

The Association between Serum Lipid Profile and Retinopathy in Type 2 Diabetes Mellitus Patients

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Abstract

Background: Blood such as VLDL, intermediate density lipoprotein (IDL), chylomicrons, chylomicron remnants and lipoprotein and therefore provides a more accurate estimate of CV risk than LDL-C alone, as shown in numerous epidemiological and clinical studies. This is particularly true for patients who are already on statin therapy or those with elevated levels of VLDL-C such as patients with obesity, metabolic syndrome and diabetes. **Subjects and Methods:** A pre-structural proforma was used to collect baseline data detailed clinical history with clinical examination and relevant investigation was done on participating individuals. **Results:** Significant correlation between HbA1c and various circulating lipid parameters and significant difference of lipid parameters in two groups (<.0% and >7.0%) of glycated haemoglobin indicates that HbA1c can be used as a potential biomarker for predicting dyslipidemia in type 2 diabetic patients. **Conclusion:** As good control of diabetes is shown to keep the lipid levels in near normal range, it appears important to aim at critical control of DM to prevent or at least postpone the onset of various complications.

Keywords: Dyslipidemia, HbA1c, Lipid Parameters.

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Received: June 2019

Accepted: June 2019

Introduction

A typical lipid profile consists of TG, TC, HDL-C and LDL-C. Most of the laboratories measure TC, TG and HDL-C directly using enzymatic assays but LDL-C is often derived indirectly from the Friedewald equation ($LDL-C = TC - HDL-C - TTTG/5$). As fasting acutely affects serum TG levels, a fasting blood sample (after 9-12h fasting) is required to estimate LDL-C accurately. This presents a practical challenge as many-a-times circumstances do not allow fasting sampling. In such settings, using non-HDL-C instead of LDL-C is a good alternative. Non-HDL-C is calculated simply by subtracting HDL-C remains accurate irrespective of fasting status. As discussed subsequently, non-HDL-C has several additional advantages over LDL-C as a CV risk marker.^[1]

Blood such as VLDL, intermediate density lipoprotein (IDL), chylomicrons, chylomicron remnants and lipoprotein (a) {Lp(a)} and therefore provides a more accurate estimate of CV risk than LDL-C alone, as shown in numerous epidemiological and clinical studies. This is particularly true for patients who are already on statin therapy or those with elevated levels of VLDL-C such as patients with obesity, metabolic syndrome and diabetes.

Some prospective studies have reported that non-fasting serum triglyceride levels may be a useful predictor of CV events. However, issues such as standardizing sampling conditions and reference values are yet to be clarified.

It is a major risk factor for CVD and increases the risk of CVD by five times in women's, and three fold in men. It has been demonstrated that people with diabetes and no history of MI have a CV risk nearly equivalent to those without diabetes and a history of MI. The mechanisms postulated to cause rapid development of vascular disease in diabetes include hyperglycaemia. Hypertension, low HDL-C, high triglyceride levels, elevated small-dense LDL, increased pro-coagulant activity and a pro-inflammatory milieu. It stands to reason, therefore, that lipid management is an essential part of diabetes care.^[2]

As mentioned above, people with diabetes are classified as high risk patients for vascular events. Hence, irrespective of the presence of absence of to her risk factors on history (age, gender, smoking, hypertension, family history) or physical examination (obesity, hypertension, polycystic ovary syndrome in woman), they should be screened for dyslipidemia.

A fasting lipid profile should be performed annually. The minimum investigations should include TC, LDL-C, TG, and HDL-C. Non-HDL-C should be routinely calculated in these patients given the higher prevalence of elevated triglycerides and small-dense DL among diabetics. In addition, estimation of Apo-B levels is also desirable in these patients. However, routine assessment of these markers is not mandatory.

As all patients with type 2 diabetes with evidence of target organ damage or other CV risk factors and those with type 1

diabetes with micro albuminuria are automatically designated to high risk category, they require management which is similar to that for secondary preventing of CVD. In other patients, formal risk assessment may be needed. The treatment approach is broadly same as that for any high risk individual without diabetes, as described in the previous sections. The primary target is LDL-C, while non HDL-C, HDL-C and apo B are secondary targets. The present document reiterates the fact that these goals are global, i.e. for both genders and for all adults. However, in children and adolescents, the acceptable LDL-C level is relaxed to 110 mg%.^[3]

Management of dyslipidemia in diabetes is similar to that in people without diabetes. Non-pharmacological therapy viz physical activity, cessation of smoking, and healthy nutrition therapy are important aspects of therapy and should follow the same principles as outlined in the previous sections. However, it should be noted that dietary fructose leads to hypertriglyceridemia if consumed in excess of 10% of total.⁴ The choice of drug therapy is similar in dyslipidemic persons with and without diabetes. The present guidelines strongly recommend statin therapy despite the fact that certain studies document a rise in incidence of diabetes with these drugs. Meta-analysis has shown that statin use is linked to higher(9%) risk of development of new-onset diabetes especially in older persons. However, the risk: benefit ratio of statins is strongly tilted in favour of drug use.

Although the choice of statin in diabetes is broadly similar to that in people without diabetes, there are some important differences in the impact of different statins on the glycemic control. Glucose neutral effects have been reported for pravastatin. Simvastatin has been shown to inhibit glucose-induced insulin secretion through blockade of L-type Ca²⁺ channels in B cells. Atorvastatin is thought to suppress glucose transporter GLUT4 expression in 3T3-L1 adipose cells by blocking isoprenoid synthesis. Cytotoxic effects on the B cell have also been reported for atorvastatin. Another postulated mechanism is through activation of SREBPs (Sterol Regulatory Element-Binding Proteins). Pitavastatin use has been reported to be devoid of the adverse effects on glycaemia that are reported with atorvastatin. Pitavastatin, in fact demonstrated a beneficial effect on HbA1c in subjects with diabetes who were enrolled in the LIVES study. Differences in the metabolic pathways for various statins may explain these differential effects on glycemic control. Pitavastatin is minimally metabolized by the CYP3A4 isoenzyme, unlike other statins, and this may be responsible for its glucose-neutral character.^[5]

The patients with diabetes often have multiple co-morbidities and are recognized to be in a 'poly-medicated' state. Therefore, lipid therapy in diabetics should have low risk of drug-drug interactions. While most statins are safe, one should be aware of potential drug-drug interactions. Antifungal agents such as itraconazole, commonly prescribed in diabetes, may increase atorvastatin and simvastatin concentrations by inhibiting CYP3A4, which metabolizes these statins.

Fenofibrate is the most widely used fibrate compound, and is recommended for use as add-on to statins. Addition of fenofibrate to statin therapy may benefit patients with diabetes, hyperglyceridemia and low HDL-C. Gemfibrozil can also be used in patients with TG>200mg% and HDL-

C<40mg%, who do not respond to statin monotherapy. However, it does not offer any advantages as compared to fenofibrate. Monotherapy with fibrates is suggested only in patients with isolated hypertriglyceridemia who do not tolerate statin therapy, even at low doses.^[6]

Subjects and Methods

A pre-structural proforma was used to collect baseline data detailed clinical history with clinical examination and relevant investigation was done on participating individuals.

Exclusion Criteria

- Patient with liver disorders
- Patients with BMI>30Kg/m²
- Patients on lipid lowering agents (statins, fibrates, etc.)
- Patients on treatment with medications which alter lipid profile
- Patients with age <20 years and > 80 years.
- Any situation that shortens erythrocytes survival or decreases mean erythrocyte age falsely lowers GHb (HbA1c) test results regardless of the test method.
- Iron deficiency anaemia is reported to increase test results that can subsequently be reversed by iron treatment. Hemolytic anemia has opposite effect to iron deficiency by reducing HbA1c in affected individuals.
- It has been reported that results may be inconsistent in patients who have conditions such as opiate addiction, lead poisoning, and alcoholism, ingest large doses of Aspirin.
- HbA1c assays are not recommended for use in the diagnosis of diabetes mellitus.
- It is reported that antibodies used in immuno-turbidimetric assays recognize the N-terminal glycosylated amino acid in the context of 4-10 amino acids of the Hb b-chain. These antibodies do not recognize the reversible Schiff base (aldimine) or 6 other gHb species, including chemically modified derivatives.
- HbE has little effect on the determination of glycosylated haemoglobin with immunoassay methods.
- It has been documented that HbF has little or no immunoreactivity with most antibodies used in HbA1c assays.
- Any patient with a significant change in HbA1c coinciding with a change in laboratory HbA1c methods should be evaluated for the presence of variant or derivative Hb.
- All HbA1c methods are inadequate for the assessment of long-term glycemic control in patients homozygous for HbS, HbC or HbSC disease

Results

Table 1: Sex with Retinopathy

Gender	Retinopathy		Total
	Absent	Present	
Female	11 (28.20%)	28 (71.79%)	39 (100%)
Male	14 (22.95%)	47 (77.04%)	61 (100%)
Total	25 (25%)	75 (75%)	100 (100%)

Table 2: Age with Retinopathy

Gender	Retinopathy		Total
	Absent	Present	
< +35	2	1	3
36-45	5	5	10
46-55	11	24	35
56-65	5	31	36
66+	2	14	16
Total	25	75	100

Mean + SD: 57.29 + 11.144

Table 3: Correlation coefficient between retinopathy and lipid

Lipid profile	Retinopathy
TC	0.091**
LDL	0.056**
TG	0.116**
HDL	0.000**
VLDL	0.123**

** Correlation is significant at p<0.01. * correlation is significant at p<0.05.

Table 4: Association between retinopathy, nephropathy with lipid profile

Lipid profile with Retinopathy	Mean + SD	p-value
TC	196.97 ±48.18	*p<0.01
LDL	122.75 ±49.36	*p<0.01
TG	160.93 ± 56.21	*p<0.01
HDL	39.64 ±10.50	*p<0.01
VLDL	32.21 ± 11.32	*p<0.01

* p<0.01 significant

Discussion

Significant correlation between HbA1c and various circulating lipid parameters and significant difference of lipid parameters in two groups (<.0% and >7.0%) of glycated haemoglobin indicates that HbA1c can be used as a potential biomarker for predicting dyslipidemia in type 2 diabetic patients in addition to glycemic control hence early diagnosis can be accomplished through relatively inexpensive blood testing.^[7]

Dyslipidemia in diabetes is a major problem and a major risk factor for cardiovascular diseases. A significant proportion of diabetic individuals are dyslipidemic. Males were found to be a higher risk of developing dyslipidemia than females. Diabetic individuals frequently have to monitor their lipid profile to prevent themselves from the risks associated with dyslipidemia as in this study 92 (63.8%) of diabetic subjects were found to have dyslipidemia.^[8]

A cluster of interrelated plasma lipid and lipoprotein abnormalities associated with alterations in VLDL metabolism contribute to the risk for atherosclerosis and CHD in the majority of patients with type 2 diabetes. Insulin resistance plays a key role in the development of diabetic dyslipidemia. Each of the lipid abnormalities (low HDL, small dense LDL, and elevated triglycerides) is associated with an increased

Features of this dyslipidemia can be improved by a variety of therapeutic modalities, including weight loss and physical activity, and the use of statins, fibrates, nicotinic acid, and TZDs. Additionally, evidence from angiographic trials indicates that reduction in small dense LDL particles can contribute significantly to reduced coronary disease progression observed with these treatments.^[9]

Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The characteristic

features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. The availability of multiple lipid-lowering drugs and supplements provides new opportunities for patients to achieve target lipid levels.

A study in Allahabad concluded that Hypercholesterolemia, hypertri-glyceridaemia and lipoprotein are the main lipid abnormalities found in diabetes which is risk for coronary artery disease. In diabetes sex plays a significant effect on risk of coronary artery disease.

Present study showed common lipid abnormalities during diabetes induced dyslipidemia are hypercholesterolemia hypertriglyceridemia and elevated LDL-C results suggest a high prevalence of dyslipidemia, which might be playing a major role in the development of cardiovascular disease among diabetic patients. The optimal care of diabetic patients should include routine monitoring of blood sugar and serum lipid profile. Aggressive lifestyle changes, such as weight reduction and physical exercise should be initiated first followed by medication with lipid lowering drugs. The optimum treatment with antidiabetic drugs to obtain fair glycaemic control should go hand in hand with lipid-lowering drugs.^[10]

It was found that TG and TG/HDL-C were independent DM risk factors, with the odds ratios being 1.292 (P=0.47) and 1.341 (p=.010), respectively although they were poor in their DM discriminatory power (area under the receiver operating characteristic curve, 0.662 and 0.672, respectively). Combined with other risk factors (fasting plasma glucose, waist circumference, and family history of DM), the DM discriminatory power of TG and TG/HDL-C was improved (area under the receiver operating characteristic curve, 0.764 and 0.767, respectively). The DM incidence increased with ascending risk score. Single HDL-C seems unable to predict future DM. Triglycerides and TG and TG/HDL-C were independent DM risk factors; and of the two TG and TG/HDL-C was a stronger risk factor. The DM discriminatory power of TG and TG/HDL-C was poor; therefore, it is recommended that they be used in combination with other risk factors. Diabetes mellitus incidence increased with ascending risk score.

Majority of the type 2 diabetes mellitus patients in Africa do not maintain a good glycemic control. Diabetic dyslipidemia characterized by high plasma triglycerides, high LDL-cholesterol and low HDL-cholesterol is tightly associated with glycemic control. Good glycemic control could result in improvement in the lipid profile and the patients could be spared from the high cardiovascular risk. Combination therapy is better than mono-therapy in controlling the glycemic load in type 2 diabetes mellitus. Metformin added to the other hypoglycaemic drugs gives added benefit in the form of reduced glycemic load and improvement in the lipid profile.

A study in Yemen concluded The overall prevalence of type II diabetes Mellitus was 4.6% (7.4% in males and 2% in females). Impaired glucose tolerance (LGT) and impaired fasting glucose (IFG) were found in 2% and 2.2% of the study population. Factors independently related to any abnormality in glucose tolerance, using logistic regression

analysis, were sex, hyperlipidaemia, hypertriglyceridaemia, and hypertension; whereas sex and age related to DM. More than 80% of the type II diabetics were over the age of 40, 35% being hyperlipidaemic, 22% being hypertensive and 18% obese. Sixty percent of IGT subjects were hyperlipidaemic and 20% were obese. Approximately 78% of obese individuals (≥ 30 kg/m²) had normal glucose tolerance.^[11]

With comparable glycemic control, the fixed PM (Pioglitazone +metformin) combination was more efficacious on HDL cholesterol improvement than the GM (glimepiride+metformin) combination. Additional positive effects were observed for biomarkers of lipid metabolism, B-cell function, activity of the visceral adipose tissue, and chronic systemic inflammation.

It is concluded from the results of the present study that type 2 diabetics were either overweight or type I obese and dyslipidaemia was very common. Results strongly suggest that further investigations should related the effects of dyslipidaemia and abnormalities of insulin resistance in type 2 diabetics. And ethnic specific patterns of lipid profile in type 2 diabetics regardless of their glucose levels, suggesting that ethnic specific strategies and guidelines on risk assessment and prevention of CVD due to dyslipidemia are required.^[12]

Conclusion

Diabetic patients with complications tend to have higher levels of lipid fractions (TGs, cholesterol, and LDL-C) and lower levels of HDL-c. This suggests that there appears to be some relation between the genesis of various vascular complications (micro vascular and macro vascular), and the presence of lipid abnormality. It is difficult to point out a particular factor as the cause as multiple mutually interacting factors determine the presence or development of these

complications.

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How to cite this article: Karan VN, Mohan V. The Association between Serum Lipid Profile and Retinopathy in Type 2 Diabetes Mellitus Patients. Acad. J Med. 2019;2(1):22-25.

DOI: dx.doi.org/10.21276/ajm.2019.2.1.7

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