THE CORRELATION OF GLYCOXYLATED HEMOGLOBIN AND NON-HDL CHOLESTEROL IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

BACKGROUND: Adults with diabetes have a two to four times higher risk of experiencing cardiovascular events than adults without diabetes. Many factors account for increased CVD risk in diabetes, but lipid abnormalities are major contributors. Non-HDL cholesterol measurement (calculated as total cholesterol minus HDL cholesterol) provides a single index of all the atherogenic, apolipoprotein (apo) B-containing lipoproteins. It has been shown conclusively that better glycemic control decreases diabetic complications and glycosylated hemoglobin (HbA1c) is a routinely used marker for long term glycemic control.

AIM: To study the glycosylated haemoglobin levels (HbA1c) and the Non HDL cholesterol levels in patients with Type 2 Diabetes mellitus.

METHOD: 50 diabetic patients admitted to Vinayaka Mission’s Medical College and Hospital, Karaikal were recruited in this study and their detailed history and laboratory investigations were obtained and statistical analysis was done.

RESULTS: Out of 50 patients, 52% (26) were males and 48% (24) were females with a mean age of 54.96 years. The mean±SD HbA1c value was 9.078±1.39 and the mean±SD for Non HDL Cholesterol was 165.18±71.55. There was found to be a statistically significant relationship (p<0.0001) between the HbA1c and Non HDL Cholesterol values of the patients.

CONCLUSION: As there is an extremely significant relationship between the HbA1c values and the Non HDL levels in a diabetic patient, HbA1c can be useful as a surrogate marker for the atherogenic dyslipidemia in diabetes.

Keywords: HbA1c, Non HDL Cholesterol

INTRODUCTION:
The prevalence of type 2 diabetes mellitus is rising much more rapidly than any other type, presumably because of increasing obesity, reduced activity levels as countries become more industrialized and aging of the population. It is estimated that close to one-fifth of all adults with diabetes in the world live in the South-East Asia region which gives a figure of 72.1 million people. Of this, 65.1 million live in India.¹ In 2013, it was estimated that $548 billion or 11% of health care expenditures worldwide were spent on individuals with diabetes.² The Crude prevalence rate of diabetes in urban areas of India is estimated to be 9 per cent of the total population. In rural areas, the prevalence is around 3 per cent of the total population.³ The Chennai Urban Population Study [CUPS] reported that among subjects who had a normal glucose tolerance at baseline, the incidence rate of diabetes was 20.2 per 1000 person years.⁴
The UK Prospective Diabetes Study (UKPDS) was a randomised, multicentre clinical trial of glycaemic therapies in newly diagnosed type 2 diabetics and it recruited 5,102 patients. It showed conclusively that in people with improved blood glucose control, the risk of laser treatment of the eye was reduced by a quarter and early kidney damage was reduced by a third. In addition, there was some evidence, though not very conclusive, that it reduced the risk of myocardial infarction and it reduced the risk of the need for an operation for a cataract. Reducing the glucose exposure (HbA1c 7.0 % versus 7.9 % over median 10.0 years), with therapy either by sulphonylurea or insulin, reduced the risk of “any diabetes-related endpoint” by 12%, microvascular disease by 25% and 16% trend to a reduced risk of myocardial infarction (P=0.052)\(^{5}\)

Hemoglobin A (HbA) constitutes 90% hemoglobin of adults and children above 6 months age. When HbA is passed through a chromatographic column it separates into HbA\(_1a\), the major component and minor components – HbA\(_1b\), HbA\(_1c\) and HbA\(_2\), collectively called HbA\(_c\).\(^{6,7}\) From structural and biosynthetic information available it is clear that HbA\(_1c\) is slowly formed and almost irreversibly by the decomposition of glucose and hemoglobin in the red blood cells. With simultaneous accumulation of HbA\(_1c\), it is evident that the amount of this component should be a reflection of average glucose concentration seen by the RBCs during their life span.\(^8\)\(^{-}\)\(^9\) of HbA\(_1c\) was reported to represent 35mg% of blood glucose levels.\(^{9}\)When properly assayed, the percent of Hb A1C provides a good retrospective, cumulative index of glycemic control for the preceding 3 month period. Adults who have diabetes have a two to four times higher risk of experiencing cardiovascular events than those adults who do not have diabetes, and their relative risk of dying from cardiovascular disease (CVD) is about twice as high.\(^{10,11,12}\)Although many factors account for increased CVD risk in diabetes, lipid abnormalities are major contributors to this risk. In the setting of diabetes, the suppression of lipoprotein lipase and very-low-density lipoprotein (VLDL) production by insulin is defective in insulin resistance, leading to increased free fatty acid (FFA) flux to the liver and increased VLDL production, which results in increased circulating triglyceride concentrations. The triglycerides are transferred to low-density lipoprotein (LDL) and high-density lipoprotein (HDL), and the VLDL particle gains cholesterol esters by the action of the cholesterol ester transfer protein (CETP). This leads to increased catabolism of HDL particles by the liver and loss of apolipoprotein (Apo) A, resulting in low HDL concentrations. The triglyceride-rich LDL particle is stripped of the triglycerides, resulting in the accumulation of atheogenic small, dense LDL particles.\(^2\) Non–HDL cholesterol is the difference between total and HDL cholesterol and, thus, represents cholesterol carried on all of the potentially proatherogenic apoB-containing particles [primarily VLDL, LDL, and HDL as well as chylomicron remnants and lipoprotein (a)]. A routine calculated LDL cholesterol level using the Friedewald equation requires a fasting triglyceride level <400 mg/dl for the accurate calculation of LDL cholesterol. Thus, in many cases of fasting hypertriglyceridemia which is common in diabetes, the clinician has no reliable estimate of LDL cholesterol, and therefore, unless ultracentrifugation is performed, has no objective index of lipid-associated CHD risk.\(^{13}\) Non–HDL cholesterol thus represents a readily obtainable, convenient and inexpensive measure of CHD risk that may be superior to LDL cholesterol in many respects.\(^{14}\) Non-HDL cholesterol has been shown to independently predict CVD in clinical trials.\(^{15,16}\) The Strong Heart Study showed that patients with diabetes in the highest tertile of non-HDL cholesterol had a higher hazard ratio for myocardial infarction (3.17) than they did with any other lipid parameter (1.96 for LDL cholesterol and 2.04 for triglycerides) compared with those in the lowest fertile. They also had the second highest hazard ratio for coronary heart disease (CHD) (2.75 vs. 1.90 for LDL, 2.12 for triglycerides, and 3.06 for the total/HDL cholesterol ratio).\(^{17}\) In a post hoc analysis of patients with diabetes from four prospective cohort studies—the Framingham Cohort Study, the Framingham Offspring Study, the Lipid Research Clinics Prevalence Follow-Up Study, and the usual-care group of the Multiple Risk Factor Intervention Trial—the relative risk of death for diabetic (compared with non diabetic) patients was 5.7 for those with low non-HDL cholesterol (< 130 mg/dl) and elevated LDL (≥ 100 mg/dl) and it was 7.2 for those with elevated non-HDL cholesterol (≥ 130 mg/dl) and low LDL (< 100 mg/dl).\(^{18}\) HbA1c levels and non-HDL cholesterol levels are compared in this study in an attempt to show that poor glycemic control leads to increase in risk factors of cardiovascular disease.

**Methodology**

**Source of data**

This study was carried out in the Vinayaka Mission’s Medical College and Hospital, Karaikal between October 2013 and September 2015 in the inpatient department.50 patients with type 2 diabetes mellitus according to the following inclusion and exclusion criteria were recruited for this study

**Method of collection of data**

A detailed Proforma was filled up for each patient, which included age, sex, IP number and history relevant to diabetes and its complications. A detailed clinical examination was done. Laboratory parameters including fasting and postprandial blood glucose, HbA1C, renal function tests, blood routine, ECG and routine urine examination were performed.

Fasting lipid profile which included serum total cholesterol, serum triglycerides, LDL cholesterol, HDL cholesterol and VLDL were estimated in all the cases. Venous blood samples were collected from patients after overnight fasting (more than 8- hours) for lipid profile, fasting blood glucose and glycosylated haemoglobin determination.

**Results**

This study recruited 50 cases admitted in the Medical ward of Vinayaka Mission’s Medical College and Hospital, Karaikal. The average age of the sample population was 54.96 years. It was found that more number of patients (40%) fell in the age bracket of 46 to 50 years than in other age groups. Out of the 50 cases studied, 26 (52%) were males and 24 (48%) were females. The Male : Female ratio was 1.08:1 The mean age of males in the study was 52.03 years and for females it was 58.12 years. The duration of

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Type 2 diabetes in the selected cases was variable. They ranged from freshly detected cases to patients with diabetes for more than 15 years. In this study, the highest number of cases (42%) had been diabetic for 1 to 5 years followed by 28% of cases who had been diabetic for 5 to 10 years.

The lipid profile in the subjects was obtained from a venous sample after an overnight fast. The desirable level as given by the ATP III guidelines was <200 mg/dL. It was found that a majority of patients (60%) came under this category of optimal control. It was found that none of the patients had triglyceride levels in the ‘very high’ bracket. There was an almost equal number, 30% and 32%, in the ‘normal’ and ‘borderline’ ranges respectively.

It was found that there were more patients in the group with a low HDL level, especially in the male subset of the population. It was seen that a higher percentage (38%) of participants had an LDL level in the optimal range. Compared to HbA1c levels, the p value is <0.0001 which is considered extremely significant. The correlation coefficient is 0.4766 The mean Non HDL cholesterol value was 165.18 and the standard deviation was 71.55. Standard error of mean was 10.119. The lower 95% confidence limit was 144.83.

The upper 95% confidence limit was 185.53. The median value was 148.50. For males, the mean ± SD was 149.38 ± 28.53 with a median value of 147.50. For females, the mean ± SD was 182.29 ± 97.12 with a median value of 154. The FBS values for males was 168.77±89.75 and for females it was 187.08±104.45. The PPBS values for males was 268.71±126.31 and for females it was 271.71±126.74. The Glycosylated hemoglobin (HbA1c) estimation in this study was done using the Hemoglobin A1C Kit (Kit no.179C00) and is expressed in %.

It was found that the majority of patients (48%) had an HbA1c value in the range of 8.1 to 9.0%. The mean HbA1c value is 9.078 and the standard deviation is 1.389 Comparison of HbA1c and Non-HDL Cholesterol values showed two-tailed p value as <0.0001, which is considered extremely significant. The Correlation coefficient (r) was 0.4877.

Discussion

The variation in the lipid profile of a patient with Type 2 Diabetes mellitus has been well established as already discussed earlier. It has also been proven that HbA1c levels play a major role in the diagnosis as well as act as an important marker of control in diabetic patients. This present study, in attempting to compare the two, recruited 50 patients with type 2 diabetes mellitus, fulfilling the inclusion and exclusion criteria.

In the present study, the study group constituted cases from age 35 to 80 years. The majority of cases and controls were in the age group of 46-50 years with a mean age ± SD of 54.96±9.30 with mean ages of males and females being 52.03 and 58.12 respectively.

In this study 20% of the cases had newly detected type 2 diabetes mellitus or had been diagnosed within the preceding one year. The duration of diabetes in 42% of cases was between 1 - 5 years, and only 2% of cases had diabetes for more than 15 years. It was also noticed by the investigator that most patients did not have a reliable medical document for the history of detection or medication history for drug intake and hence this was not given much weightage in this study. Irrespective of age, sex or duration of diabetes, it was found that 40% of the subjects had an increased total cholesterol level. 65% of males and 54% females were found to have desirable levels of total cholesterol. However, the results of lipid profile showed that female diabetic patients had significantly higher levels of cholesterol with 20% females with high cholesterol as compared to 3% of males. When looking at the individual components of the lipid profile it was found that there was a high degree of dyslipidemia which is consistent with previous studies.

Only 18% had triglyceride levels in the optimal range with 32% in the borderline and 20% in the high ranges. It has also been repeatedly seen that hypertriglyceridemia is widespread in diabetes. The HDL cholesterol levels in this study showed majority of the cases to have a low HDL of <40 mg/dL (54%) with only 2% in the range for high HDL cholesterol which has been statistically proven and accepted by the NCEP as a “negative” risk factor in diabetes. The LDL cholesterol levels, which have been implicated as a major risk factor were found to be 32%, 26% and 28% in the optimal, near optimal and borderline high ranges as given by the ATP guidelines. The LDL cholesterol levels and the HbA1c levels were found to be closely related with p <0.0001, which is considered extremely significant. The FBS and PPBS values in this study were divided according to the existing goals set by the American Diabetes Association guidelines and it was found that only 36% of the overall population had a controlled fasting blood sugar values while in the case of the 2 hour post prandial sugar levels, only 22% of the patients had controlled blood sugar values. The mean and standard error of mean (SEM), for the fasting blood sugar values in males was 168.76 and 17.60, while for females it was 187.08 and 21.32.

There was a high degree of statistically significant correlation between the fasting blood sugar values and the glycosylated haemoglobin values (p <0.0001) In the case of 2 hour post prandial blood sugar values, the values of the present study for males was a mean of 268.71 and a SEM of 24.77, and for the female subset of the study population, the mean was 271.70 with a SEM of 25.87. In this study, the mean non HDL cholesterol was found to be 165.18 with a standard deviation of 71.55. The standard error of mean was 10.119 and the upper and lower 95% confidence intervals were 185.53 and 144.83 respectively. Mean Non HDL cholesterol was 149.38 ± 28.53 for males and 182.29 ± 97.12 for females. For HbA1c, the standard values of the laboratory of the institution were used for the present study. The mean HbA1c was found to be 9.078 with a standard deviation of 1.389. There was a statistically extremely significant correlation between the HbA1c values and the fasting and 2 hour post prandial blood sugar values. The correlation between the Non HDL Cholesterol values and the Glycosylated haemoglobin values showed a statistically extremely significant P<0.0001.

The Pearson correlation coefficient (r) for the two was 0.4877 with a one tailed P of 0.0002 which is extremely significant. This shows a statistically significant relationship between the HbA1c levels and the Non HDL levels of diabetic patients.
Conclusion

Glycosylated hemoglobin level provides a simple, rapid, and objective method to assess diabetic control. Estimation of Non HDL Cholesterol level is a cost effective and accurate way to measure all the atherogenic lipoproteins. It was found that there is an extremely significant relationship between the HbA1c values and the Non HDL levels in a diabetic patient. This indicates that HbA1c can be useful as a surrogate marker for the atherogenic dyslipidemia in diabetes.

Bibliography