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Original Research Article

Gender based differences in lipid profile and other novel atherogenic risk factors in type-2 diabetes mellitus patients

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ABSTRACT

Background: Utilization of lipids and lipoproteins gets altered in diabetes mellitus (DM) leading to atherogenic dyslipidemia. This study evaluates cardiovascular risk profile of diabetic men and women, including conventional lipid profile and novel risk factors namely lipid ratios, atherogenic coefficient and atherogenic index.
Methods: In all 200 diabetic patients (100 males and 100 females) aged 18-65 years who were under treatment were randomly sampled for the study. Socio-demographic data were collected. Glycated hemoglobin levels, lipid profile, fasting blood sugar, were estimated using standard procedures. Anthropometric variables such body mass index (BMI) was measured, systolic and diastolic blood pressures were also taken. There was no difference between men and women with respect to duration of DM and type of treatment.
Results: Lipid profile estimates showed that diabetic females had higher level of total cholesterol (TC) (198.07 vs 169.5 mg/dl) and higher level of high-density lipoprotein (HDL)-C (43.99 vs. 41 mg/dl) as compared to males. All the parameters that are raised total cholesterol, triglyceride levels and low-density lipoprotein (LDL) levels were observed in significantly higher proportion of females as compared to males. The values of atherogenic indices [CR1, CR2, AC and atherogenic index of plasma (AIP)] for both genders were higher than the baseline value. In this study females had higher mean non-HDL 154 mg/dl as compared to males mean non-HDL 129 mg/dl and this study showed that female participants held on in high-risk AIP category and so they were at a higher risk of developing coronary heart condition.
Conclusions: Dyslipidemia was observed in a greater proportion of female diabetic patients than male diabetic patients

Keywords: Diabetes, Lipid profile, Dyslipidemia, Atherogenic indices, Novel cardiovascular risk factors

INTRODUCTION

Diabetes at present affects 62 million Indians, which constitutes 7.1% of the adult population.[1] The risk of developing cardiovascular disease is 2-4 times higher among people with diabetes as weighed against people without diabetes.[2] Gender-based differences in the way cardiovascular risk factors and risk of Cardiovascular disease is distributed among patients with diabetes, has been examined by several studies which tip-off towards excess risk factor clustering among females, thus rendering them at an increased risk of Cardiovascular disease as compared to men. In women DM may meddle with protective mechanisms in the vascular wall and thereby lead to enhanced atherogenesis.[3] Cardiovascular-disease is a multifactorial condition and major risk factors (i.e., obesity, hypertension, and dyslipidemia) have all demonstrated to have a say in its occurrence.[4]

Diabetic dyslipidemia is characterized by: High triglyceride (TG) concentrations, HDL-C concentrations and increased LDL-C concentrations.

TG and HDL-C forms the bases of AIP and both of these are independent risk factors for CAD.[5,6] Other fractions involving independent risk factors for CAD are cardiac risk ratio (CRR) calculated as (TC/HDL-c) and atherogenic coefficient (AC) calculated as {(TC-HDL-c)/HDL-c}. For assessing the risk of cardiovascular disease beyond the routinely done lipid profile these calculated fractions can be used in the critical setting.

The objective of the study is to study gender-based difference of lipid profile abnormalities in type 2 DM patient and to evaluate the correlation of diabetic dyslipidemia with other novel atherogenic risk factors namely: AIP, Castellis risk index (CRI) and AC.

METHODS

This observational study recruited 200 physician diagnosed type 2 DM outpatients who consequently presented to the outpatient medicine department of GMERS hospital, Patan from July 2020 to December 2020. All procedures were approved by the committee on human research and ethics of GMERS hospital, Patan. Patients were included in this study with their informed consent, on the basis of inclusion and exclusion criteria. Patients on lipid lowering drugs statins or fibrates were excluded from study. About 6 ml of fasting blood samples (overnight fast between 8 and 12 hours) were drawn from the median cubital vein on the anterior forearm into clot activator/ separating gel tubes & fluoride oxalate tubes and EDTA tubes. The clotted blood was centrifuged (Remi 3500, Labline, India) at 2000 rpm for 5 minutes to separate the serum. The serum was used to estimate the lipid profile, total cholesterol, high density lipoprotein cholesterol and direct low-density lipoprotein and the whole blood was used for glycated hemoglobin by autoanalyzer Abbott c 4000.The fluoridated anticoagulated blood was centrifuged (Remi3500, Labline, India) at 3000 rpm for 5 minutes to separate the plasma. The plasma was used to estimate the fasting blood glucose by autoanalyzer Abbott c4000. Serum VLDL-C was calculated by formula (TG/5).[7]

The atherogenic indices were calculated as follows:[8] AIP=log (TG/HDL-c), (CRR) or Castelli's risk index CRI1= TC/HDL-c, (CRI-II) Castelli's risk index 2=(LDLc/HDLc) and AC=(TC-HDL-c)/HDL-c.

Statistical analysis was carried out using the statistical package for social sciences (SPSS 21.0 for windows). The calculation of the sample size proceeds as under for 95% confidence level Z=1.96 from a pilot survey of 20 respondents it was found that 85% is satisfactory. So, p=0.85 and Q=1-P=0.15. PQ=0.1275=measure of the sample dispersion, standard error p=0.1/1.96=0.05,

$n=z^2pq/e^2$

Here, z=value determined from z table for a confidence level, 2=variance, e^2=Error specification, $n=(1.96)^2(0.1275)/(0.05)^2$ and n=195.9216.

Therefore, approx. sample size was taken as 200.

Means are presented as values ± standard deviation. Student's t-test was used to compare quantitative data between two groups. Analysis of variance (ANOVA) was used as appropriate. P<0.05 was considered statistically significant.

RESULTS

The 200 patients with T2 DM were recruited for the study (100 males and 100 females) to assess the alteration in lipid profile and atherogenic indices. Table 1 shows that there was highly significant difference in the prevalence of DM type 2 among different age groups.

Table 1: Prevalence of DM type 2 among different age groups.

Age groups (Years)	Male patients	Female patients	P value
	N	N	
Mean ± SD	55.04± 8.42	55.64± 8.59	0.4214
≤40	8	5	0.774
41 to 50	26	23	
51 to 60	33	40	
>60	33	32	
Total	100	100	

The mean fasting blood sugar (FBS) was higher than normal 144.42 SD±38.99 and mean hemoglobin A1c (HbA1c) was 7.03 SD±0.99

Table 3 shows the control of sugar in the patients. It was observed that 61% males and 65% females had FBS>126 mg/dl and 42% males and 43% females had HbA1c levels ≥7%.

Table 2: Mean fasting blood sugar and hemoglobin A1c of the patients.

Blood sugar	Total		Male patients		Female patients		P value
	Mean	SD	Mean	SD	Mean	SD	
FBS	144.42	38.99	142.44	36.21	146.40	41.49	0.0887
HbA1c	7.03	0.99	7.00	0.92	7.07	1.05	0.0951

Table 3: Classification of patients based on FBS and HbA1c levels.

Variables	Total		Male		Female	
	N	%	N	%	N	%
FBS levels						
≤100	23	11.50	14	14	9	9
101-126	51	25.50	25	25	26	26
>126	126	63	61	61	65	65
HbA1c categorization						
<6	6	3	3	3	3	3
≥6- <7	109	54.50	55	55	54	54
≥7- <8	46	23	23	23	23	23
≥8-9	33	16.50	17	17	16	16
≥9	6	3	2	2	4	4

Table 4: Prevalence of dyslipidemia in studied diabetic patients.

Lipid type	Total (%)	Female (%)	Male (%)	P value
TC	32.5	47	18	0.0000
TG	42.5	55	30	0.0001
LDL	61.5	71	52	0.0018
HDL	29	14	44	-0.0000

For serum lipid reference level, national cholesterol education program (NCEP), adult treatment panel (ATP III) guideline was referred.[9] According to NCEP-ATP III guideline, hypercholesterolemia is defined as TC>200 mg/dl, high LDL-c when value >100 mg/dl, hypertriglyceridemia as TG>150 mg/dl and low HDL-c when value is <40 mg/dl. Dyslipidemia was defined by presence of one/more than 1 abnormal serum lipid concentration. In our study, total cholesterol was more than 200 mg/dl in 65 (32.5%) and HDL-c were<40 mg/dl in 58 (29%) of all patients. LDL level higher than 100 mg/dl were present in 123 (61.5%), while 85 (42.5%) of all patients had triglyceride level higher than 150 mg/dl.

The Table 5 revealed that diabetic females had higher level of TC (198.07 vs. 169.5 mg/dl) and higher level of HDL-c (43.99 vs. 41 mg/dl) (p<0.0129) compared to matched male patients, whereas LDL-c (p<0.0114) and TG were significantly increased in females (118 mg/dl, 71%; 164.40 mg/dl, 55%) in comparison to males (99 mg/dl, 52%; 138 mg/dl, 30%) respectively.

Table 5: Lipid profile in males and females.

Lipid profile (mg/dl)	Male	Female	P value
	Mean ± SD	Mean ± SD	
TC	169.5±36.13	198.07±40.82	0.1132
TG	138±70	164±67.1	0.3373
HDL	41±5.4	43.99±4.31	0.0129
DLDL	99±27	118±34	0.0114
Non-HDL	128.7±35.32	154.08±40.13	0.1029

Table 6: Comparison of atherogenic index of plasma (AIP) of both genders.

AIP	Male	Female	P value
High risk (AIP>0.21)	28	44	0.295
Intermediate risk AIP (0.11 to 0.21)	28	16	
Low risk (AIP<0.11)	44	40	

The results revealed that AIP value of female was greater than that for male (0.178, 0.129) respectively in comparison with baseline value of (0.11), although statistically non-significant (p=0.239).

Table 7: Atherogenic indices for both genders.

Atherogenic indices	Male	Baseline value	Female	Baseline value	P value
Cardiovascular risk (CR1)	4.182	3.50	4.507	3.00	0.270
Cardiovascular risk (CR2)	2.440	3.30	2.734	3.30	0.370
Atherogenic coefficient (AC)	3.197	3.00	3.522	3.00	0.229
AIP	0.129	0.11	0.178	0.11	0.239

Table 8: Correlation of duration of diabetes and dyslipidemia.

Row labels	Hypercholesterolemia			Hypertriglyceridemia			High LDL			Low HDL		
	N	%	P value	N	%	P value	N	%	P value	N	%	P value
≤5	2	5.9	0.0153	8	23.5	0.0225	6	17.6	0.0498	3	8.8	0.0358
>5- ≤10	4	11.8		4	11.8		4	11.8		3	8.8	
>10- ≤ 15	3	12.0		6	24.0		17	68		1	4	
>15- ≤20	3	7.7		19	48.7		37	94.9		3	7.7	
>20- ≤ 25	20	69		18	62.1		24	82.8		15	51.7	
>25	33	84.6		30	76.9		35	89.7		33	84.6	
Total	65	100		85	100		123	100		58	100	

Table 7 shows that no noteworthy difference was observed in mean percent of CRR and AC of both gender in comparison with baseline value. The mean percent of CRR and AC exceed the baseline value, these results are statistically non-significant.

We observed that there was a correlation between duration of diabetes and abnormal lipid profile. Higher proportion of patients with dyslipidemia were seen as the duration of diabetes increase.

DISCUSSION

The pathogenesis of CVD in diabetes is multifactorial and dyslipidemia is found to be a powerful risk factor.[10] Lipoprotein lipase gets reduced due to widespread vascular endothelial damage attributed to long-term hyperglycemia in diabetes, leading to increased levels of VLDL, LDL cholesterol, triglycerides and a decrease in HDL. The ratio of LDL-C/HDL-C or TG/HDL-c is a better predictor of future cardiovascular events Grover et al.[11] Log TG/HDL-C (AIP) probably serves as an indicator of the atherogenic lipoprotein phenotype, Tan et al.[12] An AIP of<0.11 is considered as low risk, 0.11-0.21 intermediate risk and >0.21 as high risk. The incidence of diabetes increases with age until about age 65 years, after which both incidence and prevalence appears to level off. In our study, the prevalence of diabetes was highest in 51 to 60 age group (Table 1) and the lowest in the under 40 years age group as reported by other researchers.[13] The risk of diabetes increases 3-4 times after the age of 44 years.[14] The reason for the rising prevalence of T2 DM with age are the deterioration of insulin resistance with age, increased inactivity and longevity of diabetes patients due to improved care.[15] The commonest lipid abnormality noted in this study was high LDL-c (61.5%) followed by hypertriglyceridemia (42.5%) (Table 4). Elevated TG levels and Low HDL-c concentrations[16] is strongly associated with an increase in the risk of coronary heart disease (CHD).[17,18] In the present study, the HDL-c levels below 40 mg/dl were present in 14% and 44 % of the female and male respectively (Table 4). Some previous studies showed that reduced HDL-c were more common in females than males.[19] Studies have shown that for each mg per deciliter increase in HDL, there was ~2% decrease in CHD risk in men, but a 3% decrease in women.[20,21] The levels of TC, TG, and LDL-c were significantly higher in females as compared to males (Table 5). Hyperlipidemia in females may be ascribed to the effects of sex hormones on body fat distribution, which leads to differences in altered lipoproteins.[22] Type 2 DM induced changes in some cardiovascular risk factors such as HDL-c, TC, TG, LDL particle size and blood pressure have been found to be more prominent in women than in men.[23,24] Juutilainen et al in a study of 1059 type 2 diabetic subjects aged between 45-and 65 years found considerably higher diabetes related relative risk factor for a major CHD event in diabetic women than in men, LDL-C, were more pronounced in women compared to men.[24] Differences in coagulation, the pattern of obesity between men and women, altered estrogen related protective mechanisms and possible role of hyperinsulinemia are among the many theories that have been proposed to account for the excess risk from diabetes in women. The AIP of male and female in this study was observed to be significantly increased when compared with baseline value (Table 7) similar to other studies.[25,26] AIP values of-0.3 to 0.1 are associated with low, 0.1 to .0.24 with medium and ≥0.24 with high cardiovascular risk. AIP has a better prediction of coronary artery disease than individual lipids, and/or TC/HDL-c, LDL-c/HDL-c ratios.[27]

There is positive correlation between AIP and the fractional esterification rate of HDL (FERHDL), and negative correlation with LDL particle size. AIP correlates inversely with measurement of insulin sensitivity.[27,28] AIP may be the diagnostic alternative in situations where other atherogenic risk parameters like TG and HDL-C appear normal.[29] Degree of dyslipidemia increases with increase in duration of diabetes as seen in this study.[30,31] CAD risk in patients with diabetes escalates significantly with disease duration.[32] The CRR was found to be significantly increased in men and women compared to baseline value (Table 7) as noticed in other studies.[33] When CRR of our patients were compared with the value of American heart association (≤3.5), both male and females show greater predilection towards cardiovascular disease. The Canadian working group has chosen the [TC/HDL-c] ratio as a secondary goal of therapy considering it to be a more sensitive and specific index of cardiovascular risk than total cholesterol, particularly in individuals with TG >300 mg/dl.[34] We observed CRR or CRI in our male and female patients was >4 in concurrence with other studies.[35 36]

Values of AC for both male (3.197) and female (3.522) show a greater tendency towards cardiovascular disease.[37,38] Measurement of non-HDL is simple eliminating any additional costs and it has been accepted as a surrogate marker for apo B in routine clinical practice. Non-HDL cholesterol serves as an index of cardiovascular risk in diabetic patients whose LDL-C may not be elevated. In individuals with hyper-triglyceridemic non-HDL-C is the second target of therapy after LDL-C as per ATP III guideline. The strong association between non-HDL-C and SD LDL-C gives non-HDL a leverage as a predictor of CVD mortality.[39] In this study females had higher mean non-HDL 154mg mg/dl as compared to males mean non-HDL 129 mg/dl. The present study revealed that all three atherogenic indices of female were higher than those for male which is similar to observations made by different investigators in their studies.[40] These findings are suggestive of women being at more risk of cardiovascular disease than men. It should be made aware to all physicians that development of diabetes is associated with a greater increase in cardiovascular risk in women than in men so that they

should, at the very least, treat women with diabetes as aggressively as they do with their male counterparts.

Limitations

Our study is limited by small number of subjects, the cross-sectional nature of the study, lack of measurement of physical activity, dietary habits and other factors affecting lifestyle. Our patient population represents only those receiving outpatient treatments and thus may not be representative of severe cases. More well-designed studies are needed to prospectively verify our findings.

CONCLUSION

This study shows that in patients of type 2 DM the lipid profile changes is more adverse in females as compared to male patients. There should be a gender-sensitive approach in planning interventions (counseling and treatment) to reduce the risk of cardiovascular disease. CRR, AC, AIP seem to have a good implication prospect in daily practice to assess cardiovascular risk in type 2 diabetes mellitus. In centers which are deficient in resources and new tests are not possible, these indices are more economic and can be calculated from the routinely done lipid profile parameters. Thus, encourage the use of these cardiovascular risk indices to complement the existing profile of tests for identifying high-risk individuals for CAD and effective drug management.

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