original article

Elevated fasting blood glucose, but not obesity, is associated with coronary artery disease in patients undergoing elective coronary angiography in a referral hospital in Jordan

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BACKGROUND: Obesity and its metabolic complications are endemic in the Middle East, but the cardiovascular consequences are not well defined in local studies.

OBJECTIVE: To assess the association between fasting blood glucose (FBG), obesity and coronary artery disease (CAD) in Jordan.

DESIGN: A cross-sectional, hospital-based study.

SETTING: A referral hospital in Amman, Jordan.

PATIENTS AND METHODS: Patients with complete anthropomorphic data who were referred for elective coronary angiography were included in the analysis. Associations between CAD, FBG and obesity were assessed in multivariate logistic regression models, adjusting for known risk factors.

MAIN OUTCOME MEASURE: The presence of CAD.

SAMPLE SIZE: 434 subjects.

RESULTS: Only those who underwent coronary angiography and had complete anthropometric data were included in the study: 291 (67.1%) had CAD and 143 (32.9%) had a normal coronary angiogram.The mean body mass index, waist circumference and FBG of the study participants was 30.0 kg/m^2, 106.0 cm and 8.8 mmol/L, respectively. The mean FBG was significantly higher in patients with CAD compared to those without CAD (9.5 vs. 7.3 mmol/L, P<.001). Waist circumference was significantly higher in women with CAD compared to women without CAD (111.0 vs. 105.9 cm, P=.036), but no significant difference was observed in men. In a multivariate analysis, FBG was a strong and significant predictor of CAD; however, none of the measures of obesity were significantly associated with CAD. The findings were robust in a sensitivity analysis that excluded patients with known diabetes mellitus.

CONCLUSIONS: Elevated FBG, but not obesity, predicted CAD in a Middle Eastern population. Improved prevention, detection and management of type 2 diabetes should be a priority in this setting.

LIMITATIONS: The cross-sectional design cannot control for temporal changes in risk factors and/or reverse causation.

CONFLICT OF INTEREST: None.

According to the Global Burden of Disease Study, cardiovascular disease (CVD) is the leading cause of disability and mortality in the world.[1] The World Health Organization (WHO) estimates that low- and middle-income countries bear more than 75% of the global CVD burden.[2] Obesity, physical inactivity, smoking, dyslipidemia, hypertension and diabetes mellitus (DM) are risk factors for CVD.[3-7] The Middle East is among the most affected areas of the world for many of these indicators. Notably, obesity is endemic in the region, and in a country like Jordan, it is estimated that 65.9% of adults above 18 years are suffering from either overweight or obesity.[8] At the same time, the prevalence of DM is steadily increasing in Middle Eastern countries, from 5.9% in 1980 to an all-time high 13.7% in 2014.[9]

The impact of obesity on CVD is well documented, and previous studies have suggested that waist circumference (WC), as a measure of abdominal adiposity, might be more important than body mass index (BMI), which does not distinguish muscle mass from fat.[10,11] Large WC, in combination with increased blood pressure, elevated fasting blood glucose (FBG), reduced high-density lipoprotein (HDL) cholesterol and elevated triglyceride level, defines the clinical syndrome known as the metabolic syndrome, which is associated with an increased risk of CVD, coronary artery disease (CAD) and overall mortality.[12,13] In Jordan, a study among 1121 healthy volunteers found that 28.7% of men and 40.9% of women met the diagnostic criteria for metabolic syndrome, which is considerably higher than most other countries of the world.[14]

Elevated FBG is an independent risk factor for CAD also in the absence of the metabolic syndrome. Results from the Framingham study found that the presence of DM doubled the risk for CVD in men and tripled it in women.[15] Similar data were reported in the Multiple Risk Factor Intervention Study in the USA.[16] Interestingly, a study of more than 24 000 non-diabetic individuals from the United States found that elevated FBG increased the risk of CAD also in this group of apparently healthy adults, after adjusting for other known risk factors.[17]

Since most studies of cardiovascular risk factors have been carried out in Europe and North America, the cardiovascular consequences of unhealthy lifestyle factors in the Middle East are not well described. Given the higher prevalence of obesity, DM and the metabolic syndrome in the region,[8,9,14] local studies are needed to better understand the interplay between these risk factors in a Middle Eastern setting. The present study aimed to assess the relative contribution of obesity and abnormal glucose metabolism on the occurrence of CAD in Jordan, and might provide new insight into how to best design preventive public health programs in the region.

PATIENTS AND METHODS

Study setting and participants

Between January and December 2015, participants who underwent elective coronary angiography at Prince Hamzah Teaching Hospital, a referral hospital in Amman, Jordan, were consecutively enrolled in a cross-sectional study. Pregnant or lactating women, and patients with kidney disease, liver disease or gastrointestinal disease were excluded. Written informed consent was obtained from all participants. The study protocol conformed to the ethical guidelines of the 1964 Helsinki declaration and its later amendments, and the study was approved by the Institutional Review Board Ethics Committee at Prince Hamzah Hospital.

Data collection

Patients were admitted the day before undergoing coronary angiography. Socio-demographic data, previous health issues, smoking status, and anthropometric measurements were recorded by trained research assistants using standardized questionnaires. Venous blood samples were drawn after 12 hours overnight fasting. Serum samples were separated from the whole blood and stored at −80 °C until subsequent analysis. Fasting blood glucose was measured with the ARCHITECT ci8200 assay (Abbott, Abbott Park, IL, USA).

Anthropometric measurements

Body weight was measured using a manual, calibrated scale (Seca, Hamburg, Germany), and height was measured using a calibrated measuring rod. BMI was calculated using the following equation: weight in kilograms divided by height in meters squared. Cutoff values established by the National Institutes of Health were used: normal body weight, 18.5 to 24.9;[9] overweight, 25.0 to 29.9; and obese, >30.0.[18] WC was measured by tape at the narrowest level between the lowest rib and the iliac crest at the end of normal expiration in standing position. Individuals with a WC above the established sex-specific threshold (88 cm for women and 102 cm for men) were categorized as high risk.[18] All anthropometric measurements were carried out by a trained dietitian.

Cardiac catheterization

The procedure was performed by standard percutaneous technique. In brief, the catheter was inserted into the radial artery and advanced to the aortic sinus cusp. Radiocontrast was given through the catheter, and the arterial tree was visualized by the contrast distribution within the coronary arteries. By comparing to an adjacent normal artery, the degree of stenosis could be quantified as percentage of the arterial lumen. Consistent with prior studies, CAD was defined as ≥20% stenosis of one or more coronary arteries.[19,20]

Statistical analysis

Differences in baseline variables between patients with and without coronary artery disease were estimated using chi-square tests for categorical variables and t tests for continuous variables. Fasting blood glucose was divided into categories based on clinically relevant thresholds: ≤6.0 mmol/L (normal), 6.1-6.9 mmol/L (impaired fasting glucose), 7.0-11.0 mmol/L (diabetes) and ≥11.1 mmol/L (grossly elevated).[9] Odds ratios (OR) for CAD were estimated using logistic regression models, and adjusted for known risk factors (age, sex, smoking, hypertension, dyslipidemia, family history of CVD) using the backward Wald method. Data were analyzed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided and the significance level was set at $P<.05$. The results were reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement guidelines.[21]

RESULTS

Baseline characteristics

Of 557 participants who underwent coronary angiography, 434 had complete anthropometric data and were included in the present analysis. Of these 434 subjects, 291 (67.1%) had CAD and 143 (32.9%) had a normal coronary angiogram. Of 291 patients with CAD, 103 (35.4%) underwent stent placement during the diagnostic procedure.

Most participants (n=307, 70.7%) were male, and the median age was 55 years (interquartile range 48-64). Previous hypertension, DM and dyslipidemia were reported by 208 (47.9%), 173 (39.9%) and 26 (6.0%) study participants, and 230 (53.0%) were current or previous smokers.

Compared to individuals with a normal coronary angiogram, CAD patients were more likely to be male (78.4% vs. 55.2%; $P<.001$), older (mean age 57.7 years vs. 50.3 years, $P<.001$), previous/current smokers (57.4% vs. 44.1%; $P=.009$) and have been previously diagnosed with DM (45.4% vs. 28.7%; $P=.001$).

Measures of obesity

The mean (SD) BMI and WC of the study participants was 30.0 (6.5) kg/m^2 and 106.0 (15.8) cm, respectively. Both the mean BMI (32.1 vs. 29.1 kg/m^2, $P<.001$) and WC (108.4 vs. 105.0 cm, $P=.038$) were significantly higher in women compared to men. Among women, 115 (90.6%) had a WC above the high-risk threshold (>88 cm), whereas 158 (51.5%) men had a high-risk WC (>102 cm). With regard to BMI, 83 women (65.4%) and 100 men (32.6%) were in the obesity range (≥30 kg/m^2). As expected, there was a significant correlation between BMI and WC (Pearson correlation coefficient 0.61, $P<.001$) (**Figure 1**).

Fasting blood glucose

The mean FBG of the study participants was 8.8 mmol/L (SD 5.2), with no significant difference between men and women (8.7 vs. 9.0 mmol/L, $P=.621$). In total, 176 individuals (40.6%) had a FBG within the normal range (≤6.0 mmol/L), 60 (13.8%) were in the impaired fasting glucose range (6.1 to 6.9 mmol/L), and 198 (45.6%) were above the diabetes threshold (≥7.0 mmol/L).

There was a significant association between WC and FBG; among those with a high-risk WC, the mean FBG was significantly higher than among patients with a low-risk WC (9.3 vs. 7.9 mmol/L, $P=.008$). The difference was more pronounced in women (9.3 vs. 5.8 mmol/L, $P<.001$) than in men (9.3 vs. 8.1 mmol/L, $P=.047$) (**Figure 2**). There was no significant

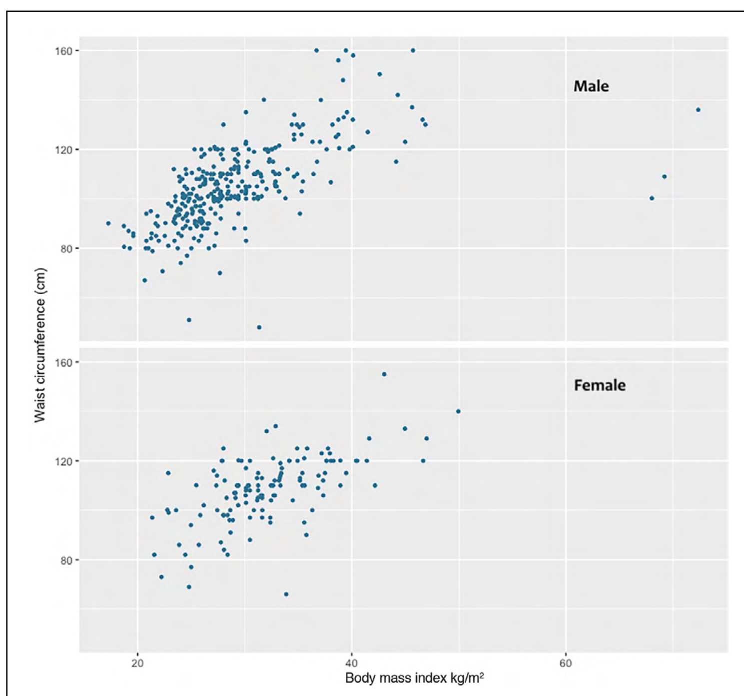

Figure 1. Correlation between body mass index and waist circumference in men and women.

association between BMI and FBG; the mean FBG was 9.0 mmol/L in those with a BMI <30 kg/m² and 8.4 mmol/L in individuals with a BMI ≥30 kg/m² (P=.220).

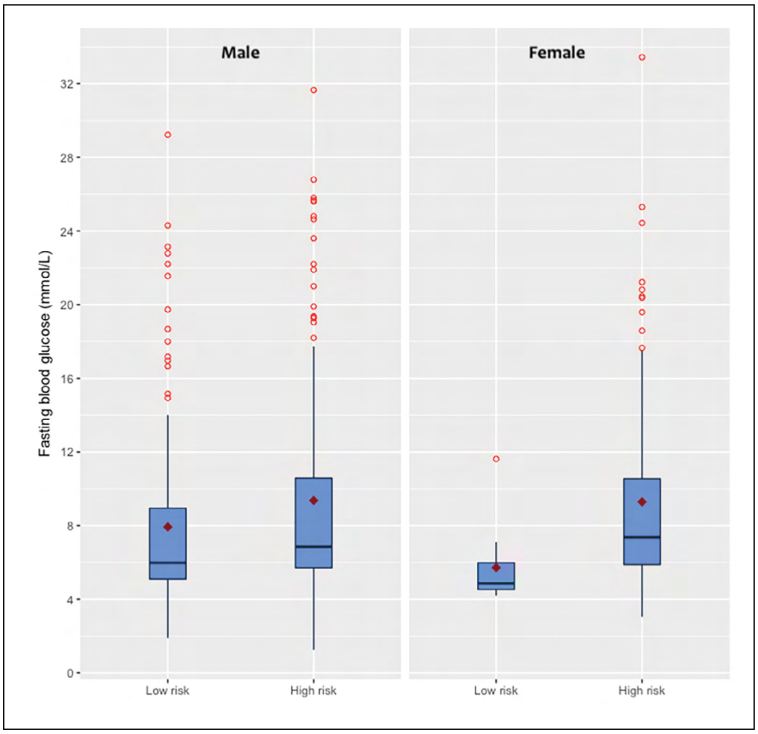

Figure 2. Fasting blood glucose by waist circumference risk category for men and women (median, first and third quartiles, red circles: >1.5 * IQR; red diamonds: mean). Differences in means (high vs. low risk) for males (8.1 vs 9.3 mmol/L, P=.047) and females (5.8 vs 9.3 mmol/L, P<.001). High-risk was defined as a waist circumference above 102 cm for men and 88 cm for women.

Table 1. Fasting blood glucose and measures of obesity in 434 patients with and without coronary artery disease.

	CAD (n=291)	Normal (n=143)	*P*
Fasting blood glucose (mmol/L)	9.5 (5.8)	7.3 (3.3)	<.001
Women	10.5 (5.9)	7.5 (3.5)	.001
Men	9.3 (5.7)	7.1 (3.2)	<.001
Body mass index (kg/m²)	29.6 (6.8)	30.7 (5.6)	.101
Women	32.3 (5.9)	32.0 (4.8)	.722
Men	28.9 (6.9)	29.7 (6.1)	.361
Waist circumference (cm)	106.2 (16.1)	105.5 (15.4)	.667
Women	111.0 (14.1)	105.9 (13.2)	.036
Men	104.9 (16.3)	105.2 (17.0)	.877

Data are mean (standard deviation). CAD, coronary artery disease.

Associations with CAD

The mean FBG level was significantly higher in patients with CAD compared to those without CAD (9.5 vs. 7.3 mmol/L, P<.001) (**Table 1**). Waist circumference was significantly higher in women with CAD compared to women without CAD (111.0 vs. 105.9 cm, P=.036); however, no significant difference was observed in men (104.9 vs. 105.2 cm, P=.877). There were no significant differences with regard to BMI.

In the univariate logistic regression analysis, increasing FBG was significantly associated with an increased risk of CAD: patients with a FBG above 11.0 mmol/L had an OR of 3.21 (95% confidence interval [CI] 1.75-5.89, P<.001) and those with a FBG between 7.0 and 11.0 mmol/L had an OR of 2.14 (95% CI 1.28-3.60, P=.004) for CAD compared to individuals with a normal FBG (≤6.0 mmol/L). There did not seem to be any increased risk of CAD in patients with impaired fasting glucose (FBG 6.1-6.9). With regard to BMI, individuals with obesity (BMI ≥30 kg/m²) appeared to have a reduced risk of CAD in univariate analysis (OR 0.44, 95% CI 0.25-0.79, P=.006). No significant associations were found between WC risk groups and CAD.

In the multivariate analysis, adjusting for age, sex, smoking, hypertension, dyslipidemia and a family history of CVD, none of the measures of obesity were significantly associated with CAD. FBG above 11.0 mmol/L, however, remained a strong and significant predictor of CAD (OR 3.02, 95% CI 1.51-6.05, P=.002) (**Table 2**).

In a sensitivity analysis, 173 patients with a known diagnosis of DM were excluded. Although the statistical power was diminished in this model, the significant association between FBG and CAD remained in the multivariate analysis: patients with a FBG between 7.0 and 11.0 mmol/L had an OR of 2.79 (95% CI 1.04-7.47, P=.042) for CAD compared to individuals with a normal FBG (≤6.0 mmol/L). Only 13 patients fell in the highest FBG category (≥11.0 mmol/L), and thus, the difference did not reach statistical significance (OR 1.49, 95% CI 0.37-6.01, P=.578).

DISCUSSION

In the present study, a high FBG was a strong and independent predictor of CAD. Although it is well-known that DM is a risk factor for CAD,[4] several studies have found that elevated FBG is an independent risk factor even in people without DM. Indeed, in a large meta-analysis of 217 150 individuals it was found that increased fasting glucose level was a significant risk factor for CVD among apparently healthy individuals

Table 2. Associations between fasting glucose, body mass index and waist circumference with coronary artery disease.

	CAD (n=291) N (%)	Normal (n=143) N (%)	Crude[1]		Adjusted[2]	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Fasting glucose (mmol/L)						
≤6.0	99 (34.0)	76 (53.1)	1		1	
6.1-6.9	40 (13.7)	21 (14.7)	1.46 (0.80-2.68)	.220	1.48 (0.74-2.94)	.265
7.0-11.0	81 (27.8)	29 (20.3)	2.14 (1.28-3.60)	.004	1.82 (0.99-3.33)	.052
≥11.1	71 (24.4)	17 (11.9)	3.21 (1.75-5.89)	<.001	3.02 (1.51-6.05)	.002
Body mass index (kg/m²)						
<25.0	60 (20.6)	20 (14.0)	1		1	
25.0-29.9	127 (43.6)	44 (30.8)	0.96 (0.52-1.77)	.901	0.97 (0.46-2.01)	.923
≥30.0	104 (35.7)	79 (55.2)	0.45 (0.30-0.68)	.006	0.56 (0.25-1.28)	.172
Waist circumference (cm)						
Low-risk	114 (39.2)	47 (32.9)	1		1	
High-risk[3]	177 (60.8)	96 (67.1)	0.76 (0.50-1.16)	.202	1.14 (0.60-2.18)	.683

CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

[1]Univariate logistic regression analysis. [2]Multivariate logistic regression analysis, adjusted for age, sex, smoking, hypertension, hyperlipidemia and a family history of cardiovascular disease. [3]Defined as >88 cm for women and >102 cm for men. Model summary for multivariate adjusted analysis: -2log likelihood: 435,255; Cox & Snell square: .233; Nagelkerke R square: .324

without DM.[22] This also applies to fasting glucose levels in the upper normal range; Nielson and colleagues reported a 53.9% higher risk of myocardial infarction among nondiabetic individuals with a FBG between 5.6 and 7.0 mmol/L, compared to those who have a FBG below 5.6 mmol/L.[17] Furthermore, a large study from the Asia Pacific region found a continuous association between blood glucose and CVD risk, which extended down to about 4.9 mmol/L, well below the usual FBG threshold for diagnosis of DM and impaired glucose tolerance.[23] Our study confirms the association between FBG and CAD in a region of the world where obesity, physical inactivity and type 2 diabetes are endemic.

Of note, BMI was not a significant predictor of CAD in our study. This is in contrast to an older study from the region, in which BMI was significantly associated with CAD in patients from (pre-war) Syria; however, the study was confined to men and other measures of obesity were not assessed.[24] The relationship between obesity and CAD has been subject to a lot of debate. Although obesity is associated with increased risk of CAD,[6,10,11] several observational studies have reported that the prognosis in patients with established CAD appears to be better in individuals with obesity compared to those with a normal or low body weight. Mortality after myocardial infarction and coronary revascularization is lower,[25,26] and the prognosis of congestive heart failure is more benign.[27] This so-called "obesity paradox" might have many explanations, including confounding and bias in epidemiological studies.[28] We did not prospectively study the prognosis in our study subjects, but the absence of an association between BMI and CAD in our cohort suggests that other factors than BMI per se might be more important in this population.

WC was significantly higher in women with CAD compared to women without CAD in the present study; however, in the multivariate analysis, the effect of WC was no longer apparent. Individuals with a high-risk WC had significantly higher FBG compared to those who had a normal WC, suggesting that any negative impact of a large WC could be, at least partly, explained by its effect on the blood glucose. This is in line with previous studies, which have shown that a large WC is associated with increased FBG and increased risk of manifest DM.[29-31]

Our study suggests that there is a huge potential for prevention of CAD in Jordan. In our study, about 60% had abnormal fasting blood glucose, although "only" 40% had a known DM diagnosis. Improved detection and management of type 2 diabetes, leading to better metabolic control, might have a major effect on the incidence of CAD in the country. Public health interventions to encourage physical activity and weight reduction can be expected to reduce the prevalence of both DM and CAD. This potential for prevention was underscored in the Prevention of Recurrences of Myocardial Infarction and Stroke (WHO-PREMISE) study, which included 10000 patients in 10 low- and middle-income countries, of whom nearly half of the patients had at least two modifiable risk factors.[32]

Our study has some limitations. First, selection bias cannot be excluded as this was a hospital-based study. Second, even if we controlled for other risk factors in the statistical analysis, there might have been residual confounding from factors not accounted for in our analysis, such as the effect of physical activity. Third, misclassification bias might have occurred as some patients with well-controlled DM might have had lower FBG because of antidiabetic medication. Fourth, we did not have prospective data in our study, and a follow-up study is being planned to assess long-term survival and identify prognostic factors. Finally, a cross-sectional study design might miss out important temporal changes in risk factors, and our findings should be confirmed, preferably in a population-based cohort study from the Middle Eastern region.

In conclusion, elevated FBG – but not obesity – was significantly associated with CAD in a Jordanian population where obesity is endemic. Given the high prevalence of modifiable cardiovascular risk factors in the region, this provides a useful target for future public health interventions. Future studies should aim to identify effective and culturally appropriate interventions to promote weight reduction, physical activity and diabetes control in the Middle East.

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