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

**Haji Muhammad Rashid*, Hiza Hassan, Mudassar Khan, Jamal Khan, Hasanat Khan**  
Department of Medical Lab Technology, University of Haripur, Khyber Pakhtunkhwa, Pakistan

**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 wildly 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 (56.4 ± 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 (r² = 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.

**Address of Correspondence**  
4849487@gmail.com

**Article info.**  
Received: August 09, 2020  
Accepted: August 22, 2020

**Cite this article:** Rashid HM, Hassan H, Khan M, Khan J, Khan H. Small Dense Low-Density Lipoprotein as Risk Factor for Atherosclerosis in Type 2 Diabetes Mellitus. RADS J Biol Res Appl Sci. 2020, 11(1):15-18.

**Funding Source:** Nil  
**Conflict of Interest:** Nil

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

**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 2 DM is associated with relative insulin deficiency or insulin resistance. Type 2 DM is the most prevalent form of diabetes in adults and it induces many complications; diabetic dyslipidemia being one of them, with the prevalence of 95% in T2DM patients. 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 dyslipidemia, 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). 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-C. 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 Program. 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 particles.

In T2DM, there is a possibility to develop CAD without the increase in LDL-C. LDL-C is one of the major risk factors for CAD as it is the primary target for CAD risk reduction therapies. 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 ranges.

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 kit.

**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.

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

| 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          | <0.0001      | <0.0001           | <0.0001  | <0.0001  | <0.0001   |

| 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. High levels of sdLDL-C in T2DM is a major complication of diabetes that can induce atherosclerosis in diabetic patients. 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.

Glycemic status of T2DM patients contributes to the severity of diabetic dyslipidemia and TG has a strong positive association with HbA1c. 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 in the diabetic population. SdLDL also induces thickness in intima-media of blood vessels and numbers of sdLDL particles are associated with insulin resistance in T2DM. Glycation rates are associated with increased atherosclerosis, morbidity and mortality in cardiovascular diseases (CVD). 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.

**ACKNOWLEDGEMENTS**

I would like to thank CEO of Asia Diagnostic Center Islamabad for moral, financial and technical support.

**LIST OF ABBREVIATION**

| Abbreviation | Full Form |
|--------------|-----------|
| 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 |

**REFERENCES**

1. A Ali. Determination of plasma fibrinogen level in diabetic patients in Shendi Town: Omkalthoum Osman Hamad; 2018; 1-59.
2. Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. World J Diabetes. 2017; 8(4):120-9.
3. Abdel-Aal NM, Ahmad AT, Froelicher ES, Batieha A, Hamza MM, Ajlouni KM. Prevalence of dyslipidemia in patients with type 2 diabetes in Jordan. Saudi Med J. 2008; 29(10):1423-8.

4. Pontrelli L, Parris W, Adeli K, Cheung RC. Atorvastatin treatment beneficially alters the lipoprotein profile and increases low-density lipoprotein particle diameter in patients with combined dyslipidemia and impaired fasting glucose/type 2 diabetes. Met Clin Exp Sci. 2002; 51(3):334-42.

5. Bando Y, Toyama H, Kanehara H, Hisada A, Okafuji K, Toya D, et al. Switching from atorvastatin to rosuvastatin lowers small, dense low-density lipoprotein cholesterol levels in Japanese hypercholesterolemic patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2016; 111:66-73.

6. Khan SH, Fazal N, Gilani SAA, Manzoor SM, Asif N, Ijaz A, et al. Correlation between cholesterol, triglycerides, calculated, and measured lipoproteins: Whether calculated small density lipoprotein fraction predicts cardiovascular risks. J Lip. 2017; 1-9.

7. Koba S, Hirano T, Ito Y, Tsunoda F, Yokota Y, Ban Y, et al. Significance of small dense low-density lipoprotein-cholesterol concentrations in relation to the severity of coronary heart diseases. Atherosclerosis. 2006; 189(1):206-14.

8. Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, et al. The role of lipids and lipoproteins in atherosclerosis. Endotext [Internet]: MDText. com, Inc.; 2019.

9. Gidding SS, Allen NB. Cholesterol and atherosclerotic cardiovascular disease: A lifelong problem. Am Heart Assoc; 2019; 8(10):1-5.

10. Bhatt A, Rohatgi A. HDL cholesterol efflux capacity: Cardiovascular risk factor and potential therapeutic target. Curr Atherosclerosis Rep. 2016; 18(1):2-14.

11. Bandyopadhyay D, Qureshi A, Ghosh S, Ashish K, Heise LR, Hajra A, et al. Safety and efficacy of extremely low LDL-cholesterol levels and its prospects in hyperlipidemia management. J Lip. 2018; 4:13-23.

12. Renjith R, Jayakumari N. A simple economical method for assay of atherogenic small dense low-density lipoprotein-cholesterol (sd-LDL-C). Indian J Clin Biochem. 2011; 26(4):385-8.

13. Joshi SR. Saroglitazar for the treatment of dyslipidemia in diabetic patients. Exp Opin Pharmacoth. 2015; 16(4):597-606.

14. Zuhroiyyah SF, Sukandar H, Sastradinanja SB. The relationship between physical activity and total cholesterol levels, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol in the Jatinangor community. J Health Sys. 2017; 2(3):23-32.

15. Khalil RMAZ, Al-Azab DAM, Akl OA. Is sd-LDL a valuable screening tool for cardiovascular disease in patients with metabolic syndrome? Alex J Med. 2017; 53(4):299-305.

16. Khan M. Small dense LDL: New marker for cardiovascular risk assessment and its therapeutic inflection. Biochem Anal Biochem. 2012;16(1):1-4.

17. Rawal JR, Mehelli Irani P. Atherogenic dyslipidemia. Indian J Endocrinol Metabol. 2013; 17(6): 969-76.

18. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nature Rev Endocrinol. 2009; 5(3):150-9.

19. Taskinen M-R. Diabetic dyslipidaemia: From basic research to clinical practice. Diabetol. 2003; 46(6):733-49.

20. Alzahrani SH, Baig M, Aashi MM, Al-shaibi FK, Alqarni DA, Bakhamees WH. Association between glycated hemoglobin (HbA1c) and the lipid profile in patients with type 2 diabetes mellitus at a tertiary care hospital: A retrospective study. Diabetes, metabolic syndrome and obesity: Targets and therapy. 2019; 12:1639-48.

21. Rodriguez-Gutierrez R, Mancillas-Adame LG, Rodriguez-Tamez G, Diaz Gonzalez-Colmenero A, Solis-Pacheco RC, Elizondo-Plazas AS, et al. Hypertriglyceridemia and its association with HbA1c test: A prospective in vivo controlled study. Int J Endocrinol. 2019; 1-7.

22. Shen H, Xu L, Lu J, Hao T, Ma C, Yang H, et al. Correlation between small dense low-density lipoprotein cholesterol and carotid artery intima-media thickness in a healthy Chinese population. Lipids Health Dis. 2015; 14(1):137-43.