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Original Article

Study of the features of coronary artery atheromatous plaque using intravascular ultrasound in patients with impaired glucose tolerance

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Abstract

Objective: We used intravascular ultrasound (IVUS) to analyze the features of coronary artery atheromatous plaque in patients with impaired glucose tolerance and mild-to-moderate angiographic coronary stenosis. The aim was to determine the clinical significance of plaque characteristics as well as the relationship between hemoglobin A1c (HbA1c) levels and coronary artery lesions.

Methods: HbA1c levels were evaluated in 85 patients (96 lesions), of whom 46 had impaired glucose tolerance (IGT Group) and 39 had normal blood glucose (NBG Group). IVUS was used to analyze the lesion vessel of both groups qualitatively and quantitatively. The external elastic membrane area (EEMA), minimal lumen area (MLA), plaque area (PA), and plaque burden (PB) were measured for both the target lesion and the reference segments (reference external elastic membrane area (REEMA), reference minimal lumen area (RMLA), reference plaque area (RPA), and reference plaque burden (RPB), respectively).

Results: HbA1c levels were significantly higher in the IGT Group than in the NBG Group ($P < 0.05$). In the IGT Group there was more soft plaque, eccentric plaque, and positive remodeling, and less calcification, while in the NBG Group there was much harder plaque and calcification, no reconstruction, and negative remodeling ($P < 0.05$). MLA was smaller in the IGT Group than in the NBG Group, while EEMA, PA, and PB were clearly greater ($P < 0.05$). In the meantime, RMLA was clearly smaller in the IGT Group than in the NBG Group, while RPA and RPB were greater ($P < 0.05$). HbA1c levels were positively correlated with PA and PB, and negatively correlated with MLA.

Conclusion: IVUS is very valuable for the evaluation of mild-to-moderate coronary lesions. The coronary artery lesions in patients with IGT are more serious and widespread than those in patients with NBG. HbA1c levels might be of some value in assessing the severity of coronary artery lesions.

Keywords: Atherosclerosis; Intravascular ultrasound; Coronary angiography; Impaired glucose tolerance

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Introduction

Impaired glucose tolerance is a transitional phase between normal glucose tolerance and diabetes. It is associated with a significantly increased risk of microvascular and macrovascular complications. The risk of serious adverse cardiovascular events increases further when impaired glucose tolerance coexists with coronary atherosclerosis.[1]

In recent years, research has shown that the severity of an atherosclerotic lesion has only a weak correlation with its clinical sequelae, the majority (60%−70%) of which are caused by the rupture of the atherosclerotic plaque and the secondary thrombus. Traditional coronary angiography (CAG) has demonstrated that most clinical events were associated with mild-to-moderate stenosis.[2−4]

In the present study, CAG was used to evaluate patients who had both coronary artery disease and impaired glucose tolerance. In those cases that showed mild-to-moderate stenosis on CAG, intravascular ultrasound (IVUS) was used to classify the pathological changes in coronary plaque and assess their clinical significance.

Methods

Subjects

Between July 2009 and December 2010, we evaluated 85 patients with stable or unstable angina, of whom 46 had impaired glucose tolerance (IGT Group) and 39 had normal blood glucose (NBG Group). All patients had at least one 50−70% vessel diameter stenosis in an epicardial coronary artery or its main branch, as confirmed by CAG. No patients in either group were taking hypoglycemic drugs.

Coronary angiography

The normal reference segments and the lesion segment were identified for each coronary vessel. A "normal" reference segment was defined as a 5−10 mm segment without pathological changes in the proximal or distal part of the target lesion vessel. The lesion segment was the one with the most severe stenosis, according to images from different angiographic projections, and as assessed by quantitative coronary angiography (QCA).

IVUS images

Quantitative indicators: All data for analysis were collected from the segment with the worst stenosis according to IVUS. The external elastic membrane area (EEMA), minimal lumen area (MLA), plaque area (PA), and plaque burden (PB) were measured for both the target lesions and the reference segments (reference external elastic membrane area (REEMA), reference minimal lumen area (RMLA), reference plaque area (RPA), and reference plaque burden (RPB), respectively), together with any vascular calcification.

Qualitative indicators: Based on the ultrasonic echo, plaque can be divided into four types: soft plaque, fibrous plaque, calcific plaque, and mixed plaque. Eccentric plaque refers to plaque that builds up unevenly on the wall of the arteries, so that its maximum thickness is more than twice the minimum.

Statistical methods

SPSS 14.0 statistical software (SPSS Inc. Chicago, IL, USA) was employed. The Chi-square test was used to compare numerical data, which were expressed as mean values. The *t*-test was used for between-group comparisons and Pearson analysis was used to test correlations between two factors. A P-value < 0.05 represented the level of statistical significance.

Results

The clinical data showed that the IGT Group had significantly higher levels of hemoglobin A1c (HbA1c) than the NBG Group ($P < 0.05$) (Table 1).

In this study, 96 pathological lesions were evaluated and found to have a mean area stenosis of $53.68 \pm 2.58\%$ by CAG and $59.66 \pm 4.66\%$ by IVUS ($P < 0.05$); Angiography identified a total of 96 lesions in the 85 patients. According to the IVUS data for these lesions, MLA was less in the IGT Group than in the NBG Group, while EEMA, PA, and PB were clearly greater in the IGT Group ($P < 0.05$). However, RMLA was clearly less in the IGT Group than in the NBG Group, while RPA and RPB were higher ($P < 0.05$) (Table 2).

In the IGT Group, there were 52 plaques, including 36 eccentric plaques, while in the NBG Group, there were 44 plaques of which 20 were eccentric. The difference was statistically significant ($P = 0.019$). The IGT Group showed more soft plaque, eccentric plaque, and positive remodeling of the coronary artery, but less calcification, while the NBG Group showed more fibrous plaque, calcification, and either no remodeling or negative remodeling ($P < 0.05$) (Table 3).

Table 1
Clinical data of the two groups.

Items	IGT group ($n = 46$)	NBG group ($n = 39$)	P value
Male/female, n	38/8	30/9	0.514
Age, years	61.1 ± 2.6	61.4 ± 2.5	0.684
Smoking, n	28	25	0.759
History of high blood pressure, n	35	28	0.653
TC, mmol/L	4.8 ± 1.2	4.7 ± 0.9	0.719
TG, mmol/L	2.3 ± 1.4	2.2 ± 2.0	0.751
LDL-C, mmol/L	2.8 ± 0.6	2.6 ± 0.6	0.163
HDL-C, mmol/L	1.4 ± 0.7	1.6 ± 0.6	0.175
EF, %	56 ± 5	55 ± 4	0.220
LAD, n (%)	20 (38.5)	19 (43.2)	0.639
RCA, n (%)	17 (32.7)	14 (31.8)	0.927
LCX, n (%)	15 (28.8)	11 (25.0)	0.673
QCA, %	53.8 ± 1.7	53.4 ± 1.2	0.128
HbA1c, %	5.96 ± 0.32	5.4 ± 0.26	0.000

IGT: impaired glucose tolerance; NBG: normal blood glucose; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; EF: ejection fraction; LAD: left anterior descending coronary artery; RCA: right coronary artery; LCX: left circumflex coronary artery; QCA: quantitative coronary angiography; HbA1c: hemoglobin A1c.

Table 2
Quantitative comparison of coronary plaque between the two groups.

Items	IGT group	NBG group	P value
EEMA, mm^2	14.3 ± 1.0	13.9 ± 0.6	0.016
MLA, mm^2	5.5 ± 0.7	5.9 ± 0.5	0.002
PA, mm^2	8.8 ± 1.1	8.0 ± 0.7	0.000
PB, %	61.2 ± 4.9	57.6 ± 3.5	0.000
REEMA, mm^2	13.5 ± 1.1	13.7 ± 1.1	0.351
RMLA, mm^2	9.2 ± 0.8	10.1 ± 0.9	0.000
RPA, mm^2	4.3 ± 1.2	3.7 ± 1.3	0.008
RPB, %	31.9 ± 7.2	26.1 ± 8.2	0.001
RI	1.1 ± 0.8	1.0 ± 0.8	0.008

IGT: impaired glucose tolerance; NBG: normal blood glucose; EEMA: external elastic membrane area; MLA: minimal lumen area; PA: plaque area; PB: plaque burden; REEMA: reference external elastic membrane area; RMLA: reference minimal lumen area; RPA: reference plaque area; RPB: reference plaque burden; RI: remodeling index; RI > 1.05 represents positive remodeling; RI < 0.95 represents negative remodeling; and 0.95 < RI < 1.05 represents non-remodeling.

Linear correlation analysis was performed to compare levels of HbA1c with MLA, PA, and PB ($P < 0.05$) (Table 4).

Fig. 1 shows an IVUS image of a mild-to-moderate lesion as identified by CAG.

Discussion

Compared with CAG, IVUS can provide more detailed information about the coronary plaque and vascular wall, such as the volume of plaque, its composition, calcification, stability, rupture, and the volume as well as the shape of vascular walls. Ninety six pathological lesions were evaluated and found to have a mean area stenosis of 53.68 ± 2.58% by CAG and 59.66 ± 4.66% by IVUS ($P < 0.05$); the statistically significant difference indicates that pathological changes in the coronary arteries may be underestimated by CAG. The following reasons may be considered: (1) Even though the proximal or distal part of a reference segment may be perfectly normal according to CAG, IVUS images may show different levels of intimal hyperplasia or even plaque within the segment, indicating the presence of atherosclerosis. (2) To protect the lumen, an atherosclerotic coronary vessel may undergo compensatory expansion, as a part of positive vascular remodeling. (3) CAG can only provide a two-dimensional image of the lumen structure, while IVUS can examine the luminal cross-section through a 360° rotation. (4) Projection angle and overlapping vessels can make a difference to the results of CAG. (5) There may be some subjective factors that influence an observer's assessment. As IVUS provides more accurate information, it can be used for diagnosis when there are doubts regarding the stenosis diagnosed by CAG, when it is necessary to decide whether revascularization is required, or when angiographic results are inconsistent with the clinical manifestations.

Table 3
Qualitative comparison of coronary plaque between the two groups (n).

Groups	Lesions	Plaque				Level of calcification				Remodeling		
		Soft	Fibrous	Calcific	Mixed	0	I	II	III	Negative	Positive	None
IGT	52	28	14	5	5	32	12	7	1	12	27	13
NBG	44	13	14	14	3	14	19	9	2	18	11	15

IGT: impaired glucose tolerance; NBG: normal blood glucose.
Note: If the composition of a plaque was predominantly (>80%) soft, fibrous, or calcific, then the plaque was classified as the corresponding type; otherwise, it was classified as mixed plaque. Level 0: no calcification; Level I: calcification <90°; Level II: calcification 91–180°; Level III: 181–270°.

Table 4
Correlation analysis comparing HbA1c levels with MLA, PA, and PB.

Groups	HbAlc	
	r	*P* value
MLA	−0.395	<0.01
PA	0.675	<0.01
PB	0.615	<0.01

HbA1c: hemoglobin A1c; MLA: minimal lumen area; PA: plaque area; PB: plaque burden.

Ko et al,[5] following 109 patients with coronary heart disease using IVUS, found that the main features of plaque in ACS patients were a heavy burden and positive remodeling. The present study produced similar findings: based on the observed pathological changes, it was found that the MLA of the IGT Group was strikingly lower than that of the NBG Group, while the EEMA was notably higher. Thus, it can be seen that both the burden and the area of plaque were clearly larger in the IGT Group than in NBG Group, indicating that coronary lesions in IGT patients were apparently more aggravated. For the reference segments, there were no differences in REEMA between the IGT Group and the NBG Group, but the lumen of reference segments in the IGT Group was much smaller. Thus, the plaque area and plaque burden of reference segments were significantly greater in the IGT Group than in the NBG Group. Similarly, there were lesions in reference segments. Compared with the NBG Group, patients in the IGT group showed lesions that were extensive and all-pervading, similar to the coronary lesions of diabetes patients.

The stability of plaque is directly related to the occurrence of acute coronary syndrome, since plaque rupture accompanied with thrombosis may lead to serious myocardial ischemia, which is the main cause of acute myocardial infarction. Acute myocardial infarction may occur when the coronary artery stenosis is not so serious, or the lesion may be responsible for coronary spasm, causing angina pectoris. Pathological

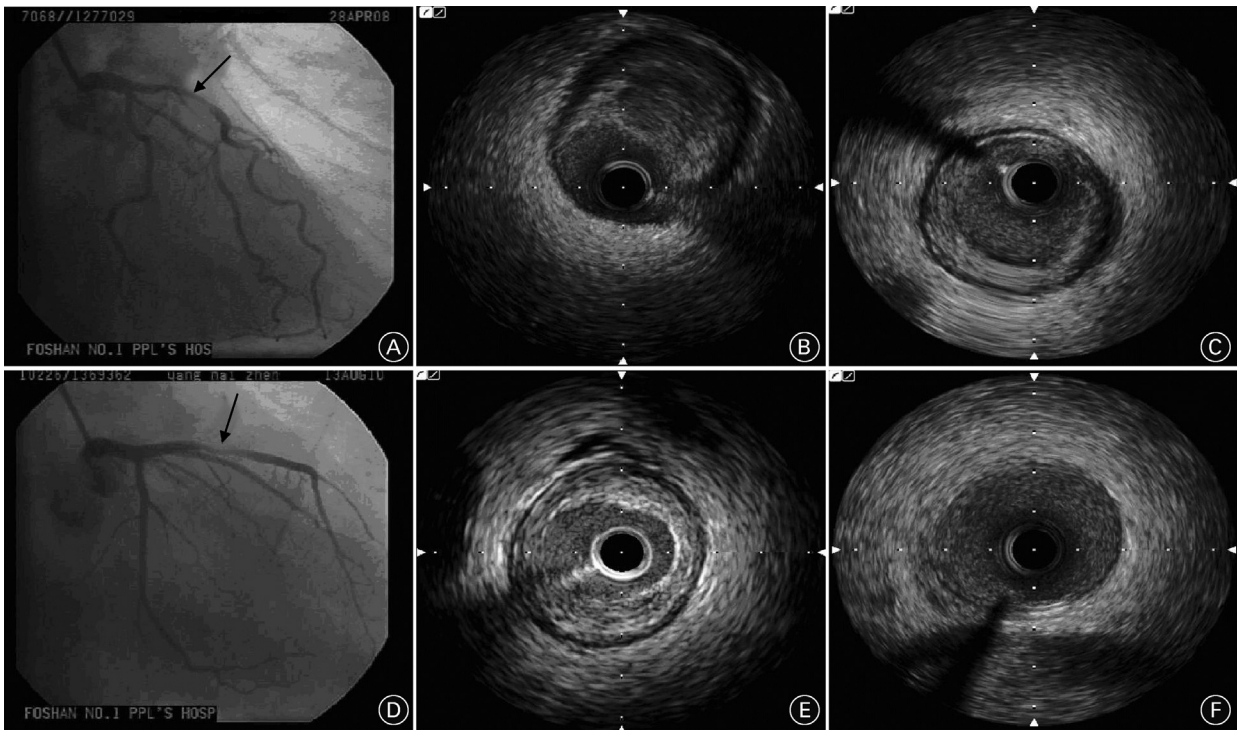

Fig. 1. Angiographic and intravascular ultrasound (IVUS) images from the impaired glucose tolerance (IGT) Group (top) and the normal blood glucose (NBG) Group (bottom). a: The proximal end of the left anterior descending artery (LAD) in the IGT group had eccentric 60% stenosis. b: IVUS image of the IGT Group showing that the proximal end of the LAD had eccentric and soft plaque (10-3 spots); the lumen area was 4.48 mm^2 and the rate of area stenosis was 68.14%. c: a reference vessel in the IGT Group. NBG Images: d: The proximal end of the LAD in the NBG Group had 50% stenosis. e: IVUS image of the NBG Group showing centralized, fibrous plaque; minimal lumen area was 6.04 mm^2 and the rate of area stenosis was 52.31%. f: a reference vessel in the NBG Group.

research has found that the histological feature of vulnerable plaque is a large lipid core, eccentric plaque with a thin fibrous cap, and a large plaque area; however, this does not necessarily result in a large occlusion of the lumen. Eccentric plaque and positive remodeling imply that the plaque is vulnerable, given that more lipids and macrophages are present during the pathological changes of positive remodeling, and that to be rich in lipids and infiltrated by a large number of macrophages is a mark of plaque vulnerability. Kato et al[6] followed 110 patients with acute coronary syndrome, using IVUS to observe the changes in their coronary arteries. In 60 patients, rupture of the culprit plaque occurred. The remodeling index of the rupture group was markedly higher than that of the non-rupture group ($P < 0.05$), showing that plaque rupture was associated with more positive remodeling. In the present study, the IGT Group had more eccentric plaque, more lipid plaque, more positive remodeling, but less calcification, indicating that IGT patients with mild-to-moderate stenosis may still have vulnerable plaque that can easily rupture, resulting in acute coronary syndrome.

The ARIC[7] study found that the level of HbA1c was related to the occurrence of cardiac events when HbA1c was $\geq$6.0%. Berry et al reported that the increase in HbA1c was related to the occurrence and severity of coronary atherosclerosis, and that it was beneficial to impose strict controls on HbA1c levels in patients with coronary artery disease who also had IGT or diabetes mellitus. Patients who had poor control of HbA1c had clearly more aggravated coronary artery lesions compared to those with good HbA1c control.

HbA1c levels show an increasing trend with the severity of coronary artery lesions, indicating that HbA1c could serve as a warning marker for the progress of coronary heart disease. However, it needs to be combined with the results of other examinations, such as clinical findings, electrocardiography, and coronary arteriography. What kind of role HbA1c plays in the development of coronary artery lesions remains to be determined; however, some possibly related factors are as follows: (1) HbA1c can produce red blood cells with more viscosity, less liquidity, and much less deformability. (2) Moreover, HbA1c can slow down the dissociation of oxyhemoglobin, increase the affinity of erythrocytes for oxygen, and notably decrease the level of 2,3-diphosphoglyceric acid, resulting in hypoxia for both tissue and cell. (3) Increased HbA1c levels enhance endothelin production, while also inhibiting the release of nitric oxide (NO) and prostacyclin, damaging vasomotor capacity. In addition, the direct toxic effect of glucose impedes the replication of endothelial cells, reducing their repair capacity, and finally giving rise to damaged endothelial cells, which promote the formation of atherosclerosis.

To conclude, the present study indicates that IVUS is of great value in the evaluation of borderline lesions, showing that the coronary artery lesions of the IGT Group were more serious and widespread than those of the NBG Group. Our findings also suggest that HbA1c levels might be of assistance in the assessment of the severity of coronary artery lesions. Therefore, for those IGT patients with CAG images indicating mild-to-moderate stenosis, especially those who have poor control of HbA1c, it is very important to schedule an IVUS examination as a reference for the choice between clinical treatment strategies, with a view to preventing future adverse cardiovascular events.

Conflicts of interest

We declared that we don't have any conflicts of interest.

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