

Small Dense Low-Density Lipoprotein as Risk Factor for Atherosclerosis in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Dyslipidemia is a common complication of diabetes and a major risk factor for atherosclerosis. Small dense low-density lipoprotein cholesterol (sdLDL-C) is a subclass of low-density lipoprotein cholesterol. sdLDL-C is highly atherogenic and has been widely studied in diabetic dyslipidemia.

Objectives: The study was carried out to explore the hidden risk of atherosclerosis due to variation of sdLDL-C in Type 2 diabetic patients, whose lipid profiles were normal.

Methodology: We enrolled 126 T2DM patients and 126 age and sex-matched normal controls in this study. Fasting lipid levels in the normal range were the selection criteria for both groups. Hemoglobin A1c (HbA1c), SdLDL-C, Triglycerides (TG), Total-Cholesterol, Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL) were performed for both groups. Results were compared by two samples t-tests.

Results: SdLDL-C levels (54.6 ± 10.2) in T2DM were significantly higher than the control group (41.6 ± 8.4) with p-value <0.00001 . There was a strong positive correlation ($r^2 = 0.591$) between HbA1c and sdLDL-C of T2DM patients.

Conclusion: T2DM patients even with normal lipids profile are at risk of atherosclerosis due to a high level of atherogenic sdLDL-C.

Keywords

Small dense LDL-Cholesterol, T2DM, Dyslipidemia, Cardiovascular Diseases, Lipids Profile.

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INTRODUCTION

Diabetes Mellitus (DM) is one of the most prevalent disease which is characterized by hyperglycemia and divided into two broad categories i.e. Type 1 DM & Type 2 DM. Type 1 DM is characterized by an absolute deficiency of insulin, while Type 2DM is associated with relative insulin deficiency or insulin resistance¹. Type 2 DM is the most prevalent form of diabetes in adults and it induces many complications; diabetic dyslipidemia being one of them², with the prevalence of 95% in T2DM patients³. The trend of increase in the plasma concentration of Triglyceride (TG), total cholesterol, low-

density lipoprotein and decrease in high-density lipoprotein is known as diabetic dyslipidemia⁴, which is considered to be highly atherogenic than any other type of dyslipidemias due to a predominance of small dense low-density lipoprotein cholesterol (sdLDL-C)⁵. Based on their density, low-density lipoprotein cholesterol (LDL-C) is further divided into two subclasses i.e. large buoyant LDL-C (LbLDL-C) and small dense LDL-C (sdLDL-C). SdLDL-C is highly atherogenic than LbLDL-C⁶. Elevated levels of sdLDL-C are closely associated with coronary artery disease (CAD) and it is an accepted risk factor for

CAD by National Cholesterol Education Program⁷. sdLDL-C has high atherogenic potential due to many various mechanisms like lower affinity for LDL receptors, high penetration effects in arterial walls, high susceptibility for oxidation, and high arterial retention. These sdLDL particles are small in size and contain less cholesterol. A high level of sdLDL-C provides increased numbers of atherogenic particles⁸.

In T2DM, there is a possibility to develop CAD without the increase in LDL-C⁹. LDL-C is one of the major risk factors for CAD as it is the primary target for CAD risk reduction therapies¹⁰. It has been observed that not only elevated LDL-C is atherogenic, but the changes in its composition and variations in the concentration of its subclasses may also induce atherosclerosis even when LDL-C is in its normal ranges¹¹.

The purpose of the present study was to compare sdLDL-C and lipids parameters between diabetic and control group to explore the hidden risks of atherosclerosis in Type 2 diabetic patients with normal lipid profile.

MATERIALS AND METHODS

This study was conducted from Jan 2018 to Jan 2019 at the Pathology Lab of Asia Diagnostic, Islamabad. A total of 565 T2DM patients were screened for their lipid profile in fasting. Among them, 126 T2DM patients with normal

lipid profile and 126 age and sex-matched healthy individuals with normal lipid profile were enrolled as a control group.

The lipid profile of T2DM and control group was measured by spectrophotometric method, while HbA1c was measured with an immunofluorescence point of care testing device. Small dense LDL-C was measured with a spectrophotometric method, using the commercial kit¹².

RESULTS

After initial screening, a total of 126 T2DM patients and 126 healthy controls were enrolled in this study. Gender wise distribution is given in Table 1.

Although the inclusion criteria for both groups were normal lipids profile in fasting, however, to determine the variation of lipid parameters within the normal range, the comparison of all lipids profile parameters (like TG, total cholesterol, HDL, and LDL) between T2DM and healthy controls was performed by two-sample t-test (Table 2). Comparison of mean of sdLDL-C between T2DM and healthy control was also performed by two samples-test (Table 2). It was observed that all lipid parameters of T2DM had a significant difference from the lipid parameters of healthy controls. Small dense LDL-C was significantly higher in T2DM than in a control group with a p-value <0.0001.

Table 1. Gender-wise Frequency Distribution of Subjects.

S. No.	Subjects	Males	Females	Total
01	Diabetic Group	72	54	126
02	Control Group	68	58	126

Table 2. Comparison of Triglyceride, Total-Cholesterol, HDL, LDL and SdLDL-C between Diabetic and Control Groups.

S. No.	Subjects	Triglyceride	Total-Cholesterol	HDL	LDL	SdLDL-C
01	Diabetic Group	137 ± 11	169 ± 18	43.9 ± 4.5	98 ± 17	54.6 ± 10.2
02	Control Group	122 ± 17	154 ± 17	47.25 ± 5.5	82 ± 16	41.6 ± 8.4
03	p value	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001

Table 3. Correlation of Lipids Profile Parameters and SdLDL-C with HbA1c in T2DM.

S. No.	Parameters	Triglyceride	Total-Cholesterol	HDL	LDL	SdLDL-C
01	R2	0.516485	0.46069	0.298692	0.38454	0.591631

In the T2DM group, correlation of TG, total cholesterol, HDL, LDL and sdLDL-C with glycated haemoglobin (HbA1c) was performed by Pearson Correlation as shown in

Table 3. From lipid profile, total cholesterol, LDL and TG showed a positive correlation while HDL showed a negative correlation with HbA1c. Small dense LDL-C levels were also positively associated with HbA1c, but this correlation ($r^2= 0.591$) was stronger than lipid parameters.

DISCUSSION

In our study, we observed that sdLDL-C and all parameters of lipid profile in T2DM subjects were significantly higher with p-value <0.001 than the normal controls, except that HDL which was markedly low in T2DM with p-value <0.001 . We also found a positive correlation between HbA1c and lipid parameters except for HDL, which was negatively correlated with HbA1c levels of T2DM subjects. A strong positive correlation was observed between HbA1c and sdLDL-C.

Although our study was limited for the T2DM subjects with normal lipid profile, within normal ranges, we observed the same pattern of changes in lipid profile parameters as it can be observed in diabetic dyslipidemia, which is associated with high levels of TG, total cholesterol, LDL and low levels of HDL along with predominant sdLDL-C^{13,14}. High levels of sdLDL-C in T2DM is a major complication of diabetes that can induce atherosclerosis in diabetic patients^{6,15,16}. In the present study, high sdLDL-C levels indicate that T2DM patients may have atherogenic risk despite the lipid profile within a normal range. Diabetic dyslipidemia due to high TG, total cholesterol, LDL and low HDL levels were observed in various studies^{17,18}.

Glycemic status of T2DM patients contributes to the severity of diabetic dyslipidemia¹⁹ and TG has a strong positive association with HbA1c^{20,21}. Within normal ranges, the same type of relationships was found in our study. T2DM with increased TG levels show a greater capacity to induce sdLDL-C production, which may contribute to the high incidence of coronary artery disease (CAD) in the diabetic population²². SdLDL also induces thickness in intima-media of blood vessels and numbers of sdLDL particles are associated with insulin resistance in T2DM²². Glycation rates are associated with increased

atherosclerosis, morbidity and mortality in cardiovascular diseases (CVD)⁶. In this regard, our study (which did not include any dyslipidemic patient) demonstrated that there is a strong positive correlation between glycemic status and sdLDL-C in T2DM patients that may contribute for the induction of atherosclerosis and may lead towards CVD.

CONCLUSION

From this study, it was concluded that all lipid parameters in T2DM patients with normal lipid profile show their trend in favour of diabetic dyslipidemia. Moreover, the presence of high sdLDL-C in normal lipids profile of T2DM patients is a strong risk factor for CAD.

FUTURE PERSPECTIVE

Lipid-Lowering Therapy should be given to T2DM patients even having lipid parameters in normal reference ranges and sdLDL-C should be incorporated in lipid profile as an integrated parameter of lipid profile as now it is available on commercial diagnostic kits.

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LIST OF ABBREVIATION

CAD	Coronary artery disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
HBA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
SdLDL	Small Dense Low-Density Lipoprotein
TG	Triglyceride

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