INTRODUCTION: Metabolic disorders of lipoprotein metabolism commonly accompany diabetes. Several studies with a limited number of patients have shown that glycemic control is related to dyslipidemia. Still, the validity of these results in a larger population and diabetic Turkish patients is not well-established. Therefore, this study aimed to reveal glycemic control’s effect on lipid parameters and the relationship between Hba1c and lipid parameters in Turkish patients with non-insulin-dependent diabetes.

METHODS: Turkish patients with non-insulin-dependent diabetes mellitus aged ≥18 years were included in this cross-sectional study. The patients were divided into two groups as good (Hba1c<7) and poor glycemic control (Hba1c≥7). The lipid parameters were compared between the two groups.

RESULTS: A total of 629 patients were included in the study. Of these patients, 47.2% were male, and the mean age was 54.5±8.6. The triglyceride (TG) levels were significantly higher, and the HDL levels were significantly lower in the poor glycemic control group (p<0.001, r<0.001). Other parameters were similar (all p>0.05). There was a significant but weak positive correlation between TG and Hba1c (r=0.13) and negative correlation between HDL and Hba1c (p<0.001, r=0.11). Of the lipid parameters, only TG was an independent predictor of glycemic control (p<0.001). In ROC analyses, the AUC was found 0.60±0.02 (p<0.001) for TG and 0.58±0.02 (p<0.001) for HDL at 95% CI.

DISCUSSION and CONCLUSION: Triglyceride and HDL are correlated with poor glycemic control, and triglyceride can be a biomarker for glycemic control in Turkish patients with non-insulin-dependent diabetes.
INTRODUCTION

Approximately 80% of diabetic patients have hypertension (HT) and high cholesterol levels. Therefore, the total cardiovascular risk is much higher than for other patients. (1,2). Diabetes mellitus (DM) is commonly accompanied by metabolic disorders of lipoprotein production and clearance. The mechanism of diabetic dyslipidemia has not been fully understood, but the most crucial factor is insulin resistance. (3). Dyslipidemia is characterized by increased serum triglycerides (TG), remnant lipoprotein, low-density lipoprotein levels, and decreased high-density lipoprotein (HDL) levels in diabetic patients (4,5). The primary mechanism of the increase in TG is the inhibition of lipoprotein lipase and hepatic lipase due to insulin resistance. Insulin resistance also increases the release of non-esterified fatty acids (NEFA). High circulating NEFA levels increase hepatic triglyceride production. Increased hepatic triglyceride synthesis increases apolipoprotein B (apo B) synthesis and very-low-density lipoprotein (VLDL) levels (6,7). Recent studies have shown that a high TG/HDL-cholesterol ratio is significantly correlated with insulin resistance in type 2 DM and is a predictor for cardiovascular disease (8,9). DM affects both lipid transfer to HDL and the activity of transport proteins. HDL metabolism may also be affected, resulting in low HDL levels, which is the second most common form of dyslipidemia in these patients (10). However, there is no significant change in LDL cholesterol levels in diabetic dyslipidemia, but the content changes because it is the degradation product of increased VLDL. Non-HDL consists of atherogenic cholesterol residues, including VLDL, LDL, and intermediate-density lipoprotein (IDL). Recently, an increasing number of studies have demonstrated the role of non-HDL cholesterol in cardiovascular events. (11-13). Glycosylated hemoglobin (HbA1c) is the primary indicator of blood glucose control (reflecting the average of the last three months) and is still the gold standard. Moreover, HbA1c is accepted as a risk factor for coronary artery disease in diabetic patients. (14)

Good glycemic control means that HbA1c and blood glucose values are within the normal range. (15). Several studies have shown that poor glycemic control is related to dyslipidemia. (16) However, these studies have been conducted with limited patients, and the effect of glycemic control on the lipid parameters is not consistent. Besides, the validity of these results in diabetic Turkish patients is not well-established. Therefore, this study aimed to reveal glycemic control’s effect on lipid parameters and relationship between Hba1c and lipid parameters in Turkish patients with non-insulin-dependent diabetes. We also sought to demonstrate the value of lipid parameters for predicting glycemic control.

METHODS

This single-center cross-sectional study included a total of 629 patients, aged ≥18 years, who were admitted to the internal medicine outpatient clinic with a diagnosis of non-insulin-dependent DM between March-2018 and May 2019. Patients with known coronary artery disease, hypothyroidism, renal failure, liver failure, statin, fibrate, or insulin therapy before the study were not included. Ethical approval for the study was granted by the hospital Ethics Committee (No:2020-25-). All the study procedures were applied in compliance with the Declaration of Helsinki (2013). The demographic data and medical history of the patients were recorded from the hospital database. Venous blood samples were taken after 12 hours of fasting. HbA1c levels were measured using the high-performance liquid chromatography method (Adams HA 8180 Akray, Japan), and triglyceride, total cholesterol, LDL, and HDL levels were measured using the chemiluminescence method on a DXI 800 analyzer (Bechman Coulter, USA). The non-HDL level was calculated using the
formula of "total cholesterol – HDL." Good glycemic control is defined as HbA1c <7. The patients were separated into two groups, as good glycemic control (HbA1c <7) and poor glycemic control (HbA1c ≥7), and the lipid parameters, blood pressure values, and smoking status were compared between the two groups.

**Statistical Analysis**

Data obtained in the study were analyzed statistically using SPSS 26.0 software (IBM Corporation, Armonk, NY, USA). The conformity of univariate data to normal distribution was evaluated with the Shapiro-Wilk Francia test. According to the quantitative data, the Mann-Whitney U test was used together with Monte Carlo results to compare the low and high HbA1c groups. Kendall’s tau-b test was used to examine the correlations between the HbA1c variable and the quantitative variables. Pearson Chi-Square Exact results were used to compare the low and high HbA1c groups according to categorical variables. The odds ratio (OR) was used with 95% confidence intervals (CI) to show a higher risk factor. Sensitivity and specificity percentages were calculated using the ROC (Receiver Operating Curve) analysis for the relationship between the real classification and the classification according to the cut-off value calculated for the low and high HbA1c groups. Linear Regression analysis was used to reveal the causality between dependent variables and independent variables as a mathematical model. Quantitative variables were expressed as median values and categorical variables as number (n) and percentage (%). Variables were analyzed at a 95% confidence interval, and a value of p <0.05 was considered statistically significant.

**RESULTS**

The 629 patients comprised 52.8% females and 47.2% males with a mean age of 54.5±8.6 years. The mean total cholesterol, LDL, TG, HDL, non-HDL levels were 214.3±52.6 mg/dl, 132±43.2 mg/dl, 185.8 ±118 mg/dl, 145.7 ±11.7 mg/dl and 168.4±50.4 mg/dl, respectively. The mean Hba1c level was 7.7±2.1 mg/dl. Poor glycemic control (HbA1c ≥7) was determined in 322 patients, and good glycemic control (HbA1c<7) was determined in 307.

Blood pressure was found to be significantly higher in the poor glycemic control group (p<0.001). Glycemic control was found to be better in the non-smokers’ group (p<0.001).

The total cholesterol, non-HDL, and LDL levels were similar in the two groups (p=0.98, p=0.47, p=0.8, respectively). The TG levels were significantly higher, and the HDL levels were significantly lower in the poor glycemic control group (p<0.001, p<0.001). The baseline characteristics of the patients are listed in Table.1. A significant but weakly positive correlation was determined between SBP and DBP and Hba1c (r=0.15 and r=0.19, respectively). A significant weak positive correlation was found between TG and Hba1c (r=0.13) and a significant weak negative correlation between HDL and Hba1c (r=-0.11) (Table.2). There was no correlation between Hba1c and total cholesterol, LDL and non-HDL (p=0.92, p=0.52, p= 0.29, respectively).

In ROC analyses, the AUC was found to be 0.60±0.02 (p<0.001) for TG and 0.58±0.02 (p<0.001) for HDL at 95% CI. A cut-off value of 180 mg/dl was determined for TG to predict Hba1c with 46.9% sensitivity and 71% specificity. The cut-off value of 36 mg/dl for HDL had 28.9% sensitivity and 85% specificity (Table 3, Figure 1, Figure 2). Linear regression analyses were performed to determine predictors of glycemic control. Of the lipid parameters, only TG was found to be a predictor of glycemic control (p=0.001). Other independent predictors of Hba1c were found to be diastolic blood pressure and smoking (p<0.001, p<0.001).
DISCUSSION

This study demonstrated that triglyceride levels increased and positively correlated with Hba1c and that HDL levels decreased and negatively correlated with Hba1c in Turkish patients with non-insulin-dependent DM. Of the lipid parameters, only TG was an independent predictor of glycemic control.

Diabetic dyslipidemia is characterized by high triglycerides and low HDL (4). The current study results are consistent with some previous findings. Hyperglycemia alone cannot fully explain lipid changes, but insulin resistance is the main trigger for diabetic dyslipidemia (17). The main effect of insulin resistance is to increase the levels of triglycerides and the main carrier, very-low-density lipoprotein (VLDL) (18). Laverdy et al. found that non-HDL and triglyceride levels were significantly higher in patients with poor glycemic control, while LDL and HDL levels were similar (19). In two other similar studies, diabetic patients were divided into two groups according to glycemic control, and triglyceride, total cholesterol, and LDL levels were found to be significantly higher in the poor glycemic control group. In the first study, a significant correlation was found between Hba1c and TG and total cholesterol, and in the second one, TG, total cholesterol, LDL, and VLDL (20,21). As seen, the main findings of these studies are inconsistent. Furthermore, the number of patients is much lower, and the regression and ROC analyses were not applied in contrast to our study. Larger patient population and using statistical methods to reveal the predictive value of lipid parameters may increase our study's power compared to previous studies. In a study conducted by Karim et al., the most common form of dyslipidemia in diabetic patients was reported to be low HDL. As a result of logistic regression analyses, it was shown that poor glycemic control (Hba1c>7) was a significant predictor of dyslipidemia, similar to the current study (22).

Hypertriglyceridemia stimulates the enzymatic activity of cholesteryl ester transfer protein (CETP), facilitating triglyceride-rich lipoproteins' transformation to HDL and LDL. Therefore, the triglyceride content of HDL and LDL increases. HDL particles enriched with triglyceride have a shorter half-life. Therefore, HDL levels are lower in diabetic patients. triglyceride-rich LDL particles undergo hydrolysis through lipoprotein lipase and hepatic lipase, and the size of LDL particles decreases. (17). In a recent study, the predictive value of lipid parameters for glycemic control was evaluated in a smaller diabetic population. Unlike our study, only LDL was found to be an independent predictor of poor glycemic control (23). In another study, total cholesterol, LDL, Triglyceride, and HDL were found to be independent predictors of Hba1c in regression analyses (24). Both those studies included insulin-dependent diabetic patients, so higher Hba1c levels and a closer relationship with dyslipidemia were expected. This difference may explain the controversial findings of our study. While

Figure 1. ROC analyse for triglyceride

Figure 2. ROC analyse for HDL
triglyceride and HDL specificity was high enough to predict Hba1c, triglyceride, and HDL sensitivity were low in our study. Because the correlation between Hba1c and triglyceride and HDL levels was not strong enough.

Stern et al. examined whether glycemic control is sufficient to achieve target lipid levels in diabetic dyslipidemia and found that lipid targets could not be reached despite strict glycemic control (25). Lifestyle modification and strict glycemic control can significantly improve lipid parameters, but statin and fibrate therapy is still the most beneficial method in reducing cardiovascular risk in these patients. In addition, the relationship between diabetes and dyslipidemia is bidirectional, so monitoring lipid parameters and achieving their goals will provide significant improvement in glycemic control. The current study findings supported this hypothesis.

This study's limitations were that it was single-center and cross-sectional in design, data related to dose and duration of oral antidiabetics were not available. There was a lack of follow-up period. Therefore, there is a need for further multi-center studies, including all treatment details and follow-up processes, to provide more valuable results.

In conclusion, there is a relationship between glycemic control and specific lipid parameters. Triglyceride can be considered as a biomarker for poor glycemic control in Turkish patients with non-insulin-dependent diabetes. This study may substantially contribute to the literature since it was conducted in diabetic Turkish patients and a large patient population. The results demonstrated the importance of a holistic, simultaneous, and aggressive approach to blood glucose and lipid control in diabetic patients.

**Informed Consent:** Written consent was obtained from the participants.

**Conflict of Interest:** Authors declared no conflict of interest.

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Table 1. Baseline characteristics of the study patients

|                          | Total (n=629) | Low HbA1c (n=307) | High HbA1c (n=322) | p        |
|--------------------------|---------------|-------------------|-------------------|----------|
| Median (Q1 / Q3)         |               |                   |                   |          |
| Age (year)               | 55 (48 / 62)  | 55 (47 / 62)      | 55 (49 / 62)      | 0.627 u  |
| Gender                   |               |                   |                   |          |
| Female                   | 332 (52.8)    | 187 (60.9) B      | 145 (45.0)        | <0.001 p |
| Male                     | 297 (47.2)    | 120 (39.1)        | 177 (55.0) A      | 1.9 (1.4-2.6) or |
| Smoker                   |               |                   |                   |          |
| No                       | 300 (47.7)    | 175 (57.0) B      | 125 (38.8)        | <0.001 p |
| Yes                      | 329 (52.3)    | 132 (43.0)        | 197 (61.2) A      | 2.1 (1.5-2.9) or |
| Systolic BP (mm Hg)      | 140 (130 / 155)| 140 (130 / 145)  | 150 (130 / 165)   | <0.001 u |
| Diastolic BP (mm Hg)     | 85 (85 / 90)  | 85 (80 / 90)      | 90 (85 / 95)      | <0.001 u |
| LDL (mg / dl)            | 130 (104 / 158)| 132 (104 / 158)  | 129 (103 / 158)   | 0.820 u  |
| Triglycerides (mg / dl)  | 155 (112 / 228)| 145 (105 / 202)  | 174.5 (120 / 250) | <0.001 u |
| HDL (mg / dl)            | 44 (37 / 52)  | 46 (39 / 54)      | 43 (36 / 50)      | <0.001 u |
| Total Cholesterol (mg / dl) | 209 (179 / 245)| 210 (180 / 243)  | 206.5 (177 / 247) | 0.982 u  |
| Non-HDL (mg / dl)        | 164 (135 / 196)| 166 (135 / 192)  | 162 (135 / 198)   | 0.474 u  |

* Mann Whitney U-test (Monte Carlo), † Pearson Chi-Square Test (Exact), ‡ Odds Ratio (95% Confidence Interval), Q1: Percentile 25%, Q3: Percentile 75%, A Expresses significance according to the Low HbA1c group, B Expresses significance according to the High HbA1c group.
Table 2. Correlations between glycemic control and blood pressure, lipid parameters

|                                | HbA1c | p       |
|--------------------------------|-------|---------|
|                                | r     |         |
| Age (years)                    | 0.018 | 0.519   |
| Systolic BP (mm Hg)            | 0.153 | <0.001  |
| Diastolic BP (mm Hg)           | 0.192 | <0.001  |
| LDL (mg / dl)                  | 0.017 | 0.522   |
| Triglycerides (mg / dl)        | 0.139 | <0.001  |
| HDL (mg / dl)                  | -0.117| <0.001  |
| Total Cholesterol (mg / dl)    | 0.002 | 0.928   |
| Non-HDL (mg / dl)              | 0.028 | 0.293   |

| Median (Q1 / Q3)               |         |
|--------------------------------|---------|
| Gender                         |         |
| Female                         | 6.6 (6 / 8.4) | <0.001  |
| Male                           | 7.4 (6.4 / 9.1) |
| Smoke                          |         |
| No                             | 6.6 (6 / 8.1) | <0.001  |
| Yes                            | 7.5 (6.4 / 9.3) |

* Mann Whitney U-test (Monte Carlo), k Kendall's tau b Test, r: Correlation Coefficient, Q1: Percentile 25%, Q3: Percentile 75%

Table 3. ROC analyses of lipid parameters and blood pressure

|                                | Cut off | Sensitivity | Specificity | AUC±SE. | P     |
|--------------------------------|---------|-------------|-------------|---------|-------|
| Low HbA1c (n=307), High HbA1c (n=322) |         |             |             |         |       |
| Systolic BP (mm Hg)            | >145    | 42.0%       | 70.1%       | 0.631 ± 0.023 | <0.001 |
| Diastolic BP (mm Hg)           | >90     | 30.8%       | 94.1%       | 0.639 ± 0.022 | <0.001 |
| Triglycerides (mg / dl)        | >180    | 46.9%       | 71.0%       | 0.60± 0.023  | <0.001 |
| HDL (mg / dl)                  | ≤36     | 28.9%       | 85.0%       | 0.582± 0.023 | 0.003  |

ROC (Receiver Operating Curve) Analysis (Honley&Mc Nell - Youden index J), AUC: Area under the ROC curve, SE: Standard Error

Table 4. Linear regression analysis of variables

| Independent Variables | B (Sh.)          | P     |
|-----------------------|------------------|-------|
| Diastolic BP (mm Hg)  | 0.139 (0.013)    | <0.001|
| Smoker (yes)          | 0.838 (0.152)    | <0.001|
| Smoker (No)           | -0.838 (0.152)   | <0.001|
| Triglycerides (mg / dl)| 0.004 (0.001) | <0.001|