Glycated Hemoglobin as a Predictor of Dyslipidemia and Cardiovascular Risk in Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a globally prevalent metabolic disorder that significantly increases the risk of cardiovascular disease (CVD) through mechanisms such as dyslipidemia, characterized by elevated triglycerides, low high-density lipoprotein (HDL) levels, and small dense low-density lipoprotein (LDL) particles. Glycated hemoglobin (HbA1c) is a key biomarker of glucose control and has been associated with CVD risk. Methods: This cross-sectional study aimed to evaluate the relationship between glycated hemoglobin (HbA1c) levels and lipid profiles, specifically lipid ratios, in a Jordanian population with type 2 diabetes mellitus (T2DM). A total of 140 patients with T2DM and 20 healthy controls participated. Blood samples were analyzed for fasting blood sugar (FBS), HbA1c, total cholesterol, triglycerides, high-density lipoprotein (HDL-C), and low-density lipoprotein (LDL-C) levels. HbA1c levels were grouped: A (≤7%), B (7–9%), C (9–11%), and D (>11%). Results: The T2DM group showed significantly elevated HbA1c levels compared to controls. Patients with higher HbA1c levels (Groups C and D) exhibited abnormal lipid profiles, including increased total cholesterol and triglycerides and reduced HDL-C. The LDL-C/HDL-C ratio was notably higher in patients with HbA1c >9%, indicating a potential elevated cardiovascular risk. This correlation between HbA1c and lipid profile abnormalities supports the association between poor glycemic control and lipid metabolism dysregulation. Conclusion: HbA1c levels are significantly associated with dyslipidemia, and lipid ratios serve as sensitive indicators for cardiovascular risk in T2DM patients. These findings underscore the clinical importance of monitoring HbA1c and lipid ratios to improve risk assessment and guide intervention strategies in high-risk populations.

Keywords: Type 2 Diabetes Mellitus (T2DM), Glycated Hemoglobin (HbA1c), Lipid Profiles, Cardiovascular Risk, Dyslipidemia.

Significance | This study showed the critical role of HbA1c levels and lipid ratios in evaluating cardiovascular risk among patients with Type 2 diabetes.

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Introduction

Diabetes mellitus (DM) is a globally prevalent metabolic disorder that poses substantial health challenges across both developed and developing nations (Berry et al., 2007). It is characterized by chronically elevated blood glucose levels that disrupt the metabolism of carbohydrates, lipids, and proteins, leading to complex pathophysiological consequences (Choudhury & Rajeswari, 2021). Diabetes is primarily categorized into type 1 and type 2. Type 1 diabetes results from autoimmune destruction of insulin-producing cells in the pancreas, whereas type 2 diabetes is associated with insulin resistance and an imbalance between blood glucose levels and insulin production (Olokoba et al., 2012; Padhi et al., 2020). Among these, type 2 diabetes mellitus (T2DM) is the

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most common, constituting approximately 90–95% of diabetes cases globally (Williams et al., 2020).

T2DM is closely linked with an elevated risk of cardiovascular disease (CVD), as diabetic dyslipidemia—a lipid disorder characterized by elevated triglycerides, low high-density lipoprotein (HDL) levels, and small, dense low-density lipoprotein (LDL) particles—aggravates the progression of atherosclerosis, which is a significant cause of CVD (Bener et al., 2007; Karalis & Disease, 2008). This relationship is particularly concerning as CVD remains a primary cause of mortality among individuals with diabetes (Sultan et al., 2006). The complications associated with DM extend beyond CVD, contributing to other systemic issues such as nephropathy, retinopathy, and neuropathy, which impact multiple organs and exacerbate morbidity and healthcare costs (Nickerson & Dutta, 2012).

In managing and monitoring T2DM, HbA1c (glycated hemoglobin) serves as a valuable biomarker, providing an integrated measure of blood glucose levels over a period of 2–3 months (Khan et al., 2007; Rohlfing et al., 2002). Elevated HbA1c levels are associated with an increased risk of CVD, as they indicate prolonged periods of hyperglycemia, a key factor in developing atherosclerotic lesions (Selvin et al., 2005). Research has shown that elevated HbA1c not only correlates with fasting blood glucose levels but also serves as an independent predictor of coronary heart disease (CHD), even in non-diabetic populations (Hameed et al., 2012).

The relationship between HbA1c and lipid profiles, specifically the LDL-C/HDL-C ratio, is of particular interest as it provides insights into the metabolic imbalances associated with dyslipidemia in T2DM. Dyslipidemia is a common metabolic abnormality in individuals with T2DM and is associated with both insulin resistance and poor glycemic control (VinodMahato et al., 2011; Garimella et al., 2016). Studies have demonstrated that abnormal lipid ratios, such as an elevated LDL-C/HDL-C ratio, may serve as early indicators of dysregulated lipid metabolism, potentially preceding overt CVD symptoms (Ridker et al., 2005; Shai et al., 2004). Understanding these associations is crucial for effective risk stratification and early intervention in patients with T2DM, particularly in high-risk regions such as Jordan, where lifestyle and genetic factors contribute to increased diabetes prevalence.

This study aims to investigate the relationship between glucose intolerance, as measured by HbA1c, and various lipid indices, with a specific focus on lipid ratios as potential early markers of cardiovascular risk in Jordanian individuals with T2DM. The findings from this study may contribute to improving the understanding of how metabolic factors intersect in T2DM, aiding in the development of more targeted interventions for cardiovascular risk management.

Materials and Methods

Study Population

This cross-sectional study included a total of 140 patients diagnosed with Type 2 Diabetes Mellitus (T2DM) and 20 healthy control individuals. Of the patient cohort, 102 were male, and 38 were female, with a mean age of 51.5 years, while the control group, consisting of 14 males and six females, had a mean age of 48.7 years. Blood samples were collected from both groups at Akadya Medical Center in Jordan, covering the period from October 22, 2021, to June 27, 2022. The study protocol was approved by the Ethical Committee, and written consent was obtained from all participants. Information on age, gender, and family history of chronic diseases was documented for each participant (Sultan et al., 2006; Padhi et al., 2020).

This study was conducted in accordance with ethical standards and received approval from the Ethical Committee associated with Akadya Medical Center, Jordan. All participants, including those in the Type 2 Diabetes Mellitus (T2DM) group and the healthy control group, provided written informed consent prior to their participation. The informed consent process involved explaining the study's purpose, procedures, potential risks, and benefits to ensure participants understood their involvement.

Participant confidentiality was strictly maintained; identifying information was anonymized in the dataset to uphold privacy standards. All data collected were securely stored and accessed solely by authorized research personnel, adhering to data protection guidelines. Special consideration was given to ensuring that the selection criteria did not unfairly exclude individuals or inadvertently introduce biases that could impact study outcomes.

Exclusion Criteria

Participants were excluded from the study if they had a history of second-line antidiabetic medications or lipid-lowering treatments, including statins, fibrates, bile acid sequestrants, nicotinic acid, or ezetimibe. Additionally, patients with a documented diagnosis of familial hypercholesterolemia, renal insufficiency, or thyroid disorders were excluded to control for confounding factors in lipid profile measurements (Karalis & Disease, 2008; Choudhury & Rajeswari, 2021).

Blood Collection and Processing

Blood samples were collected between 8:00 and 10:00 a.m. after a fasting period of at least 12 hours to minimize variability in lipid levels. Samples were allowed to clot for 15 minutes at room temperature before centrifugation at 4000g for 10 minutes. Subsequently, 2.5 ml of blood was transferred into EDTA tubes with gentle mixing to prevent clotting, ensuring a sufficient volume for HbA1c analysis (Berry et al., 2007; Nickerson & Dutta, 2012). Patients were categorized based on

HbA1c levels into four groups: Group A (HbA1c ≤ 7%, n=47), Group B (HbA1c 7%-9%, n=43), Group C (HbA1c 9%-11%, n=29) and Group D (HbA1c >11%, n=21).

Laboratory Analysis

Biochemical parameters, including fasting blood sugar (FBS), HbA1c, total cholesterol, triglycerides, and HDL-cholesterol (Table2), were measured using diagnostic kits from Roche Diagnostics on the Cobas 501 auto-analyzer (Roche et al.). LDL-cholesterol and very low-density lipoprotein (VLDL) concentrations were calculated using the Friedewald equation:

LDL-C = (Total Cholesterol) − (HDL-C) − (TGs/5)

This method is validated for plasma triglyceride levels up to 400 mg/dL (Friedewald et al., 1972).

Reference Range

The lipid profile parameters in this study were analyzed with reference to established ranges. Total cholesterol levels in participants spanned from 150 to 200 mg/dl, while triglyceride levels varied between 50 and 200 mg/dl. Hdl-cholesterol levels ranged from 10 to 60 mg/dl, and LDL-cholesterol levels fell between 60 and 160 mg/dl. Additionally, the total cholesterol to HDL ratio was recorded at 4 mg/dl. VLDL levels were projected to range from 10 to 30 mg/dl. Fasting blood sugar (FBS) levels were expected to be between 70 and 110 mg/dl, with HbA1c values anticipated to reach up to 6.0%.

Statistical Analysis

Data were presented as the mean with corresponding standard deviation (SD). Statistical analyses were conducted using SPSS software version 20.0 for Windows alongside Microsoft Excel 2007. A significance level of 0.05 was applied, indicating that results with p-values below this threshold were considered statistically significant.

Results

The study included a total of 140 patients with recently diagnosed type 2 diabetes mellitus (T2DM) and a control group of 20 healthy individuals. The patients had a mean age of 51.5 years, while the control group averaged 48.7 years. Analysis showed no statistically significant differences in age, BMI, or gender distribution between the patient and control groups (Table 1).

Upon evaluating fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) levels, a significant increase was observed in the T2DM group compared to the controls (Table 3). Specifically, HbA1c levels were markedly elevated across all patient groups: Group A (HbA1c ≤ 7%), Group B (HbA1c 7-9%), Group C (HbA1c 9-11%), and Group D (HbA1c >11%). The relationship between HbA1c and dyslipidemia severity was evident, with higher HbA1c values linked to progressively abnormal lipid profiles, a pattern consistent with findings by Gao et al. (2008) and Hameed et al. (2012), which identified elevated HbA1c as an independent risk factor for coronary heart disease (CHD).

Lipid Profile Analysis

The mean values of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were significantly different between patients and controls. Elevated levels of total cholesterol and triglycerides were present in the T2DM group, particularly among individuals in Groups C and D with higher HbA1c levels. This aligns with previous findings by Garimella et al. (2016) and Schofield et al. (2016), which highlight dyslipidemia as a critical risk factor for cardiovascular disease in T2DM patients.

Conversely, HDL-C levels were significantly lower in the T2DM group, particularly among patients in Groups C and D. The low HDL-C levels contribute to an elevated LDL-C/HDL-C ratio, a sensitive indicator of lipid metabolism disorders. This ratio was notably higher in patients with HbA1c levels above 9%, indicating an increased risk of cardiovascular disease. These findings mirror those of Ridker et al. (2005) and Shai et al. (2004), who underscored the importance of lipid ratios in assessing cardiovascular risk more precisely than individual lipid values alone (Table 4).

Lipid Ratios and Cardiovascular Risk

The LDL-C/HDL-C ratio emerged as a sensitive indicator of lipid profile disturbances, with ratios rising alongside HbA1c levels. Elevated ratios in Groups C and D (with HbA1c above 9%) correlated with increased cardiovascular risk, as reported by Giansanti et al. (1999) and Sultan et al. (2006), who emphasized the heightened mortality risk among diabetic patients with cardiovascular complications.

This study also found that increased HbA1c levels in T2DM patients were positively correlated with elevated total cholesterol/HDL-C and triglyceride/HDL-C ratios. These elevated ratios, supported by studies from Khan et al. (2007) and Selvin et al. (2005), suggest that HbA1c levels could serve as a valuable biomarker in predicting dyslipidemia and cardiovascular risk in T2DM patients. Elevated lipid ratios in diabetic individuals further reinforce the utility of these metrics in identifying high-risk individuals and guiding therapeutic interventions.

Discussion

The present study sheds light on the relationship between type 2 diabetes mellitus (T2DM) and lipid abnormalities, with a specific focus on how elevated levels of HbA1c correlate with dyslipidemia in Jordanian patients. This research is especially relevant given the rising prevalence of diabetes worldwide and its association with cardiovascular disease (CVD) risk factors, particularly dyslipidemia, which significantly exacerbates the morbidity and mortality of diabetic patients (Berry et al., 2007; Choudhury & Rajeswari, 2021). As diabetes is a systemic metabolic disorder

Table 1. Demographic characteristics of the patient and control groups.

Parameters	Patient group	Control group	*p*-value
Age (year ± STD)	58.9 ± 9.7	58.7 ± 7.9	0.435
BMI ((kg/m2) ± STD)	28.7 ± 6.7	27.8 ± 8.5	0.674
Gender(male/Female)	(102/38)	(14/6)	0.356

Table 2. Biochemical parameters among patient and control groups.

Parameters	patient group	Control group	*p*-value
HbA1c %	7.8 ± 0.7 %	5.4 ± 0.6 %	0.034*
TC (mg/dl)	214 ± 18	202 ±12	0.547
TG (mg/dl)	206 ± 12	204 ± 5	0.439
LDL-C (mg/dl)	147 ± 18	146 ± 12	0.765
HDL-C (mg/dl)	37 ± 8	35 ± 6	0.436
FBG (mg/dl).	164.3 ± 13.8	88.9 ± 3.5	0.027*

Table 3. Association between blood lipid indexes and HbA1c levels across groups with varying HbA1c categories

Parameters	Group A	Group B	Group C	Group D	*p*-value
HbA1c %	≤7.0	7.0- 9.0	9.0-11.0	≥11.0	0.354
TC (mg/dl)	198 ± 8	218. ± 16	225 ± 15	235 ± 15	0.0175*
TG (mg/dl)	204 ± 12	206 ± 5	217 ± 5	217 ± 5	0.0374*
LDL-C (mg/dl)	147 ± 18	154 ± 16	169 ± 13	188 ± 13	0.0235*
HDL-C (mg/dl)	45 ± 8	43 ± 6	41 ± 4	37 ± 5	0.0276*

Table 4. Correlations between blood lipid ratios and HbA1c levels across HbA1c categories.

Parameters	Group A	Group B	Group C	Group D	*p*-value
HbA1c %	≤7.0	7.0- 9.0	9.0-11.0	≥11.0	0.354
TC /HDL -C	198 ± 8	218. ± 16	225 ± 15	235 ± 15	0.0175*
TG /HDL-C	204 ± 12	206 ± 5	217 ± 5	217 ± 5	0.0374*
LDL-C /HDL-C	147 ± 18	154 ± 16	169 ± 13	188 ± 13	0.0235*

characterized by chronic hyperglycemia, it is crucial to understand the underlying mechanisms linking it to lipid dysregulation and CVD risk (Williams et al., 2020).

The results from this study align with existing literature indicating that dyslipidemia is a common feature in T2DM, with variations in lipid profiles associated with glycemic control, as demonstrated by HbA1c levels. Elevated HbA1c is not only a reflection of poor glycemic control but also an independent risk factor for cardiovascular complications, as previously established by Sultan et al. (2006) and Schofield et al. (2016). Consistent with the current findings, previous studies have demonstrated that diabetic patients with elevated HbA1c levels frequently exhibit altered lipid profiles characterized by increased triglycerides, elevated low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C) (VinodMahato et al., 2011; Karalis, 2008). This study corroborates the notion that lipid ratios, such as the LDL-C/HDL-C ratio, may serve as sensitive indicators of dyslipidemia and potential predictors of CVD risk in diabetic patients.

In this study, the LDL-C/HDL-C ratio emerged as particularly sensitive in detecting lipid abnormalities, reflecting the findings of Ridker et al. (2005) and Shai et al. (2004) that lipid ratios provide a more precise assessment of coronary heart disease (CHD) risk than individual lipid measurements. This finding is significant because it supports the use of lipid ratios as early indicators of lipid dysregulation in T2DM patients, allowing for more targeted interventions aimed at mitigating cardiovascular risks.

Moreover, this study highlights the critical role of HbA1c as a long-term indicator of blood glucose control and a predictor of lipid profile abnormalities. Higher HbA1c levels were associated with worsened lipid ratios, especially LDL-C/HDL-C, which is consistent with findings from Gao et al. (2008) and Khan et al. (2007). Maintaining HbA1c levels below 7% is widely recommended to reduce the risk of vascular complications (Rohlfing et al., 2002). This recommendation is particularly relevant as this study demonstrated that HbA1c levels correlated directly with dyslipidemia severity, reinforcing the need for stringent glycemic control in diabetic management protocols.

A notable strength of this study is the use of rigorous methodologies, including fasting blood samples and the use of standardized assays for lipid and HbA1c measurements. These approaches ensured reliable data collection and strengthened the validity of the findings. Additionally, the use of a well-defined control group allowed for a clear comparison, further highlighting the lipid abnormalities associated with diabetes. However, some limitations should be acknowledged, such as the relatively small sample size, which may limit the generalizability of the results. Moreover, the study's cross-sectional nature restricts its ability to establish causality between HbA1c and lipid ratios. Longitudinal studies could provide further insights into how sustained glycemic control impacts lipid profiles and subsequent cardiovascular outcomes over time.

Conclusion

This study focused on the intricate relationship between glycemic control, as indicated by HbA1c levels, and lipid abnormalities in Jordanian patients with Type 2 diabetes mellitus (T2DM). Elevated HbA1c correlates with dyslipidemia and an increased cardiovascular disease (CVD) risk, highlighting HbA1c's role as both a glycemic marker and an independent risk factor for CVD. Lipid ratios, particularly the LDL-C/HDL-C ratio, emerged as sensitive indicators of lipid metabolism disturbances and potential predictors of CVD risk in T2DM. These findings advocate for comprehensive monitoring of both glycemic and lipid metrics to better assess and manage cardiovascular risks in diabetic patients. Future research should explore diverse populations to enhance the generalizability of these findings and inform targeted intervention strategies for reducing diabetes-related cardiovascular complications.

Author contributions

S.A.F. conceptualized the project, developed the methodology, conducted formal analysis, drafted the original writing, contributed to the methodology, conducted investigations, provided resources, visualized the data, and contributed to the reviewing and editing of the writing.

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Competing financial interests

The authors have no conflict of interest.

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