

The Association of Glycated Hemoglobin With Lipid Profile Indices in Type 2 Diabetic Patients

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Abstract- The high risk of lipid abnormalities in type 2 diabetic (T2D) patients with uncontrolled hyperglycemia may be associated with an increased risk of cardiovascular complications. The aim of the current study was to investigate the association between glycated hemoglobin (HbA1c) and lipid profile levels in T2D patients. This cross-sectional study was conducted on 802 T2D patients, aged ≥ 40 years, visiting the Abu Reyhan Clinic of Shahid Mohammadi Hospital in Bandar Abbas, Iran. Serum lipid profiles were measured by the enzymatic method. Diabetes was defined based on the criteria of the American Diabetes Association. The association of HbA1c and estimated glomerular filtration rate (eGFR) with lipid profile indices was assessed using the Spearman correlation coefficient test and linear regression model. The mean \pm SD age of participants (27.7% of men) was 53.55 ± 5.56 years. The mean \pm SD of HbA1c and eGFR for all subjects were 8.97 ± 2.14 and 86.30 ± 17.48 , respectively. In this study, a positive association was observed between HbA1c and fasting blood glucose ($r=0.619$, $\beta=0.635$), total cholesterol ($r=0.165$, $\beta=0.188$), triglycerides ($r=0.103$, $\beta=0.095$), and low-density lipoprotein cholesterol ($r=0.162$, $\beta=0.173$), ($P<0.01$). Also, an inverse association has been observed between eGFR level and TGs ($r=-0.08$, $\beta=-0.096$) and FBS ($r=-0.123$, $\beta=-0.172$), ($P<0.05$). Our findings suggested that HbA1c is not only an applicable predictor of long-term glycaemic control but also can be considered as a potential biomarker for predicting lipid abnormalities in T2D patients.

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Introduction

Type 2 diabetes (T2D) is an important health problem that leads to a greater risk of comorbidities and mortality worldwide (1). As a growing public health problem, the overall prevalence of diabetes in the adult population was 8.8% (415 million people), and also estimated that about 642 million people would have T2D by 2020 (1,2). Previous reports suggested that 75% of these diabetic patients live in low and middle-income countries such as Iran (1,2). In 2015, International Diabetes Federation (IDF) had reported that health systems of countries spent the US \$673 billion (12% of global health expenditure) for the management of T2D and its related complications (3). This high global health expenditure of diabetes is mostly attributed to both macrovascular complications (including coronary artery

disease, myocardial infarction, hypertension, peripheral vascular disease) and microvascular complications (including retinopathy, nephropathy, and neuropathy) (4-6).

This disease is a multi-cluster of metabolic dysfunction secondary to decreased insulin secretion or insulin resistance. Research in endocrinology sciences indicates that poor glycemic control predisposing to the above-mentioned micro- and macro-vascular complications. The risk of cardiovascular diseases (CVD) is very high in T2D patients (7,8), so that studies revealed that T2D patients tend to have more than a two-fold increased risk of CVD and its mortality compared with those without diabetes (9,10). Research showed that increased risk of CVD in diabetes is mainly determined by dyslipidemia and hypertension (7,8). Indeed, patients with poorly managed T2D tend to have

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elevated triglycerides (TGs), low-density lipoprotein-cholesterol (LDL-C), and decreased high-density lipoprotein (HDL-C) levels compared with the general population (11).

It is suggested that HbA1c not only is used for the diagnosis of diabetes, the determination of long-term glucose control, and prediction of the risk of developing diabetic complications but also it is an independent risk factor of dyslipidemia and CVD in T2D patients (12,13). Some studies have assessed the association of long term glycemic control status or HbA1c level with lipid profiles concentration among T2D patients (7,14-17). Studies conducted on T2D patients in different countries, including Afghanistan (14), Saudi Arabia (15), Bosnia and Herzegovina (7), and Nepal (17), showed that a high value of HbA1c is positively related to higher levels of cholesterol, TGs, and LDL-C. However, investigation on Nepal diabetic population suggested that patients with HbA1c >7.0% did not have different HDL-C compared to the patients with HbA1c ≤7.0% (17). Furthermore, Klisic *et al.*, study revealed that inappropriate levels of lipid profile might predict high HbA1c value (16).

Also, some investigations reported that nephropathy and kidney dysfunction, characterized by a lower glomerular filtration rate (GFR) level, may be associated with the risk of dyslipidemia in T2D patients. Cross-sectional studies on Chinese CKD patients reported that lower level of eGFR is related to higher TGs and increased risk of dyslipidemia (4,18).

In this study, we aimed to investigate the association of HbA1c and eGFR levels with lipid profiles levels among Iranian T2D patients.

Materials and Methods

Study population

The current study has a cross-sectional design which was conducted on 802 patients with diabetes visiting the Abu Reyhan Clinic of Shahid Mohammadi Hospital in Bandar Abbas, Iran, from May 2016 to May 2018. According to the inclusion and exclusion criteria, the patients were selected, and their medical records were assessed. Also, the clinical parameters of individuals and study variables were measured and recorded. Patients for whom a definitive diagnosis of type-2 diabetes had been made by an endocrinologist or an internist based on the ADA criteria, belonging to the 40-60-year-old age group and from whose onset of diabetes five years or more had passed were included in this study. Participants with a history of other known renal diseases

(except for those related to diabetes) with acute renal failure and GFR <30 or ≥180 were excluded. Subjects were also excluded if they had the following exclusion criteria; due to the possible confounding effect of some variables in the interpretation of HbA1c (19), the patients with a history of transfusion or hemolytic anemia in the past three months, those who had developed anemia after acute blood loss in the past three months, those with a history of hypertriglyceridemia >1750 mg/dl, those with a history of taking ribavirin and interferon-alpha in the past three months, those with a history of severe hyperbilirubinemia >20 mg/dl, those with GFR <30, pregnant women and those with Hb <7 were also excluded from the study.

The protocol of this study was approved by the institutional ethics committee of the Shahid Mohammadi Clinical Research Center, Hormozgan University of Medical Sciences, Bandar-Abbas, Iran. Written informed consent was obtained from all participants included in the study.

Measurements and definitions

A digital scale with an accuracy of up to 100 was used to measure and record the weight of participants in light clothing without shoes or socks. We also measure height in standing position without shoes, using a stadiometer, to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height (m²). We took a blood sample in a sitting position after 12-14 h of overnight fasting based on a standard protocol. The blood samples were centrifuged within 30-45 min of collection. The analyses of blood samples were performed at the Abu Reyhan Clinic of Shahid Mohammadi Hospital laboratory on the day of blood collection. We analyzed the samples using the Selectra 2 auto-analyzer (Vital Scientific, Spankeren, and the Netherlands). The enzymatic colorimetric method with glucose oxidase was used to measure fasting blood sugar (FBS). Both inter- and intra-assay coefficients of variations were 2.2% for FBS. These analyses were performed using commercial kits (Pars Azmoon, Tehran, Iran). Serum TGs were determined by an enzymatic colorimetric method with glycerol phosphate oxidase. Inter- and intra-assay coefficients of variations (CV) for TGs were 0.6% and 1.6%, respectively. Total cholesterol was assessed with cholesterol esterase and cholesterol oxidase using the enzymatic colorimetric method. We measured HDL-C with phosphotungstic acid after precipitation of Apolipoprotein β. Inter- and intra-assay CVs for both TC and HDL-C were 0.5% and 2%, respectively. We also calculated the LDL-C from

the serum and TC, TG, and HDL-C concentrations and expressed it in mg/dl using the Friedewald formula.

We measure the serum creatinine by standard colorimetric Jaffe_Kinetic reaction method. Both intra- and inter-assay coefficients of variation were <3.1%. The mean creatinine was measured at least twice over six months, and if a ±10% difference did not exist, eGFR was calculated based on the mean creatinine level using the MDRD method (Modification of Diet in Renal Disease) (20).

MDRD: $eGFR = 175 \text{ (or } 186) \times \text{Serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if Female}) \times (1.212 \text{ if Black})$

We also defined diabetes based on the criteria of the American Diabetes Association (ADA) as FPG ≥ 126 mg/dl or 2-h post 75-gram glucose load ≥ 200 mg/dl or current therapy for a definite diagnosis of diabetes (21).

Statistical analysis

The Statistical Package for Social Sciences program (SPSS) (version 23.0; SPSS Inc., Chicago, IL, USA) was used to analyze data. $P < 0.05$ were considered as statistically significant. We checked the normality of variables by the Kolmogorov–Smirnov test and histogram chart. The characteristics of participants were reported as mean ± SD for quantitative variables. We

used independent two samples T-test for comparison of continuous variables among participants. Also, the correlation coefficient of HbA1c and eGFR with lipid profile levels was assessed using Spearman’s correlation coefficient test. The estimated β for lipid profile levels according to HbA1c status and eGFR level was estimated by the linear regression model. Linear regression models were adjusted for potential confounding variables, including age, sex, and BMI.

Results

A total of 802 T2D patients (27.7% men) were included in the current study. The mean ± SD age of the total population, men, and women were 53.55 ± 5.56, 53.38 ± 5.78, and 53.61 ± 5.48 years, respectively. The mean ± SD of HbA1c and eGFR for all subjects were 8.97 ± 2.14 and 86.30 ± 17.48, respectively.

The characteristics of the study population are shown based on gender classification in Table 1. Compared with male subjects, female patients had a higher level of HDL-C, BMI, and lower Hb and creatinine. However, no significant differences in TGs, LDL-C, FBS, TC concentration, eGFR, and HbA1c were observed between male and female subjects.

Table 1. Baseline characteristics of the study population based on gender categories

Variable	Total population	Male	Female	P
Age (year)	53.55 ± 5.56	53.38 ± 5.78	53.61 ± 5.48	0.820
Body mass index (kg/m ²)	25.82 ± 4.72	24.44 ± 3.82	26.35 ± 4.92	< 0.001
Hemoglobin (g/dl)	12.59 ± 1.63	13.68 ± 1.58	12.17 ± 1.44	< 0.001
HbA1c	8.97 ± 2.14	9.16 ± 2.24	8.89 ± 2.10	0.113
Fasting blood glucose (mg/dl)	196.80 ± 82.14	193.77 ± 84.41	197.96 ± 81.30	0.380
Triglyceride (mg/dl)	159.87 ± 93.09	159.38 ± 99.69	160.05 ± 90.54	0.560
Cholesterol (mg/dl)	171.98 ± 43.98	170.22 ± 43.23	172.64 ± 44.28	0.550
Low density lipoprotein- cholesterol (mg/dl)	95.30 ± 36.13	96.98 ± 35.46	94.77 ± 36.39	0.420
High density lipoprotein- cholesterol (mg/dl)	42.79 ± 11.69	40.21 ± 11.66	43.78 ± 11.56	< 0.001
Creatinine (mg/dl)	0.84 ± 0.22	0.99 ± 0.23	0.79 ± 0.19	< 0.001
Glomerular Filtration Rate	86.30 ± 17.48	86.16 ± 17.69	86.35 ± 17.42	0.891

Data are presented as mean ± standard deviation

Also, in Table 2, the characteristics of the study population were examined and compared based on HbA1c level classification. In comparison to subjects with HbA1c ≤ 8 mg/dl, participants with HbA1c > 8 mg/dl had significantly higher levels of TC, LDL-C, TG, and FBS, and lower levels of creatinine and eGFR ($P < 0.05$). However, there is no significant difference in age, HDL-C, BMI, and Hb among diabetic patients based on HbA1c classification.

In the current study, the association of HbA1c with FBS (Figure 1) and lipid profile levels (Figures 2A-D) among T2D patients was assessed using Spearman’s correlation coefficient test and linear regression model (Table 3). A positive association was observed between HbA1c and FBS ($r = 0.619$, $\beta = 0.635$), TC ($r = 0.165$, $\beta = 0.188$), TGs ($r = 0.103$, $\beta = 0.095$), and LDL-C ($r = 0.162$, $\beta = 0.173$), ($P < 0.01$). However, there was no significant association between HDL-C and HbA1c

($r=0.002$, $\beta=0.042$), ($P=0.300$). We also have assessed the association of eGFR with the levels of mentioned biochemical characteristics in participants; an inverse association has been observed between eGFR level and

TGs ($r=-0.08$, $\beta=-0.096$) and FBS ($r=-0.123$, $\beta=-0.172$), ($P<0.05$). However, there was no significant association between eGFR and other lipid profiles levels.

Table 2. Baseline characteristics of the study population based on HbA1c level classification

Variable	HbA1c ≤ 8	HbA1c >8	P
Age (year)	53.75 \pm 5.49	53.43 \pm 5.60	0.435
Body mass index (kg/m ²)	25.68 \pm 4.62	25.90 \pm 4.78	0.344
Hemoglobin (g/dl)	12.48 \pm 1.65	12.66 \pm 1.61	0.120
Fasting blood glucose (mg/dl)	145.88 \pm 48.92	227.56 \pm 82.88	< 0.001
Triglyceride (mg/dl)	153.92 \pm 92.87	163.46 \pm 93.13	0.046
Cholesterol (mg/dl)	165.57 \pm 42.33	175.86 \pm 44.55	0.002
Low density lipoprotein- cholesterol (mg/dl)	90.32 \pm 33.80	98.32 \pm 37.18	0.005
High density lipoprotein- cholesterol (mg/dl)	42.36 \pm 11.10	43.06 \pm 12.03	0.526
Creatinine (mg/dl)	0.8681 \pm 0.24	0.8471 \pm 0.22	< 0.001
Glomerular Filtration Rate	88.45 \pm 15.96	84.99 \pm 18.23	0.005

Data are presented as mean \pm standard deviation

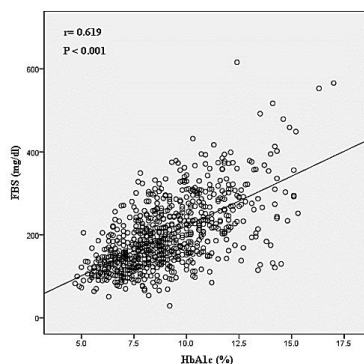


Figure 1. The correlation coefficient of fasting blood sugar according to HbA1c status was estimated by Spearman's correlation coefficient test

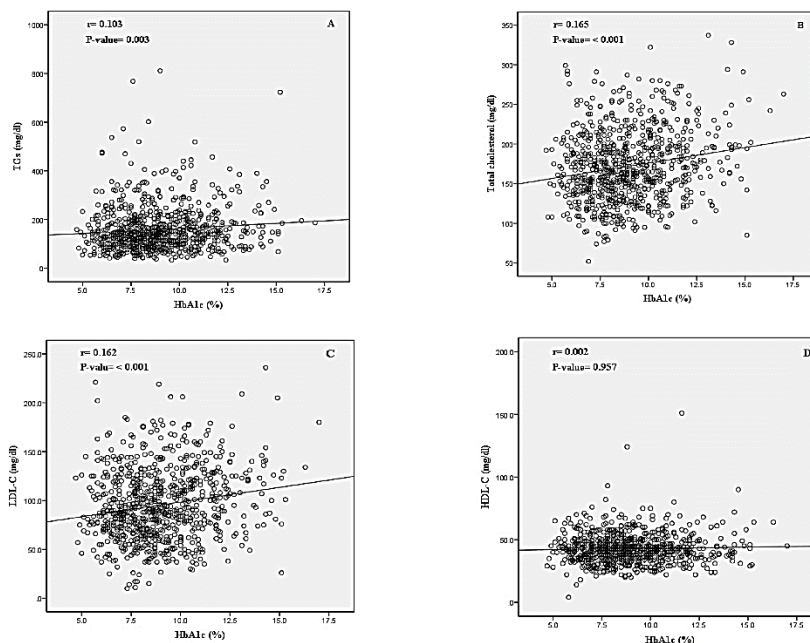


Figure 2. The correlation coefficient of lipid profile levels, including triglycerides (Figure 2A), total cholesterol (Figure 2B), low-density lipoprotein-cholesterol (Figure 2C), and high-density lipoprotein-cholesterol (Figure 2D) according to HbA1c status was estimated by Spearman's correlation coefficient test

Table 3. Finding of the Spearman correlation coefficient and linear regression models assessing the association of HbA1c levels and eGFR with lipid profiles concentration and fasting blood glucose

Variables	HbA1c				eGFR			
	R	P*	β Coefficient	P†	r	P*	β Coefficient	P†
Age	-0.040	0.250	-0.038	0.277	-0.254	< 0.001	-0.254	< 0.001
Fasting blood glucose	0.619	< 0.001	0.635	< 0.001	-0.123	< 0.001	-0.172	< 0.001
Triglyceride (mg/dl)	0.103	0.004	0.095	0.008	-0.080	0.030	-0.096	0.005
Cholesterol (mg/dl)	0.165	< 0.001	0.188	< 0.001	-0.017	0.633	-0.041	0.231
Low density lipoprotein-cholesterol	0.162	< 0.001	0.173	< 0.001	0.013	0.711	-0.010	0.781
High density lipoprotein-cholesterol	0.002	0.957	0.042	0.300	0.022	0.529	0.025	0.467

* P was determined using the Spearman correlation coefficient test

** P was determined using a linear regression model

The linear model was adjusted for age, body mass index, and sex

Discussion

In the current study, the association of HbA1c and eGFR with lipid profile parameters levels has been assessed in T2D patients. Although there was no significant correlation between HDL-C levels and HbA1c, the levels of TC, FBS, TGs, and LDL-C were significantly higher in participants with a high level of HbA1c in comparison to those with low HbA1c. Also, a negative association was observed between eGFR status and levels of FBS and TG.

The results of the present study are in agreement with the findings of previous studies conducted in other populations (7,14-17). Hussein *et al.*, study report that an HbA1c value greater than 7.0% is positively related to higher levels of TC, LDL-C, and LDL-C/HDL-C ratio (14). Also, a study conducted on the Saudi Arabia population indicated that HbA1c had direct correlations with levels of TC, TG, and LDL-C and an inverse correlation with HDL-C; also, a linear relationship was existence between HbA1c and risk of dyslipidemia (15). Investigation of Nepal diabetic population suggested that HbA1c have a positive correlation with TC, LDL-C, and non-HDL-C; however, patients with HbA1c value >7.0% did not have a different value of HDL-C, in comparison to the patients with HbA1c ≤ 7.0% (17). Klisic *et al.*, study revealed that inappropriate levels of lipid profiles could predict high HbA1c levels in T2D patients (16). Furthermore, findings of a study on Bosnia and Herzegovina individuals reported that there is a significant positive association between HbA1c and TGs and TGs/HDL-C ratio in T2D patients and early diagnosis of dyslipidemia, as well as appropriate management, can be applied as a preventive measure for suitable long-term glycemic control (7).

Overall, findings of studies reported that patients with elevated HbA1c and poorly-controlled T2 diabetes characteristically tend to have increased TGs, LDL-C, and reduced HDL-C levels compared with the general population. Previous reports suggested supporting reasons and pathways which can explain the detrimental effects of high HbA1c and hyperglycemia on levels of lipid profiles and increased risk of dyslipidemia or CVD incidence (7,4). Insulin resistance and uncontrolled blood glucose in diabetic patients are led to increased free fatty acids (FFAs) release present in insulin-resistant fat cells. Increased FFAs promote the production of TGs, which subsequently increase the secretion of apolipoprotein B (ApoB) and very LDL (VLDL-C) cholesterol. High serum levels of ApoB and VLDL have both can play an important role in increased the risk of CVD (18,22,23). Also, it has been suggested that hyperinsulinemia and insulin resistance are associated with low HDL-C levels in diabetic patients (24). Hyperinsulinemia and hyperglycemia can also have a negative effect on lipoproteins, especially LDL and VLDL, via increased glycosylation and oxidation, reducing vascular compliance, and facilitating the progression of atherosclerosis (25). Therefore, high levels of FFAs and TGs through increased stimulation of ApoB and VLDL-C, reducing HDL-C, and modification of lipoproteins likely contribute to the increased risk of CVD in T2D patients.

This study, with an assessment of the association of eGFR level with lipid profile concentration in T2D patients, showed that a lower level of eGFR is related to higher TGs. Our results are in agreement with the findings of previous studies that were conducted on Chinese CKD patients (7,18). The Hou *et al.*, study reported that TGs and LDL-C levels were significantly

increased, but HDL-C levels were significantly decreased in middle-aged and elderly Chinese subjects with lower eGFR level (18). Also, one other study in Chinese on patients with reduced kidney function, characterized by lower GFR, is more likely to have higher serum TGs and greater risk of dyslipidemia (7). Although the association between reduced eGFR levels with dyslipidemia is still far from fully understood, potential mechanisms linking reduced eGFR and kidney dysfunction with dyslipidemia have been previously reported. One mechanism may be a change in the metabolism of lipoproteins, which indicated in studies conducted on CKD patients with dyslipidemia (22,23). In patients with kidney dysfunction, there is reduced catabolism and elimination of triglyceride-rich apo B-containing lipoproteins because of the impaired lipolysis. Also, the decline of apo A-containing lipoproteins is occurred by decreasing of lipoprotein-A-I (4). Change in the metabolism of other triglyceride-rich lipoproteins (TRL), changes in the route of reverse cholesterol transport, structural alteration in lipoproteins, increased lipoprotein (a), post ribosomal modifications in lipoproteins, insulin resistance, and proteinuria are other potential mechanisms underlying dyslipidemia in patients with kidney dysfunction (24,25).

The high risk of lipid abnormalities or dyslipidemia in T2D patients (especially with reduced eGFR) in comparison to healthy subjects can explain why patients with diabetes have a significantly greater risk of CVDs than those without diabetes (7,11). Therefore, management of dyslipidemia in T2D patients is an essential practice; The ADA recommends that serum lipid profiles should be checked at least annually in individuals with diabetes (11), also based on the recommendation of some organizations, including the ADA and the American Heart Association (AHA), modifications of lifestyle are essential in decreasing the risk of dyslipidemia in all T2D patients (especially with renal dysfunction) (26). These changes include modifying the dietary pattern, medication use (mostly statins), weight loss, increased physical activity, and smoking cessation, and each can be helpful in some patients to achieve better lipid levels. Also, management of other risk factors, including obesity, hypertension, and hyperglycemia, plays a key role in CVD risk reduction among T2D patients (11,26). The current study has some limitations; this study has cross-sectional nature, which limited us from establishing a causal relation of HbA1c and eGFR level with FBS and lipid profiles. Also, despite controlling for the confounding effect of various variables in our analysis, residual

confounding due to unknown or unmeasured confounders cannot be excluded.

In conclusion, we found that the HbA1c level was closely associated with increased levels of lipid profiles, including TGs, TC, and LDL-C in T2D patients. Also, an inverse relation has been observed between eGFR and TGs and FBS concentration. Results of the current study provided evidence that HbA1c is not only an applicable predictor of long-term glycemic control but also can be considered as a potential biomarker for predicting dyslipidemia in T2D patients. Therefore, HbA1c can be used as a proper predictor to identify diabetic patients who are at a higher risk of CVD incident.

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