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Prevalence of Dyslipidemic Phenotypes Including Hyper-apoB and Evaluation of Cardiovascular Disease Risk in Normocholesterolemic Type 2 Diabetic Patients

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Abstract: Diabetic patients are vulnerable to different lethal diseases including cardiovascular disease, which is still ranked as the number one killer disease in the world. In the present study, the vulnerability of diabetic patients to cardiovascular disease was evaluated considering apoB level as a predictor. Randomly selected Bangladeshi 96 type 2 diabetic patients (M = 48, F = 48) and 49 healthy non-diabetic individuals (M = 37, F = 12) were recruited to compare their anthropometric and biochemical features. Among the diabetic subjects 32 were hypercholesterolemic (LDL-C>150 mg dL^{-1}) and 64 were normocholesterolemic (LDL-C<150 mg dL^{-1}). The biochemical parameters compared were total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C) and apolipoprotein B (apoB). The values for the diabetic patients vs. control were: TC, 214±46 vs. 186±18 mg dL^{-1}; LDL-C, 143±40 vs. 120±18 mg dL^{-1}; TG, 192±79 vs.141±33 mg dL^{-1} and HDL-C, 35±6 vs. 39±7 mg dL^{-1}; with all p value<0.05. The values for the normocholesterolemic diabetic patients vs. control were: TC, 189±28 vs.186±18 mg dL^{-1}; LDL-C, 120±23 vs. 120±18 mg dL^{-1}; TG, 184±84 vs. 141±33 mg dL^{-1} and HDL-C, 35±7 vs. 39±7 mg dL^{-1}; of which values of TG and HDL-C were significant. Serum apoB level for the diabetic patients vs. control was 1.15±0.28 vs. 0.926±0.25 g L^{-1} ($p<0.05$) and the normocholesterolemic diabetic patients vs. control was 1.06±0.26 vs. 0.926±0.25 g L^{-1} ($p<0.05$). 47% (n = 30) of the normocholesterolemic diabetic patients had hyper-apoB, of which 22% were hypertriglyceridemic and 25% were normotriglyceridemic. Surprisingly, hyper-apoB was also found in 14% of control. Thus apoB identified the high-risk phenotypes in normocholesterolemic diabetic patients and it should be used to evaluate the lipidic pattern of these patients.

Key words: Type 2 Diabetes, hyperlipidemia, Apolipoprotein B

INTRODUCTION

Diabetes is a leading cause of morbidity and mortality worldwide, primarily through an increased incidence of Coronary Heart Disease (CHD). It is likely that diabetic dyslipidemia, in particular, contributes to the increased risk of CHD observed in patients with type 2 diabetes. Dyslipidemias that frequently occur in diabetes might play a critical role in producing the accelerated macrovascular atherosclerotic disease that is, unfortunately, so common. Recent studies have shown that the lipid abnormalities associated with diabetic dyslipidemia begin to develop prior to the clinical onset of type 2 diabetes, at a time when blood glucose concentrations are relatively normal (Isomaa *et al*., 2001). It follows that the implementation of effective antihyperlipidemic treatment to the diabetic population requires an intensive approach.

Diabetic dyslipidemia comprises multiple lipoprotein disorders. The most typical of them are high level of triglyceride (TG), low level of high density lipoprotein-cholesterol (HDL-C) and normal or slightly increased level of low density lipoprotein-cholesterol (LDL-C) (Haffner, 1998; Kannel, 1985; Taskinen, 1990). Although LDL-C levels are the main therapeutic goal of diabetic and non-diabetic dyslipidemia, their concentrations do not stand for the whole mass of lipoproteic particles that also include intermediate-density lipoproteins (IDLs) and very low-density lipoproteins (VLDLs), whose atherogenicity have been demonstrated (Phillips *et al*., 1993). The number and composition abnormalities of VLDL and IDL particles in type 2 diabetes is also

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associated with other atherogenic disorders such as low HDL-C (Syvanne and Taskinen, 1997; Taskinen, 1990). Thus, the sole measurement of LDL-C levels may underestimate the risk associated with atherogenic lipoproteins. Moreover, it has been established that small dense cholesterol-depleted LDL particles are more atherogenic than normal and more buoyant cholesterol-enriched LDL particles and are highly susceptible to glycation and oxidation, both processes are central to the development of an atherosclerotic plaque (Sniderman *et al*., 2001). But unfortunately, the size of LDL particles cannot be measured directly in routine clinical laboratories. For clinical purpose, therefore, the number of LDL particles can be inferred from the plasma apoB.

ApoB (apolipoprotein B100) is the principal protein moiety of LDL, IDL and VLDL. Of the total apoB, >90% are LDL particles or, more precisely, IDL and LDL particles (Young, 1990). ApoB binds to the LDL receptor and is a crucial link in the normal pathway by which LDL is removed from plasma (Brown and Goldstein, 1986). Because each apoB-containing lipoprotein secreted by the liver contains one molecule of apoB, therefore, it reflects the total mass of atherogenic particles (VLDL, IDL and LDL) and its increase is associated with cardiovascular disease independently of LDL-C levels (Elovson *et al*., 1988; Westerveld *et al*., 1998). Recently, the Quebec Cardiovascular Study showed a higher prevalence of hyper-apoB with normo- or hyper-triglyceridemia in men who developed ischemic heart disease (Lamarche *et al*., 1996, 1995) and apoB levels have shown an association with the number of stenotic coronary vessel in normo- and dyslipidemic women (Westerveld, *et al*., 1998). Thus, in addition to hypercholesterolemia, low HDL-C and hypertriglyceridemia, hyper-apoB appears to be a candidate condition to be recognized for the correct evaluation of cardiovascular risk of lipidic origin in patients with type 2 diabetes. Therefore, the aim was to determine the prevalence of dyslipidemic phenotypes, including those dependent on apoB in a group of normocholesterolemic type 2 diabetic patients and those obtained for apoB from a normolipidemic control group and consequently to evaluate their cardiovascular risk.

MATERIALS AND METHODS

Subjects: Randomly selected 96 Bangladeshi type 2 diabetic patients of age 20-65 were examined against 49 healthy non-diabetic subjects of age 18-60. The study was conducted at the Popular Diagnostic Centre Ltd., Dhanmondi, Dhaka, from November, 2003 to August, 2004. Type 2 diabetic patients under medications that affect lipoprotein metabolism were excluded from this study. Patients with hyperchylomicronemia and dysbetalipoproteinemia were also excluded.

Sample collection: Blood samples were collected from randomly selected diabetic and healthy non-diabetic subjects after their overnight fast (10-12 h). The serum were then prepared from whole blood within 3 hours and tested within 24 h.

Estimation of serum TC, HDL-C and TG: Serum total-cholesterol (TC) was measured enzymatically using a commercially available assay kit (The CHOL Flex® reagent cartridge, Cat. No. DF27, Dade Behring Inc., USA). High-density lipoprotein-cholesterol (HDL-C) was measured by the same procedure using an assay kit for HDL-C after precipitating low density lipoprotein (LDL) and very low density lipoprotein (VLDL) with magnesium sulfate and phosphotungstic acid (HDL-Cholesterol liquicolor, Human GMBH, Germany). Serum triglyceride (TG) was also measured enzymatically using a commercially available reagent kit (TGL Flex® reagent cartridge, Cat. No. DF69A, Dade Behring Inc., USA).

Determination of serum LDL-C: Serum low-density lipoprotein-cholesterol (LDL-C) was measured indirectly using the following equation:

$$[\text{LDL-C}] = [\text{TC}] - ([\text{HDL-C}] + [\text{TG}]/5)$$

The factor [TG]/5 is an estimate of VLDL-C concentration and is based on the average ratio of TG to cholesterol in VLDL.

Assay of serum ApoB: Serum apoB was measured using Turbox® apoB reagent kit (Cat. No. 67562, Orion Diagnostica, Finland). The Orion Diagnostica Turbox apoB (apolipoprotein B) assay is a liquid-phase immunoprecipitation assay with nephelometric end-point detection. In this assay antiserum to apoB was diluted in buffer and then added to an aliquot of patient's serum. The light scattering caused by antigen-antibody complexes was measured after incubation, which was directly proportional to the apoB concentration in the sample.

Statistical analysis: Results are expressed as the mean±SD (standard deviation). Student's t-test was performed as the test of significance using the SPSS (Statistical Package for Social Science) program for windows. $p<0.05$ was considered statistically significant.

RESULTS

Anthropometric features of the study subjects: Anthropometric features, including age and BMI of different groups of the study subjects were determined and compared. Values of age (year) and BMI (kg m^{-2}) in diabetic patients (n = 96; M = 48, F = 48) vs. control (n = 49; M = 37, F = 12) were: 50.15±10.52 vs. 43.19±10.36 and 24.65±1.15 vs. 23.07±1.33 respectively, while in case of normocholesterolemic diabetic patients (n = 64; M = 30, F = 34) vs. control (n = 49; M = 37, F = 12), these values were: 49.41±9.60 vs. 43.19 ±10.36 and 23.63±1.23 vs. 23.07±1.33, respectively. However, the BMI was significantly higher in the diabetic subjects while only slightly but not significantly higher in the normocholesterolemic diabetic subjects than that of the control.

Lipid profile of control and patients: Table 1 shows the lipid profile of the control and the diabetic subjects. In the diabetic subjects, serum TC, LDL-C and TG levels were increased by 15, 19 and 36%, respectively while the serum HDL-C level was decreased by 10% than that of the control. All values were significant between the study groups when compared using Student's t-test.

Table 2 shows the lipid profile of the control and the normocholesterolemic diabetic subjects. In the normocholesterolemic diabetic subjects, serum TC and LDL-C levels were same while serum TG level was increased by 30.5% and HDL-C level was decreased by 10% when compared to that of the control, both of which were significant between the study groups.

ApoB status of the study subjects: Figure 1A shows apoB (apolipoprotein B) levels of the control (n = 49) and the diabetic patients (n = 96). Serum apoB level (g L^{-1}) was increased significantly (by 24%) in the diabetic subjects than that of the control. In the normocholesterolemic diabetic subjects serum apoB level (g L^{-1}) was also increased (by 14%, $p<0.05$) than that of the control (Fig. 1B), but was not as higher as that of diabetic group.

Percentage (%) of dyslipidemia among the study subjects: Hypercholesterolemia, hypertriglyceridemia and low HDL-C were found in 33, 44 and 67% of the diabetic patients, respectively (Table 3). Hypertriglyceridemia and low HDL-C were also found respectively in 44 and 69% of the normocholesterolemic diabetic patients. Hyper-apoB was the most prevalent lipidic abnormality as it was found in 65% of the diabetic subjects. Among the diabetic subjects all the hypercholesterolemic patients (n = 32) and

Table 1: Lipid profile of the control and the diabetic subjects

Groups	TC (mg dL^{-1})	LDL-C (mg dL^{-1})	TG (mg dL^{-1})	HDL-C (mg dL^{-1})
Control (n = 49)	186±18	120±18	141±33	39±7
Diabetic patients (n = 96)	214±46	143±40	192±79	35±6

Results are expressed as mean±SD. Student's t-test was performed as the test of significance at 5% significance level. TC = Total-cholesterol, LDL-C = Low density lipoprotein-cholesterol, TG = Triglyceride and HDL-C = High-density lipoprotein-cholesterol

Table 2: Lipid profile of the control and the normocholesterolemic diabetic subjects

Groups	TC (mg dL^{-1})	LDL-C (mg dL^{-1})	TG (mg dL^{-1})	HDL-C (mg dL^{-1})
Control (n = 49)	186±18	120±18	141±33	39±7
NCD patients (n = 64)	189±28	120±23	184±84	35±7

Results are expressed as mean±SD. Student's t-test was performed as the test of significance at 5% significance level. TC = Total-cholesterol, LDL-C = Low density lipoprotein-cholesterol, TG = Triglycerides, HDL-C = High density lipoprotein-cholesterol and NCD patients = Normocholesterolemic diabetic patients with LDL-C<150 mg dL^{-1}

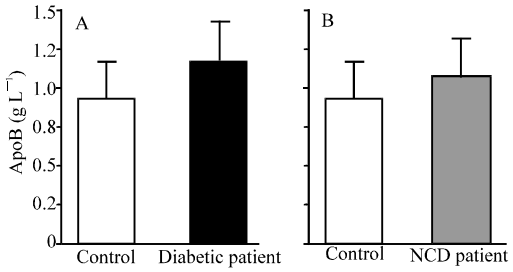

Fig. 1: A. ApoB status of the control and the diabetic patients. B. ApoB status of the control and the normocholesterolemic diabetic (NCD) patients. Results are expressed as mean ±SD. Student's t-test was performed as the test of significance at 5% significance level

30 of the 64 normocholesterolemic patients (47%) had hyper-apoB. Unexpectedly, in the control the frequency of hyper-apoB was 14% (7 of 49 subjects).

Dyslipidemic phenotypes among the patients: Dyslipidemic phenotypes obtained among all the type 2 diabetic patients studied are shown in the following figures.

Figure 2A shows the prevalence of different dyslipidemic phenotypes among all the type 2 diabetic patients. Using the conventional approach, of the total 96 diabetic patients, 19% (n = 18) showed phenotype IIa (Hyper LDL-C, Normo TG), 14.5% (n = 14) showed phenotype IIb (Hyper LDL-C, Hyper TG), 29% (n = 28) showed phenotype IV (Normo LDL-C, Hyper TG) and 37.5% (n = 36) was apparently normolipidemic (Normo LDL-C, Normo TG). All hypercholesterolemic diabetic subjects (both phenotype IIa and IIb) had hyper-apoB (apoB>1.0 g L^{-1}).

Table 3: Percentage (%) of dyslipidemia among different study groups

Groups	HC (%)	Hyper TG (%)	Low HDL-C (%)	Hyper-apoB (%)
Control (n = 49)	-	-	-	14
Diabetic patients (n = 96)	33	44	67	65
NCD patients (n = 64)	-	44	69	47

HC = Hypercholesterolemia, HyperTG = Hypertriglyceridemia, Low HDL-C = Low level of high-density lipoprotein-cholesterol, Hyper-apoB = Hyper-apolipoproteinB, NCD patients = Normocholesterolemic diabetic patients with LDL-C<150 mg dL^{-1}

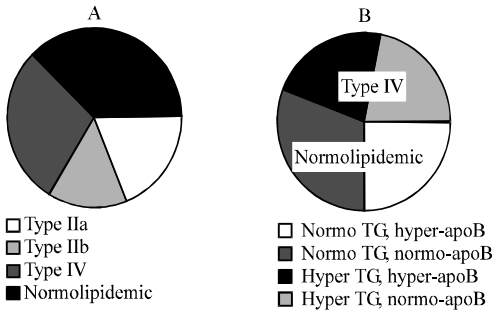

Fig. 2: A. Phenotype frequencies based on LDL-C and TG in the diabetic patients. B. Phenotype frequencies based on TG and apoB in the normocholesterolemic diabetic patients

The distribution of the normocholesterolemic diabetic patients (n = 64) into the different dyslipidemic phenotypes, including those dependent on apoB, is displayed in Fig. 2B. Hyper-apoB was the most frequent lipid disorder, allowing the identification of subgroups normotriglyceridemic hyper-apoB and normotriglyceridemic normo-apoB in the apparently normolipidemic patients. 25% (n = 16) and 31% (n = 20) of the normocholesterolemic diabetic patients were included in these subgroups, respectively. Among the patients with phenotype IV, subgroups hypertriglyceridemic hyper-apoB (22% of normocholesterolemic; n = 14) and hypertriglyceridemic normo-apoB (22% of normocholesterolemic; n = 14) were also identified.

DISCUSSION

Type 2 diabetes is associated with cardiovascular disease (Assmann and Schulte, 1988), which might be due, at least in part, to abnormalities in lipid and lipoprotein metabolism (Syvanne and Taskinen, 1997; Stamler *et al*., 1993). Both elevated levels of low-density lipoprotein-cholesterol (LDL-C) and low levels of high-density lipoprotein-cholesterol (HDL-C) predispose to premature atherosclerosis (Sniderman *et al*., 2001). But low HDL-C levels and hypertriglyceridemia are much more common in patients with coronary disease than are elevations in total and LDL-C levels; thus, from an epidemiologic perspective, both are important risk factors for premature vascular disease. The HDL-C level appears to be the more important factor; both univariate and multivariate analyses usually show it to be a significant risk factor, whereas hypertriglyceridemia is often not significant on multivariate analyses (Austin, 1999; Gotto, 1998). However, some cross-sectional studies show that hypertriglyceridemia with increased apoB level is associated with an increased risk for coronary disease, whereas hypertriglyceridemia with a normal apoB level is not (Kwiterovich *et al*., 1993; Sniderman *et al*., 1982). Thus, a high level of apoB indicates an increased risk of coronary heart disease. The measurement of apoB may therefore be useful to evaluate the cardiovascular risk.

Ninety six Bangladeshi type 2 diabetic patients (of which 64 were normocholesterolemic and 32 were hypercholesterolemic) and 49 healthy non-diabetic subjects were examined in this study. When age (year) and BMI (kg m^{-2}) were compared between the diabetic patients and the control and also between the normocholesterolemic diabetic patients and the control, it has been found that age was significantly higher in both cases than the control. BMI was significantly higher in the diabetic patients while it was only slightly but not significantly higher in the normocholesterolemic diabetic patients when compared to that of the control. Values for BMI in all study subjects including control were slightly higher than the cut off value 22.5 kg m^{-2} (Whitney and Hamilton, 1987). So, it has been found that all the study subjects were slightly overweight.

Increased emphasis is being given to recognizing and treating dyslipidemia in patients with type 2 diabetes and to reduce their high cardiovascular risk. The NCEP recommends aggressive treatment with lower goals for serum LDL-C in diabetic patients (NCEP, 1993). The usual lipidic parameters recommended for the evaluation of lipid-related cardiovascular risk are TC, LDL-C, TG and HDL-C. All these parameters were found significant between the diabetic patients and the control (Table 1). In the case of the normocholesterolemic diabetic patients, values of TG were significantly increased and HDL-C were significantly decreased while values of TC and LDL-C were, expectedly, the same when compared to that of the control. TG is increased in type 2 diabetes, most often due to the increased secretion of VLDL particles by the liver rather than to the impaired clearance of VLDL by the reduced amounts of lipoprotein lipase (Cummings *et al*., 1995; Malmstrom *et al*., 1997). Increased assembly and secretion of VLDL by the liver may result from the complex, post-transcriptional regulation of apoB

metabolism in the liver. The overproduction of VLDL results in the low level of serum HDL-C via an exchange process mediated by Cholesterol Ester Transfer Protein (CETP). However, the above parameters that are usually recommended for cardiovascular risk do not reflect the total amount of atherogenic particles. Therefore, additional parameters that do so are needed.

It has been shown that measurements of the apoproteins are better indicators of the risk of coronary heart diseases than the determination of HDL-C and LDL-C. ApoB (apolipoprotein B100) is the major protein constituent of low-density lipoprotein (LDL). Its synthesis is required for the hepatic secretion of VLDL and remains linked to the particle until its clearance from the circulation as IDL or LDL (Young, 1990). When the catabolism of TG-rich lipoprotein is impaired, as happens in type 2 diabetes, several lipoprotein disorders associated with hypertriglyceridemia occur, such as increased VLDL remnants, low HDL-C and preponderance of small dense particles (Syvanne and Taskinen, 1997). Because there is only one apoB molecule per particle, measuring plasma apoB is roughly equivalent to quantifying the number of apoB-containing lipoprotein particles secreted by the liver, mostly LDL particles, that account for, 95% of circulating apoB. Therefore, apoB reflects the total mass of atherogenic particles (VLDL, IDL and LDL) and its increase is associated with cardiovascular disease independently of LDL-C level (Elovson *et al*., 1988; Westerveld *et al*., 1998). Thus, for a given cholesterol concentration, a high concentration of apoB reflects the presence of an elevated number of apoB-containing lipoproteic particles. In agreement with this statement, it has found that having almost same LDL-C levels, serum apoB level in the normocholesterolemic diabetic patients vs. control was 1.06±0.26 vs. 0.926±0.25 g L^{-1} ($p<0.05$) (Fig. 1B) and hyper-apoB was found, respectively, in 47 and 14% of the normocholesterolemic diabetic patients and the control (Table 3). The main lipidic difference between these groups was the concentrations of TG (184±84 vs. 141±33 mg dL^{-1}, $p<0.05$) and HDL-C (35±7 vs. 39±7 mg dL^{-1}, $p<0.05$) (Table 2). Thus, apoB concentrations may provide information for a more complete lipidic evaluation than LDL-C alone in type 2 diabetic patients.

In this study the cutoff point obtained for apoB from control group, following the procedure used in the Framingham Study, showed a lower value (1.0 g L^{-1}) than the value found in Framingham Study (1.2 g L^{-1}) (Contois *et al*., 1996) and proves that regional reference values are still needed, despite international standardization of the measure. According to the cutoff value in the present study, hyper-apoB was the most prevalent (65%) lipidic abnormality in diabetic patients. When 64 normocholesterolemic diabetic patients were considered, hyper-apoB remained the most prevalent lipoproteic disorder (47%) and was more frequent than the percentage found in the control group (14%) (Table 3). It was also found that 67% diabetic patients and 69% normocholesterolemic diabetic patients had low HDL-C when compared to the cutoff point for HDL-C (for men HDL-C, 35 mg dL^{-1} and for women HDL-C, 45 mg dL^{-1}) (Table 3).

The present study analyzed the impact of apoB level for the classification of the type 2 diabetic patients with normal LDL-C level into different dyslipidemic phenotypes (Fig. 2). Patients under lipid lowering medication were excluded in the study so that the prevalence of frequent dyslipidemic phenotypes (IIa, IIb and IV) can be identified easily. The measurement of serum apoB level allowed the identification of the subgroups, hypertriglyceridemic hyper-apoB (22%) and normotriglyceridemic hyper-apoB (25%) in normocholesterolemic diabetic subjects (Fig. 2B) and thus reflects their increased cardiovascular risk (Lamarche *et al*., 1997). Thus the measurement of apoB may help to identify a group of subjects who should be treated, especially those with moderate hypertriglyceridemia, because increased apoB levels confer a two to three-fold increase in cardiovascular risk (Lamarche *et al*., 1995).

The measurement of apoB level in this study thus assessed the lipidic-cardiovascular risk in the normocholesterolemic type 2 diabetic patients that are not obtained from conventional lipoproteic evaluation. However, additional prospective studies are necessary to identify various dyslipidemic phenotypes in the normocholesterolemic type 2 diabetic patients and to evaluate their cardiovascular risk, bearing in mind the independent association of apoB with cardiovascular disease.

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