ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Assessment of lipid abnormalities and cardiovascular risk indices in type 2 diabetes mellitus

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Submitted: 24-08-2019 Revised: 14-10-2019 Published: 01-11-2019

ABSTRACT

Background: Incidence of cardiovascular events is increased to two to four times among diabetic patients when compared with non-diabetic. Dyslipidaemia in diabetes is major risk factor for cardiovascular events. Atherogenic indices have been used as major laboratory measures in clinical practice to assess cardiovascular risk. Recent studies, have shown that non-high-density lipoprotein cholesterol and other atherogenic indices is like or better than LDL-C alone in the prediction of CVD incidence and mortality. **Aim and Objectives:** The aim of this study is to assess the lipid abnormalities with cardiovascular risk using atherogenic coefficient (Ac), Cardiac Risk Ratio (TC/HDLc and LDLc/HDLc), TG/HDLc and Non- HDL in diabetes patients. **Materials and Methods:** A cross-sectional descriptive study conducted at Bir hospital (tertiary care center) Nepal. Patients diagnosed as diabetes with age 30 years or above were selected in this study during a period of 1 yr. **Results:** The mean age of the patients enrolled was 55.08 ± 1.11 (34-81) year with male (52 %) to female (48%) ratio is 1.08:1. In this study the mean Non HDLc was 165.24 ± 43.40 mg/dl (65-323) and AC was 4.0 ± 1.09. The finding of AC was slightly higher in female compare to male i.e mean ± S.D 4.07 ± 1.31 and 3.94 ± 1.15. This study show the strong correlation of Non HDLc with total cholesterol (r = .990, p = 0.000), LDLc(r = .602,p = 0.000),TG (r = .411,p = 0.000), LDLc/HDLc (r = .580,p = 0.000),TC/HDLc ((r = .866,p = 0.000), TG/HDLc (r = .390,p = 0.000) and AC (p = 0.866). **Conclusion:** The association between abnormal lipid levels and cardiovascular risk is evident among patients with diabetes mellitus. In this study there is the correlation with FBS, Non HDL-c cholesterol, Cardio risk ratio, TG/HDLc, Atherogenic coefficient. Hence Non-HDL cholesterol and Atherogenic indices proves to be more sensitive and a better predictor of cardiovascular events in diabetes patients.

Key words: Atherogenic coefficient (AC); High density lipoprotein (HDL); Low density Lipoprotein (LDL); Triglyceride (TG)

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v10i6.25337
E-ISSN: 2091-0576
P-ISSN: 2467-9100

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease resulting from insulin deficiency and/or insulin resistance. It is one of the leading causes of death worldwide. Incidence of cardiovascular events is increased to two to four times among diabetic patients when compared with non-diabetic. About 78% percent of type 2 diabetic patients succumb to death from due to premature atherosclerosis which involves dyslipidemia,[1,2,3]

The cardiovascular diseases (CVD) risk of DM increases further if it is associated with dyslipidemia. Dyslipidemia in diabetes is characterized by elevated triglyceride (TG), low levels of high density lipoprotein cholesterol (HDL-C) and increased prevalence of small dense low density lipoprotein

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cholesterol (LDL-C) particles. Serum total cholesterol (TC) and LDL-C have been used as major laboratory measures in clinical practice to assess cardiovascular risk. Recent studies, however, have shown that non-high density lipoprotein cholesterol (non-HDL-C) concentration is similar to or better than LDL-C alone in the prediction of CVD incidence and mortality.[3]

Evaluating CVD risk measures include the use of atherogenic indices which are less expensive and non-invasive techniques.[4] In predicting CVD risk especially when absolute values of lipid parameters are not markedly deranged atherogenic indices contribute significantly.[5,6] Atherogenic indices considered in this study include TG/HDL ratio, Non-High-density lipoprotein cholesterol (NHDL-C), Atherogenic coefficient (AC), Castelli risk index 1 (CRI-1) and Castelli risk index 2 (CRI-2).

CRI-1 and CRI-2 were calculated as TC/HDL-C and LDL-C/HDLC respectively as described by Koleva et al.[7] Non HDL-C was calculated as TC – HDL-C as described by Devadawson[8] et al while AC was calculated as TC – HDL-C)/HDL-C as described by Brehm et al[9]. Castelli risk index (CRI) is also used as a predictor of CVD risks and it is based on lipid parameters i.e: TG, LDL-C and HDL-C which are in turn independent risk factors for CVD.[9]

CRI-1 and CRI-2 are more sensitive and specific indices of CVD risk than TC, LDL-C and particularly in individuals with hypertriglyceridemia of >300 mg/dl. CRI-1 is also known as cardiac risk ratio (CRR). It is defined as the ratio of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C). CRI-2 is a molar ratio, defined as the ratio of low density lipoprotein (LDL-C) to high density lipoprotein (HDL-C).[10]

CRI-1 and CRI-2 were observed to be high in individuals with metabolic syndrome when compared with healthy individuals, thus was reported to be indicative of risk to CVD. A CRI-1 value ≤3.5 is seen as normal while a value >3.5 indicates a high risk of CVD. A CRI-2 value ≤3.0 is normal while ≥3.0 is indicative of CVD risk.[7,11]

Triglyceride/HDL-C ratio predicts CHD and CVD mortality, A TG/HDL-C ratio of 3.5 or greater to be highly correlated with insulin resistance and atherogenic dyslipidemia in men; this threshold was also associated with metabolic syndrome. They proposed that the TG/HDL-C ratio provides a simple way to identify insulin-resistant, dyslipidemic patients who are likely to be at increased risk for CVD.[12-14]

Therefore, the aim of this study is to assess the lipid abnormalities with cardiovascular risk using atherogenic coefficient (Ac), Cardiac Risk Ratio (TC/HDLc and LDLc/HDLc), TG/HDLc and Non- HDL in diabetes patients.

MATERIALS AND METHODS

This was a hospital based cross-sectional descriptive study conducted at Bir hospital, Nepal. Patients diagnosed as diabetes with age 30 years or above were selected in this study during a period of 1 yr. Blood sample was taken from the patients admitted and the patient attending outpatient department center at Bir hospital.

Diagnosis of DM: Diabetes is defined as per the guidelines of ADA.

Inclusion criteria

Patients with glycated hemoglobin level of ≥6.5 % or fasting plasma glucose of ≥126 mg/dl (7.0 mmol/l) or 2-hour post-load glucose ≥200 mg/dl (11.1 mmol/L) during an OGTT were recruited as a research participants. However, the research participants had to further fulfil two more criteria:

- Patients with age ≥30 years
- Sex- male or female
- Diagnosed patients of diabetes ≥3 years and under oral anti-diabetic agents and/or insulin or under dietary controls.

Exclusion criteria

- Diabetic patients with age below 30 years
- Diabetic patients with duration of less than 3 years
- Patients with known diagnosis of type-1 DM

Data collection

Blood sampling was taken for patients admitted and attending (outpatient) in our Center (Bir Hospital). This was done with clinical and biochemical evidence during the study period after obtaining informed consent.

Data was collected using a structured Proforma covering the relevant details. Patients fulfilling the inclusion criteria were explained about the nature of the study and informed written consent was obtained from those willing to get enrolled.

Laboratory analysis

Blood Glucose: Determination of blood glucose was done by glucose oxidase method.

HbA1c: It was measured by Nycocard kit reader method.

Uric acid: Serum uric acid was measured by uricase method.

Triglyceride: Serum triglyceride was estimated by Fossati and Prencipe method associated with Trinder reaction.

Total Cholesterol: Total cholesterol was estimated by enzymatic method.

HDL-C: The chylomicrons, VLDL-C and LDL-C was precipitated by addition of phosphotungstic acid and magnesium chloride. After centrifugation the supernatant fluid contains the HDL (high density lipoproteins) fraction, which was assayed for cholesterol as described above.

LDL-C was calculated using the Friedewald formula[15]

LDL-C (mg/dl) = Total cholesterol – (Triglyceride/5 + HDL cholesterol)

Non HDL-C: Non HDL-C was calculated as Non-HDL-C= Total cholesterol - HDL cholesterol

Castelli risk index (CRI)-1 calculated by Total Cholestorol/HDLc. Castelli risk index (CRI)-2-calcualted by LDLc/HDLc.Atherogenic coefficient-calculated by TC-HDLc/HDLc. Also, TG/HDLc- calculation was done.

Data analysis

All the collected data was entered into Microsoft Excel (Microsoft office 2007) and Statistical Package for Social Service (SPSS) for Window version was used. Data were expressed as Median and inter quartile range. Correlation between the parameters was assessed by using Spearman's rho. All the *p*- values were two-tailed, and those <0.05 (95% Confidence interval) were considered as statistically significant.

RESULTS

Total 125 patients with diagnosis of type 2 Diabetes mellitus were enrolled in the study. The enrolled patients met the inclusion criteria and they were either from OPD or admitted at wards of Bir Hospital. The mean age of the patients enrolled was 55.08±1.11 (34-81) year with male (52 %) to female (48%) ratio is 1.08:1 The highest numbers of the patients were found to be in the age ranges from 40 to 50. (Figures 1 and 2).

Table 1 shows the difference between male and female in various biochemical parameter in which the mean Fasting Blood Sugar and total cholesterol was higher in female compare to male.

In this study, desirable cholesterol was 44% with borderline and very high risk was 29.6% and 26.4% respectively. Similarly, 33.6 % had normal LDL level and near optimal, borderline and high risk was 44 %,16% and 5.6%. In this study 36% of patients had decreased HDLc level and TG was elevated in 68.8% as in Table 2.

Table 3 shows the cardiovascular risk indices difference between male and female diabetes patients in which AC,TG/HDL,TC/HDLc are higher in female diabetes patients.

The study showed that AC and CRI-1 was high in 80%,CRI-2 and TG/HDLc was increased in 23.2% and 78.6% respectively (Table 4)

Table 1: Mean distribution of lipid parameters in different sex

Parameters	Male	Female
FBS	170.9±59.7	193.6±56.4
Cholesterol	205.4±43.9	209.63±43.5
TG	203.6±64.5	201.8±80.0
HDLc	42.09±5.9	42.3±6.4
LDLc	108.7±29.7	106.0±29.44

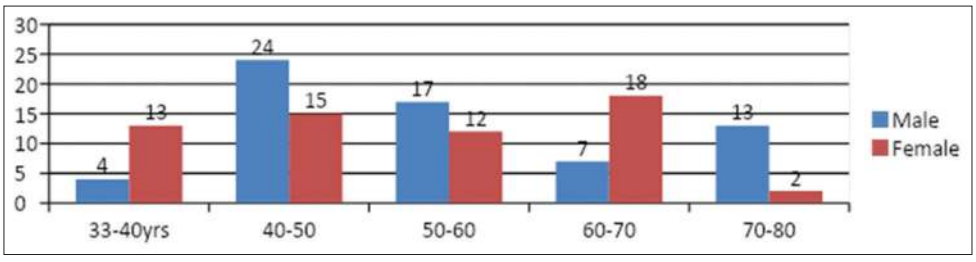

Figure 1: Age distribution

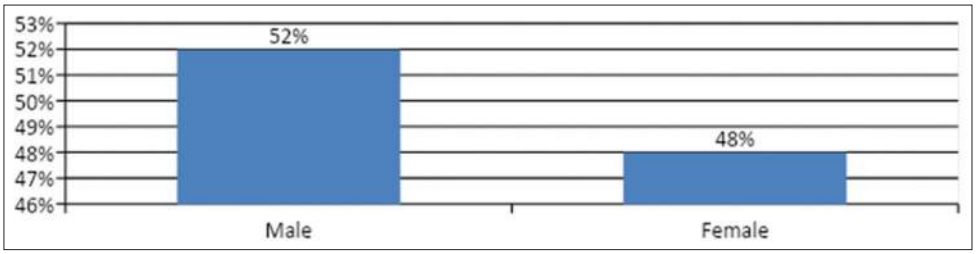

Figure 2: Sex distribution

High significant correlation was observed between Atherogenic indices as shown in Table 5. This shows that there was association between cardiovascular risk indices in diabetes patient.

DISCUSSION

It is well known that diabetes patients have a high incidence of CVD. The pathogenesis of CVD in diabetes is multifactorial and among them dyslipidemia is found to be a powerful risk factor along with Atherogenic indices.

In this study, 125 patients of diabetes with 3 years or more duration were included and assessment of lipid abnormalities and Cardiovascular Risk were observed. Diagnosed cases of type 2 diabetes aged between 34 to 81 years were taken in the study. In this study the mean age was 55.08±1.11 (34-81) year with male (52 %) to female (48%) ratio of 1.08:1. Shrestha SS et al reported the Mean (S.D) age of the diabetes patients was 58.1 years (±11.6).[16]

Similarly, Jbour AS et al[17] report the Males accounted for 52% of patients and the mean age was 56.1 years which was similar in our study. Chhetri, MR et al,[18] study shows the higher proportion of diabetes was demonstrated in male than female. The mean fasting plasma glucose was 181.84±59.08 mg/dl and mean post-prandial blood glucose was 269.48±78.24 mg/dl. This finding of fasting blood sugar and PPBS was comparable with Swetha NK study.[19]

This study showed that 42.6% of the patients enrolled into the study had normal fasting lipid profile. The cut-off values for dyslipidemia were those not falling into the desirable range as per ADA criteria or use of lipid lowering agents. As per this value total cholesterol <200 mg/dl, TG <150 mg/dl, LDL <100mg/dl and HDL >40 mg/dl for males and >50 mg/dl for females were taken normal values. The lipid values above those were considered dyslipidemia.

Taking these reference ranges the prevalence of dyslipidemia in this study was 57.4%. Among the individual lipid levels total cholesterol was normal in 44% and increased in 56% of patients. Similarly, the LDL levels were normal in 33.6% and increased in 66.4%. HDL on the other hand was normal in 64 % and decreased 36% of subjects. Lastly TG levels were normal in 31.2% and deranged in 68.8%.

The mean total cholesterol, LDLc, HDLc and TG in our study was 207. 44±43.62 mg/ dl,

Table 2: Lipid variables according to NCEP ATP III classification

Lipid Profile	Frequency	Percent (%)
Total Cholesterol		
Desirable	55	44.0
Borderline	37	29.6
Very High Risk	33	26.4
LDL		
Desirable	42	33.6
Near Optimal	55	44.0
Borderline	20	16
High Risk	7	5.6
Very High Risk	1	0.8
HDL		
Normal	80	64
Decreased	45	36
TG		
Desirable	39	31.2
Borderline	25	20.0
High Risk	61	48.8
Very High Risk	0	0

Table 3: Cardiovascular Disease Risk Indices of Diabetic patients

Sex		Atherogenic coefficient (AC) TC-HDL/HDL	Castelli Risk Index-2 LDL/HDL	TG/HDL	Castelli Risk Index-1 TC/HDL	Non-HDLc
Male	Mean±S.D	3.94±1.15	2.60±0.73	4.94±1.71	4.94±1.15	163.32±42.98
Female	Mean±S.D	4.07±1.31	2.56±0.080	4.83±1.89	5.07±1.31	167.33±44.12

Table 4: Atherogenic indices

Indices	Range	Frequency	Percentage (%)
Atherogenic coefficient	Desirable <3	25	20
	High >3	100	80
CRI-1 (TC/HDL-c)	Normal <4	25	20
	High >4	100	80
CRI-2 (LDLc/HDLc)	Normal <3.0	96	76.8
	High >3.0	29	23.2
TG/HDLc	Normal <3.5	27	21.6
	High >3.5	98	78.4
Non-HDL-c	Normal <130 mg/dl	25	20
	High >130 mg/dl	100	80

Table 5: Association between Atherogenic indices

	TC-HDL/HDL	Non-HDLc	LDL/HDL	TG/HDL	TC/HDL
TC-HDL/HDL	1	0.866**	0.640**	0.465**	1.000**
Non-HDLc		1	0.580**	0.390**	0.866**
LDL/HDL			1	0.305**	0.640**
TG/HDL				1	0.465**
TC/HDL					1
N	125	125	125	125	125

**Correlation is significant at the 0.01 level (2-tailed).

107.45±29.53 mg/ dl,42.19±6.16 mg/dl and 202.78±72.12 mg/dl respectively which was similarly to Samatha P et al[20] and Jayarama N et al study.[21] Samatha P et al concluded that the diabetic patients had a higher prevalence of high serum cholesterol, high triacylglycerol and high ldl-c than the controls, indicating that diabetic patients were more prone to cardiovascular diseases.

In this study the mean Non HDLc was 165.24±43.40 mg/ dl (65-323). This study show the strong correlation of Non HDLc with total cholesterol (r=.990, p=0.000), LDLc (r=.602, p=0.000), TG (r=.411,p=0.000), LDLc/HDLc (r=.580,p=0.000), TC/HDLc ((r=.866,p=0.000), TG/HDLc (r=.390,p=0.000). A study by Liu and his colleagues concludes that non-HDL cholesterol is a stronger predictor of CHD death among those with diabetes[22]. Sengho A et al reported found that LDLc and Non-HDLc were statistically significant compared to TC, TC/HDLc and LDLc/HDLc ratios which was similar to our finding.

Bodhe C et al[23] reported that several lipoprotein-related indices plasma concentrations of lipids (LDL-C, HDL-C, and TGs), molar ratios (TG/HDLC and LDL-C/HDL-C), and particle size (LDL and HDL)] have been used to predict CHD risk. The total cholesterol/HDL-C and LDL-C/HDL-C molar ratios have good predictive value for future cardiovascular events.

The mean AC in our study was 4.0±1.09. Similarly, the finding is slightly higher is female compare to male i.e mean±S.D 4.07±1.31 and 3.94±1.15. Ranjit et al[24] in their study, found a mean value of 4.62 ± 0.19 in coronary artery disease (CAD)-positive diabetic subjects which was similary to our finding. Study conducted by Shilpa Bhardwaj et al[25] found high Atherogenic Coefficient (AC) is a measure of cholesterol in LDL, VLDL, IDL fractions with respect to good cholesterol or HDLc. All the findings suggest that AC reflects atherogenic potential of the entire spectrum of lipoprotein fractions and hence indicates the CV risk. Atherogenic coefficient is a measure of all lipoproteins that are considered to be atherogenic (VLDL, LDL, IDL, Lpa) with respect to good cholesterol or HDLc.[26]

CONCLUSION

The association between abnormal lipid levels and cardiovascular risk is evident among diabetes mellitus. In this study there is the correlation with FBS, Non HDL-c cholesterol, Cardio risk ratio,TG/HDLc, Atherogenic cofficient. Hence Non-HDL cholesterol and Atherogenic indices proves to be more sensitive and a better predictor of cardiovascular events.

Limitation of study

It is a tertiary hospital-based study with small sample size may not represent the general population though it reflects the people from different parts of Nepal.

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SB- Designed the study, analysed data and prepared the first draft;
SB, HAB, SKBK, SG, MS and LPM- Reviewed the multiple versions of the manuscripts and read and approved the final version for submission.

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Source of Support: None, **Conflict of Interest:** None.