Original Article

Is the Extent of Coronary Artery Stenosis in Prediabetic Patients Similar to That in Diabetics?

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ABSTRACT

Background: Some studies have shown that prediabetes may be associated with a greater incidence of coronary artery disease (CAD). Since there is a conflict concerning the relationship between CAD and optimal glucose level, this study focused on the relationship between CAD in different groups of diabetes, prediabetes (impaired fasting glucose [IFG]), and normal through fasting blood glucose classification.

Methods: This is a case-control study carried out on 98 patients in each group of prediabetes, diabetes, and normal glycemia referred to the coronary angiography clinics of Chamran and Khorshid hospitals in 2014. The multiple logistic regression tests were used for statistical analysis in SPSS, version 20.

Results: Comparison of CAD between the groups showed a higher risk of CAD in the diabetic group than in the normal group (P<0.001, OR=2.314). Also a higher risk of CAD was found in the prediabetic group than in the normal group (P=0.001, OR=1.630).

Conclusions*:** Our results provide further strong evidence that glucose evaluation should be a part of standard testing for the prevention of cardiovascular diseases. ***(Iranian Heart Journal 2016; 17(1): 38-44)

Keywords: ■Coronary artery stenosis ■Prediabetic ■Diabetic ■Normal glycemic

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The incidence of coronary artery disease (CAD) is high all over the world, and diabetes is a major risk factor for CAD. The risk for death among people with diabetes is about twice that of people of a similar age but without diabetes.[1,2] However, epidemiologic evidence suggests this morbidity–mortality relationship begins early in the progression from normal glucose tolerance to overt diabetes.

Prediabetes (intermediate hyperglycemia) is a condition with a high risk of developing diabetes. Annually 5% to 10% of prediabetics progress

toward diabetes, and it is estimated that more than 470 million people in 2030 will be suffering from prediabetes. According to the American Diabetes Association (ADA), prediabetes is defined as fasting plasma glucose ranging from 100 to 125 mg/dL.
If patients with CAD undergo a 2-hour glucose tolerance test, two-thirds will indicate abnormal tests or within the diabetes range, which puts both impaired glucose tolerance and diabetes at risk of increased cardiovascular morbidity and mortality rates.[(12)]
Although micro-retinopathy has been observed in 2.4% of prediabetics, there is a controversy concerning whether prediabetes increases atherosclerosis or cardiovascular complications.[6-7] Ertan et al.[(10)] concluded that there was a relationship between HbA1C and the size of the coronary arteries whether in normal people or those with CAD. The coronary artery size in prediabetics tends to be smaller than that in those with normal glycemia.[(10)]
In another study, patients with CAD were subjected to angiography so as to compare the atherosclerotic plaque characteristics between those with diabetes, prediabetes, and normal glycemic state; the results revealed that atherosclerosis and plaque instability in patients with prediabetes were higher than those in the normal subjects and were comparable to those in the diabetics.[11]
Hence, it can be argued that prediabetes is a risk factor for CAD.[(12)] However, there is a conflict concerning the relationship between CAD and the glucose level.
On the other hand, there are low-cost screening tests such as impaired fasting glucose (IFG) and there are simple recommendations to control the glucose level like changing lifestyles and controlling cardiovascular risk factors in classified prediabetics.
We focused on the relationship between CAD and different groups of patients with diabetes, prediabetes (IFG), and normal glycemic state through fasting blood sugar classification.

METHODS

This is a case-control study carried out on patients referred to the coronary angiography clinics of Chamran and Khorshid hospitals in Isfahan (2014). The exclusion criteria comprised previous organ transplantation, dialysis procedure, cancer, and history of revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). All the consecutive patients who were referred for coronary angiography for any reason and did not meet the exclusion criteria were recruited in the study (provided that they gave informed consent) until the sample size was full. The sample size was approximately 100 patients in each group.
For each patient, a questionnaire was filled out covering gender; age; height; weight; blood pressure; educational level; history of cardiovascular disease, diabetes, and hypertension; family history of ischemic heart disease and diabetes; status of physical activity; smoking status; and medications. In addition, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), cholesterol, and FBS tests were recorded.
Blood pressure was taken after 5 minutes of rest. Hypertension was defined as known hypertensive patients, antihypertensive drug consumption, or blood pressure ≥140.90 mm Hg in 2 measurements with a minimum interval of 24 hours and a maximum interval of 1 week.
BMI was obtained from the division of weight in kilograms by height in meters powered by 2.
In order to take the tests after 14 hours of fasting on the morning of or on the morning after the angiographic tests, we administered the above tests at Chamran Hospital's laboratory. The lipid profile of the patients was required since it was a confounding factor. Hyperlipidemia in this study referred to LDL≥130, HDL≤40, or a history of hyperlipidemia.
Physical activity was defined as activities for at least half an hour a day for at least 5 days a week.
FBS was employed to classify the patients into groups: normal blood glucose, prediabetes, and diabetes. FBS<100 was considered normal, and FBS between 100 and 125 was regarded as pre-diabetes. Testing was replicated if prediabetes was diagnosed, and FBS≥126 was considered as diabetes. Nevertheless, a patient was considered diabetics if already diagnosed. If the patient had for the first time a sugar level ≥126 without being symptomatic, the test had to be replicated on another day. However, if the patient was symptomatic, there was no need to replicate the test.

After angiography, the angiography films were read by 2 cardiologists separately so as to record the percentage of stenosis, as well as the involvement zone—the severity of which was then quantified through the Gensini scoring system. The Gensini scoring criteria were applied to determine the extent of CAD (based on the anatomical location of the stenosis) and to provide a method for quantifying the severity of CAD. Based on these scoring criteria, a severity score of 1 was considered for 25% stenosis, 2 for 50% stenosis, 4 for 75% stenosis, 8 for 99% stenosis, and 16 for 100% stenosis. Each segment was assigned a value from 0.5 to 5—by multiplication of which into the involvement in terms of the severity score, a value is obtained to derive the Gensini score. In addition, the patients were divided into 2 groups based on the percentage of their coronary artery stenosis. In this study, stenosis ≥70% was considered CAD.
Simple and multiple logistic regression tests were used to compare and evaluate correlations. The entire analysis was conducted with SPSS, version 20, and all the tests were considered statistically significant at a P value<0.05.

Due to an increased cardiovascular risk in prediabetics, it is generally recommended that these individuals be screened through a low-cost test such as IFG. Moreover, it is recommended to change lifestyle and control the cardiovascular risk factors in classified prediabetics. Apart from prediabetes control through the above measures, it is recommended to apply drug therapy in this group of patients. Furthermore, patients' awareness regarding the importance of screening tests and preventive procedures even when they are not diagnosed with diabetes should be raised.

RESULTS

The subjects were first evaluated from the perspective of the existence of CAD: 116 (38.7%) patients were negative and 184 (61.3%) were positive. The status of the subjects was then evaluated in terms of several variables—including sex, hyperlipidemia, BMI, smoking, hypertension, low physical activity, family history, LDL, HDL, cholesterol, and TG (Table 1).

Table 1. Characteristics of the subjects

		Group			
		Normal N (%)	Prediabetic N (%)	Diabetic N (%)	Total N (%)
Coronary artery disease	-	56 (57.7)	32 (31.4)	28 (27.7)	116 (38.7)
	+	41 (42.3)	70 (68.6)	73 (72.3)	184 (61.3)
Sex	Male	57 (58.8)	67 (65.7)	51 (50.5)	175 (58.3)
	Female	40 (41.2)	35 (34.3)	50 (49.5)	125 (41.7)
Hyperlipidemia	-	69 (71.1)	74 (72.5)	65 (64.4)	208 (69.30)
	+	28 (28.9)	28 (27.5)	36 (35.6)	92 (30.7)
Hypertension	-	45 (46.4)	44 (43.1)	46 (45.5)	135 (45.0)
	+	52 (53.6)	58 (56.9)	55 (54.5)	165 (55.0)
Low physical activity	-	73 (75.3)	75 (73.5)	61 (60.4)	209 (69.7)
	+	24 (24.7)	27 (26.5)	40 (39.6)	91 (30.3)
Family history	-	82 (84.5)	95 (93.1)	88 (87.10)	265 (88.3)
	+	15 (15.5)	7 (6.9)	13 (12.9)	35 (11.7)
Age	Mean ± SD	60.57±11.84	59.71±11.86	60.08±10.32	60.11±11.33
Gensini Score		12.64±19.42	20.01±19.32	23.67±25.39	18.86±21.99
Low-density lipoprotein		100.33±34.83	99.55±34.03	100.10±32.70	99.99±33.74
High-density lipoprotein		43.20±11.22	40.41±9.20	40.40±7.78	41.31±9.54
Cholesterol		170.28±46.27	167.52±43.16	170.39±40.94	169.38±43.35
Triglyceride		132.70±78.16	135.53±90.77	148.02±76.68	138.82±82.19
Body mass index		24.73±7.86	23.71±9.20	26.94±6.90	25.13±8.05
Smoking (pack/y)		4.59±10.58	3.10±8.71	4.79±s12.10	4.15±10.54

At the next stage, the simple logistic regression test was used to assess the relationship between the confounding variables and CAD status and determine the significant variables correlated with CAD. The results showed that except for HDL and TG, all of these variables had a direct significant relationship with CAD (P<0.05, OR>1).

As the major objective of this study, the multiple logistic regression relationship was used to analyze the relationship between diabetic status (normal, prediabetes, and diabetes) and CAD status, after adjusting for the confounding variables (Table 2). The results showed that the odds of CAD were significantly different between the 3 groups (P<0.001). Comparison of CAD between the groups showed a higher risk of CAD in the diabetic group than in the normal group (P<0.001, OR=2.314). Also, a higher risk of CAD was observed in the prediabetic group than in the normal group (P=0.001, OR=1.630). However the risk of CAD in the diabetic group was not significantly higher than that in the prediabetic group (P=0.272, OR=1.426).

Table 2. Results of the multiple logistic regression analysis for the assessment of the correlation between diabetes and coronary artery disease after adjusting for the role of the confounding variables

	B	P value	OR
Sex (male)	0.655	0.019	1.926
Age	0.001	0883	1.001
Diabetic status*		<0.001	
Normal	1		1
Prediabetic	0.696	0.000**	1.630
Diabetic	0.839	<0.001**	2.315
Hyperlipidemia (+)	-0.635	0.061	0.530
Body mass index	-0.027	0.082	0.974
Smoking	0.002	0.878	1.002
Hypertension (+)	0.017	0.948	1.017
Low physical activity (+)	0.319	0.276	1.376
Family history (+)	0.493	0.221	1.637
Low-density lipoprotein	0.002	0.813	1.002
High-density lipoprotein	0.028	0.081	1.028
Cholesterol	-0.003	0.632	.997
Triglyceride	0.002	0.339	1.002

* Reference category is the normal group.

** P value for comparing each group with the reference group

DISCUSSION

Risk assessment is aimed at classifying the population into those at different levels of CVD risk and at intensifying preventive approaches in the individual.[1] Diabetes mellitus is known as one of the major risk factors associated with a significantly higher risk of morbidity and mortality of CVD.[2] Some guidelines recommended that for CVD prevention, patients suffering from diabetes mellitus with at least 1 other CV risk factor be considered at very high risk and other patients with diabetes mellitus be regarded at high risk.[3] Also, prediabetes is another risk factor, and the mean estimated 10-year risk of CVD in prediabetics has been reported to be 16.2%.[4] In our study, CAD was detected in 72.3% of the diabetic patients, 68.6% of the prediabetic individuals, and 42.3% of the individuals with a normal glucose level. Other findings in our study showed that CAD was significantly correlated with the presence of diabetes mellitus and the odds of CAD in these patients were significantly higher than those in the individuals with normal glucose regulation. Nevertheless, the odds of CAD were not significantly different between the diabetic patients and the prediabetic individuals.

According to some previous studies, the link between the glucose level and the development of coronary atherosclerosis is controversial. Some of these studies[5-9] have reported a significant independent relationship between the glucose level and CAD. One of these studies reported that in individuals with both fasting plasma glucose (FPG) and 2-hour plasma glucose, a high 2-hour plasma glucose level was associated with increased CVD mortality.[11-12] Also, a strong association has been reported between FPG and CAD in a few studies after multivariate adjustment.[15] In one study, a significant increase in the prevalence of CAD in prediabetic individuals was reported according to the ADA's diabetes criteria[14] and the WHO's criteria.[15] Another study by Gui et al.,[16] chiming in with our results, showed that the prevalence of CAD was significantly different between subjects with normal glucose tolerance and those with IFG. These results are in contrast to those reported by Yan et al.,[17] who reported no significant difference between these subjects. A linear increase in age-adjusted ischemic heart disease mortality rates with fasting glucose in normal men was reported by Scheidt-Nave et al. [18] Glycemia was reported to be a continuous risk factor for CVD and mortality by a meta-analysis.[18] A higher risk of cardiovascular mortality in subjects with plasma glucose levels >85 mg/dL was reported in another study.[19] In line with these findings, our results showed that the frequency of patients with CAD increased according to their insulin resistance status. Accordingly—based on our results and previous studies, there is an urgent need to implement culturally competent interventions in individuals with diabetes mellitus and prediabetes with a view to reducing the risk of progression of prediabetes to diabetes mellitus and its complications.

In a study, the patients who were referred for angiography and had at least 1 narrowed main artery were evaluated. The results suggested that coronary blood flow in the patients with prediabetes declined compared with that in the patients with normal glycemia.[20]

The results of a study by Prakash et al.[21] showed the CAD was 2 to 5 times higher in IFG and diabetes compared to the normal group.[21]

The importance of the examination of prediabetes complications lies in the fact that a good understanding of the condition can provide early diagnosis and treatment of people with IFG or impaired glucose tolerance so as to reduce the number of people with diabetes, as well as to curtail the incidence of cardiovascular complications.[22]

The Gensini score, as a tool to assess the severity of CAD, in our study was significantly associated with diabetes. Also, in the multiple regression analysis—after adjustment for age, sex, BMI, smoking, TG, TC, HDL, and LDL—the differences were still significant. Yan et al.[17] found that FPG was a significant determinant of the Gensini score. Similarly, Gui et al.[16] in their study showed that the Gensini score correspondingly increased with the FPG levels and the differences still existed after adjustment for age, sex, and BMI. The association between FPG levels and the severity of CAD was reported by Dong et al.,[23] but these authors did not use the Gensini score to assess the severity of coronary atherosclerosis.

Our study had some limitations, first and foremost among which is that it was a single-center study on individuals scheduled for coronary angiography due to chest pain. Accordingly, the fact that our subjects were at high risk of CVD might have resulted in a higher prevalence rate of CAD in this study population than the rate in the general population. Our data are, therefore, not applicable to the general population. The limited number of individuals with prediabetes constitutes the salient operational problem in the design and method of solving the problem. Another limitation of this study is the division of the patients into diabetics, prediabetics, and normal only based on their FBS levels and not their HbA1c, which was due to the forbidding cost of HbA1c testing in our lab. Another drawback of note is that the duration of diabetes in our study population is unknown in our investigation bearing in mind that the length of diabetes influences CAD.

In conclusion, the results of the present study demonstrated that diabetes was more prevalent in the CAD patients than in those with prediabetes and those with normal glucose regulation. In addition, the odds of CAD were higher in the diabetic individuals than those in the individuals with normal glucose regulation. So, our results provide further strong evidence that screening for glucose evaluation should be a part of standard testing for the prevention of CVD.

REFERENCES

1. Oliveira CSV, Giuffrida FMA, Crispim F, Saddi-Rosa P, Reis AF: ADIPOQ and adiponectin: the common ground of hyperglycemia and coronary artery disease? Arc Bras Endocrinal Metabol 2011; 55:446-54.

2. Fox CS, Coady S, Sorlie PD, D'Agostino RB Sr, Pencina MJ, Vasan RS, et al, Increasing cardiovascular disease burden due to diabetes mellitus: The Framingham Heart Study. Circulation 2007; 115:1544-50.

3. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012; 33:1635–1701.

4. Robinson JG, Stone NJ. The 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk: a new paradigm supported by more evidence. Eur Heart J 2015 Aug 14; 36 (31): 2110-2118.

5. DECODE Study Group, The European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001; 161 (3):397-405.

6. Kim HK, Lee SK, Suh CJ, Yoon HJ, Lee KY, Park HY, Kang MH. Post challenge hyperglycemia but not hyperinsulinemia is associated with angiographically documented coronary atherosclerosis in Korean subjects. Diabetes Res Clin Pract 2003; 59(2):129–136.

7. Gui MH, Hong J, Lu¨ AK, Chen Y, Shen WF, Li XY, Ning G. High sensitive C-reactive protein, adiponectin, and urine albumin excretion rate in Chinese coronary artery disease patients with different glucose tolerance status. Chin Med J (Engl) 2008; 121(24):2509-16.

8. Sourij H, Saely CH, Schmid F, Zweiker R, Marte T, Wascher TC, Drexel H. Post-challenge hyperglycaemia is strongly associated with future macrovascular events and total mortality in angiographied coronary patients]. Eur Heart J 2010; 31(13):1583-90.

9. Ford Es,Zhao G,Li C. Pre diabetes and the Risk for cardiovascular Disease.journal of the American college of cardiology. 2010; 55(13):1310-7.

10. Ertan C, Ozeke O, Gul M, Aras D, Topaloglu S, Kisacik HL, et al. Association of pre-diabetes with diffuse coronary narrowing and small vessel disease. Journal of cardiology.2014; 63(1):29-34.

11. Ning F, Tuomilehto J, Pyorala K, Onat A, So¨derberg S, DECODE Study Group. Cardiovascular disease mortality in Europeans in relation to fasting and 2-h plasma glucose levels within a normoglycemic range. Diabetes Care 2010; 33(10):2211–16.

12. Chu CS, Lee KT, Cheng KH, Lee MY, Kuo HF, Lin TH, et al. Post challenge responses of nitrotyrosine and TNF-alpha during 75-g oral glucose tolerance test are associated with the presence of coronary artery diseases in patients with prediabetes. Cardiovasc Diabetol 2012; 11(1):21

13. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology, ESC Committee for Practice Guidelines. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27(11):1341–1381.

14. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26(11):3160–67.

15. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15(7):539–553.

16. Gui MH1, Li X, Lu ZQ, Gao X. Fasting plasma glucose correlates with angiographic coronary artery disease prevalence and severity in Chinese patients without known diabetes. Acta Diabetol 2013; 50(3):333-40.

17. Yan Q, Gu WQ, Hong J, Zhang YF, Su YX, Gui MH, Zhang Y, Chi ZN, Zhang YW, Li XY, Ning G. Coronary angiographic studies of impaired glucose regulation and coronary artery disease in Chinese nondiabetic subjects. Endocrine 2009; 36(3):457–463

18. Scheidt-Nave C, Barrett-Connor E, Wingard D.L, Cohn B.A, Edelstein S.L. Sex differences in fasting glycemia as a risk factor for ischemic heart disease death, Am. J. Epidemiol 1991;133:565–576.

19. Coutinho M, Gerstein H.C, Wang Y, Yusuf S, The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years, Diabetes Care 1999; 22:233-40.

20. Kadi H, Cayhank K, Karayakali M, Celik A, Ozturk A, Koc F, et al. Effects of prediabetes on coronary collateral circulation in patients with coronary artery disease. Coronary artery disease.2011; 22(4):233-237.

21. Deedwania PC, Fonseca VA, Diabetes-prediabetes and cardiovascular risk. The American journal of medicine. 2005; 118(9)939-947

22. Konstantinou DM, Chatzizisis YS, Louridas GE, Parcharidis GE, Giannoglou GD. Non-diabetic hyperglycemia correlates with angiogeraphic coronary artery disease prevalence and severity. Diabetes and metabolism.2010; 36(5):402-8.

23. Dong X, Zhou L, Zhai Y, Lu B, Wang D, Shi H, Luo X, Fan W, Hu R. Impaired fasting glucose and the prevalence and severity of angiographic coronary artery disease in high-risk Chinese patients. Metabolism 2008; 57(1):24-29.