Predictive value of fasting blood glucose for serious coronary atherosclerosis in non-diabetic patients

Tong Zhao, Hui-Ping Gong, Zhao-Qiang Dong,
Yi-Meng Du, Qing-Hua Lu and
Hui-Qiang Chen

Abstract

Objective: To determine if high fasting blood glucose (FBG) level is an independent predictor of serious coronary lesions in patients with coronary artery disease (CAD).

Methods: We enrolled 64 patients who had symptoms of chest discomfort and who underwent coronary angiography. FBG was determined from blood samples and the extent of coronary artery lesions was analyzed according to Gensini score. We examined the relationships among diabetes, FBG, and coronary artery severity.

Results: Diabetes and FBG were significantly and positively related to Gensini score. Diabetes, but not FBG, was independently correlated with the occurrence of a Gensini score >41. However, FBG was significantly associated with Gensini score >41 in non-diabetic patients.

Conclusion: Hyperglycemia is an independent predictor of severe CAD in non-diabetic patients. Clinicians should be aware of this and should carry out appropriate early interventions.

Keywords

Fasting blood glucose, coronary artery disease, Gensini score, diabetes mellitus, hyperglycemia, prediction

Introduction

Diabetes mellitus (DM) is known to be a major risk factor for coronary artery disease (CAD), which is the main cause of death in diabetic patients. Diabetic patients

Department of Cardiology, the Second Hospital of
Shandong University, Shandong University, Ji-nan,
Shandong Province, China

Corresponding author:
Hui-Qiang Chen, Department of Cardiology, the Second
Hospital of Shandong University, Shandong University,
Ji-nan, Shandong Province, China.
Email: hqchen361@sdu.edu.cn

have more extensive, diffuse, calcified, and severe coronary artery lesions compared with non-diabetic patients,[1] which is closely related to the poor prognosis of DM. Coronary artery lesions can also be detected in the pre-diabetic state, including in patients with impaired fasting glucose (IFG) and impaired glucose tolerance.[2,3] There is thus a need to identify the early signs of atherosclerosis in patients with DM and pre-DM, to allow early interventions to treat the atherosclerotic process.

Glycosylated hemoglobin (HbA1c) level is an indicator of the average blood glucose concentration over the past 3 months. Recent studies demonstrated that high HbA1c levels could predict the prevalence and complexity of CAD in patients with not only DM, but also those with pre-DM.[4–6] Notably however, the HbA1c level may be affected by multiple factors including anemia, pregnancy, hypertriglyceridemia, and chronic liver disease,[7] which might have a marked impact on the predictive value of HbA1c for CAD. Fasting blood glucose (FBG) is a cheap and convenient measure of glucometabolism, and could thus be a good candidate or a beneficial addition to HbA1c for screening for severe coronary artery lesions in patients with DM or pre-DM. Growing evidence suggests that hyperglycemia in non-diabetic patients is closely related to the presence and severity of CAD,[8–11] raising the possibility that high FBG level might be a useful predictor of serious coronary lesions. However, the value of FBG as an independent predictor of serious coronary lesions currently remains unclear.[4,6,12]

This study aimed to investigate the significance of FBG for predicting a Gensini score >41, as a marker of coronary artery lesion severity, in hospitalized patients undergoing coronary angiography.

Patients and methods

Patient selection

The study population was selected from patients with symptoms of chest discomfort who underwent coronary angiography at the Second Hospital of Shandong University in China from November 2014 to January 2015. Patients were diagnosed with CAD if they had at least one significant stenosis (>50%) of the arterial lumen in any of the major coronary arteries, including the left main coronary artery, left anterior descending artery, left circumflex coronary artery, and right coronary artery, or in the main branches of the vascular system.[13] The present study did not include patients with coronary artery spasm angina, valvular heart disease, systemic inflammatory disease, autoimmune disorders, neoplastic disease, or severe hepatic or renal dysfunction. A total of 64 patients were included in this study. The study protocol was approved by the ethics review board of The Second Hospital of Shandong University, Ji-nan, China and carried out in accordance with the Declaration of Helsinki. Informed written consent was obtained from each patient.

Blood sampling and definitions

All blood samples were collected during hospital stay after an overnight fast (12 hours) for measurement of FBG, total cholesterol, and total triglycerides. Diabetes was defined as a FBG ≥ 7.0 mmol/L, a history of diabetes, or current treatment with hypoglycemic medications. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, a history of hypertension, or current treatment with antihypertensive medications. Hyperlipidemia was defined as a fasting total cholesterol concentration

≥ 6.21 mmol/L or total triglycerides ≥ 2.26 mmol/L, a history of hyperlipidemia, or the use of lipid-lowering medications. Smoking status was determined from the patient's medical history.

Coronary angiography

Selective coronary angiography was performed using the standard Judkin's technique, by filming multiple views of each blood vessel. Coronary angiograms were analyzed by two experienced interventional physicians blinded to the clinical characteristics of the patients.

The severity of coronary artery stenosis was assessed using the Gensini scoring system, as described previously.[13] The Gensini score was calculated by assigning a severity score to each coronary narrowing on the basis of the degree of luminal stenosis and its geographic importance. Decreases in luminal diameter of 25%, 50%, 75%, 90%, 99%, and total occlusion were given scores of 1, 2, 4, 8, 16, and 32, respectively. The score was then multiplied by a factor symbolizing the functional significance of the lesion in the coronary arterial tree, e.g. 5 for the left main coronary artery, 2.5 for the proximal left anterior descending artery or left circumflex coronary artery, 1.5 for the mid-left anterior descending artery, and 1 for the right coronary artery or the distal left anterior descending artery.[13,14]

On the basis of the calculated Gensini scores, the subjects were divided into two subgroups: low and intermediate Gensini score (≤ 41, n = 38) and high Gensini score (> 41, n = 26).[13]

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

Continuous data are shown as mean ±standard deviation and were compared by analysis of variance (ANOVA) when the data were normally distributed. Categorical data were expressed as number of cases (n) and percentage (%), and compared by χ^2 tests. Relationships among DM, FBG, and coronary artery severity were investigated by Pearson's correlation analysis. Logistic regression analyses were performed to evaluate the relationship between FBG and a Gensini score > 41. Power analyses were conducted using PASS software version 11.0.7 (NCSS, LLC, Kaysville, UT, USA). A P value < 0.05 was considered to be significant.

Results

A total of 64 patients were included in this study. The mean age of the patients was 60.3±10.9 years and 44 (69%) of the patients were men. The percentages of patients with smoking, DM, hypertension, and hyperlipidemia were 47%, 33%, 58%, and 33%, respectively. The demographic and clinical characteristics of the patients classified according to Gensini score are shown in Table 1. There were no significant differences between the groups in terms of age, gender, smoking history, blood pressure, or blood lipids. However, patients with a high Gensini score were more likely to have a history of DM and more likely to have a higher FBG.

Gensini score was positively correlated with DM (r = 0.514, $P < 0.001$) and FBG (r = 0.312, $P = 0.012$). There was no significant correlation between Gensini score and age, gender, smoking, hypertension, or hyperlipidemia. However, Gensini score was significantly related to FBG in nondiabetic patients (r = 0.387, $P = 0.010$).

We evaluated the value of FBG for predicting a high Gensini score, as a marker of

Table 1. Baseline clinical characteristics based on Gensini score.

Variable	Low and intermediate GS (≤41, n=38)	High GS (>41, n=26)	P value
Age (year)	60.2 ± 11.8	60.6 ± 9.5	0.255
Male (n, %)	25 (66%)	19 (73%)	0.537
Smoking (n, %)	16 (42%)	14 (54%)	0.355
Diabetes (n, %)	5 (13%)	16 (62%)	<0.001
Hypertension (n, %)	20 (53%)	17 (65%)	0.310
Hyperlipidemia (n, %)	11 (29%)	12 (46%)	0.159
FBG (mmol/L)	5.6 ± 1.3	7.3±3.7	<0.001

GS, Gensini score; FBG, fasting blood glucose.

Table 2. Independent predictors of Gensini score >41 in multivariate logistic regression analysis.

Variable	OR, 95% CI	P value
Age	1.034 (0.972–1.100)	0.293
Sex	1.008 (0.212–4.791)	0.992
Smoking	0.877 (0.200–3.849)	0.862
Diabetes	10.240 (2.156–48.636)	0.003
Hypertension	1.190 (0.333–4.248)	0.789
Hyperlipidemia	1.459 (0.412–5.171)	0.558
FBG	1.098 (0.815–1.479)	0.537

GS, Gensini score; FBG, fasting blood glucose.

Table 3. Independent predictors of Gensini score >41 in non-diabetic patients according to multivariate logistic regression analysis.

Variable	OR, 95% CI	P value
Age	1.070 (0.972–1.178)	0.166
Sex	1.392 (0.167–11.616)	0.760
Smoking	1.087 (0.108–10.979)	0.944
Hypertension	4.232 (0.596–30.025)	0.149
Hyperlipidemia	1.046 (0.173–6.330)	0.961
FBG	5.779 (1.382–24.161)	0.016

GS, Gensini score; FBG, fasting blood glucose.

CAD severity, by multivariate logistic regression analysis. Multiple logistic regression identified DM (odds ratio [OR] = 10.240, 95% confidence interval [CI] 2.156–48.636, $P = 0.003$), but not FBG (OR = 1.098, 95% CI 0.815–1.479, $P = 0.537$), as an independent correlate of high Gensini score (Table 2). The power of the logistic regression analysis was 77.5%.

We further explored the predictive value of FBG for high Gensini score in non-diabetic patients by conducting multivariate logistic regression analysis based on traditional risk factors impacting on high Gensini score. There was a significant association between FBG and high Gensini score (OR = 5.779, 95% CI 1.382–24.161, $P = 0.016$) when confounding factors including age, gender, smoking, hypertension, and hyperlipidemia were analyzed in the logistic regression model (Table 3). The power of the logistic regression analysis was 73.6%.

Discussion

This study demonstrated that hyperglycemia was closely linked to the complexity of CAD in non-diabetic patients, and that non-manipulated FBG could independently predict severe CAD in these patients.

DM is an important risk factor for, and indeed is often considered to be equivalent to, coronary heart disease. Compared with non-diabetic patients, patients with DM tend to have more inflammatory infiltration (macrophages and T lymphocytes), larger

necrotic core size, and more diffuse atherosclerosis in the coronary lesions.[15] A systematic review by Ford et al.[16] revealed that IFG increased the relative risk of cardiovascular disease by about 1.12 to 1.37 times, indicating that IFG could moderately increase the risk of cardiovascular disease. In the current study, we demonstrated that DM and high FBG were positively related to the severity of coronary artery stenosis, in line with the results of previous reports.[8–11]

Basic research supports an important role for hyperglycemia in the progression of atherosclerosis. Mounting evidence has shown that hyperglycemia could induce the overproduction of mitochondrial reactive oxygen species in cardiovascular cells, and excessive reactive oxygen species could then promote atherosclerosis by activating multiple pathways, including increased substrate conversion by aldose reductase (AKR1B1), increased formation of methylglyoxal, the major advanced glycation product precursor, activation of protein kinase C isoforms β, δ, and θ, and increased protein modification by O-linked β-N-acetylglucosamine.[17] Hyperglycemia might also accelerate atherosclerosis by inducing endothelial cell dysfunction, reducing nitric oxide bioavailability, promoting a vasoconstrictive or prothrombotic state, and boosting nuclear factor-κB expression.[18]

The extent and severity of CAD can be evaluated using the Synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) score[19] or the Gensini score.[13] These scores, together with several clinical variables, can predict the likelihood of fatal and non-fatal cardiovascular events in patients with CAD.[20] Yang et al.[12] demonstrated that SYNTAX scores were higher in subjects with type 2 DM or IFG compared with those with normal FBG. In a study by Karakoyun et al.,[4] high FBG and a SYNTAX score

>22 were significantly correlated in patients with type 2 DM, while a further study found that either DM or IFG could predict a SYNTAX score >22.[12] However, no association between fasting glucose levels and SYNTAX score >22 was found in non-diabetic patients in a study by Arbel et al.[6] Notably, in terms of artery stenosis, the Gensini score starts at 25% occlusion while the SYNTAX score only begins at 50%, suggesting that the Gensini score might be a more sensitive parameter than SYNTAX score for detecting early atherosclerotic coronary artery lesions. Although previous studies demonstrated that hyperglycemia was positively related to Gensini score in non-diabetic patients,[8–11] whether hyperglycemia was closely correlated with high Gensini score in these patients remained unknown.

Using the Gensini rather than the SYNTAX scoring system, we found that high FBG in non-diabetic patients could predict the presence of severe coronary lesions, indicated by a Gensini score >41. However, further larger studies are needed to explain the discrepancies among the above studies and to determine the predictive role of FBG for severe coronary lesions.

Importantly, this study showed that both DM and high FBG were closely linked to the extent and severity of CAD. However, FBG did not predict the severity of coronary lesions in patients with DM. This could be because FBG may be influenced by antidiabetic drugs in patients with DM, while FBG in non-diabetic patients is not manipulated by hypoglycemic agents. These results thus support different predictive values for FBG in terms of coronary lesion severity between diabetic and non-diabetic patients.

This study had several limitations. First, it was a cross-sectional study and lacked long-term follow-up data. Second, the number of patients was relatively small

because of funding limitations, which might have limited its statistical power. Third, all patients in our study population underwent coronary angiography, which might have introduced selection bias.

Conclusion

High FBG is an independent predictor of severe CAD in non-diabetic patients, while the presence of DM also usually signifies serious lesions in CAD patients. The occurrence of hyperglycemia in non-diabetic patients should thus be given more attention and treated by appropriate early interventions.

ORCID iD

Hui-Qiang Chen http://orcid.org/0000-0001-6928-4687

References

1. Naito R and Miyauchi K. Coronary artery disease and type 2 diabetes mellitus. *Int Heart J* 2017; 58: 475–480.
2. Gurudevan S, Garg P, Malik S, et al. Impaired fasting glucose is associated with increased severity of subclinical coronary artery disease compared to patients with diabetes and normal fasting glucose: Evaluation by coronary computed tomographic angiography. *BMJ Open* 2016; 6: e005148.
3. Suzuki K, Takano H, Kubota Y, et al. Plaque characteristics in coronary artery disease patients with impaired glucose tolerance. *PloS One* 2016; 11: e0167645.
4. Karakoyun S, Gokdeniz T, Gursoy MO, et al. Increased glycated hemoglobin level is associated with syntax score ii in patients with type 2 diabetes mellitus. *Angiology* 2016; 67: 384–390.
5. Ashraf H, Boroumand MA, Amirzadegan A, et al. Hemoglobin A1C in non-diabetic patients: An independent predictor of coronary artery disease and its severity. *Diabetes Res Clin Pract* 2013; 102: 225–232.
6. Arbel Y, Zlotnik M, Halkin A, et al. Admission glucose, fasting glucose, hba1c levels and the syntax score in non-diabetic patients undergoing coronary angiography. *Clin Res Cardiol* 2014; 103: 223–227.
7. Malkani S and Mordes JP. Implications of using hemoglobin A1C for diagnosing diabetes mellitus. *Am J Med* 2011; 124: 395–401.
8. Dong X, Zhou L, Zhai Y, et al. Impaired fasting glucose and the prevalence and severity of angiographic coronary artery disease in high-risk Chinese patients. *Metabolism* 2008; 57: 24–29.
9. Yan Q, Gu WQ, Hong J, et al. Coronary angiographic studies of impaired glucose regulation and coronary artery disease in Chinese nondiabetic subjects. *Endocrine* 2009; 36: 457–463.
10. Konstantinou DM, Chatzizisis YS, Louridas GE, et al. Non-diabetic hyperglycaemia correlates with angiographic coronary artery disease prevalence and severity. *Diabetes Metab* 2010; 36: 402–408.
11. Gui MH, Li X, Lu ZQ, et al. Fasting plasma glucose correlates with angiographic coronary artery disease prevalence and severity in Chinese patients without known diabetes. *Acta Diabetol* 2013; 50: 333–340.
12. Yang X, Liu H, Yang F, et al. Elevated risk of an intermediate or high syntax score in subjects with impaired fasting glucose. *Intern Med* 2015; 54: 439–444.
13. Chen J, Chen MH, Li S, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of coronary artery disease: a Gensini score assessment. *J Atheroscler Thromb* 2014; 21: 1271–1282.

14. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol* 1983; 51: 606.

15. Virmani R, Burke AP and Kolodgie F. Morphological characteristics of coronary atherosclerosis in diabetes mellitus. *Can J Cardiol* 2006; 22(Suppl B): 81B–84B.

16. Ford ES, Zhao G and Li C. pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol* 2010; 55: 1310–1317.

17. Shah MS and Brownlee M. Molecular and cellular mechanisms of cardiovascular disorders in diabetes. *Circ Res* 2016; 118: 1808–1829.

18. King RJ and Grant PJ. Diabetes and cardiovascular disease: pathophysiology of a life-threatening epidemic. *Herz* 2016; 41: 184–192.

19. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009; 5: 50–56.

20. Sinning C, Lillpopp L, Appelbaum S, et al. Angiographic score assessment improves cardiovascular risk prediction: The clinical value of SYNTAX and Gensini application. *Clin Res Cardiol* 2013; 102: 495–503.