DYSLIPIDEMIA IN TYPE 2 DIABETES MELLITUS: MORE ATHEROGENIC LIPID PROFILE IN WOMEN

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Abstract- Previous studies have shown that diabetes mellitus (DM) increases the risk of cardiovascular disease in women to a greater extent than in men. It seems that DM may alter lipid profiles more adversely in women compared to men. In this study we evaluated serum lipoprotein differences in type 2 diabetic men and women. The study included 350 type 2 diabetic patients (100 men and 250 women), aged 19-82 years. Demographic data were and biochemistry tests including serum lipoproteins were measured. There was no difference between men and women with respect to duration of DM and type of treatment. Body mass index **(**BMI), systolic and diastolic blood pressures were significantly higher in women than age matched men. Women also had significantly higher plasma levels of total cholesterol (233.7 vs. 190.3 mg/dl, $P < 0.001$), triglycerides (219.7 vs. 180.6 mg/dl, $P < 0.05$), low-density lipoprotein cholesterol (LDL-C) (141.2 vs. 116.1 mg/dl, $P < 0.001$), high-density lipoprotein cholesterol (HDL-C) (47.1 vs. 39.4 mg/dl, $P < 0.001$), non-HDL cholesterol (186.1 vs. 150.8 mg/dl, $P < 0.05$), Lp(a) (50.7 vs. 38.2 mg/dl, $P < 0.05$) and apo-B (117.6 vs. 101.2 mg/dl, $P < 0.001$). All types of dyslipidemia were significantly more prevalent in females. Women had higher plasma levels of HDL-C compared to men. Higher prevalence of hypertriglyceridemia in females was due to their higher BMI, and sex was not an independent risk factor for hypertriglyceridemia. Type 2 diabetic women are exposed more profoundly to risk factors including atherogenic dyslipidemia and higher BMI, systolic and diastolic blood pressures compared to men.

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INTRODUCTION

Type 2 diabetes mellitus (DM) increases the risk of coronary heart disease (CHD) more markedly in women than men (1). However, the reported magnitudes of the diabetes-related CHD risk in men and women vary widely between different studies (2-6). The cause of the greater relative risk of CHD in diabetic women still remains incompletely understood, but several explanations can be offered. First, adverse changes induced by type 2 DM in some cardiovascular risk factors, such as high-density lipoprotein (HDL) cholesterol, triglycerides (TG), low-density lipoprotein (LDL) particle size and blood pressure have been found to be more pronounced in women than in men (7-9). In addition, DM in women may interfere with protective mechanisms in the vascular wall and thereby lead to enhanced atherogenesis. Patients with type 2 DM have two to fourfold increase in cardiovascular disease (CVD) (10, 11) and dramatically higher risk of accelerated cerebral and peripheral vascular disease (12, 13).

Although DM is a well-known independent risk factor for vascular disease, abnormalities in insulin and glucose do not seem to account entirely for high

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frequency of macrovascular disease in patients with type 2 DM. In the UK Prospective Diabetes Study (UKPDS) the typical lipid pattern in the population with DM compared with no DM showed a pattern of hypertriglyceridemia, low HDL-C, relatively unaltered total cholesterol and an increased LDL-C in women (14).

Type 2 DM is associated with a cluster of interrelated plasma lipid and lipoprotein (Lp) abnormalities that are all recognized as predictors for coronary heart disease, including reduced plasma levels of high density lipoprotein cholesterol (HDL-C), a predominance of small and dense, low density lipoprotein cholesterol (LDL-C) particles and elevated plasma levels of TG (15). Elevated levels of Lp(a), a well known independent predictor of CVD (6, 7), has also been reported in diabetic patients compared to control groups (16, 17).

The purpose of this study was to evaluate the effect of sex on lipid abnormalities in patients with type 2 DM, to determine the prevalence of dyslipidemia in these patients and to evaluate its coexistence and correlation with other known CVD risk factors.

MATERIALS AND METHODS

Patients' Data

This study recruited 600 type 2 diabetic outpatients who consecutively presented to the Diabetes Clinic of Emam Khomeini Hospital, affiliated to Tehran University of Medical Science and Health Services (TUMS), from Oct. 2002 to Oct. 2003. The diagnosis of DM was based on the American Diabetes Association criteria for type 2 DM (fasting plasma glucose level higher than 126 mg/dl and/or glucose level exceeding 200 mg/dl at 2 hours in the 75 g oral glucose tolerance test). A total of 350 patients (100 males and 250 females), aged 19-82 years (54.3 ± 10.9, mean ± SD) completed the study. Patients had been treated by diet, exercise and/or oral hypoglycemic agents *(i.e.*; biguanides and/or sulfonylureas) and/or insulin. For each patient a questionnaire including epidemiologic data such as age, gender, occupation, duration of DM and history of smoking was completed. Information was obtained about demographic characteristics and medical history of all patients concerning their age, sex, history and duration of DM, hypertension, smoking, medications and co-morbidities. Patients' drug history such as taking anti-hypertensive and lipid lowering drugs was not considered as a restriction for inclusion.

All subjects underwent physical examination, including measurements of height, weight, waist circumference and blood pressure (sitting position after at least 10 min rest). Patient with elevated serum creatinine (1.3 mg/dl for women and 1.5 mg/dl for men), clinical evidence of congestive heart failure (CHF) or liver insufficiency, poor blood glucose control, and systemic or local infections were excluded. We obtained informed consent from all participants.

Anthropometric Data

Patients' heights were measured in centimeters with shoes off and weights were measured in kilograms in indoor clothing. Body mass index (BMI) was calculated using the formula BMI= weight (kg)/ height^2 (m).

Laboratory Data

Blood samples were drawn after at least 12.00 hours of overnight fasting. Fasting blood samples were obtained for measuring fasting blood glucose (FBG), total cholesterol, LDL-C, HDL-C, TG, Lp(a), apoprotein B (apo-B) and HbA1c. Total cholesterol was measured by Trinder method. HDL-C was measured by immunoinhibitory method. Lp(a) and apo-B were measured by immunoturbidimetery. TG was measured by enzymatic method. Commercially available kit (Lipid, Pars Azmoon Co., Karaj, Iran) were used for measurements. LDL-C was calculated using Friedewald formula.

Statistical Analyses

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS 12.0 for windows). Independent *t* test was used to compare quantitative data in groups. Pearson correlation coefficient was used to determine the correlation between quantitative data. *P* value < 0.05 was considered significant.

RESULTS

A total of 350 type 2 DM patients (100 males and 250 females) were studied. Table 1 shows demographic data of the patients. Female patients had higher level of BMI (28.57 kg/m^2 vs. 25.37 kg/m^2, $P < 0.05$), systolic BP (132.93 mm Hg vs. 128.24 mm Hg, $P = 0.05$) and diastolic BP (81.40 mm Hg vs. 76.87 mm Hg, $P < 0.05$). Patients' lipid profiles are also demonstrated in table 1.

Prevalence of different types of dyslipidemia in all of the patients and in males and females are shown in table 2. Apo-B levels were more than 110 mg/dl in 56% and Lp(a) levels were more than 40 mg/dl in 49% of patients. Apo-B, LDL-C and Lp(a) had positive correlation with each other ($P < 0.05$) (Fig. 1). Non-HDL cholesterol (total cholesterol-HDL-C) levels higher than 160 mg/dl were present in 61% of patients. Non-HDL-C had positive correlation with apo-B, Lp(a), LDL-C and TG. There was no correlation between duration of diabetes and lipid profile. Forty percent of patients were smokers. No significant difference was detected regarding lipid profile between smoker and non-smoker patients. Obese patients (BMI > 30) had higher levels of systolic BP (135.08 mm Hg vs. 130.25 mm Hg, $P < 0.05$), diastolic BP (83.30 mm Hg vs. 78.63 mm Hg, $P < 0.05$) and longer duration of diabetes (7.14 years vs. 9.24 years, $P < 0.05$).

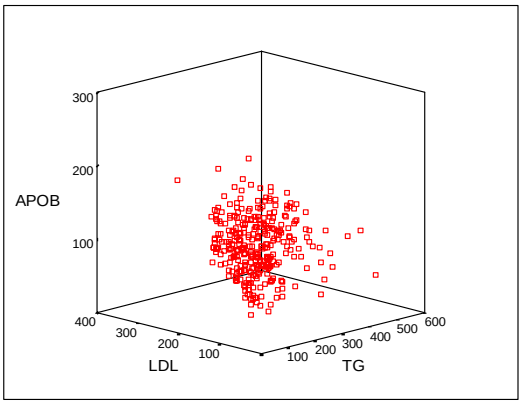

Fig. 1. Triglycerides, low-density lipoprotein cholesterol and apo-B had positive correlation with each other.

Furthermore, there was no significant difference in lipid profile between obese (BMI > 30) and non-obese patients.

Female patients had higher plasma level of total cholesterol (233.67 mg/dl vs. 190.30 mg/dl, $P < 0.05$), TG (219.7 mg/dl vs. 180.6 mg/dl, $P < 0.05$), LDL-C (141.23 mg/dl vs. 116.10 mg/dl, $P < 0.05$), HDL-C (47.14 mg/dl vs. 39.44 mg/dl, P value < 0.05), non-HDL cholesterol (186.18 mg/dl vs. 150.76 mg/dl, $P < 0.05$), Lp(a) (50.67 mg/dl vs. 38.18 mg/dl, $P < 0.05$) and apo-B (117.61 mg/dl vs. 101.17 mg/dl, P value < 0.05) compared to age matched male patients (Fig. 2).

Table 1. Demographic characteristics and serum lipoprotein levels of the studied patients

	All Patients		Female		Male	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (yr)	54.4	10.9	53.7	10.6	56.1	11.3
Duration of diabetes (yr)	8.7	7.2	8.5	6.9	9.0	7.8
BMI (kg/m^2)	27.67	5.17	28.58	5.18	25.38	4.39
SBP (mm Hg)	132	20	133	21	128	16
DBP (mm Hg)	80	11	81	12	77	10
HDL (mg/dl)	45	14.2	39.4	14.2	47.1	14
LDL (mg/dl)	133	44	116.1	40.96	141.23	43
Total cholesterol (mg/dl)	221	63	190	52	234	63
TG (mg/dl)	208	96	181	96	219	121
Lp(a)	47	37	38	33	51	38
Apo-B	112.8	30.2	101	28	117.6	30

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.

Table 2. Prevalence of different types of dyslipidemia in males and females

Lipid type*		All Patients	Female	Male	*P* value
HDL	Normal	45.1%	42.4%	52.0%	0.065
	low	54.9%	57.6%	48.0%	
LDL	Normal	30.9%	27.2%	40.0%	0.014
	high	69.1%	72.8%	60.0%	
T-Chol	Normal	65.1%	74.0%	43.0%	0.000
	High	34.9%	26.0%	57.0%	
TG	Normal	36.6%	33.2%	45.0%	0.026
	High	63.4%	66.8%	55.0%	
Lp(a)	Normal	54.9%	51.2%	64%	0.02
	High	45.1%	48.8%	36%	
Apo-B	Normal	46.6%	41.2%	60%	0.001
	High	53.4%	58.8%	40%	

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.
*Normal HDL value indicates HDL level more than 40 mg/dl in males and HDL value more than 50 mg/ml in females. LDL less than 100mg/dl, TG less than 150mg/dl and total cholesterol less than 200, Lp(a) less than 40 mg/dl, and apo-B less than 110 mg/dl were regarded as normal.

DISCUSSION

Our study provided the evidence for the presence of high prevalence of dyslipidemia in type 2 diabetic patients. Although our patients received oral hypoglycemic agents for hyperglycemia and in some cases were treated with lipid lowering agents, a significant proportion of them had abnormal lipid profile. The most frequent was hypertriglyceridemia (63.4%) and the least frequent was elevated total cholesterol (35%).

Each of the dyslipidemic features is associated with increased risk of cardiovascular disease, the leading cause of death in patients with type 2 DM. Fontbonne *et al*. in a prospective cohort study showed that elevated plasma levels of TG in diabetic patients was positively and significantly correlated with CAD events and CAD mortality (18). Hypertriglyceridemia may be the best lipid predictor of CVD in type 2 diabetic patients (18).

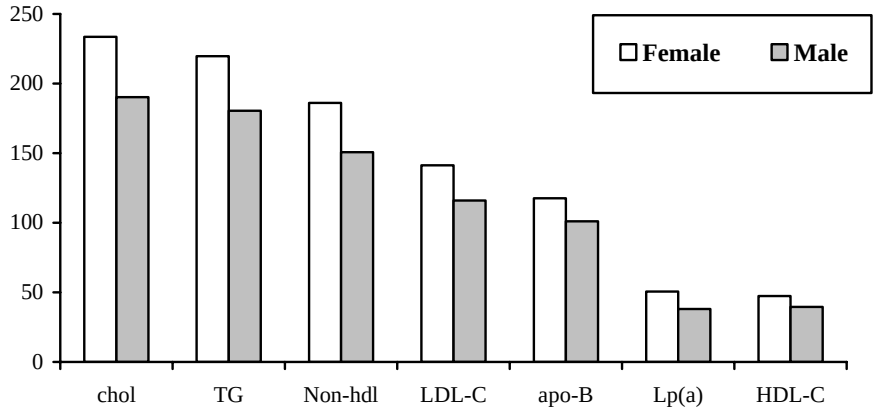

Fig. 2. Lipid profile in females compared to males in type 2 diabetic patients.

Recent studies have demonstrated that in diabetic patients TG levels is a risk factor for CVD independent of HDL-C level and despite glycemic control (19, 20). Mean levels of total cholesterol and LDL-C in those with type 2 diabetes may not differ significantly from those in non-diabetic subjects (14). Type 2 diabetic patients have an abnormally high number of small, dense LDL-C particles (21-23).

Moreover, patients with small, dense LDL-C will also typically have lower HDL-C and elevated TG blood levels, which may further increase risk of atherosclerosis (21). Although, the inaccessibility to differentiate the LDL-C subclasses was a limitation to our study, this study showed a high prevalence of hypercholesterolemia (64.2%) and high plasma level of LDL-C (about 70%) in diabetic patients which requires special consideration. Additionally, the predominance of small and dense LDL-C may clinically show itself as an increased level of non-HDL cholesterol plasma level (24) which shows a stronger association with CVD and mortality than LDL-C (25). Non-HDL-C includes all lipoprotein particles that contain apo-B and are potentially atherogenic, including LDL-C, Lp(a), Intermediate density lipoprotein (IDL-C), and very low density lipoprotein (VLDL-C) (26). Sixty one percent of patients had non-HDL plasma level more than 160 mg/dl. This may to some extent be due to predominance of small, dense LDL-C particles and in some part due to elevated plasma level of TG, Lp(a) and apo-B. Fifty six percent of patients had apo-B plasma levels more than 110 mg/dl and 49% had Lp(a) higher than 40 mg/dl that may contribute in high plasma level of non-HDL cholesterol.

Type 2 DM is also associated with low plasma levels of HDL-C (5). It is well documented that reduced HDL-C levels are associated with an increased risk of coronary heart disease (27). It may be due to a number of HDL-C particles functions that possibly will contribute to direct cardioprotective effects, including promotion of cellular cholesterol efflux and anti-oxidative and anti-inflammatory properties (15). Moreover, low HDL-C levels are often accompanied by elevated TG levels (28), and the combination has been strongly associated with an increase in risk of CHD (29-31). HDL-C levels below 50 mg/dl were present in 58% of females and below 40 mg/dl in 48% of males. Although this abnormality was more frequent in females it was not statistically significant. In this study, there was no significant correlation between TG and HDL-C levels. This may be in part due to the fact that consumption of lipid-lowering agents was not considered as exclusion criterion of the patients. Furthermore, in this study the increase in atherogenic lipoproteins including LDL-C, Lp(a) and apo-B were correlated with each other. This may expose patients to an accelerated risk for atherosclerosis.

It has been reported that type 2 DM increase the risk of CHD more markedly in women than in men (2-6). Adverse changes induced by type 2 DM in some cardiovascular risk factors, such as HDL-C, total cholesterol, TG, LDL-C particle size and blood pressure have been found to be more pronounced in women than in men (7-9). Juutilainen *et al.* in their study of 1059 type 2 diabetic subjects aged 45-64 years found a considerably higher diabetes related relative risk for a major CHD event in diabetic women than in men (1). They found that the burden of obesity, elevated blood pressure, and atherogenic dyslipidemia (low HDL cholesterol and high TG) was, in the presence of diabetes, greater in women than men. In a meta-analysis of prospective studies of coronary death among women with DM by Warren *et al.* they found that the relative risk of coronary death from diabetes was greater for women than men (32).

In this study, clustering of CAD risk factors such as high systolic and diastolic blood pressure and higher plasma level of total cholesterol, non-HDL cholesterol, TG, LDL-C, Lp(a) and apo-B, and abnormal HDL-C levels were more pronounced in women compared to men (Fig. 2). What is the reason for this difference between women and men? One popular theory to explain the sex difference relates to HDL cholesterol. Walden *et al.* suggested that HDL cholesterol levels are lower in diabetic women than men (33). In fact it has also been postulated that the inverse association between CHD and HDL levels is stronger in women than men. Gorden *et al.* showed that for each milligram-per-deciliter increase in

HDL, there was ~2% decrease in CHD risk in men, but a 3% decrease in women (21).

There are many other theories proposed to account for the excess risk from diabetes in women. These include differences in coagulation (34), the pattern of obesity between men and women (35), and possible role for hyperinsulinemia (36). Diabetes may also alter estrogen related protective mechanisms (37). Furthermore, low grade inflammation may have a greater role in perturbing insulin action in women, or inflammatory factors may interact with female sex hormones, resulting in a decrease of protective effects of estrogens on body fat distribution and insulin action (38). The discussion of these theories is beyond the scope of our study; suffice it to say that the underlying basis for the sex difference in risk from diabetes remains, for the most part, speculative.

Conflict of Interests

The authors declare that they have no competing interests.

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