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ORIGINAL ARTICLE

The relationship between glycated hemoglobin (HbA1c), hematocrit, mean platelet volume, total white blood cell counts, Visceral Adiposity Index, and Systematic Coronary Risk Evaluation 2 (SCORE2) in patients without diabetes

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Abstract

Objective Cardiovascular diseases (CVD) are the most common, deadly, noncommunicable disease group globally. This study aims to investigate the relationship between Systematic Coronary Risk Evaluation 2 (SCORE2) scores, which indicate the risk of future CVD in patients without known CVD and diabetes mellitus (DM) diagnoses, and HbA1c values.

Methods In our retrospective cross-sectional study, patients under 40 years of age and over 69 years, those with a history of any CVD, those with a history of type 1 or type 2 DM, individuals with known anemia, patients using antihyperlipidemic or antidiabetic medications, and those with HbA1c levels of 6.5 and above were excluded. The relationship between the SCORE2 risk scores and related parameters was investigated among the included 249 patients.

Results Among a total of 249 patients, with a mean age of 51.9 ± 7.5 years, 137 (55.0%) were male. Positive correlations were found between the SCORE2 (%) value of the patients and hemoglobin (rho = 0.222; $p < 0.001$), red blood cell (rho = 0.207; $p = 0.001$), hematocrit (rho = 0.267; $p < 0.001$), white blood cell (rho = 0.147; $p = 0.021$), triglyceride (rho = 0.247; $p = 0.004$), glucose (rho = 0.244; $p < 0.001$), HbA1c (rho = 0.208; $p < 0.001$), waist circumference (rho = 0.204; $p = 0.001$), and Visceral Adiposity Index (VAI) (rho = 0.145; $p = 0.023$) values.

Conclusion A significant relationship was found between HbA1c and the current CVD risk score, SCORE2, in our patient group without DM. Our study is the first to examine this relationship in the literature. While no relationship was found between SCORE2 and body mass index (BMI), a significant relationship was found with the VAI. This indicates that CVD risk is more associated with visceral fat accumulation than total weight. Evaluating patients with normal BMI based on VAI will be beneficial in demonstrating CVD risk.

Keywords Cardiovascular · Risk · Glycated hemoglobin · Adiposity · Mean platelet volume

Introduction

Cardiovascular diseases (CVD), including coronary heart disease and stroke, accounted for an estimated 18.6 million deaths in 2019, making it the most common and deadly noncommunicable disease group globally [1]. Various risk scores are used to predict CVD that causes high mortality and morbidity. American College of Cardiology/American Heart Association (ACC/AHA), Framingham Risk Score, Systematic Coronary Risk Evaluation (SCORE), and Systematic Coronary Risk Evaluation 2 (SCORE2) are some of the scales used. SCORE2 is an updated scoring system published in 2021 and has some advantages over SCORE. While the risk of fatal CVD in the next 10 years is calculated

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with the SCORE risk score published in 2003, all the fatal and non-fatal CVD risks are calculated in SCORE2. It is important for preventive medicine to calculate the non-fatal CVD burden seen especially in young people in recent years. In SCORE2, the results were calibrated by taking into account the general CVD risk situation of the countries in Europe, and the rate of false results was reduced. SCORE2 was developed to predict the risk of CVD causing mortality or morbidity in individuals aged 40–69 years without a previous diagnosis of CVD or diabetes mellitus (DM) [2].

Glycated hemoglobin (HbA1c), which reflects the average blood sugar levels over the preceding 2 to 3 months, serves as a well-established biomarker for assessing long-term glycometabolic control. Since 2010, it has also been recommended for the diagnosis of diabetes mellitus (DM) [3]. Diabetes mellitus is acknowledged as an independent factor to coronary artery disease (CAD), with diabetic patients facing a 3–4 times higher risk of cardiovascular mortality when compared to non-diabetic individuals [4]. Although traditional risk factors for cardiovascular problems such as hypertension, atypical lipid profiles, and obesity are frequently observed in individuals with diabetes, there is an increasing body of evidence suggesting an independent impact of heightened blood glucose levels on the progression of atherosclerosis [5, 6]. The "Diabetes Control and Complications Trial" reported that there is no discernible glycemic threshold for the development of cardiovascular complications [7]. Furthermore, during a subsequent examination in the Atherosclerosis Risk in Communities (ARIC) investigation comprising non-diabetic grown-ups, it was uncovered that increased HbA1c levels were linked to an increased likelihood of heart-related ailments and fatality [8]. Moreover, several other research investigations have supplied added backing to the connection between initial serum HbA1c levels upon admission and extended-term mortality in non-diabetic individuals hospitalized for acute ST-elevation myocardial infarction (STEMI). Additionally, these studies have pointed to a heightened occurrence of coronary artery disease (CAD) among non-diabetic patients [9–12].

In a meta-analysis involving patients over 50 years of age, a significant correlation was observed between HbA1c level in patients without DM and mortality from any cause and cardiovascular mortality in patients over 65 years of age. Although the relationship significantly decreases after adjusting for age, gender, smoking, race/ethnicity, physical activity, alcohol usage, total cholesterol, high-density lipoprotein (HDL), hemoglobin (HGB), serum creatinine, albuminuria, body mass index (BMI) education, hypertension, and CVD history, it remains statistically significant [13].

When the studies in the literature were examined, it was seen that the studies examining the relationship between HbA1c and CVD were conducted using former scoring systems or by retrospective screening of patients with known CVD. It is noteworthy that there is no study using current scoring systems examining the relationship between HbA1c and CVD risk in patients without known CVD and DM diagnoses. In this study, it was aimed to investigate the relationship between SCORE2 scores and HbA1c values, which indicate the risk of CVD in the next 10 years.

Methods and Materials

Our study is a retrospective and cross-sectional study conducted with the data of patients who applied to the family medicine outpatient clinics of our tertiary hospital between 1 December 2020 and 1 December 2021. In accordance with the group criteria in which SCORE2 was used, patients under 40 years of age and over 69 years of age, those with a history of CVD, those with a history of type 1 or type 2 DM, those using antihyperlipidemic drugs or antidiabetic drugs, and those with a HbA1c of 6.5 and above in their blood were excluded [2]. Since it is known that anemia can affect HbA1c, individuals with an HGB value below 13 g/dl in men and 12 g/dl in women were not included in the study [14–16].

The data of 1169 patients who applied in a 1-year period were examined; 137 patients under the age of 40 and 112 patients aged 70 and over were excluded because they did not meet the age criteria in the study criteria.

When the data of 920 patients who fit the age limit were examined, it was observed that 338 of them had one or more of type 1 DM, type 2 DM, use of antihyperlipidemic or antidiabetic drugs, anemia, and previous CVD. In the laboratory examinations of the remaining 582 patients, 27 had HbA1c values of 6.5 and above. Of the remaining patients, 306 were excluded from the study due to lack of data. The research was carried on with 249 patients who fulfilled all the criteria.

The patient's anamnesis, physical examination information, and laboratory results at the time of application were scanned from the registry system of our hospital and noted. Patient's age, gender and active smoking status, and previous CVD (coronary angiography results at any time in their lives, peripheral vascular diseases, and previous ischemic or hemorrhagic stroke diagnoses) were recorded by scanning from the declared anamnesis information. From the physical examination information of the patients, blood pressure measurements were recorded as mm-Hg, waist circumference (WC) and height measurements as cm, and body weight measurements as kg.

The hemogram parameters (HGB, red blood cell (RBC), hematocrit (HCT), mean erythrocyte volume (MCV), red cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), white blood cell (WBC)), absolute lymphocyte count (LYM#), absolute neutrophil count (NEUT#)), some biochemical parameters (glucose,

triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol), and HbA1c values were recorded during the medical history taken on the specified date. The hemogram parameters were measured with the Beckman Coulter LH 700 Hematology Analyzer (Beckman Coulter Inc., Brea, CA, USA). Glucose, LDL, HDL, TG, and total cholesterol measurements were examined using the enzymatic colorimetric method performed by Beckman Coulter AU5800 (Beckman Coulter Inc., Brea, CA, USA) autoanalyzer. HbA1c was measured by high-performance liquid chromatography (HPLC) (Tosoh Corporation, Tokyo, Japan). BMI and Visceral Adiposity Index (VAI) values of the patients were calculated and recorded. Formulas of Amato et al. were used to calculate VAI [17]. This was defined as

$$\text{For males, VAI} = \left[\text{WC}/(39.68 + (1.88\text{BMI}))\right](\text{TG}/1.03)(1.31/\text{HDL})$$

$$\text{For females, VAI} = \left[\text{WC}/(36.58 + (1.88\text{BMI}))\right](\text{TG}/0.81)(1.52/\text{HDL})$$

Statistical analysis

For statistical analysis, IBM-SPSS (Statistical Package for the Social Sciences) 23.0 (Armonk, NY: IBM Corp.) package program was used. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and range where appropriate). The study employed the Kolmogorov–Smirnov test to assess the normal distribution of the study's parameters. The chi-square test and Fisher's exact test were used for comparing categorical variables. Mann–Whitney *U* test was used to analyze the differences between the groups. Pearson correlation test was used for parametric data to determine the relationship between continuous measurement values, and Spearman correlation test was used for non-parametric data. Statistical significance level was taken as 0.05 in all tests.

Results

The data of 249 patients included in our study were analyzed. According to the examination, the mean age of the patients was 51.9 ± 7.5 years, while 137 (55.0%) of the patients were male and 112 (45.0%) were female.

Active smoking was detected in 19 (7.6%) patients; hypertension findings were found in 62 (24.9%) of the patients.

WC was observed to be 97.8 ± 10.8 cm on average; mean weight was 82.6 ± 13.8 kg. The mean BMI was found to be 29.7 ± 4.5 kg/m^2 in patients. The mean systolic blood pressure was 112.5 ± 15.5 mm-Hg (Table 1).

Table 1 Examination of demographic data, anthropometric measurements, and systolic blood pressure values used in SCORE2 calculation of the patients included in the study ($n = 249$)

	n	Percentage (%)
Gender		
Male	137	55.0
Woman	112	45.0
	Mean ± Sd	**Med (range)**
Waist circumference (cm)	97.8 ± 10.8	98 (67–122)
Male	101.0 ± 9.1	100 (70–122)
Woman	93.9 ± 11.4	95 (67–121)
Weight (kg)	82.6 ± 13.8	82 (49–138)
Male	86.8 ± 12.6	86 (49–138)
Woman	77.5 ± 13.6	76 (53–120)
Body mass index (BMI) (kg/m^2)	29.7 ± 4.5	29 (17.8–44.6)
Systolic arterial blood pressure (mm-Hg)	112.2 ± 15.5	110 (80–160)

Mean Mean, *Sd* standard deviation, *Med* Median

Table 2 Correlation analysis of laboratory parameters and anthropometric measurements with SCORE2

	SCORE2 (%)	
	rho	*p*
HGB (g/dl)	0.222	**< 0.001**
RBC (10^6/ µl)	0.207	**0.001**
MCV (fl)	0.071	0.265
HCT (%)	0.267	**< 0.001**
PLT (10^3/ µl)	− 0.099	0.120
MPV (fl)	− 0.025	0.690
PDW (%)	− 0.016	0.804
WBC (10^3/µl)	0.147	**0.021**
NEUT# (10^3/µl)	0.115	0.071
LYM# (10^3/µl)	0.040	0.529
Triglyceride (mg/dl)	0.247	**< 0.001**
Glucose (mg/dl)	0.244	**< 0.001**
HbA1c (%)	0.208	**0.001**
Waist circumference(cm)	0.204	**0.001**
Body mass index (BMI) (kg/m^2)	0.049	0.441
Visceral Adiposity Index (VAI)	0.145	**0.023**

Patients' SCORE2 (%) values and HGB (rho = 0.222; $p < 0.001$), RBC (rho = 0.207; $p = 0.001$), HCT (rho = 0.267; $p < 0.001$), WBC (rho = 0.147; $p = 0.021$), triglyceride (rho = 0.247; $p = 0.004$), glucose (rho = 0.244; $p < 0.001$), HbA1c (rho = 0.208; $p = 0.001$), WC (rho = 0.204; $p = 0.001$), and VAI (rho = 0.145; $p = 0.023$) values were found to be positively correlated (Table 2).

There is a significant correlation between HbA1c with age (rho = 0.265, $p < 0.001$), RDW (rho = 0.166, $p = 0.008$), glucose (rho = 0.344, $p < 0.001$), WC (rho = 0.194, $p = 0.002$),

weight (rho = 0.130, $p = 0.041$), BMI (rho = 0.172, $p = 0.007$), and SCORE2 (%) (rho = 0.208, $p = 0.001$) (Table 3).

Discussion

A significant relationship was found between HbA1c and the current CVD risk score, SCORE2, in our patient group without DM. Studies show that patients with DM with an HbA1c level above 7% have significantly increased CVD and that intensive glucose control reduces this risk [18–20]. However, an increased incidence of CAD with severe and multivessel involvement has been observed in DM patients with high HbA1c [21]. A direct relationship between HbA1c and CVD was demonstrated in a meta-analysis of 46 studies examining the frequency of CVD in patients with and without DM. This meta-analysis concluded that the optimal HbA1c level should be between 6 and 8% for patients with DM and between 5 and 6% for those without DM. When the findings in this study were examined, it was observed that the mortality rate for any reason increased when the HbA1c level went beyond the level determined for patients with and without DM [22]. In a study conducted in China, a statistically significant correlation was found between HbA1c and CAD diagnosed by coronary angiography in patients who were not diagnosed with DM. In the analysis performed in the same study, a U-shaped relationship was found between the HbA1c value and the severity of CAD, and the frequency and severity of MI increased in the group with both HbA1c < 5.7 and HbA1c > 7.2 [23]. Likewise in another study, high HbA1c levels were found to be significantly associated with in-hospital and short-term mortality in patients with and without DM who were admitted to the hospital for acute coronary syndrome [24]. Studies in patients without DM have shown a significant relationship between HbA1c and the risk of CAD and the number of involved vessels [25, 26]. Studies have indicated that elevated blood sugar levels can potentially result in endothelial impairment by diminishing nitric oxide accessibility and elevating oxidative stress levels, which, in turn, can lead to inflammation and activation of prothrombotic pathways. This condition can potentially contribute to the development of atherosclerosis, distinguished by the buildup of fats, immune cells, and smooth muscle cells within the arterial wall. The relationship between HbA1c and cardiovascular risk may have emerged as a result of these mechanisms [27]. This significant relationship between HbA1c value and SCORE2 in our study conducted with the patient group without DM suggests that blood sugar regulation is important not only in the patient group with DM but also in the patient group without DM.

Obesity is one of the important causes of CVD. In a study examining the relationship of VAI with coronary diseases and ischemic cerebral diseases, 1498 patients were retrospectively screened. In this study, a significant relationship was found between VAI and all metabolic syndrome factors and CVD. Nonetheless, even though male sex, age at the occurrence, tobacco use, and VAI demonstrated separate connections with CVD, such an affiliation did not appear in the case of BMI, WC, and other recognized risk factors for cardiovascular disease. Furthermore, there existed a connection between VAI and the age at the time of the incident, particularly in cerebrovascular events. These findings can be elucidated by the fact that VAI encompasses both physical and metabolic parameters and is a valuable indicator reflecting both fat distribution and adipose tissue function without distorting the meaning [28]. Although no significant relationship was observed between BMI and SCORE2 in our study, a relationship was observed between triglyceride, WC, VAI, which is accepted as a new indicator of and visceral adiposity, and SCORE2. This shows that weight gain, which causes cardiovascular risks, is associated with accumulation around the waist and visceral fat rather than being associated with total body weight.

When a comprehensive review conducted in 2022 was examined, it was seen that there was a relationship between hemogram parameters and CVD. In the study, it is thought that WBC count indicates inflammation associated with CVD, and therefore, it is considered to be associated with both the risk of CVD and mortality related to CVD [29]. In our study, after excluding diabetes, another cause of

Table 3 Correlation analysis of laboratory parameters and anthropometric measurements with HbA1c

	HbA1c	
	rho	*p*
Age (years)	0.265	**< 0.001**
HGB (g/dl)	− 0.014	0.832
HCT (%)	0.050	0.437
RDW (%)	0.166	**0.008**
PLT (10^3/µl)	0.082	0.195
MPV (fl)	0.006	0.927
PDW (%)	0.017	0.787
HDL cholesterol (mg/dl)	0.044	0.488
Total cholesterol (mg/dl)	0.085	0.181
LDL cholesterol (mg/dl)	0.085	0.182
Triglyceride (mg/dl)	0.073	0.249
Glucose (mg/dl)	0.344	**< 0.001**
Waist circumference (cm)	0.194	**0.002**
Weight (kg)	0.130	**0.041**
Body mass index (BMI) (kg/m^2)	0.172	**0.007**
Visceral Adiposity Index (VAI)	0.061	0.338
SCORE2 (%)	0.208	**0.001**

inflammation, a significant correlation, was found between WBC and other WBC-related parameters and CVD risk in patients without known CVD. This suggests that increased inflammation in the body is associated with CVD risk even after excluding an inflammatory CVD risk factor such as diabetes. When the physiology of HGB is examined, it is thought that in cases where the intracellular HGB concentration increases, nitric oxide (NO), which causes vasodilation in the circulation, will be retained by HGB and removed from the circulation and may lead to vasoconstriction [30]. It is known that blood viscosity will increase when MCV and HCT are increased [30]. It is expected that the increase in erythrocyte parameters such as HGB, HCT, and MCV, both indirectly through NO and by increasing the viscosity, will increase the risk of CVD. In our study, a significant relationship was observed between these parameters and SCORE2.

In our study, the relationship between MPV and SCORE2, which has been more emphasized in recent years and accepted as an inflammation marker, was also examined, and no significant relationship was found between them. MPV is an easy and inexpensive parameter to reach, but it is affected by many factors related to platelet activation. For this reason, it will be more useful and meaningful to conduct studies in special patient groups. In a study conducted in the Danish general population, blood specimens collected upon arrival to the emergency room or outpatient clinic of 39,531 men and women, 1300 of whom had MI, were examined before percutaneous coronary intervention, and it has been demonstrated that MPV is linked to a heightened risk of MI regardless of known cardiovascular risk factors [31]. In a study examining the relationship between thrombocyte parameters and cardiovascular risk in the Framingham Heart Study, a significant association was found between high thrombocyte count and adverse cardiovascular risk profiles. Furthermore, in the same study, a significant but weaker association was observed between MPV and cardiovascular risk [32] Contrary to these studies, in a study examining 2872 stable coronary artery patients who underwent elective percutaneous coronary intervention, it was revealed that the group with low MPV was associated with worse clinical outcomes when long-term major adverse cardiovascular events were examined with a median follow-up of 5.6 years [33]. The studies investigating the relationship between MPV and cardiovascular risk scores demonstrate that high MPV levels in the acute phase of cardiovascular disease can serve as a valuable marker in predicting the development of complications following CVD, the risk of disease recurrence, morbidity, and mortality. However, in studies conducted during long-term follow-ups or periods without acute CVD, no significant positive relationship was found between MPV and CVD. It is thought that the fact that our study was conducted with patients who had never had CVD before caused no significant relationship between MPV and SCORE2. The relationship between MPV and CVD has been investigated in various ways in the literature, but different results have been obtained. Considering that MPV is affected by many factors, more studies are needed in more specific patient groups in this area.

Conclusion

DM and obesity are among the major problems of our age, and they are known to pose a risk for CVD. It is a very important requirement in terms of public health and preventive medicine to make recommendations to reduce the risk of CVD in patient groups known to have DM or who are obese or morbidly obese according to BMI. Although there was no correlation between SCORE2 and BMI, a significant association between VAI suggests that the risk of CVD is linked to visceral adiposity rather than overall weight. It would be effective for patients within the normal range of BMI to be reassessed and properly guided based on VAI in terms of preventive medicine in order to reduce the incidence of CVDs.

CVDs are among the most prevalent causes of mortality and morbidity in our contemporary society. Therefore, not only predicting the risks associated with CVDs using various scoring systems but also understanding the underlying factors contributing to these risks holds significant importance from a preventive medicine perspective. Our study is the first to examine the relationship between SCORE2 and HbA1c in non-diabetic patients, but it has some limitations. First of all, this single-center and retrospective study represents a limited population on its own. In order to generalize the results of the study, the study should be conducted with more patients in a multicenter manner. Additionally, since our study is retrospective, we were unable to employ dual X-ray absorptiometry (DXA), MRI, or CT imaging to calculate participants' visceral fat levels. In this study, the VAI formula was used for this purpose. While this formula is not considered the gold standard, previous research has shown correlations with MRI [28]. Patients self-reported with no objective assessment, which may have introduced an information bias. In the patient data obtained from the hospital register system, the smoking status of the patients was seen as only present or absent. This may have led to inaccuracies in calculating the SCORE2 risk scores of patients who have recently quit smoking.

Our study showed that HbA1c value is associated with CVD risk, except for patients with DM diagnosis. Patients who are not in the risk group but have high HbA1c should be informed about lifestyle changes and glucose control.

Author contribution All authors contributed to the study conception and design. Material preparation and data collection were performed by Cem Yesiloglu and Canan Emiroglu. Formal analysis was performed by Cem Yesiloglu and Cenk Aypak. The first draft of the manuscript was written by Cem Yesiloglu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability The data are available from the corresponding author on reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences Dıskapı Yıldırım Beyazıt Training and Research Hospital (Date 15.08.2022 /No.144/06) in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

Consent to participate Written informed consent was obtained from all patients.

Consent for publication Patient signed informed consent regarding publishing their data.

Competing interests The authors declare no competing interests.

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