Background: Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide. Due to increased CAD risk factors in Saudi Arabia, research on more feasible and predictive biomarkers is needed. We aimed to evaluate glycated hemoglobin (HbA1c) as a predictor of CAD in low-risk profile non-diabetic patients living in the Al Qassim region of Saudi Arabia.

Methods: Thirty-eight patients with no history of CAD were enrolled in this cross-sectional study. They provided demographic data, and their HbA1c estimation followed the National Glycohemoglobin Standardization Program parameters. All patients underwent coronary computed tomography angiography (CCTA) for evaluation of chest pain. The extent of coronary artery stenosis (CAS) was quantified as percentage for each patient based on plaques detected in CCTA.

Results: Mean blood pressure of the patients was (91.2 ± 11.9 mmHg), BMI (28.3 ± 5.8 kg/m²), serum cholesterol level (174 ± 33.1 mg/dl), and HbA1c levels (mean 5.7 ± 0.45, median 5.7 and range 4.7 – 6.4%). Eighteen patients showed no CAS (47.4%), 12 showed minimal stenosis (31.6%), 3 showed mild stenosis (7.9%), 3 showed moderate stenosis (7.9%) and 2 showed severe stenosis (5.3%). A moderate correlation was detected between HbA1c and CAS percentages (r = 0.47, p < 0.05) as well as between HbA1c and the number of affected coronary vessels (r = 0.53, p < 0.001).

Conclusion: Glycated hemoglobin can be used as a predictive biomarker for CAD in non-diabetic low-risk patients.

Keywords: HbA1c, Coronary artery disease, CAD risk factors
Each of the screening tools has its advantages and disadvantages. Unfortunately, there is no settled consensus among clinicians on which tool is more likely to accurately predict fatal and non-fatal CAD-related outcomes [7]. Therefore, there is room for assessment of additional biomarkers that can detect early metabolic changes related to atherosclerosis and CAD.

Glycated hemoglobin (HbA1c), a well-known biomarker that reflects long-term glycemic control, has been an established diagnostic test for diabetic patients since 2010 [8]. Its value for the prediction of microvascular and macrovascular complications among diabetic patients is well established [8]. However, its potential as a screener of CAD among non-diabetic patients has shown mixed results in the literature.

This controversy in the literature regarding HbA1c is still ongoing. There are recent studies that did not find a positive correlation between HbA1c and cardiovascular-related outcomes (for example, death, nonfatal myocardial infarction, stroke, or hospitalization due to heart failure) [9]. On the other hand, evidence of positive correlation was detected in other studies, including recent meta-analyses of 22 studies involving 22,428 non-diabetic patients; high HbA1c levels were associated with a higher rate of long-term death (OR = 1.76, 95% CI = 1.44–2.16) and myocardial infarction (OR = 1.69, 95% CI = 1.07–2.67). The findings for death remained the same after sensitivity analyses [10].

Moreover, HbA1c cut-off values for atherosclerosis, CAD diagnosis, and stages of coronary artery stenosis (CAS) show diverse results in the literature with evidence for increased CAD risk concomitant with increased HbA1c levels even in non-diabetic populations [11].

There is no available data regarding the above HbA1c cut-off values in the Saudi population. Our research for local HbA1c cut-off values for CAD diagnosis and its stages of severity can be of great help in optimizing the prevention of CAD and its sequelae, especially in high-CAD-risk groups like the Saudi population.

Our main aim is to investigate the role of the biomarker HbA1c as a predictor of CAD in non-diabetic patients with no previous established CAD diagnosis.

**Methods**

**Study design and participants**

This cross-sectional study included 38 patients who came to the outpatient clinic of Prince Sultan Cardiac Center, Al Qassim for evaluation of their chest pain. They were enrolled in the study between December 2017 and July 2018 after signing the informed consent that explained their rights in the study, the perceived risks and benefits of participation, and the measures taken by the investigators to keep their personal information confidential. The inclusion criterion was non-diabetic adults that had indication for CCTA. A patient was excluded from the study if he/she had any of the following: (a) previous CAD diagnosis, (b) impaired kidney function detected by urea and creatinine, (c) any end organ failure or malignancy, (d) active infection, (e) diabetes (HbA1c ≥6.5% or fasting glucose ≥126 mg/dL), (f) previous diabetes diagnosis, or (g) was using anti-diabetic medication and/or statins.

**Data collection and laboratory testing**

Upon enrollment, the patients were interviewed with a standard questionnaire for the following data: (a) age (in years), (b) gender (male, female), (c) other demography, and (d) CAD risk factors, including diabetes, hypertension, dyslipidemia, physical inactivity, previous CAD, family history, and drug/substance intake. A basic physical examination was carried out, and an average of three resting blood pressure measurements were taken by a specialized cardiology nurse using a mercury sphygmomanometer. Hypertension was defined as blood pressure ≥140/90 mmHg or receiving anti-hypertension treatment. Body mass index (BMI) was calculated by dividing weight (kg) by height (meters squared). All patients had blood samples taken before CCTA for laboratory analysis, including urea, creatinine, fasting blood glucose (FBG), lipid profile, and HbA1c. HbA1c (Tina-quant Hemoglobin A1c Gen.3 REF 05336163 190 /Roche Diagnostics GmbH-Germany) was estimated according to the National Glycohemoglobin Standardization Program (NGSP) parameters. Criteria of diabetes mellitus diagnosis was defined according to the American Diabetic Association’s diagnostic criteria [12]: pre-diabetic stage [HbA1c 5.7–6.4 / impaired fasting glucose (IFG) (100–125 mg/dL)]; diabetes mellitus (HbA1c ≥6.5 /fasting glucose ≥126 mg/dL).

**CCTA**

All patients had an appointment for evaluation of suspected ischemia via high resolution CCTA with a dual-source 256 slice scanner (Siemens Flash Definition CT scanner; Siemens, Berlin, Germany). After a calcium score scan, we used either a prospective electrocardiography (ECG) triggering or a retrospective ECG gating acquisition. Post-processing and reconstruction of the CCTA were carried out with a Multimodality Workplace (Siemens Medical Solutions, Erlangen, Germany).

**CCTA results interpretation**

CCTA images were interpreted by two cardiologists who had at least 6 years of experience in CCTA.
interpretation. Based on the plaques detected in CCTA, CAS was quantified for each patient and was expressed in percentages [13]. Additionally, patients were classified as having minimal (<25%), mild (25–49%), moderate (50–69%), and severe (≥70%) stenosis according to the degree of luminal obstruction [14].

**Statistical analysis**

Quantitative variables are presented as mean ± SD. Qualitative variables are expressed as numbers and proportion. Correlation of HbA1c levels with CAS percentages and the number of affected vessels was determined by means of Spearman’s correlation test. A receptive operative characteristics (ROC) curve was generated to assess HbA1c values with different levels of CAD stenosis. P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics, version 25 (SPSS Inc., Chicago, Illinois, USA).

**Results**

The sample’s mean age was 50.8 years (standard deviation, SD = 9.5), and mean BMI was 28.3 kg/m² (SD = 5.8). Sixty-three percent (63%) were male, 65.5% were overweight or obese, 29.4% were hypertensive, and 21.4% had an above normal cholesterol level (>200 mg/dl).

The HbA1c level was 5.7 ± 0.45% (4.7–6.4%), and the data indicated that 44.7% were normal (<5.6%) and 55.3% were pre-diabetic (5.7–6.4%) (Table 1).

Eighteen patients showed no CAS (47.4%), 12 showed minimal stenosis (31.6%), 3 showed mild stenosis (7.9%), 3 showed moderate stenosis (7.9%), and 2 showed severe stenosis (5.3%). The mean number of vessels affected was 0.84 (SD 0.95; range 0–3) (Table 2).

Figure 1 shows three examples of CCTA images with their related HbA1c levels.

HbA1c was not significantly correlated with CVD risk factors like age, systemic hypertension, or the serum cholesterol level, and it had only a mild correlation with BMI (0.4, P < 0.05).

A moderate correlation could be detected between HbA1c and CAS quantitative percentage (r = 0.470, P = 0.051) as well as between HbA1c and the number of affected coronary vessels (r = 0.5344, P = 0.0011) (Table 3).

**Discussion**

A salient finding of this study was a moderate correlation between HbA1c and CAS percentages among non-diabetic patients. This finding is in agreement with a recent study by Ikeda et al. [15] that showed a higher HbA1c level as an independent risk factor of CAS. Previous studies, some of which included meta-analysis, found a positive correlation between HbA1c and cardiovascular events in non-diabetic adults [16–18]; however, these studies did not test the correlation between HbA1c and severity of CAS based on CCTA findings.

Geng et al. [10] conducted a meta-analysis using 20 studies involving 22,428 patients to investigate HbA1c correlation with clinical CAD outcomes; they found that an elevated HbA1c level increased the risks of both long-term mortality (odds ratio 1.76, 95% confidence interval 1.44–2.16, P < 0.001) and myocardial infarction (MI, odds ratio 1.69, 95% confidence interval 1.07–2.67, P = 0.026), but not the risk of early death in non-diabetic patients with CAD. More recently, Haring et al. [19] showed a positive association between high-normal HbA1c levels and increased CVD risk and mortality. On the other hand, there are studies that do not support that notion, such as by Liu et al. [20] and Shin et al. [21], in which HbA1c was

| Table 1 | Patient characteristics of the sample (n = 38) |
|----------|---------------------------------------------|
| Variable | Mean ± SD/ N (%)                             |
| Age (years) | 50.87 ± 9.56/ 24 (63.2)                      |
| Male      | 24 (63.2)                                    |
| Overweight/Obese | 19 (65.5)                                |
| Hypertensive | 5 (29.4)                                    |
| High cholesterol | 6 (21.4)                                    |
| HbA1c (%) | Normal 17 (44.7)/ Pre-diabetic 21 (55.3)    |

| Table 2 | Distribution of CAS among patients (n = 38) |
|----------|---------------------------------------------|
| Variable           | Mean ± SD/ N (%)                           | Min-Max |
| Stenosis (%)       | 19.6 ± 19/ 18 (47.37)                      | 5–75    |
| Number of affected vessels | 0.84 ± 0.95/ 12 (31.58)                  | 0–3     |
| Stenosis severity  |                                            |         |
| Normal             | 18 (47.37)                                 |         |
| Minimal            | 12 (31.58)                                 |         |
| Mild               | 3 (7.89)                                   |         |
| Moderate           | 3 (7.89)                                   |         |
| Severe             | 2 (5.27)                                   |         |
not associated with prognosis among non-diabetic patients with myocardial infarction.

A number of factors may explain the discrepancy in results between these studies. Some studies recruited young people with favorable cardiac risk profiles, while other studies had more elderly participants with already advanced CAD complications [20]. A few studies resorted to retrospective design, and therefore, may have missed unrecorded adverse cardiac events [22]. The studies also varied in the outcomes that they were interested in, which ranged from very early changes in the arterial wall pathology [15], to short-term clinical adverse outcomes [23], to long-term morbidity and mortality [10].

This study’s finding of an HbA1c cut-off value of 5.9% to differentiate coronary stenosis among non-diabetic patients is supported by findings from other studies although there is no Saudi data available for comparison. Ashraf et al. [24] studied 299 non-diabetic patients who had coronary angiography for suspected ischemia and reported that an HbA1c level of 5.6% could be used for CAD-specific risk stratification (OR: 2.8, 95% CI: 1.3–6.2, p-value: 0.009). Tomizawa et al. [25] found that an HbA1c level above 6% was associated with significant CVD risk in non-diabetic patients.

Our study focused on pre-diabetic patients, who are usually overlooked and neglected in clinical practice although endothelial dysfunction, the main pathogenesis of both micro and macrovascular diabetic complications, starts to develop in this early stage [26]. Consequently, this study highlights the significance of sub-threshold levels of HbA1c in a pre-diabetic condition as an early predictor of CAS.

A recently published study by Engel et al. [26] compared the endothelial permeability, which is considered a hallmark of CAD, with different HbA1c levels using an albumin-binding MR probe. This cross-sectional study included 26 patients and concluded that patients with both intermediate and high HbA1c levels are associated with a larger extent of endothelial damage of the coronary arteries as compared to patients with HbA1c levels below 5.7% [27].

Abnormal glucose regulation (AGR) and insulin resistance are thought to be crucial factors for the development of subclinical atherosclerosis and, consequently, CAD. In fact, AGR has been independently associated with acute coronary events [23]. Additionally, insulin resistance and CAD have been found to co-exist in newly diagnosed patients with impaired glucose tolerance and impaired fasting glucose [28].

The increase in serum HbA1c is likely to be associated with the increase in the number of coronary vessels affected with stenosis. As the study by Haring et al. [19] found a positive link between high-normal HbA1c levels and increased risk of subclinical atherosclerosis (0.02 mm increase in the thickness of common carotid artery media per 1% increase in HbA1c), so did we find a positive correlation between serum HbA1c and the affected number of coronary vessels with stenosis. Our results further corroborated the findings of the study by Tomizawa et al. [25], who investigated the relationship of HbA1c and coronary plaque characteristics and reported that plaque formation in the coronary vessels was twice as likely (OR 2.19, 95% CI =1.37–3.45, p = 0.005) in patients with elevated HbA1c levels.

This study was the first in Saudi Arabia to assess the relationship between serum HbA1c and CAS by CCTA. Moreover, its participants were non-diabetic with relatively low CAD risk, so the study showed the role HbA1c could play in the prevention and monitoring of

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Table 3  Correlation of HbA1c with CAS percentage & number of affected vessels

| Percentage of stenosis | Number of vessels |
|------------------------|------------------|
| Spearman’s r-value     | 0.47             |
| p-value                | < 0.05           |
| N                      | 38               |

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Fig. 1  Multiplaner reconstruction CCTA images for 3 studied cases with rising HbA1c levels. a. Normal right coronary artery (RCA), HbA1c = 4.8%; b. Mild stenosis at proximal left descending coronary artery (LAD) stenosis, HbA1c = 5.8%; and (c) Severe stenosis of the left circumflex coronary artery (LCX), HbA1c = 6.3%
CAD among those who are otherwise free from cardiac events. Finally, HbA1c, which was the focus of this study, is a standardized and widely available test that can be easily employed in primary healthcare centers for early prevention of CAD events.

**Limitations**

This study has few limitations. It was a single-center study and therefore may not have enrolled a full spectrum of pre-diabetic patients. It also had a small sample size. Future studies should employ larger samples and enroll patients from multiple sites to validate the findings of this study. Finally, the cross-sectional nature of this study with no follow up of the patients precluded it from establishing a temporal relationship between HbA1c and CAD. Future studies should employ a cohort design to follow up the patients. Additionally, trials could be undertaken to test the effect of lowering HbA1c on CAS in pre-diabetic patients.

**Conclusions**

Based on our findings, we conclude that glycated hemoglobin A1c can be used as a predictive biomarker for CAD in non-diabetic patients with a cut-off value of 5.9%.

**Abbreviations**

AGR: Abnormal glucose regulation; BMI: Body mass index; CAD: Coronary artery disease; CAS: Coronary artery stenosis; CCTA: Coronary computed tomography angiography; CVD: Cardiovascular disease; ECG: Electrocardiography; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin; IFG: Impaired fasting glucose; LAD: Left anterior descending coronary artery; LCX: Left circumflex coronary artery; MPR: Multiplanar reconstruction; NFG: Normal fasting glucose; NGSP: National Glycohemoglobin Standardization Program; RCA: Right coronary artery; ROC: Receiver operator characteristic curve

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**Authors’ contributions**

ME conceived of the idea, developed the theory, supervised the findings, and wrote the manuscript. HS shared in the methodology structure and analytical plan, and provided critical feedback. SB developed the theoretical formalism, performed the computations and the numerical simulations. NS designed the model and the computational framework, verified the analytical methods, developed the theoretical formalism, performed the analytic calculations, and helped supervise the project. WA, OR, SE & TR collected patient data. ZA shared in the practical work of coronary CT angiography. RA was the principle investigator, conceived of the idea, shared in the practical work of coronary CT angiography, supervised the findings, and wrote the manuscript. All authors read and approved the final manuscript.
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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Ethical approval from the regional research ethics committee was taken prior to commencing the study (Al Qassim providence, KSA Ministry of Health, approval number 45/44/1508). All patients signed informed consents matching with the committee regulations prior to their participation in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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