

IS IMPAIRED FASTING GLUCOSE ASSOCIATED WITH INCREASED RISK OF CORONARY ATHEROSCLEROSIS?

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Abstract- Impaired fasting glucose identifies individuals at high risk of progression to diabetes but the role of IFG as a coronary artery disease risk factor, independent of its progression to diabetes and its association with other coronary artery disease risk factors, is unclear. A cross-sectional study was conducted to evaluate the hypothesis that impaired fasting glucose increased the likelihood of atherosclerotic plaque formation. Blood chemistry data as well as traditional coronary artery disease risk factors from 812 patients referred for coronary angiography to heart centers in Shahid-Chamran and Sina hospital, Isfahan, Iran were recorded. The population were stratified into three groups according to American Diabetes Association criteria: normal fasting glucose (n=608), impaired fasting glucose (n=92) and diabetes mellitus (n=112). We use extent, Vessel and stenosis scores to indicate the coronary artery involvement. Kruskal-Wallis test showed that the means of extent, Vessel and stenosis scores are not significantly different between three groups ($P > 0.05$). Multivariate linear regression analysis, using extent score of coronary artery disease as dependent variable and traditional risk factors and impaired fasting glucose as independent variables did not show any significant difference either. Our data suggested that impaired fasting glucose is not associated with increased risk of coronary atherosclerosis.

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INTRODUCTION

In 1997, an Expert Committee of the American Diabetes Association (ADA) proposed a set of revised criteria for the diagnosis of diabetes mellitus introducing a new category of abnormal glucose regulation, impaired fasting glucose (IFG) (1). These criteria were later adapted by the World Health Organization (WHO) (2). Impaired glucose tolerance (IGT) and IFG identify individuals at increased risk of developing diabetes, based on post challenge or

fasting challenge or fasting glucose level, respectively. Also it has been suggested that these two groups are associated with varying rates of progression to coronary artery disease (CAD) (3). Since presentation of the new criteria, several investigators have argued for retaining the oral glucose tolerance test (OGTT) for diagnosis of impaired glucose regulation (4-8). Considering that fasting glucose test is simple, easy to apply and had been widely used, also ADA suggested that this test could be used alone because it has the same accuracy as OGTT. Although the association of hyperglycemia at levels below the current diagnostic thresholds for diabetes with CAD risk, has been increasingly recognized; the specific contributions of IFG versus IGT to CAD risk remains poorly understood (9-13). Due to these findings, we evaluate

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the association between impaired fasting glucose and coronary artery atherosclerosis.

MATERIALS AND METHODS

The sampled population in this cross-sectional study was the patients referred for coronary angiography to heart centers in Shahid-Chamran and Sina hospitals, Isfahan, IRAN (812 patients). The patients were invited to participate in this study by telephone or letter. Informed consent was obtained from the patients before enrolling the study. Demographic and baseline data consisting of age, gender and drug history were recorded for each patient by trained medical students. Patients with a history of using antidiabetic drugs were excluded from our study. Systolic and diastolic blood pressures were recorded invasively during coronary angiography. Height and weight were measured and body mass index was calculated (kg/m^2), cigarette smoking was based on the self (patient) report and it was calculated on pack/year; patients who have been ceased smoking for more than 3 years considered nonsmokers. Patients who undergo coronary angiography and were fast had blood samples taken the day of admission before preparation for angiography. Blood was collected in plain tubes for enzymatic determination of glucose, total cholesterol, triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) by technical Ra1000 auto analyzer. The population was stratified into three groups based on fasting plasma glucose values using ADA criteria:

1- Diabetes mellitus (DM): FBS \geq 7.0 mmol/l or 126mg/dl.

2- Impaired fasting glucose: FBS= 6.0 to 6.9mmol/l or 110 to 125mg/dl.

3- Normal fasting glucose: FBS<6.0mmol/l or 110 mg/dl.

Scoring system for coronary artery disease

Coronary angiography was performed in patients by experienced cardiologists who were unaware of the clinical and biological data.

1- Vessel score: This score shows the number of vessels with a significant stenosis (70% or greater

reduction in lumen diameter). Scores ranged from 0 to 3, depending on the number of vessels involved. Left main artery stenosis was scored as single vessel disease.

2- Stenosis score: This was a modified Gensini score, which has been described previously. Briefly, the most severe stenosis in each of eight segments was graded according to severity; that is a grade of 1 for 1% to 49% reduction in lumen diameter, 2 for 50% to 74%, 3 for 75% to 99%, and 4 for total occlusion. The score for each of the eight segments were added together to give a total score out of 32 which indicates on the severity of stenosis.

3- Extent score: This score developed to indicate the proportion of the coronary arterial tree involved by angiographically detectable athroma. The proportion of each vessel involved by athroma, identified as luminal irregularity, was multiplied by a factor for each vessel: Left main artery, 5; LCX, 20; obtuse marginal and posterolateral vessels, 10; RCA, 20; and main PDA, 10. When the major lateral wall branch was a large obtuse marginal or intermediate vessel, this was given a factor of 20 and the LCX, a factor of 10. The scores for each vessel or branch were added to give a total score out of 100, that is the percentage of the coronary intimal surface area involved by athroma (14,15).

Statistical analysis

The data were analyzed by Multivariate linear regression and Kruskal-wallis analysis in SPSS 12 software. A $p < 0.05$ was considered as statistically significant. The study protocol was approved by the ethical committee of the Isfahan University Of Medical Science.

RESULTS

This study was conducted on 812 individuals who underwent coronary angiography. 481(59%) subjects were male. The average age was 56.229 ± 10.971 (Range: 20-94 years).

Patients were stratified into three groups according to ADA criteria: patients with normal fasting glucose ($n=549$), impaired fasting glucose ($n=65$) and diabetes mellitus ($n=43$).

Table 1. Means and standard deviations(SD) of extent, stenosis and vessel scores in three groups (Kruskal-wallis test).

FBS groups		Extent score	Stenosis score	Vessel score
<i>Normal</i>	Mean	16.1102	4.5460	.9846
	SD	26.4007	5.0684	1.1533
<i>IFG</i>	Mean	17.9891	4.6863	1.0392
	SD	27.2258	5.0060	1.0947
<i>Diabetic</i>	Mean	23.5268	5.7937	1.2381
	SD	28.5745	4.6772	1.1030

Kruskal-Wallis test was used to compare means of extent, Vessel and stenosis scores in these three groups (Table 1).

This test did not show any significant difference between groups ($P > 0.05$). Multivariate linear regression analysis with stepwise method was also performed using extent score of CAD as dependent variable and the other factors such as age, gender, BMI, smoking, blood pressure, LDL, HDL, TG, total cholesterol and IFG as independent variables. Results did not show any significant difference either.

DISCUSSION

In our cross-sectional study of patients underwent coronary angiography, the new category, IFG, based on 1997 ADA criteria was not found to have association with an increase in coronary atherosclerosis; considering CAD risk factors. Since the establishment of the two intermediate metabolic states (IFG and IGT), their identity with cardiovascular risk has been put forward (1). In the ARIC study, which defined diabetes on the basis of fasting plasma glucose concentration (≥ 7.8 mmol/l) and medical history, abnormal glucose metabolism was associated with increased carotids Intima Media Thickness (IMT) (12). The Rancho Bernardo Study suggested that fasting blood glucose < 7.8 mmol/l could be a risk factor for coronary heart disease but the study probably included two-thirds who would have been diagnosed as having diabetes only by postchallenge glucose criteria (16, 17). Thus, the

results of these studies may be biased by a linear increase of undiagnosed diabetes in parallel to the increment in fasting blood glucose (17, 18). Jarrett proposed a threshold effect for hyperglycemia with the metabolic syndrome associated with IGT and newly detected diabetes to be responsible for the increased cardiovascular risk (19). In the IRAS study it showed that IGT was only associated with a thickening of the carotid wall in non-Hispanic Whites but not in the entire population including Blacks and Mexican Americans. This study did not address IFG as a possible risk category for atherosclerosis (20). In parallel with this study Hanefeld M. and his colleagues concluded in their case-control study that IFG alone was not related to increase IMT (21). On the other hand Wannamethe G. et al concluded that random blood glucose concentration above 6.1 mmol/l was a risk factor for coronary heart disease in nondiabetic men in the British Regional Heart Study (22). Some, but not all, cross-sectional studies have suggested differences in other atherogenic traits between IGT and IFG. Elevated C-reactive protein (CRP) levels have been demonstrated in individuals with newly diagnosed type 2 diabetes and IGT, but not with IFG (23,24). A direct comparison of CRP levels in association with postchallenge glycemia versus fasting glycemia has demonstrated a greater association between CRP and postchallenge glycemia (24). On the other hand, a recent study by Hanefeld et al. did not demonstrate any differences in lipid (other than free fatty acid) or blood pressure levels between IFG and IGT, with both categories being defined using the 1997 ADA criteria (25). We must accentuate that the current work included only subjects who were referred for coronary angiography to heart centers. The other limitation of our study is that we did not perform OGTT for patients and therefore we could not compare these two tests in combination to traditional risk factors. Clearly, this cross-sectional study does not allow an answer with respect to long-term outcome of IFG as a possible risk factor for coronary heart disease as it was shown for IGT with prospective studies considering end-points such as myocardial infarction and cardiovascular death. In conclusion, our data suggested that IFG is not associated with increased prevalence of coronary

atherosclerosis. The prognostic significance of IFG as a predictor of subsequent development of atherosclerosis needs to be evaluated in prospective studies.

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Impaired fasting glucose and coronary atherosclerosis

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