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BMJ Open 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

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ABSTRACT

Objective: This study was designed to evaluate the severity of subclinical atherosclerosis in patients with asymptomatic impaired fasting glucose (IFG) compared to those with diabetes mellitus (DM) and normal fasting glucose (NFG), as measured by coronary computed tomographic angiography (CCTA).

Design: Subjects were divided into three groups: NFG (<100 mg/dL), IFG (100–125 mg/dL) and DM. Coronary artery calcium on non-contrast CT and plaque analysis on CCTA were performed.

Setting: University hospital, single centre.

Participants: 216 asymptomatic participants prospectively underwent CCTA for the evaluation of coronary artery disease (CAD).

Primary and secondary outcome measures: Atherosclerotic plaque burden in IFG compared to NFG patients.

Results: 2664 segments were analysed in 120 NFG, 44 IFG and 52 DM participants. The mean calcium scores were 178 ± 395 , 259 ± 510 and 414 ± 836 for NFG, IFG and DM, respectively ($p=0.037$). The mean plaque burdens in the NFG, IFG and DM groups were 0.31 ± 0.45 , 0.50 ± 0.69 and 0.68 ± 0.69 , respectively ($p=0.0007$). A greater proportion of patients with DM (19/52, 36.5%) and IFG (13/44, 29.5%) had obstructive CAD compared to those with NFG (16/120, 13.3%) ($p=0.0015$). The number of segments with severe disease was significantly higher in the DM (60/637, 9.4%) and IFG (42/539, 7.8%) groups compared to that in the NFG group (34/1488, 2.3%) ($p=0.0001$).

Conclusions: (1) IFG and DM have significantly higher, but comparable, calcium scores, plaque burden and obstructive CAD compared to NFG in asymptomatic individuals. (2) Pending corroboration by other reports, more intensive efforts may be devoted to the evaluation and treatment of patients with IFG.

While diabetes mellitus (DM) is considered a disease, there has been no similar classification for impaired fasting glucose (IFG),

Strengths and limitations of this study

- This is the first study to demonstrate comparable subclinical atherosclerosis in patients with DM and those with IFG.
- The study provides important implications for the large IFG population.
- The study has insufficient power, and not been designed, for clinical outcomes.

defined as a fasting blood glucose level of 100–126 mg/dL, and also known as pre-diabetes.¹ To examine its relationship with clinical coronary artery disease (CAD), a systematic literature review of 18 studies reported a significant but modest relative risk of 1.18–1.20.² In the symptomatic and asymptomatic population, there are numerous studies documenting the increased association of DM with subclinical atherosclerosis,^{3–10} but there are no data for pre-diabetes. Consequently, this study was designed to establish the role of IFG in plaque formation in asymptomatic patients compared to patients with DM and participants with normal fasting glucose (NFG), as measured by coronary computed tomographic angiography (CCTA).

METHODS

Patients

The study group consisted of 216 randomly selected, asymptomatic self-referred participants with no prior history of CAD, who voluntarily underwent MDCT between June 2005 and August 2007 as part of the investigational protocol for inclusion in this study. All participants had comprehensive

evaluation of their cardiovascular risk factors through a questionnaire and a medical chart review along with laboratory assessment. Participants were separated into three groups based on their fasting plasma glucose. Individuals were classified as DM if they reported the condition or had fasting plasma glucose levels >126 mg/dL. IFG was defined as fasting plasma glucose levels between 100 and 126 mg/dL; the remaining participants were designated as NFG.

Coronary computed tomographic angiography

All participants underwent coronary artery calcium (CAC) scoring and MDCT using a 64-slice scanner (Aquilion 64, Toshiba America Medical Systems, Tustin, California, USA). Oral β -blockers were administered by protocol to patients before the examination as needed to reduce heart rate. A 70–90 mL weight-based bolus of iohexol contrast agent (Omnipaque 350; Amersham Health, Ireland) was injected intravenously. When signal density in the descending aorta reached a predefined threshold of 180 Hounsfield units, the patient was instructed to sustain an inspiratory breath hold. The scan protocol used a gantry rotation time of 400 ms, a slice collimation of 64×0.5 mm applied at a table increment of ~7.2 mm/rotation (depending on the patient's heart rate), a tube voltage of 120 kV and a tube current of 300–500 mA (depending on the patient's weight). A scanning field of view of 320 mm was combined with a detector collimation of 64×0.5 mm and a pixel matrix of 512×512. MDCT data were transferred to an image analysis workstation (Vitrea 2, Vital Images, Minnetonka, Minnesota, USA) and digitally rendered using an automated algorithm for cardiac structural analysis.

CAC scoring using the Agatston method was performed for each participant. For the CCTA data, a per-segment analysis of CAD was performed in each participant by a Level 3 Cardiac CT reader. Coronary artery segments were identified and classified in each participant based on the standard 15-segment AHA/WHO coronary nomenclature guidelines.¹¹ For each visualised coronary artery segment, an ordinal scale was used to classify the degree of stenosis and atherosclerotic plaque: 0 for normal (no stenosis), 1 for mild plaque (stenosis <30%), 2 for moderate plaque (stenosis between 30% and 60%) and 3 for obstructive plaque (stenosis >60%). The plaques were further characterised as calcified, non-calcified or mixed. Therefore, a total plaque burden score was determined in each participant by averaging the individual plaque scores over the total number of assessable segments. To calculate plaque burden score, each assessable segment was scored 0, 1, 2 or 3. The total plaque burden score was the sum of all individual segment scores divided by the total number of assessable segments. The CCTA and CAC radiation doses were in the range of 5–10 and 1–2 mSv, respectively.

Statistics

Statistical analysis was performed using PC-based software (Graphpad 5.0, San Diego, California, USA). Continuous variables were compared, including fasting

plasma glucose, lipids, systolic blood pressure and plaque burden score in the DM, IFG and NFG groups, using the one-tailed analysis of variance (ANOVA). In addition to the three-group analysis, individual comparisons were also performed between the normal and IFG groups, normal and DM groups, and IFG and DM groups using the Mann–Whitney test for non-normally distributed variables and Student's t-test for normally distributed variables. To compare categorical variables in the per-segment analysis of coronary anatomy and the per-patient analysis of plaque burden, we used Pearson's χ^2 test.

This study was approved by the Institutional Review Board.

RESULTS

Demographics

Of the 216 patients, 52 had DM, 44 had IFG and 120 had NFG.

The demographic characteristics in each group are shown in [table 1](#). There were no significant differences in age, smoking prevalence, statin use, family history of CAD, and systolic and diastolic blood pressures among the three groups. When comparing DM with NFG, those with DM were older, had higher body mass index, lower low-density lipoprotein cholesterol (LDL) and higher prevalence of hypertension. When comparing the IFG group with the DM group, LDL was lower, triglycerides were higher and blood pressure was higher in those with DM than in those with IFG.

Coronary artery calcium

The mean calcium scores in the NFG, IFG and DM groups were 178±395, 259±510 and 414±836, respectively. There was a significantly higher CAC ($p=0.01$) in the DM group compared to the NFG group. Comparison between the IFG and DM groups and between the IFG and NFG groups revealed no significant differences ($p=0.2830$ and $p=0.2860$, respectively). However, a three-group comparison using ANOVA demonstrated a significant trend of increasing CAC from NFG to IFG to DM ($p=0.04$).

Coronary computed tomographic angiography

There was no statistically significant difference ($p=0.23$) in plaque burden score in the DM (0.68±0.69) and IFG (0.50±0.69) groups ([figure 1](#)). The IFG group's plaque burden was significantly higher than that seen in the NFG group (0.31±0.45, $p=0.04$). Finally, comparison between the DM and NFG groups yielded a markedly higher plaque burden in the DM group ($p<0.0001$).

Per-segment analysis

A total of 2664 coronary artery segments were analysed: 637 in the DM group, 539 in the IFG group and 1488 in the NFG group ([table 2](#)). Totally, 49 segments (19 DM (3.0%), 13 IFG (2.4%), 17 NFG (1.1%) and 1.8%

Table 1 Demographics

	DM	IFG	NFG	p (DM vs IFG)	p (DM vs NFG)	p (IFG vs NFG)	p (3 Groups), one-way ANOVA or χ^2
Number	52	44	120				
Male	30 (57.7%)	27 (61.4%)	79 (65.8%)				0.5794
Female	22 (42.3%)	17 (38.6%)	41 (34.2%)				
Smokers	13 (25.0%)	13 (29.5%)	28 (23.3%)				0.7180
Age	62.4±10.6	59.4±12.7	58.1±11.0	0.2133	0.0183	0.5148	0.0735
BMI	28.7±6.6	27.4±5.5	25.9±4.6	0.3638	0.0057	0.1346	0.0182
Fasting glucose	127.3±25.9	107.3±5.5	88.9±7.7	<0.0001	<0.0001	<0.0001	<0.0001
Lipid profile							
LDL	90.5±34.2	117.2±37.7	114±37.1	0.0023	0.0011	0.7034	0.0025
HDL	45.4±13.7	50.3±13.2	52.1±17.9	0.1229	0.0512	0.5496	0.1221
Blood pressure							
Hx hypertension	45 (86.5%)	27 (61.4%)	83 (69.2%)				0.0113
Systolic BP	146±19	139±17	138±19	0.0830	0.0165	0.7301	0.0465
Diastolic BP	81±11	81±9	79±10	0.9763	0.2454	0.2626	0.3627
On statins	18 (34.6%)	19 (43.2%)	46 (38.3%)				0.6907
Family history of CAD	19 (36.5%)	18 (40.9%)	35 (29.2%)				0.3144
PAD/stroke/carotid artery disease	6 (11.5%)	1 (2.3%)	2 (1.7%)				0.0093

Bold values highlight the major categories.

BP, blood pressure; BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; LDL, low-density lipoprotein cholesterol; NFG, normal fasting glucose; PAD, peripheral arterial disease.

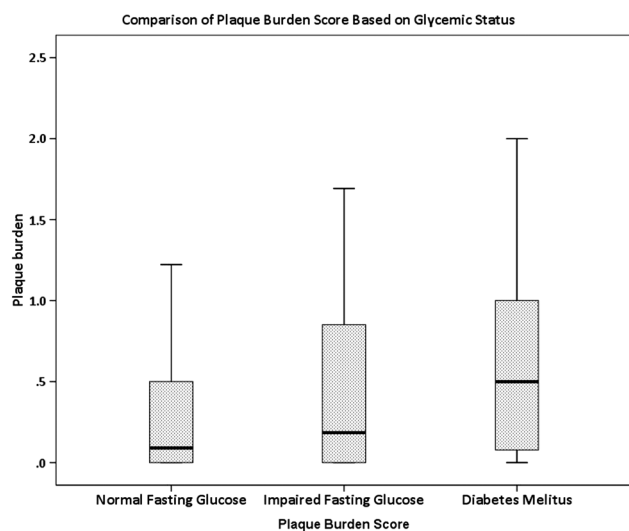


Figure 1 Plaque burden score in 216 patients separated according to their glycaemic status, with SEM shown in bars. Plaque burden was computed by scoring each assessable coronary segment as 0 for normal, 1 for mild plaque, 2 for moderate plaque and 3 for severe plaque and dividing by the number of assessable segments. * $p=0.04$, ** $p<0.0001$, ‡ $p=0.23$.

overall) could not be analysed due to motion artefacts or poor image quality, leaving a total of 2615 assessable segments (98.2%). The NFG group had a significantly fewer diseased segments (any degree of stenosis) (22.6%, 29.1% and 39.9%, respectively, $p<0.0001$ for both comparisons) compared to the IFG and DM groups. There

were a significantly ($p<0.0001$) greater number of segments with calcified plaques in participants with DM (26.7%) compared to those with IFG (15.2%) and NFG (14.6%). The IFG and DM groups had a significantly greater proportion of non-calcified plaques than the NFG group, but there were no differences between the DM (6.3%) and IFG (6.7%) cohorts. Mixed plaques were noted in similar percentages in the three groups.

Per-patient analysis

The number of participants with obstructive CAD (>60% stenosis) was significantly ($p=0.001$) higher in the DM (36.5%) and IFG (29.5%) groups than that in the NFG group (13.3%) (figure 2). When two-group comparisons were performed, there was no significant difference in the prevalence of obstructive CAD between the DM and IFG groups ($p=0.52$). There was a significantly higher proportion of individuals with obstructive CAD in the IFG versus NFG groups ($p=0.02$) and the DM versus NFG groups ($p=0.0009$). In addition, the number of individuals with very high calcium scores (>400) was significantly ($p=0.03$) higher in the DM (30.8%) and IFG (18.2%) groups than that in the NFG group (13.3%). In two-group comparisons, the DM group was significantly higher than the NFG group ($p=0.01$), but there was no significant difference between the DM compared to IFG groups ($p=0.24$) and NFG compared to IFG groups ($p=0.46$).

DISCUSSION

This study is the first to provide evidence for the association of IFG, in addition to DM, with increased objective

Table 2 Plaque severity and composition

	DM	IFG	NFG	p (DM vs IFG)	p (IFG vs NFG)	p (DM vs NFG)	p (3 groups)
<i>Plaque severity</i>							
Total segments analysed	637	539	1488				
Normal segments	383 (60.1%)	382 (70.9%)	1152 (77.4%)				<0.001
Mild plaque segments	135 (21.1%)	81 (15.0%)	223 (15.0%)				
Moderate plaque segments	59 (9.3%)	34 (6.3%)	79 (5.3%)				
Severe plaque segments	60 (9.4%)	42 (7.8%)	34 (2.3%)				
Total diseased segments	254 (39.9%)	157 (29.1%)	336 (22.6%)	0.0001	0.0029	<0.0001	<0.0001
<i>Plaque composition</i>							
Total plaques	254	157	336				
Calcified plaques	170 (26.7%)	82 (15.2%)	218 (14.6%)	0.0035	0.0099	<0.0001	0.0068
Mixed plaques	44 (6.9%)	39 (7.2%)	73 (4.9%)	0.0766	0.4890	0.4060	0.1668
Non-calcified plaques	40 (6.3%)	36 (6.7%)	45 (3.0%)	0.0877	0.00092	<0.0001	0.0270

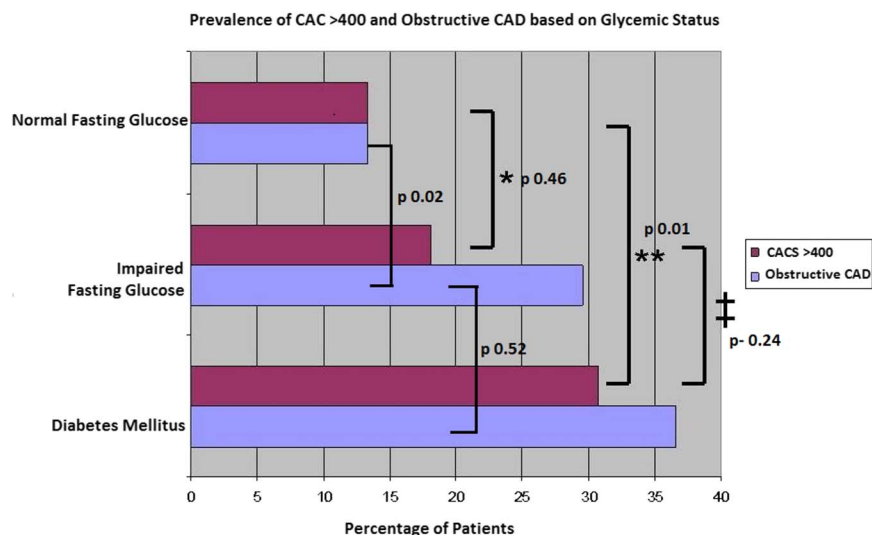
Bold values highlight the major categories.

DM, diabetes mellitus; IFG, impaired fasting glucose; NFG, normal fasting glucose.

measures of CAD compared to NFG, including significantly higher, but comparable, calcium scores, plaque burden and obstructive CAD in patients with asymptomatic IFG and DM compared to individuals with NFG. Although DM is generally regarded as a CAD equivalent,¹² more recent data indicate that this may not be the case. A recent meta-analysis of 45 108 patients reported that patients with DM and no myocardial infarction had 43% fewer events than patients with a prior myocardial infarction and no DM.¹³ In addition, it has become clear through CAC studies that patients with DM have the same spectrum of CAC scores as those with no DM, with, however, more risk at every CAC level,^{3–10} except for equivalent very low risk in those with 0 CAC.⁴

Whether these findings apply to prediabetes patients is unknown. Microvascular disease is not a sequel of IFG; several years of DM is necessary.¹ IFG does impose an 18–20% increase in macrovascular cardiovascular risk,² presumably mediated by insulin resistance and frequent association with the metabolic syndrome. The conversion rate to DM is 10% annually, thereby adding further to the rapid worldwide increase in DM prevalence, from 171 million in 2000 to a projected 366 million in 2030.¹⁴ The magnitude of the issue is apparent in the USA from the IFG prevalence of 25.7%, with an estimated affected population of 57 million adults.¹ Other countries are similarly afflicted, with 37.6% prevalence in Denmark and 37.6% in India.¹ Therefore, in the setting of a

Figure 2 Percentage of patients studied with CACS >400 and obstructive CAD (at least one coronary artery segment with >60% stenosis) separated based on their glycaemic status. *p=0.46 and 0.02 for CACS> 400 and obstructive CAD, respectively; **p=0.01 and 0.0009 for CACS >400 and obstructive CAD, respectively; ‡p=0.24 and 0.52 and for CACS >400 and obstructive CAD, respectively. CACS, coronary artery calcium score; CAD, coronary artery disease.



paucity of data and widespread prevalence, establishing the CAD risk in this large cohort is of major public health importance.

There are two prior studies correlating the degree of glycaemic derangement in diabetic participants with CAD burden by conventional angiography. Seibaek *et al* compared the results of glucose tolerance tests in a population of 99 patients with documented CAD to a control group of 112 patients without CAD.¹⁵ They found that a higher percentage of patients with CAD had abnormal glucose tolerance but were unable to demonstrate a specific correlation between the degree of hyperglycaemia and the amount of CAD. More recently, Quadros *et al* studied 145 individuals undergoing coronary angiography and divided them into four groups based on their fasting plasma glucose; they were able to demonstrate a good correlation between hyperglycaemia and CAD burden.¹⁶ Conventional angiography, however, is limited by its inability to identify the non-obstructive plaque burden. CCTA, on the other hand, is ideally suited to identify and semiquantify all plaque.

DM has been evaluated by CAC in multiple studies, and the increased prevalence of CAC in DM is well documented, as is the worse prognosis in those with CAC.^{3–10} In CCTA evaluations, Pundziute *et al*⁹ noted more diseased segments, calcified and non-calcified plaques in 215 patients with symptomatic DM compared to individuals with no DM, and Scholte *et al*¹⁰ in 70 patients with asymptomatic DM reported plaque in 80%, 41% of which were non-calcified. Neither paper evaluated patients with IFG. Until the present study, there were no CAC or CCTA evaluations of patients with IFG. The findings are consistent with the near equivalency of subclinical atherosclerosis in the DM and IFG groups. With the exception of higher percentages of diseased segments, and calcified plaques in the DM group, all other measures of atherosclerosis, including calcium score, CAC >400, plaque burden, proportion of non-calcified and mixed plaques, and incidence of obstructive disease, were no different in the DM and IFG cohorts. In contrast, most of the parameters of atherosclerosis severity were worse in the IFG group compared to the NFG group; only the frequencies of mild, moderate and mixed plaques were similar. This study does not address the mechanism of the advanced atherosclerosis in the IFG group for which further research is needed.

Weaknesses

There were several limitations to this study. First, the prevalence of hypertension was slightly higher in the DM group, which may have made a small contribution to the greater burden of CAD in this group. Second, in this asymptomatic population, the presence of CAD on CCTA was used as a surrogate end point for clinical CAD. However, this has been the rule in asymptomatic populations, in whom event rates are low and invasive angiography not warranted. Finally, this study was neither powered nor designed to examine clinical outcomes.

Clinical significance

While most physicians are familiar with the risks of DM and the metabolic syndrome, IFG remains under the radar. The near equivalency of subclinical atherosclerosis in DM and IFG should heighten awareness of the risks of IFG. Pending corroboration by other reports, more intensive efforts may be devoted to the evaluation by CAC scanning and treatment of patients with pre-diabetes.

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Contributors SG recruited patients and performed all studies with PG. PG collected all data, database and first draft. SM involved in database analysis and paper writing with PG. RK made calls for follow-ups. FS performed all studies in association with SG. HH and AD participated in discussion of results and paper editing. JN is the principal investigator, created the study plan, and participated in review of analysis and paper editing.

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