Diabetic dyslipidemia is a well-known issue, but what about lipoprotein a levels in Type 2 diabetics?

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Abstract
Type 2 DM is a worldwide endemic disease. Dyslipidemia is also a frequent disorder associated with diabetic patients. Lipid profiles can vary in distinct ethnic groups and population. There have been few trials about lipoprotein a (Lpa) levels in type 2 diabetic patients. We investigated serum lipid profiles, Lpa levels and metabolic syndrome findings in type 2 diabetic patients. In this prospective trial, 709 type 2 diabetic patients (407 F; 302 M) and 157 healthy control subjects (91F; 66M) living in the same geographic region were included. The mean age of patients was 53.4 ± 9.2 years. After 12-h overnight fasting, blood samples were obtained for analyzing the serum lipids. The serum total cholesterol, HDL, LDL, and triglycerides levels were measured by glucose enzymatic calorimetric method and apo-B, lipoprotein (a) levels by electrochemiluminescence Immunoassay. All patients were also evaluated for metabolic syndrome by NCEP ATP III criteria. Type 2 diabetic patients had higher serum total cholesterol, LDL cholesterol, triglyceride and apo-B levels and lesser HDL-cholesterol, compared with the control group ($p<0.001$). The serum Lpa was found to be similar in both type 2 diabetic and control subjects ($p=0.519$). Of the 709 diabetic patients, 516 (72.9%) had metabolic syndrome. In conclusion, as expected, dyslipidemia and metabolic syndrome was found to be higher in diabetic patients with respect to healthy controls, however, serum Lpa levels were not different in both groups.

Keywords: *Diabetes Mellitus, lipid profiles, Lipoprotein (a), metabolic syndrome.*

Introduction

The lipid abnormality (dyslipidemia) associated with type 2 diabetes typically consists of elevated triglycerides and decreased HDL cholesterol level.[1] In such individuals, LDL cholesterol levels are generally not significantly abnormal, although they maybe somewhat elevated in whites[2] and lower in other racial/ethnic groups. The frequently mild abnormality in LDL cholesterol concentration associated with diabetes belies a qualitative abnormality in the LDL structure, i.e., decreased size and increased density of the LDL particle.[3] Even when LDL cholesterol is normal or within a range that might be considered low in diabetic individuals, LDL appears to be very potent contributor to the development of coronary heart disease CHD.[4] In addition to VLDL, LDL levels are also somewhat increased in diabetic individuals under poor control, probably accounting in part for their increased risk for cardiovascular disease (CHD).

Apo-B100 and Lpa are also accepted an athoregenic lipoproteins when its plasma level is above 30 mg/dL. Lpa levels can vary in different ethnic groups. There are few studies regarding its association with type 2 diabetes. The results of serum Lpa levels are inconclusive.

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In this prospective clinical study, we investigated serum lipid levels including total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, and Lpa, in addition, the frequency of metabolic syndrome among our type 2 diabetic patients.

Material and methods

In this prospective study, total 709 (Female: 407; Male: 302) type 2 diabetic patients who were diagnosed and followed at our outpatient clinic of the University Hospital between the years 2003 and 2008 were enrolled. Past medical history, diabetes duration, chronic diabetic complications, treatment modalities of all patients were investigated. Diabetic complications such as retinopathy, neuropathy, nephropathy and peripheral arterial disease were evaluated by ophthalmic examination (by ophthalmologist), electromyography, neurological examination, 24-h microalbuminuria, and peripheral arterial pulses and doppler ultrasonograpy. BMI (body mass index) and waist circumference of the patients were measured in the fasting state.

Biochemical analyses were performed after 12-h overnight fast for blood glucose, HbA1c, BUN, creatinine, liver transaminases, and serum lipid parameters [total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, and Lpa. Serum glucose, AST, ALT, GGT, total cholesterol, HDL, LDL, triglyceride levels were analyzed via a modular system using enzymatic calorimetric method. Serum apo B, Lpa levels were measured by a modular apparatus with ECLIA (Electrochemiluminescence Immunoassay).

Those subjects who have renal failure, liver failure, known malignant disease, acute infection, alcohol abuse, hypothyroidism and taking medication affecting serum lipid levels were excluded from the study.

As a control group, 157 (Female: 91; Male: 66) healthy subjects living in the same geographical area with diabetic patients were enrolled. The Local Ethical Committee approved the study.

Statistical analyses were performed with a packed program of SPSS, version 16.0. Parametric and nonparametric tests were used. Values were given mean ± SD. Nonparametric data was compared by Ki-square test. T-test for comparing of different group and logistic regression test for determining risk factors were used. P<0.05 was accepted as positive.

Results

Mean age of the patients (N=709) was 53.4 ± 9.2 years. Mean duration of diabetes was 7.61±5.81 years. Mean age of the control subjects (N=157) was 49.4± 10.1 years. The main characteristics of the patients and control group and their comparisons are shown in Table 1.

The serum lipid profiles of the patients and control groups are shown in Table 2. Of the 709 type 2 diabetic patients, 355 (50.1%) had high total cholesterol level (>200 mg/dl, p<0.01), 248 (35%) had high LDL levels (>130 mg/dl, p<0.016) (Fig. 1), 419 (59.1%) had high triglyceride level (>150 mg/dl, p<0.001) (Fig. 2), 38 (5.4%) had higher apo B level than control subjects (p<0.001) (Fig. 3), 240 (33.9%) had serum Lpa over 30 mg/dl (p=0.298) (Fig. 4), 393 (55.4%) had low (<40 mg/dl) HDL cholesterol (p<0.001).

HDL-cholesterol levels of the patients and controls are shown in figure 5 with respect to the gender. The HDL level of diabetic females was found lower than the control subjects (48.6±14.1mg/dl vs. 55.7±15.8 mg/dl, p<0.001), respectively. HDL level of diabetic males was non-significant than control males (p=0.138).

The relationship between the serum lipid parameters and gender of the patients is given in Table 3. Total cholesterol, HDL, LDL, apoB, and Lpa levels of the females were significantly higher than those of the males.

There was no significant relation between diabetes duration and lipid parameters.

The mean BMI of type 2 diabetics and control group were 30.4±5.3 kg/m^2 and 29.1±3.9 kg/m^2 (p<001), respectively. In comparison to other lipid parameters, serum triglyceride and apo B levels showed correlation with BMI (p<0.001). No relation was found between Lpa and BMI (p=0.61).

No significant relation was found between HbA1c and serum lipid parameters.

Diabetic complications found in patients were as follows; coronary artery disease 12.6%, peripheral arterial disease 4.8%, neuropathy 51.9%, retinopathy 29.7%, nephropathy 23.9%; microalbuminuria 18.5% and macroalbuminuria 5.4%. When compared to the serum lipid parameters, no correlation was found with the presence of diabetes complication.

The frequency of metabolic syndrome considering the NCEP ATP III criterions was found as follows: metabolic syndrome found in the 83.5% of the diabetic females and 58.6% of the diabetic males (p<0.001).

Discussion

An increased levels of Lpa >30 mg/dl has been accepted as an isolated risk factors for CAD and myocardial infarction (MI).[5] Several studies have shown that Lpa is high in type 2 diabetic patients.[6-11] In these studies, performed in different population, serum Lpa levels were reported to be between 0-100 mg/dl with over 50% in the range of 0 and 50 mg/dl.[12-14] In contrast, many other studies have reported no difference in the serum Lpa levels between type 2 diabetics and control subjects.[15-17]

In the present study, serum Lpa levels of diabetic patients were not significantly different from the control group [(33.3 ± 46.4 mg/dl, range 0 to 122 mg/dl) vs. (35.9 ± 46.7 mg/dl, range, 0 to 125 mg/dl) p=0,519], respectively. However, serum Lpa levels in women were higher than that of men (37.3 ± 54.1mg/dl vs. 27.8 ± 32.6 mg/dl, p < 0.004). The underlying cause of this gender difference is not known, but it is speculated that Apo(a) phenotype, or ethnical characteristics could have an influence. However, in another study from Tunus including 200 type 2 diabetic patients and 100 control group, Lpa levels of male diabetic patients revealed positive correlation with CAD contrary to female diabetic patients, and they found no correlation between Lpa levels and serum glucose and HbA1C levels.[18] In our study, we also found no difference between Lpa levels and diabetes duration, BMI and HbA1c levels. In two studies from Turkey including a total of 55 type 2 diabetics and 32 control subjects, Lpa levels were not different between diabetics and non-diabetic control subjects.[19,20]

In certain studies, it was reported that apo (a) phenotype could affect the serum Lpa levels.[21-24] As a result, racial variations in Lpa levels were suggested,[12,13,25] but, unfortunately, in the present study, we could not analyze apo a phenotypes.

The total cholesterol was normal to high in type 2 diabetic patients.[26] In the present study the total cholesterol of 709 diabetic patients was significantly higher than that of control group (202.2 ± 41.5mg/dl vs. 189.0 ± 30.5 mg/dl, p<0.001), respectively.

In a study on lipid profiles of healthy Turkish population including 9,000 subjects between 1990 and 1993, total cholesterol level was found to be between 160 and 190 mg/dl. Total cholesterol levels of 68 per cent of Turkish males and 78 per cent of Turkish females were lower than 200 mg/dl. However, HDL levels of the Turkish population were reported to be lower than target levels. Therefore, an

Table 1: The characteristics of type 2 diabetic patients and control subjects

Parameters	Type 2 DM (N=709) Mean± SD	Control group (N=157) Mean ± SD	*p* value*
Age (year)	53.4 ± 9.2	49.4 ± 10.1	<0.001
Diabetes duration (year)	7.61±5.81	-	-
BMI (kg/m^2)	30.4 ± 5.3	29.1±3.9	<0.001
Waist circumference (cm)	98.0 ± 11.6	85.0± 9.5	<0.001
HbA1c (%)	7.75 ±1.85	5.2±0.35	<0.001
Glucose (mg/dl)	158.4 ± 64.4	91.6±25.3	<0.001
Total cholesterol (mg/dl)	202.2 ± 41.5	189.0± 30.5	<0.001
HDL (mg/dl)	46.2 ± 13.0	51.3±14.8	<0.001
LDL (mg/dl)	118.1 ± 34.7	111.6±29.0	<0.015
TG (mg/dl)	196.9 ± 21.9	123.7±76.1	<0.001
Apo B (mg/dl)	92.4±24.5	81.8±19.4	<0.001
Lp (a) (mg/dl)	33.3±46.4	35.9±46.7	0.519

**p* value: type 2 diabetics vs. control subjects

Table 2: Serum lipid profiles of type 2 diabetic and control subjects.

Parameters	Type 2 DM (N=709)	Control (N=157)	p
T. Cholesterol (mg/dl)			
<200	354 (49.9%)	108 (68.8%)	<0.001
200–239	227 (32%)	38 (24.2%)	
>240	128 (18.1%)	11 (7.0%)	
HDL (mg/dl)			
<40	393 (55.4%)	61 (38.9%)	<0.001
>40	316 (44.6%)	96 (61.1%)	
TG (mg/dl)			
<150	290 (40.9%)	115 (73.2%)	<0.001
150–199	155 (21.9)%	20 (12.7%)	
200–499	246 (34.7%)	22 (14.0%)	
>500	18 (2.5)%	0	
LDL (mg/dl)			
<100	219 (30.9%)	53 (33.8%)	<0.016
100–129	242 (34.1%)	66 (42.0%)	
130–159	154 (21.7%)	29 (18.5%)	
160–189	78 (11.0%)	7 (4.5%)	
>190	16 (2.3%)	2 (2%)	
Apo B			
0–66	86 (12.1%)	37 (23.6%)	<0.001
66.1–133	585 (82.5%)	120 (76.4%)	
>133	38 (5.4%)	0	
Lp (a)			
<30	469 (66.1%)	97 (61.8%)	<0.298
≥30	240 (33.9%)	60 (38.2%)	

Table 3. Serum lipid profiles of type 2 diabetic patients according to gender.

Parameter	Gender	N=709	Mean ± SD	Range (Min; Max)	*p*
Total Cholesterol	F	407	209.37±40.966	(98;310)	0.001
	M	302	192.71±40.526	(98; 301)	
	F	407	48.66±14.176	(24; 65)	0.001
HDL	M	302	42.99±10.559	(24; 64)	
	F	407	121.90±33.997	(62; 210)	0.001
LDL	M	302	113.11±35.210	(60; 193)	
	F	407	201.83±127.736	(70; 514)	0.204
TG	M	302	190.26±113.434	(70; 434)	
	F	407	95.19±25.279	(36; 209)	0.001
Apo B	M	302	88.79±23.096	(30; 167)	
	F	407	37.38±54.159	(0; 114)	0.004
Lpa	M	302	27.87±32.620	(0; 122)	

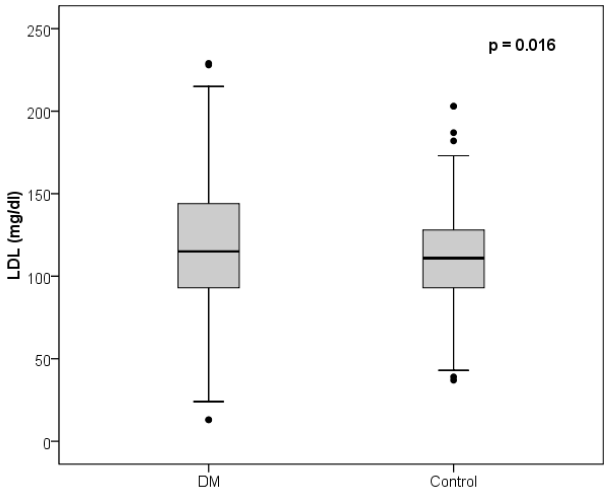

Figure 1: Comparison of the LDL cholesterol levels of type 2 diabetic patients with control subjects (p <0.016).

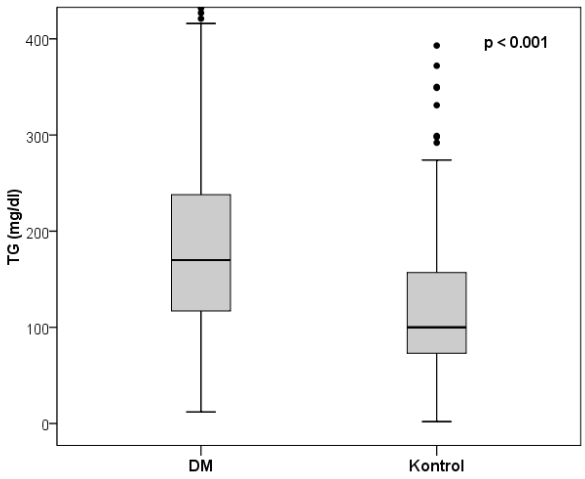

Figure 2: Comparison of the triglyceride levels of type 2 diabetic patients with control subjects (p<0.001).

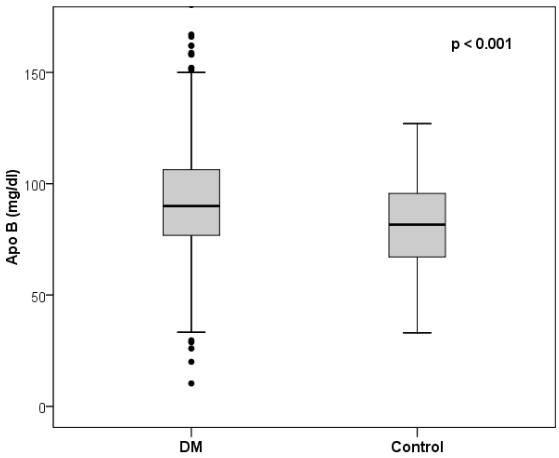

Figure 3: Comparison of the apo B levels of type 2 diabetic patients with control subjects (p<0.001).

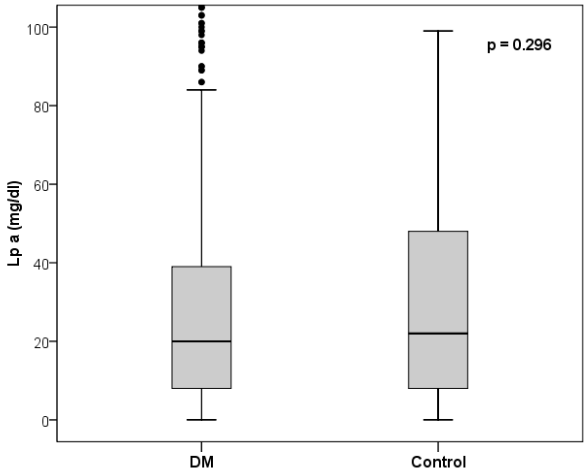

Figure 4: Comparison of the Lpa levels of type 2 diabetic patients with control subjects (p <0.296).

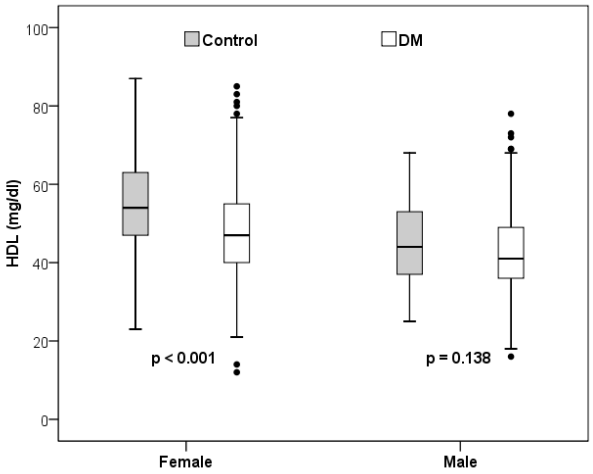

Figure 5: Comparison of the HDL cholesterol levels of type 2 diabetic patients with control subjects according to the genders.

increased CAD risk was suggested due to the increased total cholesterol/HDL ratio.[27-29] In our study, the total cholesterol levels of our control group were consistent with the study of Kadıoğlu and associates, but the total cholesterol level of diabetic patients was higher than our control group.[20]

In a study by Daghash associates, including 180 type 2 diabetic and 180 control subjects aged between 25 and 65, the total cholesterol level was significantly higher in diabetics than control subjects (204.2 ± 39.7 mg/dl vs.194.9 ± 41.6 mg/dl), respectively.[15] In another study from Africa, consisting 401 type 2 diabetic patients, it was reported that 35% of patients had hypercholesterolemia, and a study from England showed that serum total cholesterol level was greater than 200 mg/dl in 73% of type 2 diabetic patients.[30,31] In the present study, 50% of diabetic patients had serum total cholesterol level of over 200 mg/dl. Racial and nutritional factors have been suggested to explain these variations.

Another problem in type 2 diabetic patients is a low HDL, a common finding, which is a risk factor for CAD. A partial

cause of low HDL in diabetic patients is the glycation of HDL and as a result an increase in HDL turnover.[26] A number of studies on HDL levels in type 2 diabetic patients reported that low HDL levels were common findings in comparison to non-diabetic control groups.[30, 32-35] In the present study we also found the HDL levels in type 2 diabetics were lower than non-diabetic control group (46.2 ± 13.0 vs. 51.3 ± 14.8, p<0.001). HDL levels in diabetic women were found to be 48.6 ± 14.1mg/dl, and in diabetic men 42.9 ± 10.5 mg/dl, which was significantly lower than control group. Likewise, a study by Mahley and associates,[13,28] and another study by Onat and associates [29,50] showed that low HDL was a frequent finding among Turkish population. In these studies, mean HDL levels of women were reported to be between 37 and 45 mg/dl, and in men, between 34 and 41 mg/dl and the HDL levels of 70% of men and 50% of women were reported to be below 40 mg/dl. Genetic factors were suggested as the underlying cause for the explanation of low HDL in Turkish population.[36]

Hypertriglyceridemia is also a common finding in type 2 diabetic patients and the mean serum triglyceride level has been given as 186-197 mg/dl.[30-33,37] Over production of VLDL and a decreased activity of serum lipoprotein lipase activity were suggested in the pathogenesisis of hypertriglyceridemia.[37,38] In a study by Reaven and associates, they showed a significantly positive correlation between serum insulin level and VLDL secretion.[39] However, in several other studies, it was shown that acute hyperinsulinemia decreased VLDL synthesis in the liver of non-diabetics. [40,41] In the present study, serum triglyceride level of diabetics was found to be significantly higher than that of control (196.9 ± 121.9 mg/dl vs. 123.7 ± 76.1 mg/dl, p<0.001). More than fifty nine (59.1%) of diabetic patients had hypertriglyceridemia (>150 mg/dl) and we did not find any relation between gender and serum triglyceride levels. Obesity and insulin resistance have been suggested to contribute to the pathogenesis of hypertriglyceridemia in type 2 diabetics.[40,41] It was also shown in our study that serum triglyceride levels correlated with BMI (r=0.074).

Serum LDL cholesterol is the most atherogenic lipoprotein among serum lipoproteins. LDL cholesterol in type 2 diabetics is high or normal ranges but, more atherogenic modified small, dense LDL cholesterol type is usually associated with type 2 diabetic patients.[42]According to the criteria of NCEP ATP III, LDL cholesterol level over 100 mg/dl has been accepted as increased risk factor for CAD in diabetic patients.[42] In our study, the mean serum LDL levels of type 2 diabetics was 118.1±34.1 mg/dl (range, 60 to 220), and out of all diabetic patients examined, 69.1% of subjects had serum LDL level >100mg/dl. In a study from USA on LDL levels of type 2 diabetics, they reported that 58% of diabetic patients had serum LDL cholesterol over 130 mg/dl,[35] in a similar study from India, LDL cholesterol level of 45.2% of type 2 diabetics was found to be higher than 130 mg/dl.[34] In our study, LDL cholesterol level of 35 per cent of the diabetic patients was over 130 mg/dl. Ethnicity, nutritional habitual and life styles could be a reason for the different LDL levels.

Regarding with the metabolic control of diabetes mellitus and serum lipid levels, there have been different study results. In some studies, a positive correlation between HbA1c and serum lipid profiles was reported.[43-45] However, in certain studies, no correlation was reported between serum HbA1c and cholesterol level.[6, 20, 46] In the present study we also did not find significant relation between HbA1c level and serum lipid parameters including HDL, LDL, Lpa and apoB levels.

Several studies on body weight and serum lipid levels revealed that a positive correlation between body weight and serum triglyceride and inverse correlation with HDL level.[47,48] Similarly, in the present study we also found significantly positive correlation between BMI and serum triglyceride level of diabetic patients (p<0.001), but there was no correlation between BMI and serum triglyceride level in control subjects.

Type 2 diabetes mellitus is also a parameter of metabolic and insulin resistance syndrome). In a study from Turkey in 2004, the prevalence of metabolic syndrome in adults over 20 years was 33.9% in the general population.[49] Similarly, in another study from Turkey including adults over 30 years, the prevalence of metabolic syndrome was reported to be 32.9% of the general population (27% in males, and 38.6% in females).[50]In our study the prevalence of metabolic syndrome in diabetic patients was 72.9% (58.6% in males, and 83.5% in females).

In conclusion, in this study including relatively large number of type 2 diabetic patients, it was shown that there was no relation between type 2 diabetes mellitus and serum Lpa levels in comparison to control subjects. However, despite some differences with the reported studies, as a general, serum triglyceride, total cholesterol, LDL levels were higher and HDL levels lower than in the control subjects, consistent with the literature. Further studies are needed, especially the elucidation of the role of serum Lpa levels in type 2 diabetes mellitus.

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