditions of diabetes and co morbidity of hypertriacylglycerolidemia and the extent of risk for developing coronary heart disease (CHD) and atherosclerosis.

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