Hormozgan Medical Journal

doi 10.34172/hmj.2023.968

Hormozgan Med J. 2023; 27(3): 111-117

Original Article

Association of Impaired Fasting Glucose and Coronary Artery Disease in Non-diabetic Population

Shahin Abbaszadeh[1*], Yasaman Hafezpour[1], Marzieh Nikparvar[1], Elham Bushehri[2], Hossein Abbasi[3], Mahta Moraghebi[3], Hossein Farshidi[1], Masoumeh Kheirandish[4]

[1]Cardiovascular Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[2]Medical Education Group, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[3]Student Research Committee, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[4]Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

***Correspondence to:**
Shahin Abbaszadeh,
Email: sh.abbaszadeh@humas.ac.ir

Abstract

Background: Prediabetes is associated with coronary artery disease (CAD). The current study aimed to investigate the association between impaired fasting glucose (IFG), CAD, and coronary artery stenosis severity.

Methods: This case-control study was performed on 35-70 year-old non-diabetic individuals. Patients who had coronary artery stenosis ≥ 50% at least in one coronary artery and those with stenosis < 50% on angiography were considered as case and control groups, respectively. Patients were selected from Shahid Mohammadi Educational Medical Center in Bandar Abbas in 2018-2019. Age, gender, body mass index (BMI), smoking status, history of hypertension and hyperlipidemia, family history of CAD, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), creatinine, and lipid profiles were compared between the two groups.

Results: There were 52 subjects in each case and control group. The mean age of participants (N = 104) was 54.83 ± 9.36, and 71.2% of them were male. The mean of FPG ($P < 0.0001$), low-density lipoprotein (LDL) ($P = 0.02$), triglyceride ($P = 0.007$), and the HbA1c ($P = 0.011$) were significantly higher in the case group than in the control group. Moreover, high-density lipoprotein (HDL) levels were significantly lower in the CAD group compared to the control group ($P = 0.006$). Furthermore, binary logistic regression demonstrated that the chance of IFG was (OR: 12.49), HbA1c (OR: 12.28), and LDL (OR: 1.05) in people with CAD.

Conclusion: IFG and elevated HbA1c levels are significantly associated with an increased risk of CAD in the Iranian adult population.

Keywords: Impaired fasting glucose, Prediabetes, Coronary artery disease, Angiography

Received: March 16, 2021, **Accepted:** October 26, 2021, **Published Online:** August 5, 2023

Background

Cardiovascular disease (CVD) is responsible for the high mortality rate across the world. Studies have predicted that CVD will lead to a significant increase in deaths in all populations by 2020 (1, 2). Based on the American Heart Association (AHA) consensus report, coronary artery disease (CAD) is the most common type of CVD with a prevalence rate of nearly 51% (3, 4). Early detection of CAD patients is crucial for complications and mortality prevention (5). Several studies have shown that diabetic patients have a two to four times increased risk of coronary heart disease than healthy populations (5). The epidemiologic studies revealed that CVD is responsible for about 46% of all deaths among the Iranian population (6).

Several studies have demonstrated that diabetic patients have a two to four times increased risk of coronary heart disease than healthy populations (7-9). Indeed, studies have reported an increasing role of hyperglycemia in the development of CVD. Increased plasma glucose levels and impaired glucose tolerance (IGT) tests are associated with an increased CVD risk (10-12). According to previous studies, severe atherosclerosis causes CVD when the patient is in a prediabetes condition, including IGT, impaired fasting glucose (IFG), or both. Prediabetes refers to a transition state between a normal glucose tolerance state and type 2 diabetes mellitus (T2DM). Prediabetes, by definition, is the isolated IGT, isolated IFG, or the co-existence of them. There are different etiology and pathophysiology for IFG and IGT. Prediabetes is a prelude to diabetes, and there is a continuous range from normoglycemia to T2DM (13).

Isolated IGT is associated with moderate to severe muscle insulin resistance and impaired first and second-

phase insulin secretion. In contrast, moderate insulin resistance in the liver and impaired first-stage of insulin secretion are observed in the IFG conditions. However, they have normal or approximately normal sensitivity to the insulin in their muscles (14-18). Prediabetic subjects are predisposed to T2DM and significant atherosclerotic CVD (19-22).

The IGT diagnosis requires an oral glucose tolerance test that patients are reluctant to perform (23). Based on American Diabetes Association (ADA) recommendation, IFG is defined by FPG levels ranging between 100 and 125 mg/Dl, while IGT is the blood glucose between ≥ 140 mg/dL and ≤ 199 mg/dL after 75 oral glucose load challenging in the presence of FPG < 126 mg/dL (24). Although the association between CAD risk and its associated mortality has been identified with increased glucose levels, there are controversial findings regarding lower FPG levels and CAD mortality association (25, 26). Indeed, the relationship between CAD risk and its associated mortality with different FPG levels has been less studied (27, 28).

Prediabetes is associated with complications of macrovascular organs such as CVD, stroke, and peripheral vascular disease. These conditions could be detected in patients with type 2 diabetes, but they would begin and progress during the prediabetes period (29-32). A recent meta-analysis of 35 studies that assessed the association of myocardial infarction (MI), congestive heart failure, CAD, and atherosclerosis found that the atherosclerosis process occurs in prediabetes individuals (33-35). In addition, pre-diabetic people often have dyslipidemia, that is, high triglycerides and low high-density lipoprotein (HDL) (36-40). According to the result of a long-term follow-up study, a diabetes prevention strategy by modifying lifestyle led to a reduction in CVD as well as all causes of mortality (41).

Objectives

Due to the high prevalence of CAD and diabetes as significant risk factors for CAD, this study was conducted to investigate the relationship between IFG, plasma glucose levels, and CAD in non-diabetic patients.

Materials and Methods

This case-control study has been performed on 104 patients between April 2017 and March 2017, after receiving permission from the Ethics Committee of Hormozgan University of Medical Sciences, and it complies with the statements of the Declaration of Helsinki. The study population included non-diabetic patients aged 35-70 years referred to Jorgani's Angiography Center, Bandar Abbas, Iran. The informed constant was taken, then demographic and anthropometric measurements were done by a trained nurse. Afterward, age, sex, family history of CAD, history of CAD hyperlipidemia, hypertension, and cigarette smoking were recorded.

Each group's sample size was estimated at 52 individuals with an accuracy of 50% and a reliability coefficient of 95%. Sample selection was performed by systematic random sampling. In this way, the files were first divided into two categories: CAD positive and CAD negative. Finally, the number of CAD and non-CAD cases were 250 and 300, respectively. Systematic sampling was conducted in each category to achieve the target sample size. Then, cardiovascular risk factors and demographic data were assessed using a researcher's checklist.

The average weight of the subjects was computed using a digital scale, which had a measurement accuracy of 0.5 kg. The height was also measured with the subjects standing barefoot, and body mass index was calculated as weight in kilograms divided by the square of the height in meters.

Before angiography, the blood samples were taken after 10 hours of fasting condition. This sample was kept at -70°C for analysis. The serum glucose, lipids, creatinine, and glycated hemoglobin (HbA1c) were assessed immediately after admission. Standard enzymatic methods determined total cholesterol, triglyceride, HDL cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glucose. The turbid inhibition immunological assay was used to measure HbA1c. CAD was considered stenosis of at least 50% of the diameter of one of the main epicardial coronary arteries or branches, and CAD positive was defined as more or equal to 50% of the stenosis, which was estimated visually.

The presence of CAD was classified as one, two, and three vessels, or left main artery disease with a minimum of 50% stenosis. Depending on the number and severity of involved arteries, patients were classified as non-CAD or with one, two, three-vessel, or left main disease. The subjects diagnosed without or minimal CAD after angiography (no stenosis or less than 50% stenosis) were counted in the control group, and CAD patients were included in the case group.

People who had a history of diabetes, and/or being on anti-hyperglycemic agent treatment, and/or the HbA1c equal or more than 6.5%, and/or 2 hours post-challenge, and 75 grams glucose equal or greater than 200 mg/dL, regardless of fasting glucose level, were diagnosed with diabetes mellitus.

Hypertension was defined by the history of high blood pressure or the use of antihypertensive drugs or systolic blood pressure of at least 140 and/or diastolic blood pressure of at least 90 mmHg in two separate measurements. Hyperlipidemia was considered using blood lipid-lowering drugs or triglycerides greater than 150 mg/dL or total cholesterol more than 200 mg/dL.

The data analysis was done by SPSS version 18 software. The Smirnoff-Kolmogorov test was used to evaluate the normal distribution of quantitative data. Statistical

analysis methods such as independent t-test, Chi-square, and logistic regression were used to determine the relationship between the quantitative and qualitative variables, respectively. Then, the Mann-Whitney test was used to compare variables lacking a normal distribution in both case and control groups. Binary logistic regression was then used to predict the roles of the variables in CVD subjects. The variables with a *P* value less than 0.25 were included in regression analysis, and the *P* values less than 0.05 were considered statistically significant cut points.

Results

A total of 104 non-diabetic patients were enrolled in this study. The mean age of these individuals was 56.52 ± 9.97 and 53.13 ± 9.00 years in the case and control groups, respectively, and the men consisted of 74 (71.2%) participants. The distribution of quantitative variables based on the mean and standard deviation is presented in Table 1. According to Table 1, there was no significant difference between the age case and control groups ($P = 0.073$). The case group had higher statistically significant FPG ($P < 0.001$), HbA1c ($P = 0.011$), and LDL-C ($P = 0.02$) levels but a lower HDL ($P = 0.006$) level compared to control subjects.

Table 2 displays the logistic regression analysis for multiple variable risk estimation by odds ratio (OR) both crude and adjusted. There were no statistically considerable differences between the two groups in the variables with regard to age, weight, height, body mass index, smoking, history of hypertension, history of hyperlipidemia, and family history of CAD, but there was a significant relationship between the presence of IFG (OR:12.49; 1.6-95.5, $P = 0.015$), HbA1c (OR: 12.28; 2.5-58.5, $P = 0.002$), and LDL-C (OR: 1.05; 1.01-1.10, $P = 0.020$). The chance of IFG, high HbA1c, and high LDL-C in CAD subjects while controlling other influential variables was 12.5, 12.28, and 1.05 times higher, respectively, compared to their counterparts. As Tables 3 and 4 depict, there was no significant difference in the relationship between IFG, HbA1c, and severity of CAD in the case group ($P > 0.05$).

Table 1. Anthropometric and Demographic Characteristics in Case and Control Groups

	Case	Control	Total	*P* Value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)	56.52 ± 9.97	53.13 ± 9.00	54.83 ± 9.62	0.073
Weight (kg)	70.67 ± 12.88	70.10 ± 12.63	70.38 ± 12.70	0.979
Height (m)	1.65 ± 0.09	1.65 ± 0.08	1.67 ± 0.08	0.239
BMI (kg/m²)	25.0 ± 4.43	25.49 ± 4.20	25.25 ± 4.30	0.576
FPG (mg/dL)	105.23 ± 13.35	93.04 ± 14.58	99.13 ± 15.20	< 0.001
HbA1c (%)	5.38 ± 0.48	5.21 ± 0.40	5.29 ± 0.44	0.011
Hb (g/dL)	12.8 ± 1.55	12.90 ± 1.68	12.85 ± 1.61	0.786
Cr (mg/dL)	0.98 ± 0.23	0.95 ± 0.17	0.96 ± 0.20	0.654
TC (mg/dL)	173.79 ± 48.93	163.40 ± 35.07	168.60 ± 42.68	0.272
HDL (mg/dL)	40.10 ± 8.53	46.25 ± 11.26	43.17 ± 10.41	0.006
LDL (mg/dL)	105.38 ± 37.69	86.24 ± 27.88	95.81 ± 34.36	0.020
TG (mg/dL)	146.94 ± 67.21	116.69 ± 72.14	131.82 ± 71.03	0.007

Note. SD: Standard deviation; BMI: Body mass index; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c, Hb: Hemoglobin; Cr: Creatinine, TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides.

Discussion

In the present study, 104 non-diabetic people aged 35-70 years were evaluated. The present study mainly aimed

Table 2. Binary Logistic Regression Analysis of Impaired Fasting Glucose, Anthropometric Indices, Laboratory Measurements, and Coronary Artery Disease

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Age (y)	1.03 (0.99-1.08)	-	
Weight (kg)	1.00 (0.97-1.03)	-	
Height (m)	1.03 (0.98-1.08)	-	
BMI (kg/m²)	0.97 (0.89-1.06)	-	
Hb (g/dL)	0.96 (0.76-1.22)	-	
Cr (mg/dL)	2.10 (0.31-14.1)	-	
TC (mg/dL)	1.00 (0.99-1.01)	-	
HDL (mg/dL)	0.94 (0.90-0.98)	-	
LDL (mg/dL)	1.01 (1.00-1.03)	1.05 (1.01-1.10)	0.020
TG (mg/dL)	1.01 (1.00-1.02)	-	
FPG (mg/dL)	1.06 (1.03-1.09)	-	
HbA1c (%)	2.41 (0.97-5.99)	12.28 (2.5-58.5)	0.002
Gender			
Female (Reference)			
Male	1.76 (0.74-4.17)	-	
IFG			
No (Reference)			
Yes	6.17 (2.62-14.51)	12.49 (1.6-95.5)	0.015
Smoking status			
No (Reference)			
Yes	1.66 (0.734-3.48)	-	
History of HLP			
No (Reference)			
Yes	0.48 (0.21-1.07)	-	
History of HTN			
No (Reference)			
Yes	1.17 (0.53-2.55)	-	
Family History of CAD			
No (Reference)			
Yes	0.88 (0.34-2.31)	-	

Note. OR: Odds ratio; IFG: Impaired fasting glucose; CAD: Coronary artery disease; BMI: Bods mass index; Hb: Hemoglobin; Cr: Creatinine; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; HLP: Hyperlipidemia; HTN: Hypertension; * Reference.

Table 3. Relationship between Severity of CAD and IFG in the Case Group

		Severity of the Disease				*P* Value
		Single Vessel (%)	Two Vessels (%)	Three Vessels (%)	Left Main Artery	
IFG	Yes	13 (76.5)	10 (62.5)	16 (84.2)	5 (83.3)	0.331
	No	4 (23.5)	6 (37.5)	3 (15.8)	1 (16.7)	

Note. CAD: Coronary artery disease; IFG: Impaired fasting glucose.

Table 4. The Relationship between the Severity of CAD and the Frequency, Mean, and SD of HbA1c in the Case Group

		Severity of the Disease				*P* Value
		Single Vessel	Two Vessels	Three Vessels	Left Main Artery	
HbA1c	<5.7%	12 (70.6)	10 (62.5)	15 (78.9)	5 (83.3)	0.595
	5.7-6.4 %	5 (29.4)	6 (37.5)	4(21.1)	1 (16.7)	
	Mean ± SD	5.31 ± 0.48	5.46 ± 0.41	5.39 ± 0.58	5.28 ± 0.44	0.798

Note. CAD: Coronary artery disease; HbA1c: Hemoglobin A1c; SD: Standard deviation.

to investigate the relationship between IFG and CAD. According to the results obtained after logistic regression analysis, patients with CAD had an almost 12.5-fold risk of IFG. The results of the present study were concordant with those of Stratton et al. who investigated the association between glycemia and atherosclerotic lesions. They concluded that increased plasma glucose levels and IGT were associated with an increased risk of CVD (12).

In three key studies (i.e., DECODE, DECODA, and Funagata Diabetes), mortality from CVD in people with IGT was close to patients with type 2 diabetes and much higher than in people with IFG (15, 42, 43).

Genuth and colleagues' study showed that IGT is a risk factor for CVD, but its diagnosis requires the oral glucose tolerance test, which has been reported undesirable by patients (44). Barr et al found in a study that after 2.5 years of follow-up, the risk of CVD-related mortality increased in people with IFG compared to people with normal FBS, and 65% of those who died of CVD had diabetes, IFG, or IGT. Furthermore, age, gender, and other common risk factors for CVD in diabetes and IFG were independent predictors of CVD mortality. Nevertheless, there was no case with IGT (45). In the study by Dong et al, the relationship between angiographic CAD and FPG level was more substantial than the relationship with normal FPG level. IFG and increasing FPG levels were associated with a moderate prevalence of angiographic CAD and stenosis in the left anterior descending artery. In general, FPG levels were an independent risk factor for CAD (46). The present study results indicated a significant relationship between IFG and CAD in non-diabetic individuals; therefore, the rate of IFG in patients with CAD was significantly higher than in patients without CAD or with minimal CAD.

The important finding in the present study was a significant HbA1c chance (OR: 12.28) in CAD prediction. Arbel et al also showed that HbA1c is the only factor associated with glucose-metabolic. HbA1c also had a significant association with CAD intensity with MI and angina pectoris. Further, there was an association between HbA1c and measured CAD intensity using the SYNTAX score in nondiabetic patients with MI or angina pectoris (47). Simultaneously, there was no association between glucose at the beginning of hospitalization or FPG and CAD intensity (47). It is obvious that HbA1c has several limitations. First, it is affected by the red blood cell life span. Hemolytic anemia and biotin are the most critical factors that significantly influence the red blood cell life span in non-anemic people who are normoglycemic or diabetic (48). Second, the HbA1c must be checked by a standard method that the ADA suggests. This method is unavailable in most medical laboratories. Hence, the correlation between HbA1c and the dependent variable should be interpreted with caution. In Khaw and colleagues' study, an increase in HbA1c (within the normal range) was associated with an increase in 10-year cardiovascular mortality (49).

Hashemi et al found that IFG is not associated with an increased prevalence of coronary artery stenosis. They did not find any significant difference between diabetic, IFG, and non-diabetic patients concerning coronary stenosis. Their study was cross-sectional and was not suitable for exploring the association between IFG and coronary outcomes (50). Increased mortality can be justified because, in most patients with prediabetes, insulin resistance syndrome (metabolic syndrome) such as abdominal obesity, hypertriglyceridemia, low HDL, and hypertension are found. Components of metabolic syndrome are often found in people with prediabetes years before the diagnosis of type 2 diabetes. These findings suggested advanced vascular atherosclerosis, generally preceded by endothelial-dependent vasodilation, vascular smooth muscle dysfunction, and increased arterial stiffness (32, 49, 51-53). This finding contradicts the findings of our study which detected a relationship between FPG and coronary artery severity. Differences between the two studies may be due to the demographic characteristics of the studied populations,

the role of disruptive factors, and different designs (using the SYNTAX score to assess the intensity of CAD Arbel and colleagues' study). Some limitations of this study are the lack of glucose tolerance testing, lack of nutritional information, and physical activity.

Conclusion

According to the study findings, IFG and HbA1c are significantly associated with CAD. However, there was no significant association between the severity of coronary artery stenosis and IFG. It is suggested that further studies should be designed to evaluate the relationship between isolated IGT, IFG /IGT, and CAD.

Author's Contribution

Conceptualization: Shahin Abbaszadeh.
Data curation: Yasaman Hafezpour.
Formal analysis: Elham bushehri.
Investigation: Yasaman Hafezpour.
Methodology: Elham bushehri.
Project administration: Shahin Abbaszadeh.
Resources: Hossein Farshidi.
Supervision: Shahin Abbaszadeh.
Validation: Masoumeh kheirandish.
Visualization: Marzieh Nikparvar.
Writing–original draft: Hossein Abbasi, Mahta Moraghebi.
Writing–review & editing: Masoumeh Kheirandish.

Competing Interests

The authors declared that they have no competing interests.

Ethical Approval

This study was approved by the ethical committee of Hormozgan University of Medical Sciences (Ethics code: IR.HUMS.REC.1398.157).

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