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Original Article

Ox LDL and its Correlation with HbA1C in Newly Diagnosed T2DM Patients

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ABSTRACT
Background: Routine lipid profile fails to explain morbidity and mortality due to cardiovascular complications of Type 2 Diabetes Mellitus (T2DM) and its need of hour to find statistically and metabolically better parameter to assess risk of cardiovascular diseases (CVD) in T2DM. **Aims and Objectives**: To evaluate values of oxidized Low Density Lipoproteins (ox LDL) in T2DM and find its correlation with glycated hemoglobin (HbA1C). **Materials and Methods**: 80 newly diagnosed T2DM patients and equal number of age and gender matched healthy individuals were included in the study. Ox LDL along with routine lipid profile, fasting and post prandial blood sugar (FBG & PPBG)) and HbA1c were estimated in all subjects. **Results**: The values of FBG, PPBG, triglycerides (TG), total cholesterol (TC), low density lipoproteins(LDL), very low density lipoproteins(VLDL), ox LDL and HbA1c were significantly ($p<0.001$) higher in newly diagnosed diabetic cases as compared to controls. In newly diagnosed T2DM cases, HbA1c had strong positive correlation with TG, TC, LDL, VLDL, oxLDL ($r=0.895$, $r=0.921$, $r=0.881$, $r=0.895$, $r=0.788$, respectively) and a strong negative correlation with HDL ($r=-0.578$). **Conclusions:** ox LDL shows a strong correlation with HbA1C and is metabolically a better parameter than routine lipid profile. In our study oxLDL is significantly increased in newly diagnosed T2DM patients and its increased levels are proven risk factor of CVD in T2DM patients. We concluded that ox LDL is a promising risk marker for atherosclerosis. It can help in the prompt and early detection of CVD in T2DM patients.

Keywords: T2DM, ox LDL, Cardiovascular diseases.

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INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia due to insulin deficiency or insulin resistance resulting in altered metabolism of carbohydrates, lipids and proteins. It is the most common endocrinal disorder worldwide with high incidence and prevalence. According to international diabetic federation, in the year 2017, the number of diabetics in the world between the age group 20-79 years is expected to be 425 million i.e 8.8 % of the entire population. It is expected to rise to 628.6 million i.e 9.9% of the entire population, by the year 2045.[1] By the year 2045 India is expected to become the diabetic capital of the world, with almost 134.3 million diabetics according to the estimates of International Diabetic Federation.[1] Out of all diabetes types, Type 2 DM has a maximum prevalence and accounts for 91% cases of all diabetic patients.[2] Various complications of diabetes leads to high morbidity and mortality associated with diabetes. Hypercholesterolemia[3] and high levels of LDL cholesterol are the major risk factor for atherosclerosis. But it has been found that certain people having normal lipid profile develop cardiovascular diseases.[4] Patients of type 2 DM and metabolic syndrome having control of various risk factors of CVD like LDL-C were found to have cardiovascular events.[5] So, the lipid profile assessed routinely was found to be inadequate in assessing the risk of cardiovascular complications in diabetic patients. Oxidation and glycation of lipoproteins play an important role in various steps of atherogenesis and this eventually leads to cardiovascular diseases. So, in this study we estimated the values of ox LDL in newly diagnosed T2DM and correlated them with HbA1C. There is increased oxidative stress in patients with T2DM.[6,7]

Hyperglycemia leads to glycation of LDL and this glycated LDL is more prone to oxidation.[8] Oxidation of low density lipoprotein is a key process in the early progression of atherosclerosis. LDL on oxidation induces monocyte infiltration, smooth muscle cell proliferation and atheromatous plaque formation. Binding of ox LDL to CD36 (a scavenger receptor) on macrophages increases the production of inflammatory cytokines, thus playing a critical role in atherogeneisis and CVD.[9] ox LDL is not recognized by LDL receptor but by the scavenger receptor (SR) receptor present on the macrophages. The SR on macrophages is not regulated and leads to the accumulation of cholesterol and hence formation of foam cells. Also, the ox LDL down-regulates the scavenger receptors on the macrophages and decreases the extent of reverse cholesterol transport (RCT) and it cannot be taken by HDL.[10,11] This study is an attempt to find a correlation between HbA1C and ox LDL in newly diagnosed type 2 DM patients. In this study we assessed the conventional lipid profile (TC, TG, LDL, HDL and VLDL) and ox LDL. We correlated the values of conventional lipid parameter and ox LDL with glycated hemoglobin (HbA1c).

MATERIALS & METHODS

The study was conducted in the Departments of Biochemistry and Medicine of SGT Medical College, Hospital & Research Institute, Budhera, Gurugram after taking ethical clearance from the ethical commitee. It was a hospital based study which included 80 newly diagnosed Type 2 DM patients attending medicine OPD and 80 age and gender matched healthy individuals from general population were taken as controls. The diagnosis of new patients of T2DM was based on American Diabetic Association criteria[12] i.e Fasting blood sugar level ≥ 126 mg/dl (7 mmol/L), Random blood glucose ≥ 200 mg/dl (11.1 mmol/L) or HbA1c ≥ 6.5 % with classical symptoms of diabetes (polyuria, polydipsia, polyphagia, weight loss) or hyperglycemic crisis and two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/ L) following a 75g oral glucose load. Patient with history of smoking and chronic alcoholism and on medications such as hypolipidemic drugs, hormone replacement therapy, steroids, drugs that induce hyperglycemia, liver or kidney diseases and those suffering from acute or chronic inflammatory disorders, dyslipidemias and HIV were excluded from the study. Written and informed consent was taken from all the subjects included in the study after explaining the details of the study and its purpose. 5ml of venous blood was drawn after 12-14 hours of overnight fasting, under aseptic conditions in suitable vaccutainers from the selected cases and controls. The plasma/serum was separated by centrifugation at 3000 rpm for 15 minutes. Plasma/ Serum were used for analysis of FBG, PPBG, TG, TC, LDL, HDL, HbA1c and ox LDL. FBG, PPBG and lipid parameters were measured on Erba Mannheim EM-200 Fully-automatic analyser with ERBA XL System Pack. HbA1c was measured by Ion Exchange Resin Method. and Ox LDL was measured by ELISA kit (Elabscience). Data was collected and mean and SD for all the parameters was calculated. Statistical analysis was performed by SPSS 21 program for Windows. Continuous variables were summarized in the form of Mean ± SD and categorical variables are presented as frequencies and percentages. Graphically data was presented by bar diagrams. Student independent t tests were employed for comparing continuous variables. Chi square tests or Fisher's test, whichever appropriate, was applied for comparing categorical variables. A p value <0.001 was considered highly significant.

RESULTS

The mean age of newly diagnosed T2DM cases was 52 years and the mean age of controls was 52.3 years. The difference of age between cases and controls was not significant (p= 0.678). (Table: 1) 65% of cases were males and 35% were females while 57% of patients control group were males and 23% of healthy controls were females. There was no significant correlation between cases and healthy people on the basis of sex of individuals. The values of were significantly higher (p<0.001) in newly diagnosed T2DM cases as compared to controls. (Table: 2) The values of serum TG, TC, LDL, VLDL, ox LDL were significantly higher (p<0.001) while the levels of serum HDL was significantly lower (p<0.001) in newly diagnosed Type 2DM cases as compared to controls. (Table: 2 & Fig: 1) In newly diagnosed T2DM cases, HbA1c had strong positive correlation with FBG, PPBG, TG, TC, LDL, VLDL, oxLDL (r=0.937, r=0.930, r=0.895, r=0.921, r=0.881, r=0.895, r=0.788, respectively). HbA1c had a strong negative correlation with HDL (r=-0.578). (Table: 3)

Table 1: Showing mean age (years) among cases and controls

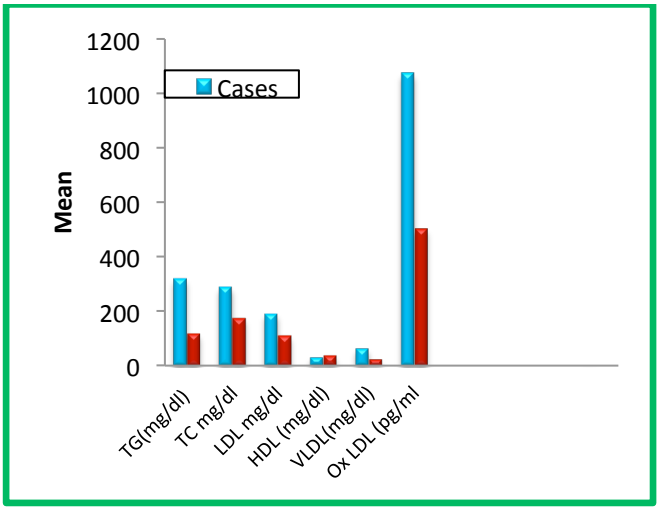
Age (years)	N	Mean	SD	Range
Cases	80	52.0	3.75	46-62
Controls	80	52.3	2.56	47-59

Table 2: Comparison of various biochemical parameters between cases and controls

Parameter	Cases		Controls		p-value
	Mean	SD	Mean	SD	
FBG (mg/dl)	279.05	25.97	87.95	6.13	<0.001*
PPBG (mg/dl)	310.00	31.45	120.73	6.86	<0.001*
HbA1C (%)	6.95	0.46	5.09	0.37	<0.001*
TG(mg/dl)	320.6	38.99	118.5	16.05	<0.001*
TC(mg/dl)	289.4	27.12	174.9	16.63	<0.001*
LDL(mg/dl)	192.3	28.38	111.5	16.71	<0.001*
HDL (mg/dl)	32.6	4.68	39.7	4.96	<0.001*
VLDL(mg/dl)	64.1	7.80	23.7	3.21	<0.001*
ox LDL (pg/ml)	1072.8	205.91	501.3	130.56	<0.001*

Table 3: Correlation of HbA1c with FBG, PPBG and lipid parameters

Parameter	Pearson Correlation (r)	p-value
FBG(mg/dl)	0.937	<0.001*
PPBG(mg/dl)	0.930	<0.001*
TG(mg/dl)	0.895	<0.001*
TC(mg/dl)	0.921	<0.001*
LDL(mg/dl)	0.881	<0.001*
HDL(mg/dl)	-0.578	<0.001*
VLDL(mg/dl)	0.895	<0.001*
Ox LDL(pg/ml)	0.788	<0.001*



Graph 1: Showing lipid parameters in cases and controls

DISCUSSION

Diabetes Mellitus is the most common endocrinal disorder worldwide with high incidence and prevalence. American Diabetes Association predicted approximately 4 million deaths due to diabetes in the year 2017.[1] Diabetics have two to three times higher rate of cardiovascular diseases than those without diabetes.[13] In our study the levels of FBG, PPBG and HbA1c were significantly higher in newly diagnosed T2DM patients as compared to controls. In newly diagnosed T2DM cases the mean values of HbA1c was 6.95±0.46 % whereas the mean value of HbA1c in controls was 5.09% ±0.37%. Fasting blood sugar is the cheapest biomarker to separate diabetic from non diabetic individuals. Our study showed a marked increase in FBG and HbA1c in the diabetic patients as compared to the controls, which is similar to study of Ghazanfari Z et al[14] (2010) who presented that FBG and HbA1c are used as diagnostic biomarker to separate diabetic from non-diabetic subjects. Hyperglycemia leads to formation of sorbitol, glycosylation of hemoglobin and various lipoproteins and later formation of advanced glycosylated end products (AGEs). The AGEs form cross links with extracellular matrix proteins like collagen and cause endothelial dysfunction, reduces nitric oxide (NO) synthesis and accelerate atherosclerosis. In our study ox LDL was found to have significantly higher values in newly diagnosed T2DM cases (1072 ± 205.8 pg/ml) as compared to controls (501.3± 130.56 pg/ml). Also, the correlation between HbA1c and ox LDL was highly significant (r=0.509, p<0.001). Our study was similar to studies of Njajao Omer et al[15] (2009) who concluded that ox LDL was positively associated with T2D (OR=1.3,95% CI:1.1–1.5), fasting glucose (β=0.03±0.006), HbA1c (β=0.02±0.004), fasting insulin (β=0.12±0.02). Ganjifrockwala Farzana et al[16] (2016) found that statistically significant increase in ox LDL was seen in T2DM with retinopathy patients as compared to controls. They found that there is no significant increase in ox LDL in diabetic non retinopathic individuals as compared to controls. Nakhjavani Manouchehr et al[17] (2010) found that ox LDL was directly related to the duration of diabetes (r = 0.519, p=0.001). ox LDL was significantly higher in patients with prolonged diabetes (81.43 ± 1.65) than values of ox LDL in newly diagnosed patients (45.50 ± 1.49). Hyperglycemia leads to glycation of LDL-C and the glycated LDL-C is more prone to oxidation. They suggested that, diabetes is a chronic inflammatory condition, the oxidative stress increases with increase in diabetic duration. Meisinger Christa et al[18] (2005) studied chronic heart disease (CHD) patients and concluded that ox LDL was a powerful risk factor for atherosclerosis. Also, similar study was done by Bansal Sanjiv Kumar[19] (2016) who found significant higher values of ox LDL in CAD patients as compared to healthy people. T2DM and insulin resistance leads to reduced insulin mediated uptake of fatty acids which are delivered to liver and result in the formation of triglyceride rich large sized VLDL particles which are not cleared from the plasma due to decreased activity of lipoprotein lipase resulting from insulin resistance. These large sized VLDL also lead to formation of small dense low density lipoproteins (sd LDL). Both large sized VLDL and sd LDL are more prone to glycation and the glycated lipoproteins are more prone to oxidation, resulting in the formation of ox LDL. Our study showed a strong association of ox LDL with glycemic status in T2DM cases. This leads to increased formation of glycated LDL and glycated sd LDL. These glycated lipoproteins are more prone to oxidation as there is increased oxidative stress in patients with T2DM.[6,7] Ox LDL has many atherogenic properties and plays a key role in the atherosclerotic lesions. HbA1c is a good parameter for predicting hypercholesterolemia in diabetic patients. Our results show that HbA1c is predictor of ox LDL concentration. So, if proper glycemic control in maintained, the levels of ox LDL can be controlled. Our study clearly showed difference between the levels of risk factors of CVD in T2DM patients and healthy people. Our study showed a higher value of risk factors for atherosclerosis in T2DM patients as compared to controls. Ox LDL is metabolically better and a strong risk factor for atherosclerosis. As, ox LDL plays an important role in the progression of atherosclerosis, it would be wise to reduce the level of ox LDL, lipid profile and blood glucose to control the complications of diabetes to prevent future risk of CVD.

CONCLUSION

Ox LDL has statistically a strong correlation with HbA1C and is a metabolically better parameter than routine lipid profile in assessing the risk of CVD in T2DM patients. Ox LDL is a promising risk marker for CVD. Possibly more attention should be focused on ox LDL in the management of lipids in diabetic patients. The findings need to be validated in more patients.

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