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 (HbA1c) is a routinely used marker for long-term glycemic control**.**

Objective: to investigate the role of HbA1c 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. .HbA1c 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 HbA1C 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 HbA1c with triglycerides (TG) was positive and statistically significant (P=0.033). Patients with HbA1c 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 HbA1c ≤ 7.0%. However, there was no significant difference in value of HDL-C between the two groups.

Conclusion: 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.

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

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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 (HbA1c) as the gold standard of glycemic control, with levels ≤ 7% deemed appropriate for reducing the risk of vascular complications (5) HbA1c 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 HbA1c 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 HbA1c 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).HbA1c 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 HbA1c 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 HbA1c 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 HbA1c value ≤7.0 % and second group consists of patients with HbA1c value >7.0%. Patients with HbA1c 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 HbA1c value ≤ 7.0%.

Statistically significant positive correlation was observed between FBG and HbA1c (P=0.000,r =0.58). HbA1c 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 HbA1c with TG was positive (P=0.033, r =0.033) and statistically significant (Figure 1).) HbA1c showed statistically non significant negative correlation with HDL-C (p=0.8)

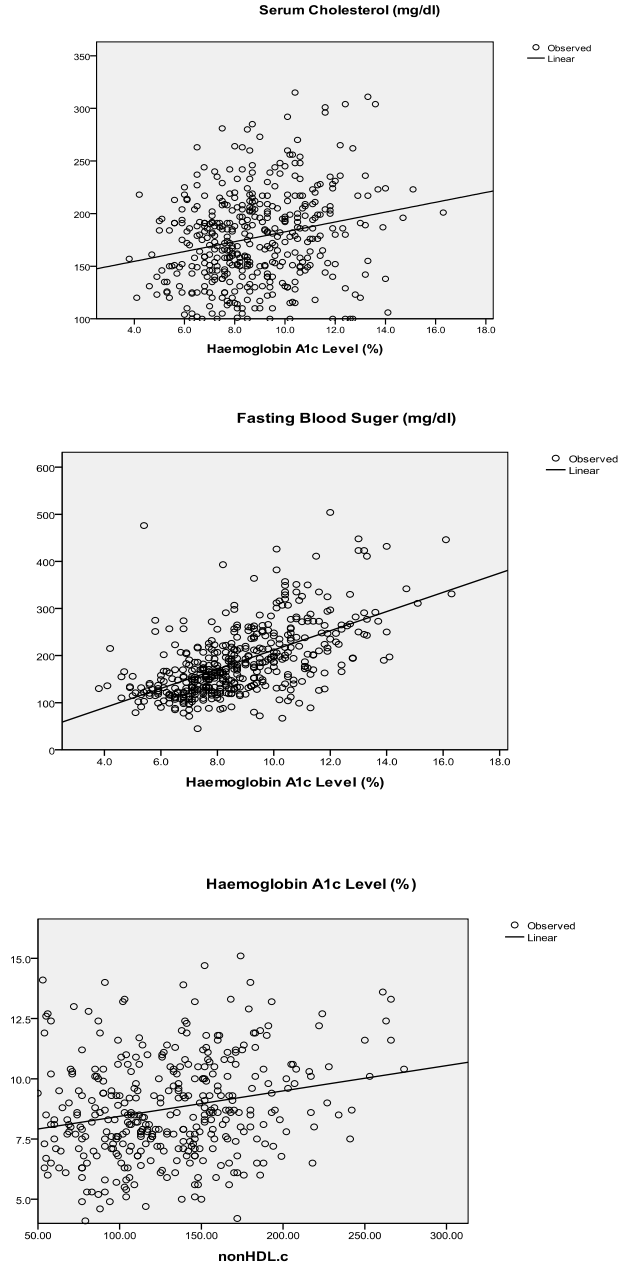
Table 1. Lipid Profile parameters result of Male and Female Type 2 Diabetic Patients

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
HbA1c (%)	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 (HbA1c)

Parameters	Glycated Hemoglobin (HbA1c)		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*



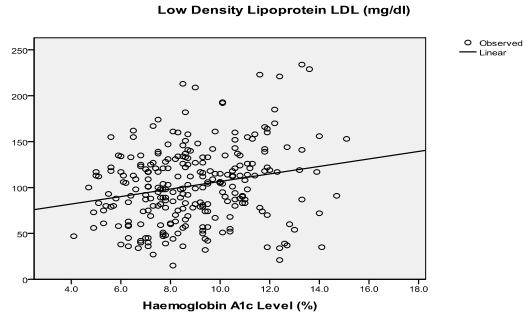


Figure 1: Correlations between HbA1c,FBG ,TC,LDL-C,NON HDL-C

Discussion:

The distribution of subjects according to gender and specific HbA1c cutoffs showed that most of the type 2 diabetic patients experience poor glycemic control irrespective of their gender (Table 1). A significant correlation between HbA1c and FBG (Fig. 1) is in agreement with earlier reports [11, 12]. We also observed significant correlations between HbA1c and cholesterol, triglycerides, HDL and LDL in diabetic patients (Fig. 1). Several investigators have reported significant correlations between HbA1c and lipid profiles and suggested the importance of glycemic control in normalizing dyslipidemia [13–14]. Although the levels of HbA1c 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 HbA1c 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 HbA1c 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 HbA1c cutoff of 7.0%. The diabetic patients with HbA1c 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 HbA1c 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 HbA1c value. As elevated HbA1c and dyslipidemia are independent risk factors of CVD, diabetic patients with elevated HbA1c 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 HbA1c level by 0.2% could lower the mortality by 10% (29)

Conclusion:

Significant correlation between HbA1c and various circulating lipid parameters and significant difference of lipid parameters in two groups (≤7.0% and >7.0%) of glycated hemoglobin 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**.**

References:

1. Berry C, Tardif JC, Bourassa MG . Coronary heart disease in patients with diabetes: part I: recent advances in prevention and noninvasive management. J Am Coll Cardiol 2007, 49:631–642

2. Sultan A, Thuan JF, Avignon A Primary prevention of cardiovascular events and type 2 diabetes: should we prioritize our interventions? Diabetes Metab (2006) 32:559–567

3.Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229-234.

4.Windler E. What is the consequence of an abnormal lipid profile in patients with type 2 diabetes or the metabolic syndrome? Atheroscler Suppl 2005;6: 11-14.

5.Gotto Cardiologist's role in improving glucose control and global cardiovascular risk in patients with type 2 diabetes mellitus. Am J Cardiol (2007) 99:3–5

6. Haseeb A. Khan. Clinical significance of HbA1c as a marker of circulating lipidsin male and female type 2 diabetic patients. Springer-Verlag 2007

7.. Ravipati G, Aronow WS, Ahn C, Sujata K, Saulle LN, Weiss MB Association of hemoglobin A1c level with the severity of coronary artery disease in patients with diabetes mellitus. Am J Cardiol (2006) 97:968–969

8. Kawasumi M, Tanaka Y, Uchino H, Shimizu T, Tamura Y,et al.Strict glycemic control ameliorates the increase of carotid IMT in patients with type 2 diabetes. Endocr J (2006) 53:45–50

9. Woodward A, Wallymahmed M, Wilding J, Gill G Improved glycemic control: an unintended benefit of a nurse-led cardiovascular risk reduction clinic. Diabet Med (2005)22:1272–1274

10. Nakamura K, Yamagishi SI, Adachi H, Kurita-Nakamura Y, Matsui T, Yoshida T, Sato A, Imaizumi T Elevation of soluble form of receptor for advanced glycation end products (sRAGE) in diabetic subjects with coronary artery disease. Diabetes Metab Rev (2007) 23(5):368–371.

11. Rosediani M, Azidah AK, Mafauzy M Correlation between fasting plasma glucose, post prandial glucose and glycated haemoglobin and fructosamine. Med J Malaysia(2006) 61:67–71

12. Ito C, Maeda R, Ishida S, Sasaki H, Harada H Correlation among fasting plasma glucose, two-hour plasma glucose levels in OGTT and HbA1c. Diabetes Res Clin Pract 2000;50:225–230

13. Faulkner MS, Chao WH, Kamth SK, Quinn L, Fritschi C, Maggiore JA, Williams RH, Reynolds RD Total homocysteine,diet and lipid profiles in type 1 and type 2 diabetic and nondiabetic adolescents. J Cardiovasc Nurs2006 ; 21:47–55

14. Chan WB, Tong PC, Chow CC, So WY, Ng MC, Ma RC, Osaki R, Cockram CS, Chan JC Triglyceride predicts cardiovascular mortality and its relationship with glycemia and obesity in Chinese type 2 diabetic patients. Diabetes Metab Res Rev 2005 ;21:183–188

15. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339:229–234.

16. Gu K, Cowie CC, Harris MI) Diabetes and decline in heart disease mortality in US adults. JAMA 1999; 281:1291–1297

17. Steinberg HO, Paradisi G, Cronin J, Crowde K, Hempfling A,Hook G, Baron AD Type II diabetes abrogates sex differences in endothelial function in

pre-menopausal women. Circulation2000; 101:2040–2046

18. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. Diabetes Care 2005; 28:514–520.

19. Esteghamati A, Abbasi M, Nakhjavani M, Yousefizadeh A, Basa AP, Afshar H Prevalence of diabetes and other cardiovascular risk factors in an Iranian population with acute coronary syndrome. Cardiovasc Diabetol2006; 5:15

20.Sibley SD, Thomas W, de Boer I, Brunzell JD, Steffes MW Gender and elevated albumin excretion in the Diabetes Control and Complications trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort: role of central obesity. Am J Kidney Dis2006; 47:223–232.

21. Goldberg IJ. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. J Lipid Res 1996; 37: 693-707.

22..Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC, et al. Glycated hemoglobin and cardiovascular risk fac-tors in Chinese subjects with normal glucose tolerance. Diabet Med 1998;15: 573-578.

23..Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes Care 2003; 26: 16-23.

24. .Gimeno-Orna JA, Faure-Nogueras E and Sancho-Serrano MA. Usefulness of total cholesterol/HDL-cholesterol ratio in the management of diabetic dyslipi-daemia. Diabet Med 2005; 22: 26-31

25 Lemieux I, Lamarche B, Couillard C, Pascot A, Cantin B, Bergeron J, et al. Total cholesterol /HDL cholesterol ratio vs LDL cholesterol /HDL cholesterol ratio as in-dices of ischemic heart disease risk in men. The Que-bec Cardiovascular Study. Arch Intern Med 2001; 161: 2685-2692.

26.Peters AL. Clinical relevance of non-HDL cholesterol in patients with diabetes. Clinial Diabetes 2008; 26:3-7

27..Khan HA, Sobki SH, Khan SA. Association between glycaemic control and serum lipids profile in type 2 diabetic patients: HbA1c predicts dyslipidaemia. Clin Exp Med 2007; 7: 24-29.

28. Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care 2006; 29: 877-882.

29.Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Pro-spective Investigation of Cancer and Nutrition (EPIC-Norfolk). Br Med J 2001; 322: 15-18.