

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

M. Hashemi, H. Taheri, N. Amiri, M. Yavari, I. Shaigannia, L. Moghadas, Z. Talaei, E. Shirzadi and B. Soleimani

Medical Students Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

**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.

© 2008 Tehran University of Medical Sciences. All rights reserved.

*Acta Medica Iranica*, 46(1): 38-42; 2008

**Key words:** Atherosclerosis, coronary artery disease, impaired fasting glucose, angiography.

### 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

Received: 25 Apr. 2006, Revised: 28 May 2006, Accepted: 1 Jul. 2006

**\* Corresponding Author:**

Elham Shirzadi, Medical Students Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran  
Tel: +98 311 6732149  
Fax: +98 311 6732149  
E-mail: elhamshirzadi@yahoo.com

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 ( $\text{kg}/\text{m}^2$ ), 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  $56.229 \pm 10.971$  (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 ( $\geq 7.8$  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.

### Acknowledgment

This work was supported by Research in assistant and Medical Students Research Center of Isfahan University Of Medical Sciences. The authors gratefully acknowledge the special effort by Dr.Montazeri H, cardiologist; Dr.Shamsolkottabi H, cardiologist and Dr.Baghaii H, pathologist. We also thank Shahid-Chamran and Sina hospitals staff for their help in collecting the outcome data.

### REFERENCES

1. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2000 Jan; 23 Suppl 1:S4-19.
2. 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. *Diabetes Med*. 1998 Jul; 15(7):539-53.
3. Blake DR, Meigs JB, Muller DC, Najjar SS, et al. Impaired glucose tolerance, but not impaired fasting glucose, is associated with increased levels of coronary heart disease risk factors: result from the Baltimore longitudinal study on Aging. *Diabetes*. 2004 Aug; 53(8): 2095-2100.
4. Meigs JB, Larson MG, D'Agostino RB, et al. Coronary artery calcification in type 2 diabetes and insulin resistance: the framingham offspring study. *Diabetes care*. 2002 Aug; 25(8):1313-1319.
5. Heldgaard PE, Olivarius NF, Hindsberger C, Henriksen JE. Impaired fasting glucose resembles impaired glucose tolerance with regard to cardiovascular risk factors: population-based, cross-sectional study of risk factors for cardiovascular disease. *Diabetes Med*. 2004 Apr; 21(4):363-370.
6. DECODE Study Group, European Diabetes Epidemiology Study Group. Will new diagnostic criteria for diabetes mellitus change the phenotype of patients with diabetes? *Br Med J*. 1998; 317: 371-375.
7. The DECODE study group. European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet*. 1999 Aug 21; 354(9179):617-621.
8. Tominaga M, Eguchi H, Manaka H, Igarashi K, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care*. 1999 Jun; 22(6):920-924.
9. Rewers M, Shetterly SM, Baxter J, Marshall JA, et al. Prevalence of coronary heart disease in subjects with normal and impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a biethnic Colorado population. The San Luis Valley Diabetes Study. *Am J Epidemiol*. 1992 Jun 15; 135(12):1321-1330.
10. Balkau B, Shipley M, Jarrett RJ, Pyorala K, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care*. 1998 Mar; 21(3):360-367.
11. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999 Feb; 22(2):233-240.
12. Hanefeld M, Koehler C, Schaper F, Fuecker K, et al. Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis*. 1999 May; 144(1): 229-235.
13. Rodriguez BL, Lau N, Burchfiel CM, Abbott RD, et al. Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. *Diabetes Care* 1999 Aug; 22(8):1262-1265.
14. Sullivan DR, Norwick TH, Freedman SB. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. *Am Heart J*. 1990; 119: 1262-1268.
15. Reardon MF, Nestel PJ, Craig IH, Harper RW. Lipoprotein: Factors of the severity of coronary artery disease. *Atherosclerosis*. 1983; 49:1-7.

16. Scheidt-Nave C, Barrett-Connor E, Wingard DL, et al. Sex differences in fasting glycemia as a risk factor for ischemic heart disease death. *Am J Epidemiol.* 1991; 133:565-576.
17. Barrett-Connor E. Does hyperglycemia really cause coronary heart disease? *Diabetes Care.* 1997; 20:1620-1623.
18. Stern MP. Glycemia and cardiovascular risk. *Diabetes Care.* 1997; 20: 1501 -1502.
19. Jarrett RJ. The cardiovascular risk associated with impaired glucose tolerance. *Diabetic Med.* 1996; 13: S15- S19.
20. Wagenknecht LE, D'Agostino RB, Haffner SM, et al. Impaired glucose tolerance, type 2 diabetes, and carotid wall thickness: the Insulin Resistance Atherosclerosis Study. *Diabetes Care.* 1998; 21: 1812-1819.
21. Temelkova-Kurktschiev T, Henkel E, Koehler C, et al. Subclinical inflammation in newly detected type II diabetes and impaired glucose tolerance. *Diabetologia.* 2002; 45: 151.
22. Wannamethee G, Shaper AG. The association between heart rate and blood pressure, blood lipids and other cardiovascular risk factors. *J Cardiovasc Risk.* 1994; 1: 223-230.
23. Ford ES. Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care.* 1999; 22:1971-1977.
24. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM. C-Reactive protein is more strongly related to post-glucose load glucose than to fasting glucose in non-diabetic subjects: the Insulin Resistance Atherosclerosis Study. *Diabet Med.* 2002; 19 :939 - 943.
25. Hanefeld M, Koehler C, Fuecker K, Henkel E, et al. Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose: the Risk Factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes Study. *Diabetes Care.* 2003; 26: 868 -874.