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Original article

Discordance between lipid markers used for predicting cardiovascular risk in patients with type 2 diabetes

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SUMMARY

Aims: Non-high density lipoprotein cholesterol (non-HDL-C) is gaining importance over low density lipoprotein cholesterol (LDL-C) as cardiovascular risk marker in patients with type 2 diabetes. It represents the overall lipid burden and is a surrogate marker for the apolipoprotein B. We studied the discordance between the old (LDL-C) and the new (non-HDL-C) lipid markers in a large group of diabetes patients.

Methods: The lipid profile data of all diabetes (T2DM, aged 18–75, using oral or injectable anti diabetic agents) patients was analyzed in this study. We excluded patients with type1 diabetes, secondary forms of diabetes and gestational diabetes. Elevated lipid parameters (LDL > 100 mg/dL and non HDL-C > 130 mg/dL) were defined as per the guidelines of Adult Treatment Panel III.

Results: The study participants (409 M:360 F) had a mean age of 47.3 ± 12.4 years, BMI of 28.4 ± 5.6 kg/m^2 and an A1c of 8.8 ± 2.2%. Elevated LDL-C was observed in 383 patients (49.8%) and elevated non HDL-C in 418 (54.4%) patients. Of the 383 patients with elevated LDL-C, 346 (90.3%) had corresponding elevated levels of non-HDL-C and out of 418 patients with elevated non HDL-C, 346 (83%) had elevated LDL-C. Discordance between the elevated LDL-C and non-HDL-C values were greater among patients with low triglyceride levels when compared with those with high triglycerides (Pearson's χ^2 test = 67.7; $P < 0.001$).

Conclusion: Our data suggest a significant discordance between the LDL-C and non-HDL-C in patients with diabetes. This discordance leads to the residual cardiovascular risk in diabetes patients.

1. Introduction

The comprehensive management of type 2 diabetes involves achievement of the ABC (A1c, Blood pressure and Cholesterol) goals appropriate for the individual. Many landmark clinical trials have shown the reduction in mortality, microvascular and macrovascular complications with good glycemic control [1–3]. Atherosclerotic vascular conditions are associated linearly with the prevalent LDL-C (low density lipoprotein cholesterol), making it a major target for curtailing the cardiovascular risk [4]. However, few authors have noted the occurrence of recurrent cardiovascular events despite reaching the recommended goal of LDL cholesterol [5,6]. This phenomenon is termed as the "residual risk" and is seen more commonly in patients with diabetes [7]. Multiple mechanisms are responsible for the residual risk which includes an LDL particle number, apolipoprotein B, Lipoprotein (a), the size of the LDL particle and other fractions of the atherogenic lipoproteins [8]. The major contributing risk factor for the residual risk is the difference between the estimated LDL value and the actual quantity of circulating atherogenic LDL particles.

LDL cholesterol is the main target in estimating the cardiovascular risk, but the same measure is actually not measured directly in majority of the samples. The LDL-C value is derived from the Friedewald formula assuming a fixed interrelationship between the lipoproteins [9]. Apolipoprotein B (Apo B) is proposed as a better marker than LDL-C, because of its presence on each of the atherogenic lipoprotein molecule in the circulation [10]. The measurement of apolipoproteins requires more advanced laboratory facilities and is not widely available in resource poor countries. Non-HDL cholesterol (non HDL-C) is proposed as an alternate risk marker as a better predictor of cardiovascular risk in the patients. Previous studies suggest that the non HDL-C is an

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acceptable surrogate marker for Apo B and these two markers are more closely associated with cardiovascular outcomes than the traditional LDL-C [11,12]. The advantages of non HDL-C include the ease of calculation and measurement irrespective of the fasting state. Previous reports suggest a minor degree of discordance between these two lipid markers. An extensive search of the literature did not reveal any similar papers from our country, prompting us to undertake this study. In this report, we analyzed the discordance between the LDL-C and non HDL-C in a large sample of type 2 diabetes patients.

2. Materials & methods

2.1. Study population

We conducted this cross sectional study on patients with type 2 diabetes, who are undergoing regular consultation at our clinic. The patients (aged 18–75 years, duration of more than 1 year, receiving either oral or injectable anti diabetic agents, irrespective of using hypolipidemic drugs) were included in the study. The exclusion criteria were patients with any major illness, surgery or diabetic ketoacidosis in last 6 months, type 1 diabetes, secondary diabetes, untreated thyroid dysfunction and the presence of any other disease with potential to alter the lipid parameters. All the patients with available record for the lipid profile and HbA1c are included in the study. We included patients irrespective of their glycemic and cardiac status or lipid lowering medication history. Participant recruitment for the study was started from January 2014 with an aim to include a total of 750 patients in the study. The patients were divided into four groups for the final analysis: Group 1 (Normal LDL-C and non HDL-C), Group 2 (Elevated LDL-C and normal non HDL-C), Group 3 (Normal LDL-C and elevated non HDL-C) and Group 4 (Elevated LDL-C and non HDL-C). Informed consent was obtained from all the patients to include their data in the study and the protocol was approved by the institutional ethics committee.

2.2. Study measures

All patients were subjected for lipid profile estimation after a 12 h overnight fasting from routine clinical practice. Apart from the complete lipid profile, their glycemic parameters like fasting blood glucose, postprandial blood glucose and HbA1c were also analyzed. Blood glucose and lipid parameters were measured with fully automated analyzer (Turbochem, CPC, India) and HbA1c was estimated using the high performance liquid chromatography method. LDL-C measurement is a derived value from the Friedewald equation and all samples with triglycerides more than 400 mg/dL were not included in the study. The coefficients of variation for A1c, serum cholesterol, and fasting blood glucose were 10, 9, and 7.5%, respectively, at our laboratory. The targets for LDL-C (<100 mg/dL) and non HDL-C (<130 mg/dL) were defined as per the latest guidelines [13,14]. Concordance was defined as the presence of both LDL-C and non HDL-C in the appropriate category and discordance is defined when they assign the patient to different risk categories. Non HDL-C is estimated by subtracting the HDL-C from total cholesterol.

2.3. Statistics

Data are presented as mean ± S.D. and descriptive statistics were used for the data analysis. Pearson's Chi-Square test was used to compare the data of the study parameters. Comparison between the groups is done using the ANOVA method and a P value of less than 0.05 was considered significant for all the tests. The statistical analysis and graph generation was done using the Graph Pad Prism Software, Version 6 (Graph Pad Software, San Deigo, CA, USA).

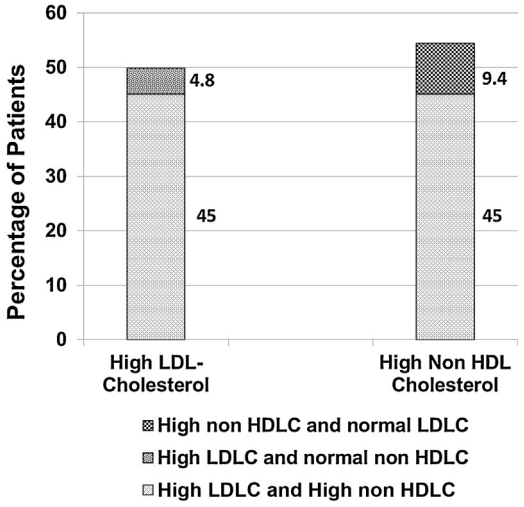

Fig. 1. Concordance/discordance between LDL-C and non HDL-C.

3. Results

The study participants (409 M:360 F) had a mean age of 47.3 ± 12.4 year, BMI of 28.4 ± 5.6 kg/m^2 and an A1c of 8.8 ± 2.2%. Concordance or discordance between LDL and non-HDL-C levels for the whole cohort are shown in Fig. 1 Elevated LDL-C was observed in 383 patients (49.8%) and the elevated levels of non HDL-C is seen in 418 (54.4%) of the patients. Of the 383 patients with elevated LDL cholesterol (>100 mg/dL), 346 (90.3%) had correspondingly elevated levels of non-HDL-C (>130 mg/dL) and 37 (9.7%) patients had normal non HDL-C levels. Of the 418 patients with elevated non HDL-C, 346 (83%) had corresponding elevated levels of LDL-C and 72 (17%) patients had normal LDL-C level.

We stratified the patients as per the triglyceride level to assess the concordance or discordance between the lipid parameters as shown in Table 1. Discordance between the elevated LDL-C and non-HDL-C values were greater among patients with low triglyceride levels when compared with those with high triglycerides (Pearson's χ^2 test = 67.7; $P < 0.001$). Similarly, the discordance between low LDL-C and non-HDL-C values were greater among patients with high triglyceride levels (Pearson's χ^2 test = 18.2; $P < 0.001$). We compared the entire data divided into four groups as shown in Table 2. Briefly, the data suggests that the age and blood pressure distribution are similar between all the groups. Patients with elevated non HDL-C have a higher A1c and lower HDL-C levels when compared to others.

4. Discussion

Our data suggest a significant discordance between the LDL-C and non HDL-C values. The discordance is more in patients with higher triglyceride levels when compared with normal triglyceride

Table 1
Patients grouped according to the LDL-C and non HDL-C levels stratified by the triglyceride value.

	Patients (*N*)	Non HDL-C < 130	Non HDL-C > 130
Triglycerides < 150			
LDL-C < 100	230	218 (95)	12 (5)
LDL-C > 100	224	34 (15)	190 (85)
Triglycerides > 150			
LDL-C < 100	156	96 (62)	60 (38)
LDL-C > 100	159	3 (2)	156 (98)

N (%).

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Table 2
Comparison between the clinical and biochemical parameters of all the four groups.

Parameter	Units	Group 1 (n = 314)	Group 2 (n = 37)	Group 3 (n = 72)	Group 4 (n = 346)	P value
Definition of the group		LDL-C–N Non HDL-C–N	LDL-C–↑ Non HDL-C–N	LDL-C–N Non HDL-C–↑	LDL-C–↑ Non HDL-C–↑	
Age distribution	Years	47.5 (12.9)	45.7 (15.5)	47.3 (10.7)	47.3 (11.9)	0.8764
BMI	kg/m^2	28.4 (5.7)	29.5 (7.9)	30 (6.8)	27.9 (4.9)	**0.0192**
Systolic BP	mmHg	122.8 (6.9)	121.4 (3.5)	122.6 (7.5)	122.7 (6.6)	0.6600
Diastolic BP	mmHg	80.6 (7.8)	79.7 (6.6)	79.3 (6.8)	80.3 (7.9)	0.6306
HbA1c	%	8.5 (1.9)	8.2 (1.9)	8.8 (2.1)	9.1 (2.4)	**0.0006**
Total cholesterol	mg/dL	137.8 (23.2)	166.6 (32.2)	184.2 (25.7)	215.2 (40.4)	**<0.0001**
Triglycerides	mg/dL	135.5 (72.6)	95.2 (52.3)	289.1 (180.3)	165.9 (115.8)	**<0.0001**
HDL cholesterol	mg/dL	42.3 (14.5)	41.5 (14.3)	36.9 (12.5)	41.2 (13.6)	**0.0350**
LDL cholesterol	mg/dL	71.4 (16.6)	112.4 (23.4)	82.9 (17.7)	141.6 (31.7)	**<0.0001**
Non HDL C	mg/dL	95.6 (20.2)	120.5 (8.9)	148.7 (24)	173.9 (37.5)	**<0.0001**
Non HDL–LDL	mg/dL	24.2 (15.4)	8.2 (26.7)	65.8 (34.7)	32.3 (19.7)	**<0.0001**

Mean (S.D.).

level. Our report suggests identification of an additional 5% of patients with higher cardiovascular risk using the non HDL-C when compared with LDL-C. In the subgroup analysis of patients with low LDL-C (n = 386), 81% had a corresponding low level of non-HDL-C, while the remaining 19% had high levels of non-HDL-C. In spite of the availability of this simple tool, the use of non HDL-C is very limited to measure the cardiovascular risk estimation [15]. Our data suggest that the LDL-C alone may give a false sense of security with one fifth of the subjects still at higher cardiovascular risk despite having normal LDL-C value. Previous reports from a different population database suggest that the concordance is only 58% amongst diabetes patients [16]. The higher concordance in our report could be due to patients receiving hypolipidemic agents.

Our report also confirms the widely published high residual risk of cardiovascular disease in diabetes despite the LDL-C level within the target. Amongst all the lipid parameters, non HDL-C represents an overall lipid burden excluding the HDL [17]. This includes the contributions from the small, dense cholesterol in low-density lipoproteins (LDL), triglyceride-rich lipoproteins, including very-low density lipoproteins (VLDL) and their remnants, intermediate-density lipoproteins (IDL), chylomicron remnants and lipoprotein (a). Apolipoprotein B is present on each of these particles and gives a better estimate about the cardiovascular risk in patients. The data from the Framingham study suggests that it has a better correlation with cardiovascular risk at all levels than LDL-C [18].

LDL-C remains the first target to achieve in all patients and ATP III guidelines have suggested the use of non HDL-C as secondary target after LDL [13]. For every 1 mmol (39 mg/dL) reduction in LDL, cardiovascular risk is reduced by 23%. The residual risk of 9–14% remains even after adequate correction of LDL. Strategy of targeting HDL to more than 40 mg/dL also yields benefits of 2–3% cardiovascular risk reduction for every 1 mg/dL (0.03 mmol/L) elevation in HDL [19]. The use of novel marker non HDL-C instead of the traditional LDL-C may further decrease the residual risk in diabetes patients. Target for non-HDL-C is 30 mg in addition to the LDL target. The difference of 30 mg/dL is more applicable when the serum triglyceride level is more than 200 mg/dL and this difference varies based on the underlying triglyceride levels. Diabetic patients with high serum triglyceride levels are benefited with fibrates or glitazars after their LDL cholesterol level is brought under control [20]. Recent lipid guidelines by cardiovascular societies have ignored the concept of non HDL-C and are not endorsed by the diabetes associations [21].

The strength of our study is the observation of concordance/discordance in the clinical practice scenario irrespective of the statin use. Previous reports suggest that "on treatment" ApoB is a better predictor of cardiovascular risk than the LDL-C value [22]. The discordance could have been more if we had included statin naïve patients, which is a major limitation of our study. Other limitations include small sample size and data from a single centre may not represent the diabetes population.

5. Conclusion

In conclusion, our data suggest a significant discordance between the LDL cholesterol and non-HDL-C in patients with diabetes. This highlights that a significant number of type 2 diabetic patients have higher residual cardiovascular risk due to high triglyceride level. Further large studies are required to study the discordance patterns and suggest recommendations for hypolipidemic drug therapy beyond statins.

Conflicts of interest

The authors declare that they have no conflict of interest.

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