

Glycated haemoglobin as a dual biomarker Association between HbA_{1c} and dyslipidemia in type 2 diabetic patients

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Summary:

Background: Diabetic patients with accompanied dyslipidemia are soft targets for cardiovascular diseases. An early intervention to normalize circulating lipids has been shown to reduce cardiovascular complications and mortality. Glycated hemoglobin (HbA_{1c}) is a routinely used marker for long-term glycemic control.

Objective: to investigate the role of HbA_{1c} as a marker of circulating lipids in type 2 diabetic patients

Subjects and Methods: A total of 450 type 2 diabetic patients (214 males and 236 females), mean age was 55.5 ± 9.35 , who attended the National Diabetic Center, Al-Mustansiria university during the period from December 2010 to May 2011 were included in this study. Fasting venous blood samples were collected from all the subjects. HbA_{1c} was estimated by high performance liquid chromatography. The Serum was used for analyzing Fasting Blood Glucose (FBG), Total cholesterol (TC), HDL-cholesterol (HDL-C), Triglycerides (TG). Dyslipidemia was defined as per the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines. Diabetes was defined as per American diabetes association criteria. The statistical analysis was done by SPSS statistical package version 17.

Results: Statistically significant positive correlation was observed between HbA_{1c} and Total Cholesterol ($P=0.000$), LDL-C ($P=0.000$), LDL-C/HDL-C ratio ($P=0.001$), Non-HDL-C ($P=0.000$) and Risk ratio ($P=0.000$). The correlation of HbA_{1c} with triglycerides (TG) was positive and statistically significant ($P=0.033$). Patients with HbA_{1c} value > 7.0 had significantly higher value of TC, TG, LDL-C, LDL-C/HDL-C ratio, non-HDL-C and risk ratio (TC/HDL-C) as compared to the patients with $HbA_{1c} \leq 7.0\%$. However, there was no significant difference in value of HDL-C between the two groups.

Conclusion: HbA_{1c} 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.

Keywords: Diabetes mellitus, Dyslipidemia, Glycated hemoglobin, Lipid Profile panel, Biomarker

Introduction:

Diabetes is a global endemic with rapidly increasing prevalence in both developed and developing countries (1) there is a high risk of cardiovascular disease (CVD) in People with type 2 diabetes, Diabetic patients with accompanied dyslipidemia are soft targets for cardiovascular deaths which represent the top killer in this population [2]. Patients with type 2 diabetes often exhibit an atherogenic lipid profile, which greatly increases their CVD risk compared with people without diabetes, glycemia is the apparent feature of diabetes due to diagnostic dependency of patients on blood glucose measurements. However, most of the individuals may also carry unnoticed dyslipidemia, characterized by increased levels of triglycerides and LDL and decreased HDL. Individuals with coexisting diabetes and metabolic syndrome (dyslipidemia + hyperglycemia + hypertension) have

the highest prevalence of CVD. Early therapeutic interventions, aiming to reduce triglycerides and LDL and to increase HDL, significantly reduce mortality in type 2 diabetic patients (3, 4). A significant association between dyslipidemia and systolic blood pressure has been observed in type 2 diabetic patients, suggesting their increased susceptibility to vascular diseases associated with LDL. It is likely that the combination of hyperglycemia, diabetic dyslipidemia, insulin resistance and hypertension produces an enhanced atherogenic environment within the circulation (5). Infiltration of lipoproteins in arterial wall and dermal tissue has been implicated in atherosclerosis and xanthoma, respectively. Severe hyperlipidemia in diabetes may also lead to lipid infiltration into the retina, causing macular edema, retinal hard exudates, and blindness (6).

The Diabetes Complications and Control Trial (DCCT) established glycosylated hemoglobin (HbA_{1c}) as the gold standard of glycemic control, with levels $\leq 7\%$ deemed appropriate for reducing the risk of vascular complications (5) HbA_{1c} is

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directly related to the severity of coronary artery disease (CAD) in diabetic patients (7). Whereas, improving the glycemic control can substantially reduce the risk of cardiovascular events in diabetics (8). Moreover, attempts to reduce cardiovascular risks resulted in the improvement of HbA_{1c} even in the absence of any specific intervention targeted at improving glycemic control (9). A soluble form of receptor for advanced glycation end products (sRAGE) in type 2 diabetic patients with CAD was found to be elevated with significant association between sRAGE and HbA_{1c} as well as serum lipids (10).

Subjects and methods:

A total of 450 type 2 diabetic patients (214 males and 236 females), mean age was 55.5± 9.35 who attended the National Diabetic Center, Al-Mustansiria university during the period from December 2010 to May 2011 were included in this study. Fasting venous blood samples were collected from all the subjects. The serum was used for analyzing Fasting Blood Glucose (FBG), Total cholesterol (TC), HDL-cholesterol (HDL-C), Triglycerides (TG). HbA_{1c} was estimated by high performance liquid chromatography(supplied by Variant company, USA). Glucose level was determined using kits supplied by Randox, UK, total cholesterol, triglycerides, high density lipoprotein were determined using kits (Biomaghrab, Sa, France), LDL-cholesterol was calculated by Friedwald and Frederickson formula, Non-HDL-C, Risk ratio(TC/HDL-C), LDL-C/ HDL-C were calculated. For serum lipid reference level, National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guideline was referred. According to NCEP-ATPIII guideline, hypercholesterolemia is defined as TC>200 mg/dl, high LDL-C when value >100 mg/dl, hypertriglyceridemia as TG >150 mg/dl and low HDL-C when value <40 mg/dl. Non HDL-C<130mg/dl, risk ratio less than 4.5 Dyslipidemia was defined by presence of one or more abnormal serum lipid concentration. Diabetes was defined as per American Diabetes Association (ADA) criteria. Value of HbA_{1c} was given as percentage of total hemoglobin and values of all other parameters were given in mg/dl.

Statistical analysis: Statistical analysis was done by SPSS version 17.0. Pearson's correlation test was performed to examine correlations between various parameters. Independent samples t-test (2-tailed) was used to compare means of different parameters. All Values are expressed as mean ± standard error of mean. The results were considered statistically significant when P < 0.05.

Results:

Among total 450 type 2 diabetic individuals included in this study, 214 were male and 236 were female. The mean age ± SEM of male and female subjects were 55.22± 9.5 and 55.95 ± 9.2 years respectively. The mean value of HbA_{1c} and FBG

were slightly higher in females in comparison to male patients but the differences were not significant. Among the circulating lipids, TC and LDL-C were significantly higher (P<0.05) in females patients. Although the mean level of TG was slightly lower and of HDL-C slightly higher in females than males, these differences were statistically non-significant (Table 1).

Hypercholesterolemia was found in 129(28.7 %) individuals, hypertriglyceridemia was found in 160(35.5%) individuals, decreased HDL-C was found in 39(8.5%) individuals and increased LDL-C was found in 231(51.3%) individuals.

Among the diabetic individuals, 111(23.5 %) individuals had only one abnormal lipid profile parameter, 87(18.4%) had two abnormal lipid parameter and 41(8.7 %) individuals had three abnormal lipid profile parameter. According to NCEP-ATPIII guideline, 128(54.2%) females out of 236 and 158 (73.8 %) males out of 214 were dyslipidemic.

In table 2; diabetic patients were classified into 2 groups as per their glycemic index; first group consists of patients with HbA_{1c} value ≤7.0 % and second group consists of patients with HbA_{1c} value >7.0%. Patients with HbA_{1c} value >7.0% had significantly higher value of TC (P=0.004), TG (P=0.006), LDL-C (P=0.02), Non-HDL-C, LDL-C/HDL-C ratio and Risk ratio as compared to patients with HbA_{1c} value ≤ 7.0%.

Statistically significant positive correlation was observed between FBG and HbA_{1c} (P=0.000, r =0.58). HbA_{1c} also demonstrated direct and significant correlations with Total Cholesterol (P=0.000, r =0.228), LDL-C (P=0.000, r =0.219), LDL-C/HDL-C ratio (P=0.001, r = 0.211), Non-HDL-C (P=0.000, r = 0.228) and Risk ratio (P=0.000, r =0.223). The correlation of HbA_{1c} with TG was positive (P=0.033, r =0.033) and statistically significant (Figure 1.) HbA_{1c} showed statistically non significant negative correlation with HDL-C (p=0.8)

Table 1. Lipid Profile parameters result of Male and Female Type 2 Diabetic Patients

Parameters	Males (n=214)	Females (n=236)	P-value
	Mean ± SEM	Mean ± SEM	
Age(years)	55.22± 9.5	55.95 ± 9.2	0.9
HbA _{1c} (%)	8.61±0.15	8.97 ±0.13	0.08
FBG(mg/dL)	182.9 ± 5.2	191.07± 4.8	0.25
TC(mg/dL)	170.03 ± 2.9	183.68 ± 3	0.002*
TG(mg/dL)	151.5 ± 5.2	144.6 ±4.6	0.32
HDL-C(mg/dL)	44.46±0.22	44.85 ±0.22	0.50
LDL-C(mg/dL)	95.70 ±3.7	107.80 ±3.5	0.020*

*statistically significant

Table 2: Biochemical Parameters categorized by patients' glycemic control (HbA_{1c})

Parameters	Glycated (HbA _{1c})		P-value
	≤7.0 (n=79)	>7.0 (n=340)	
	Mean ± SEM	Mean ± SEM	
Total Cholesterol(mg/dL)	165.62±4.2	179.65±2.4	0.004*
Triglycerides(mg/dL)	132.0± 6	152.31 ±4	0.006*
HDL-C(mg/dL)	44.68±0.3	44.75±0.1	0.84
LDL-C(mg/dL)	91.43±5	104.47±2.9	0.02*
Risk ratio (TC/HDL-C)	3.69 ±0.11	4.03 ± 0.6	0.01*
Non HDL-C(mg/dL)	119 ±4.8	134 ± 2.6	0.009*
LDL-C/HDL-C	2.04 ± 0.11	2.31± 0.6	0.04*
FBG (mg/dL)	143.2±6	196.7±3.8	0.000*

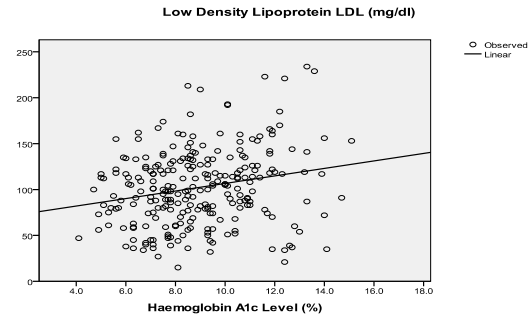


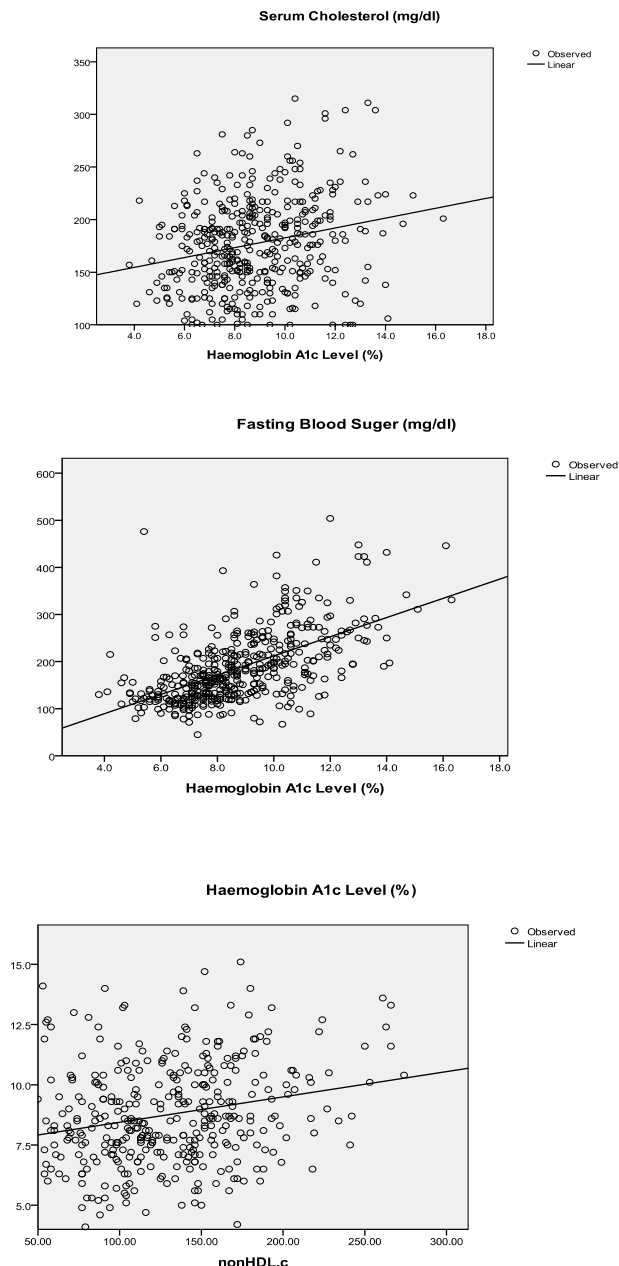
Figure 1: Correlations between HbA_{1c},FBG ,TC,LDL-C,NON HDL-C

Discussion:

The distribution of subjects according to gender and specific HbA_{1c} cutoffs showed that most of the type 2 diabetic patients experience poor glycemic control irrespective of their gender (Table 1). A significant correlation between HbA_{1c} and FBG (Fig. 1) is in agreement with earlier reports [11, 12]. We also observed significant correlations between HbA_{1c} and cholesterol, triglycerides, HDL and LDL in diabetic patients (Fig. 1). Several investigators have reported significant correlations between HbA_{1c} and lipid profiles and suggested the importance of glycemic control in normalizing dyslipidemia [13–14]. Although the levels of HbA_{1c} and FBS did not differ significantly between the two genders, female patients showed higher levels of both (Table 1). Diabetes confers a markedly increased risk of cardiovascular events in both males and females [15]. However, women with diabetes are more susceptible to increased cardiovascular mortality [16]. Diabetic women may be subject to more adverse changes in coagulation, vascular function and cardiovascular risk factors than diabetic men [17]. The results of lipid profile showed that female diabetic patients had significantly higher levels of cholesterol and LDL, which is in agreement with earlier reports [18, 19]. Hyperlipidemia in females may be attributed to the effects of sex hormones on body fat distribution, leading to differences in altered lipoproteins [20].

This study reveals high prevalence of hypercholesterolemia, hypertriglyceridemia, high LDL-C and low HDL-C levels which are well known risk factors for cardiovascular diseases; Insulin affects the liver apolipoprotein production. It regulates the enzymatic activity of lipoprotein lipase (LpL) and Cholesterol ester transport protein. All these factors are likely causes of dyslipidemia in Diabetes mellitus [21]. Moreover, insulin deficiency reduces the activity of hepatic lipase and several steps in the production of biologically active LpL may be altered in DM [22].

The study also showed a statistically significant correlation between HbA_{1c} and non-HDL-C, Non-HDL-C was shown to be the stronger predictor of CVD in diabetic [23], National Cholesterol Education Program Adult Treatment Panel III has



recommended using Non-HDL cholesterol in assessing CVD risk in patients with diabetes, the measurement of Non-HDL-C is simple and can be conducted even in non-fasting state of patients and can be determined regardless of TG concentration. Hence, Non-HDL cholesterol can be of great value in determining dyslipidemia in diabetic subjects. Risk ratio also showed strong correlation with HbA_{1c} in our study, similar to the finding of other study [24], some studies revealed that the predictive power of the TC/HDL ratio was found to be higher than that of Non-HDL cholesterol and that TC/HDL-C can be used as a treatment guides for diabetic dyslipidemia. Total number of apo-B containing particles and small LDL-C Particles are increased in diabetes and these metabolic abnormalities are better reflected by TC/HDL-C ratio and Non-HDL-C than LDL-C alone (25, 26)

In the present study, diabetic patients were divided into 2 groups as per the HbA_{1c} cutoff of 7.0%. The diabetic patients with HbA_{1c} value > 7.0% exhibited a significant increase in TC, LDL-C, TG, LDL-C/HDL-C ratio, Non-HDL-C and Risk ratio without any significant alteration in HDL-C in comparison to patients with HbA_{1c} value ≤7.0%. Khan HA et al (27) showed the impact of glycaemic control on various lipid parameters in which Severity of dyslipidemia increases in patients with higher HbA_{1c} value. As elevated HbA_{1c} and dyslipidemia are independent risk factors of CVD, diabetic patients with elevated HbA_{1c} and dyslipidemia can be considered as a very high risk group for CVD. Improving glycaemic control can substantially reduce the risk of cardiovascular events in diabetics (28). It has been estimated that reducing the HbA_{1c} level by 0.2% could lower the mortality by 10% (29)

Conclusion:

Significant correlation between HbA_{1c} and various circulating lipid parameters and significant difference of lipid parameters in two groups (≤7.0% and >7.0%) of glycated hemoglobin indicates that HbA_{1c} 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.

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