International Journal of Science and Healthcare Research
Vol.3; Issue: 2; April-June 2018
Website: www.ijshr.com
Original Research Article *ISSN: 2455-7587*

Characterization of Lipid Abnormalities in Type 2 Diabetes Mellitus

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ABSTRACT

Different patterns of dyslipidemia can be observed in T2DM patients apart from the most common lipid triad viz high TGs, low HDL-c and high small LDL-c. Characterization of lipid abnormalities is important as it can guide physicians to individualize lipid lowering intervention. Also, newer indices like atherogenic index of plasma, Apo B and non-HDL levels and various lipid ratios can be more conclusive than just the absolute levels of lipid parameters. The aim of our study was to observe the presence of various patterns of dyslipidemia and use of aforementioned indices and various lipid ratios to characterize dyslipidemia in Nepalese T2DM patients. The study is a hospital based retrospective study comprising 336 patients. The commonest pattern of dyslipidemia found was Isolated Hypertriglyceridemia (23.8%) followed by CHL (23.2%), AD (21.4%), isolated low HDL (17.9%) and Isolated Hypercholestrolemia (10%). Isolated Hypercholestrolemia was found to be highest in males where as females had high but equal prevalences of CHL, AD and Isolated Hypertriglyceridemia. The commonest abnormality observed among deranged absolute lipid parameter was increased TG (58.3%), followed by TC (38.1%), low HDL (36.9%) and high LDL (35.1%). Considerably high percentage of patients (58.3%) had abnormal Apo B. Higher percentage of younger cohort had abnormal absolute lipid values than the elderly cohort. 48.6% of patients having normal LDL-C level had high TG/HDL followed by 47.7%, 25.5% and 14.7% of patients who had normal LDL-C but high values of Apo B, AIP and Non- HDL cholesterol suggesting use of additional parameters to LDL-c level in stratifying CVS risk in these patients. Differences in pattern of dyslipidemia among patients of T2DM should not be overlooked while deciding the lipid lowering therapy. Other lipid indices should be used in addition to absolute levels of lipid profile parameters to understand actual CVS risk imposed by diabetic dyslipidemia.

Key words: Type 2 Diabetes, Dyslipidemia characterization, Nepal.

INTRODUCTION

Lipid abnormalities are commonly found with Type 2 Diabetes mellitus (T2DM) adding to the CVS risk. Moreover, metabolic abnormalities, such as predominance of small dense LDL particles and increased glycation of LDL, raise the atherogenic risk in these patients. Hence, regular lipid profile assessments comprising levels of Total Cholesterol (TC), HDL-c, LDL-c and TGs have been recommended in these patients. Combined hyperlipidemia (CHL), a common phenotype, is characterized by increased levels of LDL cholesterol (LDL-c) and triglycerides (TGs) and low level of HDL cholesterol (HDL-c). [1] Although this lipid triad is commonly associated with T2DM, due to complex pathways of lipoprotein metabolism, the other patterns of dyslipidemia such as isolated low HDL-c, other isolated dyslipidemias and atherogenic dyslipidemia are not uncommon. Pokhrel et al have stated presence of isolated dyslipidemias like isolated hypercholesterolemia, isolated hypertriglyceridemia and isolated high LDL in Nepalese T2DM adults. [2] The third report of National Cholesterol Education Program Adult Treatment Panel (NCEP

ATP III) [3] defines Isolated low HDL-c as levels of HDL-c and TGs less than 40 mg/dl and 150 mg/dl respectively and Atherogenic dyslipidemia as levels of HDL-c <40mg/dl and TG >150mg/dl. Also, the lipoprotein particles associated with T2DM are different than seen in dyslipidemia in non-diabetic individuals. These are smaller and denser and documented to be more atherogenic than their normal sized counterparts. Although concentration of LDL-c has been recommended by several authorities to be primary target for lipid lowering therapy in T2DM, the LDL-c may remain in normal range obscuring need for therapy. Alternatively, levels of non-HDLc and Apo B can be used to assess CVS risk in these cases. Several large prospective studies have shown Apo B to be better predictor of future CVS events than LDL-c. [4-6] and Apo B to be a better predictor of CVS risk in individuals with low LDL-c level. [7] Also, ESC/EAS 2016 guidelines describe the goal of Apo B <100mg/dl in T2DM patients as secondary target for lipid lowering therapy. [8] The LDL-c particle size should be taken in to account in conditions when LDL-c level comes normal. In cases where measuring particle size is unavailable, Log (TG/HDL), known as Atherogenic Index of plasma (AIP) can be used as a surrogate tool for LDL particle size. [9] Many times ratios like TC/HDL and TG/HDL give a better impression of dyslipidemia than absolute levels of parameters of lipid profile.

Recognition of patterns of dyslipidemia are beneficial while deciding on the lipid lowering drugs to be prescribed, for example VA-HIT study [10] suggested Gemfibrozil therapy for Isolated low HDL in T2DM patients instead of regular statins which are commonly prescribed in these patients. Also, indices like non-HDLc, AIP, Apo B and lipid ratios like TC/HDL and TG/HDL should be used in addition to absolute values of lipoprotein levels to reveal the actual malignant nature of diabetic dyslipidemia and direct the lipid lowering therapy as per the individual requirement.

This study describes the presence of different patterns of dyslipidemia and various lipid ratios in T2DM patients attending a tertiary care centre in eastern part of Nepal.

MATERIALS AND METHODS

This study was conducted as a hospital based retrospective study at B.P.Koirala Institute of Health Sciences, Nepal after taking ethical clearance from the institutional research committee. Records of Type 2 Diabetes adults attending opd were reviewed and data was collected. Patient's data enrolled were irrespective of duration of diabetes, presence of any complications and any treatment being taken. Altogether, data from 336 cases of T2DM are included in the study. Dyslipidemia was defined according to the third report of National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria [3] as follows: hypercholesterolemia-serum T. Cholesterol (TC) level ≥200 mg/dl; hypertriglyceridemia–serum Triglycerides (TG) level ≥150 mg/dl; low HDL-C level ≤40 mg/dl for both men and women; high LDL-C level ≥100 mg/dl, high TC/HDL-C ratio ≥5, high non-HDL-C ≥ 130 mg/dl and high ApoB ≥ 90 mg/dl. Combined hyperlipidemia was defned as serum HDL-C <40 mg/dl (male and female), LDL-C≥100 mg/dl and TG level ≥150 mg/dl and Atherogenic Dyslipidemia (AD) as serum HDL-C <40mg/dl (male and female) and TG >150mg/dl. Isolated dyslipidemias were defned as follows: isolated hypercholesterolemia-serum TC ≥200 mg/dl and TG <150 mg/dl; isolated hyper-triglyceridemia–serum TG ≥150 mg/dl and TC < 200 mg/dl, and isolated low HDL-serum HDL-C < 40 mg/dl (male and female) without hypertriglyceridemia. Non-HDLc was calculated by subtracting HDL-C from TC and Apo B was calculated as ApoB = 0.65 × TC-0.59 × HDL-C + 0.01 × TG when TG < 270 mg/dl and ApoB = 25.6 + 0.58 × TC-0.38 × HDL-C-0.06 × TG when

TG > 270 mg/dl. [11] Cut off for TG/HDL ≥ 3.5 was taken to define high CVS risk. [12] Atherogenic Index of Plasma (AIP) was calculated as log (TG/HDL) where TG and HDL were in their molar concentration and a cut off of >2.4 were taken to be associated with high CVS risk. [13] Data was analysed in SPSS. Normality of data was checked by Smirnov Kolmogorov test. Quantitative data was analysed by Student t test and Mann Whitney U test for parametric and non parametric variables respectively. Categorical data was analysed by chi square test. Correlation was calculated using Pearson correlation test and spearman rho test in parametric and non parametric data respectively. P value was considered significant at <0.05.

RESULTS

Data from 336 T2DM patients were enrolled in the study. There were 154 (45.8%) males and 182 (54.16%) females. The mean age of patients (in yrs) was 52.28±11.9. Females had higher values of TC, HDL-C and TG and lower value of LDL-C than males, the difference was not significant. Table 1 describes patterns of dyslipidemia among males and females. Patterns of dyslipidemia viz CHL, AD, Isolated hypercholesterolemia and Isolated hypertriglyceridemia were common in females than in males. Whereas Isolated low HDL was a common finding in males. Chi square test was conducted to test the significance. Isolated low HDL significantly differed gender wise, rest all differences were not significant.

Table 1 Gender wise distribution of dyslipidemia patterns.

	Male (154)	Female (182)	P value
Combined hyperlipidemia (CHL)	30 (19.5%)	44 (24.2%)	0.08(NS)
Atherogenic dyslipidemia	28 (18.2%)	44 (24.2%)	0.11(NS)
Isolated Hypercholestrolemia	14(9.1%)	20 (11%)	0.34(NS)
Isolated Hypertriglyceridemia	36 (23.4%)	44 (24.2%)	0.48(NS)
Isolated low HDL	34 (22.1%)	26 (14.3%)	0.04(S)

S, NS= significant and non significant at the level of <0.05 respectively.

As age is a non modifiable CVS risk factor, we looked into its effect on the patterns of dyslipidemia and various parameters of lipid profile and lipid ratios. We formed three age groups viz <40 yrs, 40-59 yrs and ≥60yrs. Table 2 and 3 summarize the respective results. Chi square test was applied. Difference in occurrence of various patterns of dyslipidemia among the three age groups was statistically significant except for isolated low HDL. Various parameters of lipid profile and lipid ratios significantly differed among three age groups.

Table 2 Patterns of Dyslipidemia among different age groups (in yrs).

	<40 (48)	40-59 (180)	≥60 (108)	P value	Total (336)
Combined hyperlipidemia(CHL)	30 (62.5%)	32(17.8%)	16(14.8%)	S	78(23.2%)
Atherogenic dyslipidemia	24 (50%)	32 (17.8%)	16 (14.8%)	S	72(21.4%)
Isolated Hypercholestrolemia	6 (12.5%)	24 (13.3%)	4 (3.7%)	S	34 (10%)
Isolated Hypertriglyceridemia	10 (20.8%)	28 (15.6%)	42 (38.9%)	S	80 (23.8%)
Isolated low HDL	8 (16.7%)	36 (20%)	16 (14.8%)	NS	60 (17.9%)

S, NS= significant and non significant at the level of <0.05 respectively.

LDL-C has been often used as primary target goal for lipid lowering therapy in T2DM patients. But many times its value is normal. Hence there is requirement of other parameters and indices to define CVS risk in such patients. We divided the data into two groups according to target goal of LDL-C (<100mg/dl and ≥100mg/dl). Patients having LDL-C <100mg/dl are supposed to have lower CVS risk than the other group. Table 4 summarizes the frequency of occurrence of high level of Non-HDLc (≥130 mg/dl), Apo B (≥90 mg/dl), TC/HDL (≥5), TG/HDL (≥3.5) and AIP (>0.24) among these two groups. Chi square test showed the difference was statistically significant.

Table 3 parameters of lipid profile and lipid ratios among various age groups (in yrs).

	<40 (48)	40-59 (180)	>60 (108)	P value	Total (336)
T. cholesterol (≥ 200 mg/dl)	28 (58.3%)	88 (48.9%)	12 (11.1%)	S	128 (38.1%)
HDL-c (<40 mg/dl)	32 (66.7%)	64 (35.6%)	28 (25.9%)	S	124 (36.9%)
LDL-c (≥100 mg/dl)	36 (75%)	62 (34.4%)	20 (18.5%)	S	118 (35.1%)
Triglycerides (≥150 mg/dl)	32 (66.7%)	96 (53.3%)	48 (44.4%)	S	176 (52.4%)
Non-HDLc (≥130 mg/dl)	36 (75%)	58 (32.2%)	28 (25.9%)	S	122 (36.3%)
Apo B (≥90 mg/dl)	36 (75%)	132 (73.3%)	28 (25.9%)	S	196 (58.3%)
TC/HDL (≥5)	32 (66.7%)	76 (42.2%)	8 (7.4%)	S	116 (34.5%)
TG/HDL (≥3.5)	36 (75%)	104 (57.8%)	52 (48.1%)	S	192 (57.1%)
AIP (>0.24)	36 (75%)	70 (38.9%)	36 (33.3%)	S	142 (42.3%)

S, NS= significant and non significant at the level of <0.05 respectively.

Table 4 CVS risk defined as LDL cut off compared to various other indices

	LDL <100 mg/dl n=218 (64.8%)	LDL ≥100 mg/dl n=118 (35.2%)	P value	Total
Non-HDLc (≥130 mg/dl)	32 (14.7%)	90 (76.3%)	S	122 (36.3%)
Apo B (≥90 mg/dl)	104 (47.7%)	92 (78%)	S	196 (58.3%)
TC/HDL (≥5)	24 (11%)	92 (78%)	S	116 (34.5%)
TG/HDL (≥3.5)	106 (48.6%)	86 (72.9%)	S	192 (57.1%)
AIP (>0.24)	56 (25.7%)	86 (72.9%)	S	142 (42.3%)

S, NS= significant and non significant at the level of <0.05 respectively.

Unavailability of Apo B measurement renders it to be impractical to be used as a CVS risk marker. We have used calculated Apo B levels in our study. The result of correlation tests is presented in Table 5. All correlations are positive and statistically significant.

Table 5 Correlation of calculated Apo B with various parameters.

	Apo B (correlation coefficients)	P value
LDL-c	0.46	S
Non-HDLc	0.50	S
Triglycerides	0.51	S*
TG/HDL	0.56	S*

S, S*=significant correlation coefficients measured by pearson and spearman rho correlation tests.

DISCUSSION

T2DM patients have an increased prevalence of lipid abnormalities which adds on to their CVS risk. This study was undertaken to describe about different other recognized patterns of dyslipidemia in these patients apart from the common triad of high TC, LDL-C and low HDL-C. This will help in choosing among different lipid lowering drugs as they work on different lipoprotein particles and orienting the lipid lowering therapy more according to the need of individual. We also intended to look into usage of various other lipid parameters like non-HDL and Apo B levels and ratios and index like TC/HDL, TG/HDL and AIP to define CVS risk. These parameters can be easily calculated from the given lipid profile values but give additional knowledge about CVS risk than absolute values of TC, HDL, LDL and TG.

We studied the frequency of occurrence of patterns of dyslipidemia like CHL, AD, Isolated Hypercholesterolemia, Isolated Hypertriglyceridemia and Isolated low HDL in patients with T2DM. Understanding these patterns is important because that directs while choosing on the type and number of lipid lowering drugs to be given. Many studies have recommended use of combination of statin and fibrates for CHL. [1] NCEP ATP III [3] recommends use of statins plus fibrates or nicotinic acid for treatment of AD with metabolic syndrome or T2DM. It also suggests non-HDL cholesterol to be secondary target of therapy when TGs are 200-499 mg/dl in these patients. It also mentions trials like Lipoprotein and Coronary Atherosclerosis Study, AFCAPS/Tex CAPS and VA-HIT study suggesting use of lovastatin for Isolated low HDL by the first two trials and gemfibrozil by the VA-HIT study. The commonest pattern of dyslipidemia found was Isolated Hypertriglyceridemia followed by CHL, AD, Isolated low HDL and Isolated Hypercholesterolemia (Table 2). This table also shows that younger people have highest and lowest prevalence of CHL and Isolated Hypercholesterolemia

respectively. Elderly group had highest and lowest prevalence of Isolated Hypertriglyceridemia and Isolated Hypercholesterolemia respectively. The gender wise distribution of pattern of dyslipidemia showed occurrence of Isolated Hypercholesterolemia to be highest in males where as females had high but equal prevalences of CHL, AD and Isolated Hypertriglyceridemia. These differences should not be overlooked while deciding on the lipid lowering therapy.

We found out that majority of patients had higher levels of TC, LDL-C, TG, TC/HDL and Apo B and lower level of HDL-C than the cut off laid by NCEP ATP III guidelines. The commonest abnormality observed among deranged absolute lipid parameter was increased TG (58.3%), followed by TC (38.1%), low HDL (36.9%) and high LDL (35.1%) (Shown in Table 3). This is in contrast with other studies done in Nepal that showed most prevalent single dyslipidemia in both central and mid-western Nepal was low HDL-C. The least prevalent single dyslipidemia was hypercholesterolemia in central Nepal and high LDL-C in mid-western Nepal. [2] Insulin resistance seen in these patients lead to increased rate of lipolysis in adipocytes and influx of free fatty acids into the liver resulting into overproduction of triglyceride rich lipoproteins and delayed clearance of such lipoproteins due to decreased activity of the endothelial bound enzyme lipoprotein lipase. [14] Age wise analysis showed higher percentage of younger cohort, <40 yrs of age had abnormal absolute lipid values than the elderly cohort, >60yrs of age. These findings were statistically significant. Similar finding has been shown by Thapa et al. in a hospital based study conducted in the central region of Nepal, Kathmandu. [15] This creates an alarming situation and younger cohort should consider it and be careful.

One component of atherogenic dyslipidemia is small LDL particles and their presence is associated with an increased risk for CHD. [3] As standard and inexpensive methodologies are not available for their measurement, NCEP ATP III does not recommend measurement of small LDL particles in routine practice. Hence, indices like TG/HDL and AIP are gaining more attention enabling easy screening for presence of small LDL particles. As the TG/HDLC ratio increases, the LDL particle size is reduced. [16] Researchers have also shown AIP, that is log arithmetically transformed ratio TG/HDL-C to be the best determinant for FERHDL and hence lipoprotein particle size and thus a better predictor of cardiovascular risk than other previously used lipid parameters. [17] Having an idea about presence of small LDL particles can be of importance as NCEP ATP III suggests consideration can be given to using nicotinic acid or fibrates as components of lipid-lowering therapy if small LDL particles accompany elevated triglycerides or low HDL cholesterol in high-risk persons like T2DM patients. Another such index is Apo B. NCEP ATP III considers Apolipoprotein B to be a potential marker for all atherogenic lipoproteins but because of presence of limited epidemiological and clinical trial evidence supporting superiority over LDL cholesterol in CVS risk prediction and lack of standardized apolipoprotein B measures, it recommends use of non-hdl cholesterol level as a surrogate for Apo B. We examined the use of TG/HDL, AIP and calculated Apo B in our study. As shown in table 3, considerably high percentage of patients (58.3%) had abnormal Apo B. It showed a declining pattern with age being highest among the younger cohort and lowest among the elderly one. Also 42.3% of patients had abnormal AIP and 57.1% had abnormal TG/HDL ratio suggesting these patients to be having a high CVS risk. Age wise analysis showed higher percentage of young patients had abnormal AIP and TG/HDL ratio. The difference was statistically significant. Only 35.1% of patients had high LDL-C levels where as higher percentage of patients had abnormal Apo B, AIP and TG/HDL ratio. Also as

shown in table 4, 48.6% of patients having normal LDL-C level had high TG/HDL followed by 47.7%, 25.5% and 14.7% of patients who had normal LDL-C but high values of Apo B, AIP and Non- HDL cholesterol. As LDL has been considered to be single most important primary target for lipid lowering therapy by different authorities, the patients having normal LDL-C can be false negatively considered to have low CVS risk. Our findings suggest assessment of these simple indices viz Apo B, TG/HDL ratio and AIP, can give a better idea about the CVS risk imposed to T2DM patients and guide the lipid lowering therapy when used in conjunction with LDL-C. In addition, as shown in Table 5, calculated Apo B correlates well with Non-HDL-C, TG and TG/HDL ratio and can be used when direct measurement of Apo B is not available.

CONCLUSION

Our study shows presence of different patterns of dyslipidemia among T2DM patients. Differences in pattern of dyslipidemia among these patients with respect to gender and age have been found. We suggest determination of the pattern of dyslipidemia should be done before starting lipid lowering therapy Use of other lipid indices should not be overlooked as these help to understand actual CVS risk imposed by diabetic dyslipidemia when used in addition to absolute levels of lipid profile parameters.

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How to cite this article: Baranwal JK, Maskey R, Sherchand O et al. Characterization of lipid abnormalities in type 2 diabetes mellitus. International Journal of Science & Healthcare Research. 2018; 3(2): 28-34.

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