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ORIGINAL SCIENTIFIC PAPER

Glycosylated haemoglobin and coronary atherosclerosis in non-diabetic patients: is it a prognostic factor?

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ABSTRACT

Background: Some studies aimed to evaluate the relationship between HbA1c and coronary artery disease (CAD). However, it is well known that long-term glycometabolic disorders put the heart at risk for CAD. Considering the inconsistencies between previous studies, this study aimed to investigate the relationship between HbA1c and coronary artery atherosclerosis.

Methods: A cross-sectional study was conducted on 411 non-diabetic patients who underwent their first coronary angiography between November 2013 and December 2014 in Baqiyatallah Hospital. Blood samples were taken before angiography. Coronary angiograms were reported and reviewed by two cardiologists according to the Gensini score. They were not aware about the patients' HbA1c level. Severity of CAD was determined through ascertaining the prevalence of multi-vessel disease, extent of CAD (single-, two- or three-vessel disease or left main stem stenosis (>50%)). Data analysis was performed by using SPSS software.

Results: A total of 411 patients (252 men and 159 women) were evaluated. Angiography was normal in 67 patients (16.3%), 30.7% had single-vessel disease (SVD), and 29.1%, 20.7% and 3.2% had two-, three- and multivessel disease, respectively. Based on the ROC curve, the HbA1c was able to differentiate between patients with and without coronary atherosclerosis ($p < .001$, cut-off point = 5.45). The cut-off points for differentiation of severe CAD and patients with 75–100% stenosis of coronary artery were 5.55 ($p < .001$) and 5.65 ($p < .001$), respectively.

Conclusions: The present study demonstrated that HbA1c might be an independent diagnostic factor in non-diabetic patients with severe coronary atherosclerosis.

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KEYWORDS
Glycosylated haemoglobin; coronary artery disease; non-diabetic patients

Background

Glycosylated haemoglobin (HbA1c), as a marker of average blood glucose over the preceding 2–3 months, is a recommended tool in both diagnosis and screening of diabetes mellitus [1,2]. It is well known that long-term glycometabolic disorders put the heart at risk for coronary heart diseases (CHDs) [3,4].

There are a plenty of literature about the relationship between HbA1c and coronary artery diseases (CADs). This relationship has especially been evaluated among nondiabetic patients and some of the studies reported the level of HbA1c as a predictor of cardiovascular diseases (CVDs) in these subjects [5,6]. However, an interaction might exist between HbA1c levels and traditional cardiovascular risk factors. A recent study has investigated the relationship between HbA1c and CHD among women. However, the relationship was not significant when other risk factors were excluded [7]. Some investigators also proposed that a previous history of CVD might obscure the relationship between HbA1c and CHD. However, the risk of CHD was shown to be independent of such a history [8].

Some of the studies have also investigated HbA1c as an independent predictor of CAD and reported that it is a significant determinant of CAD and its severity, independent of traditional risk factors [6]. Other studies rejected this hypothesis [9]. Therefore, it can be concluded that further studies are needed to investigate the relationship between HbA1c and CVD.

Objectives

Considering the inconsistencies between previous studies, this study aimed to investigate the relationship between HbA1c and coronary artery atherosclerosis. We also tried to determine the ideal cut-off value

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of HbA1c as a prognostic factor for coronary atherosclerosis and its severity.

Patients and methods

A cross-sectional study was conducted on 411 patients without history of known diabetes mellitus who underwent their first elective coronary angiography (coronary artery angiography was performed when clinically indicated) for suspected ischaemia at Baqiyatallah hospital, Tehran, Iran. The study was conducted between November 2013 and December 2014. In addition to routine investigations, the HbA1c was measured for all patients on admission. The angiogram was reviewed by two cardiologists, both blinded to the patient's diabetes status, to assess the Gensini score.

All patients had either angina or angina-like chest pain and evidence of ischaemia (ischaemic electrocardiographic changes, positive stress or other non-invasive tests). Exclusion criteria included newly detected diabetes (defined as fasting blood sugar >126 mg/dL, HbA1c $>6.5\%$ or 2-h post-load glucose >200 mg/dL during an oral glucose tolerance test, OGTT), haemoglobin <11 mg/dL, concomitant systemic diseases such as autoimmune disease, cancer or active infection, splenectomy or acute blood loss in the last month.

The study was approved by the Institutional Review Board of Baqiyatallah University of Medical Sciences and the ethics committee of Baqiyatallah hospital. Written informed consent was obtained from all patients and they were assured of confidentiality of their personal information and the right to refuse participation. Permissions were also sought from the hospital authorities. The researchers observed all ethical issues in accordance with the ethical Declaration of Helsinki.

Laboratory measurements

Following overnight fasting, blood samples were drawn from the antecubital vein into EDTA-treated and plain tubes on the day of the coronary angiography for biochemical assay and stored at $-70\,^{\circ}$C prior to analysis. Serum glucose, lipid profile and HbA1c were assessed immediately after admission. Serum triglycerides, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and glucose level were evaluated by standard enzymatic procedures. HbA1c was assessed through turbidimetric inhibition immunoassay (Roche Tina-quant Gen.2 HbA1c on Integra 800) with inter- and intra-assay coefficient of variation (CV) of 1.3% and 0.8% at a mean level of 5.3% (34 mmol/mol) and 1.0% and 0.9% at a mean level of 10.2% (88 mmol/mol), respectively, and lower detection limit of 2.9%. HbA1c was calculated according to the National Glycohaemoglobin Standardization Program (NGSP) equivalent value. All laboratory tests were accomplished in the central laboratory of Baqiyatallah hospital.

Assessment of coronary atherosclerosis

Coronary angiography was performed using the standard Judkins technique (Siemens Artis Zee Floor, Munich, Germany) and all coronary angiograms were reported and reviewed by two cardiologists who were not aware about the patients' HbA1c level. CAD was defined as $>50\%$ luminal narrowing in at least one major epicardial vessel. Severity of CAD was determined through ascertaining the prevalence of multi-vessel disease, extent of CAD [one-, two- or three- vessel disease or left main stem stenosis ($>50\%$)]. According to the number of diseased arteries, patients were categorized as having no disease, or one-, two- or three-vessel disease. Given the small number of patients with left main disease, three-vessel and left main disease were grouped together, as a three-vessel disease.

Statistical analysis

Data analysis was performed using SPSS software (version 21, Chicago, IL). Categorical and ordinal data were summarized using percentages and compared using Chi square and Fisher's exact tests. Analysis of variance and Tukey's *post hoc* test were applied to compare the mean of quantitative variables. Pearson's and Spearman correlation coefficients were utilized to determine bivariate correlation between two quantitative variables. The normality of variables was checked by one-sample K–S test.

The receiver operating characteristic (ROC) curve was used to test the accuracy of HbA1c in the differentiation of normal and abnormal angiography findings and severe/non-severe coronary atherosclerosis. Binary logistic regression analysis with the forward Wald method was also performed to identify the r-square values for predicting normal/abnormal angiography findings and severe/non-severe coronary atherosclerosis. The variance inflation factor (VIF) was calculated to determine the collinearity of variables, and the variables were excluded from model if VIF >10.

Results

A total of 411 patients (252 men and 159 women) were evaluated. The mean age of the subjects was

60.59 ± 12.26 y and their mean BMI was 27.28 ± 4.24 kg/m^2. Results of angiography was normal in 67 patients (16.3%), 30.7% had single-vessel disease (SVD), and 29.1%, 20.7% and 3.2% had two-vessel, three-vessel and multi-vessel disease, respectively. Patients' underlying diseases, risk factors and drugs history are presented in Table 1.

Patients with different angiographic results were significantly different in terms of age, BMI, white blood cell (WBC) count, triglycerides, FBS, HbA1c and left ventricular ejection fraction (LVEF) (Table 2).

Vessel stenosis was less than 50% in 59 patients, 50–75% in 37 patients, and more than 75% in 248 patients. The severity of atherosclerosis and characteristics of atherosclerotic coronary vessels in patients with different angiographic results are presented in Table 3.

Based on the ROC curve, the HbA1c was able to differentiate between patients with and without coronary atherosclerosis ($p < .001$, cut-off point = 5.45, Figure 1). The cut-off points for the differentiation of severe CAD and patients with 75–100% stenosis of coronary artery were 5.55 ($p < .001$, Figure 2) and 5.65 ($p < .001$, Figure 3), respectively.

Seventeen variables were entered in the binary logistic regression model in predicting normal and abnormal angiography results. After six steps regressions by the forward Wald method the *r*-square amount increased from 0.205 to 0.4 and six variables remained in the model ($p < .001$, $r^2 = .400$, shown in Table 4).

Seventeen variables were entered in the binary logistic regression model to predict severe atherosclerosis. After four steps of regressions using the forward Wald method the *r*-square value increased from 0.211 to 0.345 and four variables remained in the model ($p < .001$, $r^2 = .345$).

The mean HbA1c was significantly higher in patients with an atherosclerotic left main artery (LMA) in comparison with those with normal LM (6.04 vs. 5.75, $p = .002$). However, the mean HbA1c was not significantly different in patients with and without left anterior descending (LAD) artery atherosclerosis (5.76 vs. 5.78, $p = .688$). The mean HbA1c was also significantly higher in patients with atherosclerotic left circumflex (LCX) artery compared with those with normal LCX (5.84 vs. 5.68, $p = .001$). Moreover, the mean HbA1c was significantly higher in patients with an atherosclerotic right coronary artery (RCA), compared with those with a normal RCA (5.85 vs. 5.68, $p < .001$).

Table 1. Description of patients' underlying diseases, risk factors and drugs history.

Variable	Frequency (%)
Hypertension	172 (41.8)
Hyperlipidaemia	111 (27)
Previous CABG	42 (10.2)
Previous PCI	105 (25.5)
Smoking	108 (26.3)
Drugs history	
ACE inhibitors	40 (9.7)
ARBs	153 (37.2)
Beta blockers	157 (38.2)
Nitrates	102 (24.8)
Statins	220 (53.5)
Aspirin	336 (81.8)
Calcium channel blockers	37 (9)
Diuretic	25 (6.1)
Warfarin	17 (4.1)
Clopidogrel	113 (27.5)

ACE: angiotensin-converting-enzyme; ARBs: angiotensin II receptor blockers; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention.

Discussion

The present study showed that HbA1c can be used as a marker for predicting coronary atherosclerosis in

Table 2. Comparison of demographic, laboratory and echocardiography results in the patients with normal coronary angiography results, SVD, 2VD and ≥3VD.

Variables	Normal ($N = 67$)	SVD ($N = 126$)	2VD ($N = 120$)	3VD and more ($N = 98$)	*p* Value
Age, year	50.72 ± 12.9	61.53 ± 11.4	61.73 ± 11.2	64.73 ± 10.5	<.001
Male gender	30 (44.8)	70 (55.6)	86 (71.7)	66 (67.3)	.001
BMI, kg/m^2	28.24 ± 4.9	27.46 ± 4.6	27.07 ± 3.8	27.28 ± 4.2	.101
WBC, ×10^3/mm^2	6.29 ± 1.8	6.63 ± 1.7	7.07 ± 1.8	7.28 ± 1.9	.001
Hg, mg/dL	13.48 ± 1.9	13.69 ± 1.6	14.03 ± 1.6	13.79 ± 1.5	.148
Platelet, ×10^3/mm^2	231.58 ± 62.2	219.02 ± 61.5	225.7 ± 73.1	225.22 ± 62.2	.632
Haematocrit	39.85 ± 5.2	40.85 ± 4.2	41.56 ± 4.7	41.35 ± 4.1	.074
Total cholesterol	156.46 ± 49.5	163.45 ± 53.7	151.19 ± 45.7	159.17 ± 42.1	.249
LDL	88.03 ± 36.7	92.82 ± 39.3	93.12 ± 51.5	88.31 ± 33.3	.729
HDL	39.61 ± 10.4	38.97 ± 9.8	37.10 ± 7.9	37.04 ± 7.7	.114
Triglycerides	113.8 ± 50.6	132.20 ± 57.1	112.50 ± 61.5	134.58 ± 67.7	.009
FBS, mg/dL	101.63 ± 15.1	104.10 ± 17.0	106.49 ± 17.7	109.47 ± 17.1	.019
HbA1c	5.36 ± 0.35	5.63 ± 0.41	5.75 ± 0.42	5.94 ± 0.42	<.001
LVEF	51.64 ± 6.4	50.79 ± 4.8	48.21 ± 5.6	45.05 ± 6.6	<.001

BMI: body mass index; FBS: fasting blood sugar; HbA1c: haemoglobin A1c; Hg: haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricle ejection fraction; SVD: single-vessel disease; 2VD: two-vessel disease; 3VD: three-vessel disease; WBC: white blood cell.

Table 3. Description of coronary angiography results in atherosclerotic patients.

Variables	SVD ($N=126$)	2VD ($N=120$)	3VD ($N=85$)	MVD ($N=13$)	p Value
Stenosis					.001
<50%	29 (23)	23 (19.2)	7 (8.2)	0 (0)	–
50–75%	19 (15.1)	15 (12.5)	3 (3.5)	0 (0)	–
>75%	78 (61.9)	82 (68.3)	75 (88.2)	13 (100)	–
Plaque size, mm	11.31 ± 4.1	14.50 ± 6.5	17.47 ± 6.3	19.23 ± 6.4	<.001
Severity					<.001
Mild	28 (22.2)	19 (15.8)	7 (8.2)	0 (0)	–
Moderate	21 (16.7)	21 (17.5)	4 (4.7)	0 (0)	–
Severe	77 (61.1)	80 (66.7)	74 (88.2)	13 (100)	–
Vessels					
LM	0 (0)	10 (8.3)	6 (7.1)	5 (38.5)	<.001
LAD	86 (68.3)	107 (89.2)	82 (96.5)	12 (92.3)	<.001
LCX	21 (16.7)	69 (57.5)	84 (98.8)	13 (100)	<.001
RCA	21 (16.7)	54 (45)	76 (89.4)	12 (92.3)	<.001

LCX: left circumflex; LAD: left anterior descending artery; LMA: left main artery; RCA: right coronary artery.

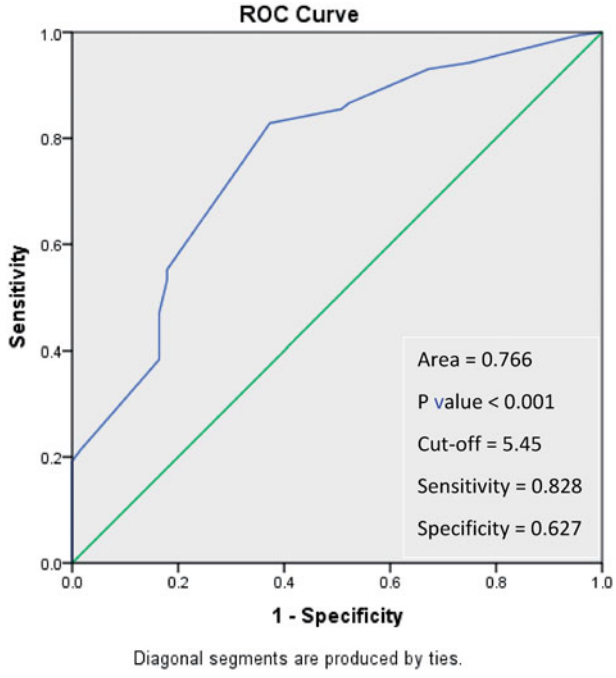

Figure 1. The ROC curve showing the sensitivity and specificity of HbA1c to differentiation of patients with coronary atherosclerosis.

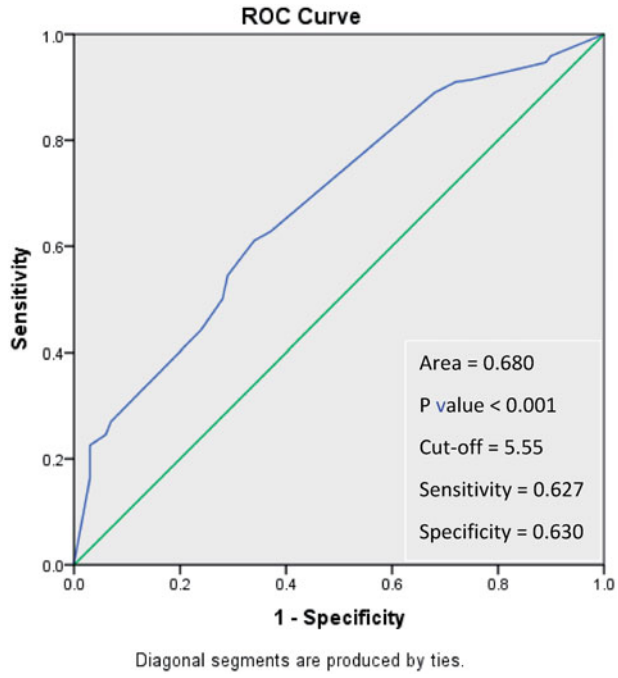

Figure 2. The ROC curve showing the sensitivity and specificity of HbA1c to differentiation of patients with severe coronary atherosclerosis.

non-diabetic patients. An increase of one percent in HbA1c was associated with a 9.7-fold increase in coronary atherosclerosis. According to the regression model, this association was independent of traditional cardiovascular risk factors such as age, gender, BMI, hypertension and hyperlipidaemia. Moreover, the present study demonstrated that HbA1c might be an independent diagnostic factor in non-diabetic patients with severe coronary atherosclerosis.

Some of the previous studies have also examined the relationship between HbA1c and coronary artery disease and also investigated the prognostic and diagnostic values of HbA1c in patients with coronary atherosclerosis. For instance, a community-based study has reported that HbA1c is a better predictor of CAD than fasting or postchallenge plasma glucose in non-diabetic women but not in men. However, the reasons for the sex difference were not discussed [10]. A prospective study has also examined the relationship between HbA1c, CVDs and total mortality in 4662 men and 5570 women. A significant relationship between HbA1c concentration and the occurrence of CVD was initially observed in this project. The relationship was present in persons without known diabetes. The lowest rate of CVD was observed in subjects with HbA1c concentration less than 5% and it was reported that one percent increase in the concentration of HbA1c can lead to 21% increase in the occurrence of CVDs.

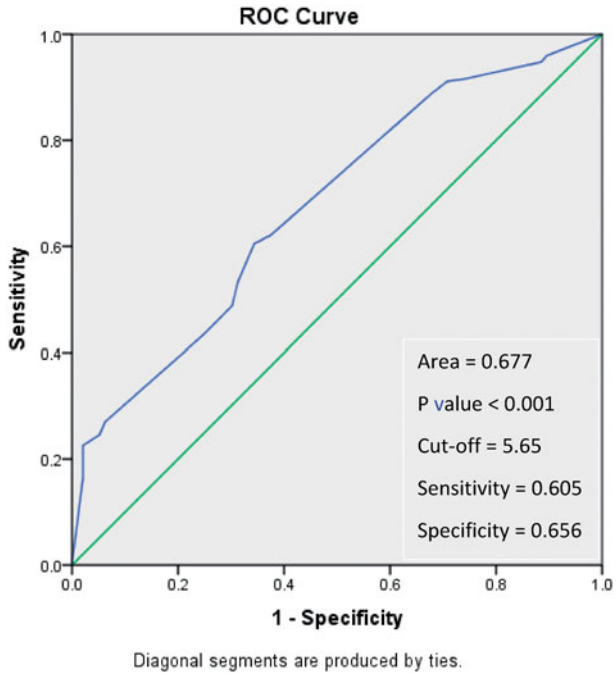

Figure 3. The ROC curve showing the sensitivity and specificity of HbA1c to differentiation of patients with 75–100% coronary artery stenosis.

Table 4. Logistic regression model for predicting coronary atherosclerosis in patients.

Variables	*p* Value	EXP (B)	95% CI for EXP (B)
Remained in model			
Gender	.001	3.08	1.58–6.00
Age	<.001	1.07	1.04–1.10
HbA1c	<.001	9.77	3.44–27.81
HTN	.027	2.26	1.09–4.64
HLP	.040	0.444	0.204–0.964
LVEF	.014	0.925	0.869–0.984
Excluded from model			
BMI[a]	.224	0.951	0.877–1.03
WBC[a]	.749	1.04	0.823–1.31
Haemoglobin[a]	.507	0.884	0.614–1.27
Platelet[a]	.329	0.997	0.992–1.00
Haematocrit[a]	.122	1.11	0.972–1.27
Cholesterol[a]	.067	0.986	0.971–1.00
LDL[a]	.117	1.014	0.997–1.03
HDL[a]	.858	0.996	0.971–1.00
TG[a]	.065	1.008	0.999–1.02
FBS[a]	.231	0.986	0.963–1.01
Smoking[a]	.366	0.707	0.333–1.50

[a]Removed from model with the forward Wald method.

However, after excluding the patients with prior CVD and those with diabetes, the relationship was no longer statistically significant [8]. In a nested case–control analysis, a risk ratio (RR) of 2.25 (95% CI: 1.59–3.19) has been reported for the occurrence of CVDs in non-diabetic women with an HbA1c concentration ≥5.5%. However, after adjustment for risk factors such as BMI, blood pressure, CRP, LDL, HDL and TG, the RR was no longer significant [7]. In contrast, a prospective study on 1321 adults without diabetes showed that HbA1c level below 4.6% was not significantly associated with the occurrence of CHD; however, a significant relationship was observed above this level. Furthermore, in an adjusted model, the RR of CHD was 2.36 (95% CI: 1.43–3.90) for every 1% increase in HBA1c concentration [11]. After these studies and because of inconsistent results, a meta-analysis was conducted on nine cohort studies (1639 non-diabetes cases) and reported an RR of 1.20 (95% CI: 1.10–1.31) for the occurrence of CHD by each 1% increase in HbA1c concentration. But the reported RR was not adjusted for traditional CHD risk factors [12]. In 2013, Ashraf et al. investigated 299 subjects without diabetes who had undergone coronary angiography and reported that HbA1c is an independent predictor of CAD (OR = 2.8, 95% CI: 1.3–6.2). In addition, using the Gensini score, they reported a significant association between HbA1c concentration and the severity of CAD. Furthermore, they showed that a cut-off value of 5.6% for HbA1c can predict CAD with a specificity and sensitivity of 52% and 60.5%, respectively [6]. In our project, the cut-off point of HbA1c was 5.45% for determining atherosclerotic patients (sensitivity: 0.828, specificity: 0.627). In a prospective nested case–control study in 2013, the risk ratio for CAD was 1.67 for every 1% increment in HbA1c concentration. The latter study suggested HbA1c as an early marker for predicting the risk of CHD in non-diabetic patients [13]. Similarly, Hong et al. have conducted a prospective study on 1433 subjects (three groups based on baseline HBA1c level including a low group < 5.7%, $n = 483$; an intermediate group 5.7–6.3%, $n = 512$; and a high group >6.3%, $n = 438$) and concluded that a high baseline level of HbA1c could be considered as an independent marker for predicting the severity and outcome of CAD [14]. On the other hand, a recent retrospective study has reported that HbA1c cannot be used as an independent marker for the severity of CAD [9]. The conflicting results of the latter study might be attributed to the analytical methods used because using the HbA1c level, the researchers stratified the patients into three groups of < 6, 6–6.4 and ≥6.5, while such high levels of HbA1c were an exclusion criterion in other studies and this type of stratification might affect the results. However, in line with this result, Rebnord et al. have also shown that there is no overall association between HbA1c and prognosis of stable angina in non-diabetic patients [15].

In the current study, we also recognized new cut-off values of HbA1c to determine patients with severe coronary artery atherosclerosis (5.55%) and those with coronary artery stenosis (5.65%). Some of the previous studies have also investigated the prognostic value of

HbA1c for determining the number of diseased vessels. These studies have also shown that an increase in the concentration of HbA1c is associated with an increase in the number of diseased vessels [16,17].

The mentioned inconsistent results on the relationship between HbA1c and CAD or occurrence of atherosclerosis might also be attributed to different study designs, different times of follow-up, different definition of CAD outcomes and events and also different methods for the measurement of HbA1c [18]. All of these factors should be considered in future studies.

To the best of our knowledge, there is no published trial on the effect of reduction in HbA1c level on the occurrence of CAD. There could be some explanations about the relationship between concentration of HBA1c and occurrence of CAD or atherosclerosis. It is known that changes in lifestyle, including changes in dietary regimens, exercise and weight loss, which are suggested ways for reducing the HBA1c level, can have beneficial effects on traditional cardiovascular risk factors [13]. On the other hand, hyperglycaemia can induce oxidative stress which together with lipid peroxidation products and soluble advanced glycation end products can lead to endothelial dysfunction. This may help to express inflammatory genes and finally higher occurrence of atherogenetic events (http://www.ncbi.nlm.nih.gov/pubmed/16829472). Also, it is reported that HBA1c in addition to representing glucose level, can be used as a marker of protein glycation and related inflammation which can lead to CAD (http://www.ncbi.nlm.nih.gov/pubmed/8194672).

The main limitation of our study is that it was a cross-sectional study, and this type of study cannot exactly examine the cause and effect relationships, including the relationship between HbA1c and CAD. Therefore, more advanced methodologies such as interventional studies are recommended.

Conclusions

In this project, we concluded that HbA1c can be used as an independent marker for determining non-diabetic patients with coronary atherosclerosis and also determining severity of the disease. It should be noted that where there are conflicting results in the literature more original studies can be useful for running different review articles and meta-analysis. Furthermore, in our study, we could not assess the physical activity and lifestyle of patients which can influence both CAD and HBA1c. This could lead to confounding variables. The effect of these variables can be evaluated in interventional studies. Finally, conducting more original studies, especially clinical trials regarding the effect of reduction in the level of HbA1c on the coronary atherosclerosis, are recommended.

Disclosure statement

No potential conflict of interest was reported by the authors.

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