Nemoto et al. Int J Clin Cardiol 2015, 2:1
ISSN: 2378-2951

International Journal of
Clinical Cardiology

Review Article: Open Access

Relationship between Insulin Levels and Coronary Atherosclerosis in Newly Diagnosed Diabetes Mellitus and Impaired Glucose Tolerance

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Abstract

Background: While some therapies implemented for newly diagnosed Diabetes Mellitus (DM) or impaired Glucose Tolerance (IGT) are effective in preventing cardiovascular events, investigations of coronary plaque in patients with newly diagnosed DM or IGT are lacking.

Methods: We evaluated 96 patients with acute coronary syndrome. The External Elastic Membrane (EEM), Lumen Cross-Sectional Area (CSA), plaque CSA, and plaque burden in the Left Anterior Descending (LAD) artery proximal to the lesion, diagnosed as normal by Coronary Angiography (CAG), were measured using Intravascular Ultrasound (IVUS). Patients were divided according to DM status (DM=35, non-DM=61). Non-DM patients underwent a 75g Oral Glucose Tolerance Test (OGTT) and were further divided into abnormal glucose tolerance (AGT; n=29) and Normal Glucose Tolerance (NGT) groups (n=32).

Results: Quantitative Coronary Angiography (QCA) showed no significant differences in EEM or vessel diameter between groups. However, the lumen CSA was significantly smaller in the DM group than in the NGT group. The plaque CSA and plaque burden were significantly greater in the DM and AGT groups than in the NGT group. Total insulin and glucose values and insulin and glucose values at 120 min after the OGTT correlated with plaque CSA; insulin values at 120 min after the OGTT showed the strongest correlation (R=0.505, $P<0.01$).

Conclusions: Coronary plaque was identified among newly diagnosed DM or IGT patients even when the CAG appeared normal, suggesting that preventive measures against atherosclerosis should be initiated prior to DM development.

Keywords

Acute coronary syndrome, Abnormal glucose tolerance, Insulin, Intravascular ultrasound, Atherosclerosis, Diabetes mellitus

Introduction

Diabetes mellitus (DM) has been identified as a risk factor for cardiovascular disease. Mortality risk is 2–3 times greater in patients with DM than in those without [1,2]. It is well known that the prevalence of multivessel disease and long coronary lesions with small reference vessel diameters is high in patients with DM. Retrospective studies have demonstrated that patients with DM have more extensive coronary plaque compared with those without [3,4].

It is believed that atherosclerosis occurs in the pre-diabetes stage [5]. Therefore, abnormal glucose metabolism, such as that seen in patients with DM or impaired glucose tolerance (IGT), is recognized in over two-thirds of patients with cardiovascular disease such as acute myocardial infarction or angina pectoris [2,6,7].

Hyperglycemia, particularly postprandial hyperglycemia, is a well-known pre-diabetic condition and a risk factor for all-cause mortality and cardiovascular disease [1,8,9]. Some investigators have reported evidence that diabetic intervention therapy during the early phase of DM or IGT can have a preventive effect on cardiovascular events [10-12]. However, assessment of coronary plaque in the pre-diabetes stage has not been sufficiently investigated.

Coronary angiography (CAG) is the standard diagnostic test for coronary disease [13]. However, measurement of vessel walls and plaque is impossible using CAG because it only provides a two-dimensional (2D) image of the vessel lumen. Moreover, early atherosclerosis can sometimes be overlooked; furthermore, the assessment of diffuse disease is difficult. Intravascular ultrasound (IVUS) can measure the vessel wall and quantify the amount of coronary plaque, and it is commonly used as a diagnostic tool and an adjuvant treatment tool [14]. We examined the relationship between coronary atherosclerosis and abnormal glucose metabolism using IVUS in patients with acute coronary syndrome.

Methods

Subjects

IVUS-guided primary angioplasty of the Left Anterior Descending Artery (LAD) was performed for 205 patients with acute coronary syndrome between October 2003 and April 2007.

A normal coronary was defined by a %diameter stenosis (%DS) of <20% according to Quantitative Coronary Angiography (QCA).

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Citation: Nemoto N, Nakajima R, Ymazaki K, Utsunomiya M, Hori M, et al., (2015) Relationship between Insulin Levels and Coronary Atherosclerosis in Newly Diagnosed Diabetes Mellitus and Impaired Glucose Tolerance. Int J Clin Cardiol 1:020

Received: December 25, 2014: **Accepted:** February 03, 2015: **Published:** February 06, 2015

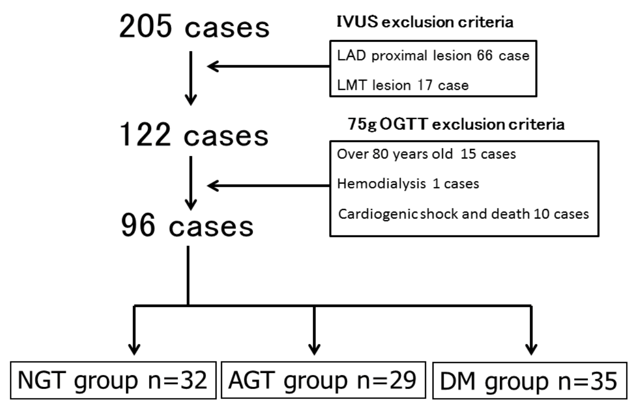

Figure 1: Enrollment criteria and study flow

DM (diabetes mellitus) group: DM was considered present if at least one of the following criteria were present: 1) DM treatment, such as diet therapy, medical therapy, or insulin use; 2) an HbA1c (National Glycohemoglobin Standardization Program; NSGP) level of ≥6.5%; or 3) a Fasting Plasma Glucose (FPG) level of ≥126mg/dl. NGT (Normal Glucose Tolerance) group: NGT was considered present if the FPG level was <100mg/dl and the 2h plasma glucose (2h-PG) level was <140 mg/dl following the 75-g oral glucose tolerance test (OGTT). AGT (Abnormal Glucose Tolerance) group: Those without DM and NGT.

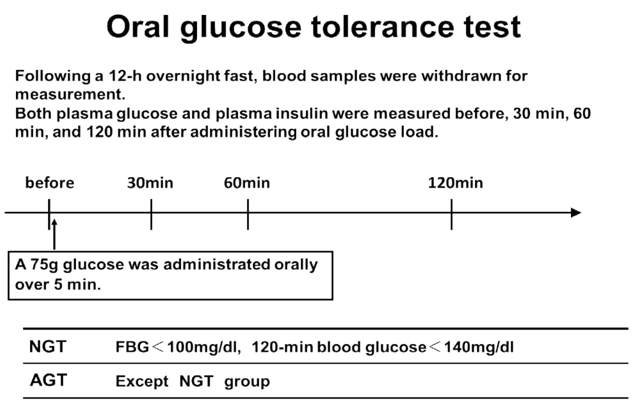

Figure 2: Oral glucose tolerance test (OGTT)

Patients with proximal LAD (n=66) and left main (n=17) coronary disease with a %DS of >20% were excluded from IVUS analysis.

Patients aged >80 years (n=15), patients with cardiogenic shock, and cases of death (n=10) and hemodialysis (n=1) were also excluded from the study. The remaining 96 patients were divided on the basis of DM status (Figure 1).

Patients were considered to have DM if they met at least one of the following criteria: 1) history of DM treatment, such as diet therapy, medical therapy, or insulin use; 2) an HbA1c (National Glycohemoglobin Standardization Program; NSGP) level of ≥6.5%, and/or 3) a fasting plasma glucose (FPG) level of ≥126mg/dl.

Patients without DM underwent a 75-g oral glucose tolerance test (75-g OGTT) before discharge from the hospital and were divided into two groups according to the results.

Normal glucose tolerance (NGT) was defined as an FPG level of <100mg/dl and a 2h plasma glucose (2h-PG) level of <140 mg/dl. Abnormal glucose tolerance (AGT) was defined as the absence of DM and NGT.

OGTT and blood sampling

Immediately after admission, baseline venous blood samples were obtained to measure ratios (%) of HbA1c (Japan Diabetes Society), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and creatinine before any medical agents or other interventions were administered.

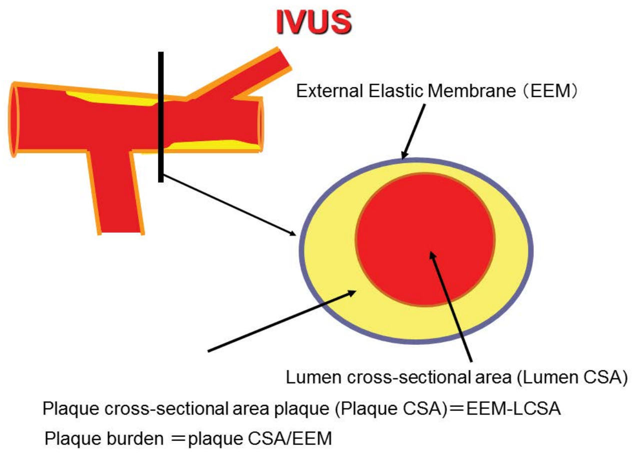

Figure 3: Cross-sectional intravascular ultrasound (IVUS) image of an atherosclerotic human coronary artery and the measured position**.** The plaque Cross-Sectional Area (CSA) was calculated as External Elastic Membrane (EEM) minus lumen CSA, and plaque burden was calculated as plaque plus media CSA divided by EEM CSA. Measured position: Left Anterior Descending Artery (LAD) proximal to the lesion, 5mm or more from a major branch such as the circumflex artery or major diagonal artery and diagnosed as normal on coronary angiography (CAG).

HbA1c was calculated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value using the following formula: HbA1c (NGSP)%=1.02×HbA1c (Japan Diabetes Society; %) + 0.25% [15].

A baseline 75g OGTT was performed 2–3 weeks after the coronary intervention to avoid the possible influence of acute coronary syndrome on glucose tolerance. Blood samples were collected after a 12h overnight fast. A total of 75g of glucose was orally administered over a period of 5 min, and plasma glucose and insulin levels were measured before administration and 30, 60, and 120 min after administration (Figure 2).

IVUS and percutaneous coronary intervention

All patients received aspirin (162–200mg) and intravenous heparin to achieve an activated clotting time of >250 s. Glycoprotein II b/III was not given to any patient. IVUS was performed with percutaneous coronary intervention and intracoronary administration of 125–250μg of nitroglycerin. Data were acquired with commercially available IVUS transducers (30MHz/3.2F, Ultracross or 40MHz/2.5F, Atlantis SR pro, Boston Scientific/SciMed, Natick, MA, USA). An imaging catheter was introduced into the mid-portion of the LAD and withdrawn to the left main by automatic pullback at a speed of 0.5mm/s. Ultrasound images were recorded on S-VHS tape for offline analysis.

Quantitative IVUS and QCA analysis

Quantitative analyses of gray-scale IVUS images were performed according to the criteria of the American College of Cardiology Clinical Expert Consensus Document on IVUS.[16] Images of the site proximal to the LAD, 5 mm or more from a major branch such as the circumflex artery or major diagonal and diagnosed as normal on CAG, were evaluated for this study (Figure 3). The External Elastic Membrane (EEM) and lumen cross-sectional area (CSA) were measured. Plaque CSA was calculated as EEM minus lumen CSA, and plaque burden was calculated as plaque plus media CSA divided by EEM CSA.

QCA, of the LAD proximal site assessed with IVUS, was performed with an automated edge detection system (CMS, Medis Medical Imaging Systems, Nuenen, The Netherlands) by experienced interventional cardiologists.

Statistical methods

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as percentages. The chi-square test and

Table 1: Baseline patient characteristics

	DM group (n=35)	AGT group (n=29)	NGT group (n=32)	*P* value
Age	65.8 ±10.2[a]	62.4 ± 12.7[ab]	58.2 ± 13.0[b]	0.04
Males (%)	23 (65.7)	26 (89.7)	24 (75.0)	0.08
Body mass index	24.8 ± 4.9	24.4 ± 3.6	23.8 ± 2.3	0.59
Hypertension (%)	28 (80.0)	16 (55.2)	21(65.6)	0.1
Dyslipidemia (%)	19 (54.3)	13 (44.8)	19 (59.4)	0.52
Smoking (%)	17 (48.6)	20 (69.0)	19 (59.4)	0.25
Family history (%)	3 (8.6)	3 (10.3)	4 (12.5)	0.92
Prior PCI (%)	4 (11.4)	2 (6.9)	4 (12.5)	0.77
Prior myocardial infarction (%)	2 (5.7)	2 (6.9)	2 (6.3)	1.00

Values are expressed as mean ± SD or number (percentage).

[ab]Cells with same superscripts within row do not differ (*P*>0.05).

DM: Diabetes Mellitus, AGT: Abnormal Glucose Tolerance, NGT: Normal Glucose Tolerance, PCI: Percutaneous Coronary Intervention

Table 2: Patient biochemical data

	DM group (n=35)	AGT group (n=29)	NGT group (n=32)	*P* value
Total cholesterol, mg/dl	197 ± 44	200 ± 29	197 ± 39	0.95
LDL cholesterol, mg/dl	122 ± 35	123 ± 28	127 ± 31	0.79
HDL cholesterol, mg/dl	47 ± 11	49 ± 14	46 ± 11	0.54
Triglyceride, mg/dl	138 ± 74	139 ± 76	120 ± 67	0.53
FPG mg/dl	168 ± 63[a]	94 ± 10[b]	88 ± 7[b]	<0.01
HbA1c (%)	8.0 ± 1.4[a]	5.7 ± 0.3[b]	5.5 ± 0.3[b]	<0.01
Serum Cr, mg/dl	0.85 ± 0.27	0.90 ± 0.18	0.82 ± 0.21	0.44

Values are expressed as mean ± SD.

[ab]Cells with same superscripts within row do not differ (*P*>0.05).

DM: Diabetes Mellitus, AGT: Abnormal Glucose Tolerance, NGT: Normal Glucose Tolerance, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, FPG: Fasting Plasma Glucose, Cr: Creatinine

Fisher's exact test were used to compare frequency ratios between groups. Continuous variables were compared by analysis of variance (ANOVA). Differences between the mean 75g OGTT results were assessed by unpaired Student's t-tests. Linear regression was used to determine whether plasma insulin and glucose levels correlated with plaque CSA. To evaluate associations between plaque CSA and other variables, stepwise forward multivariate linear regression analyses were performed. Candidate variables included all those parameters significant in univariate correlations. The entry criterion in the multivariate analyses was set at a significance level of $p<0.10$.

A probability value of <0.05 was considered statistically significant. All analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient demographics

There were 35 patients with DM, 29 with AGT, and 32 with NGT (Table 1). The mean age was 65.8 ± 10.2, 62.4 ± 12.7, and 58.2 ± 13.0 years for patients with DM, AGT, and NGT, respectively; the DM patients were significantly older than the NGT patients (P<0.05). There were no significant differences among the three groups with regard to body mass index, family history, or history of hypertension, dyslipidemia, smoking, prior myocardial infarction, and prior percutaneous coronary intervention.

Biochemical data are detailed in Table 2 and 3. There were no significant differences among the three groups with regard to total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and serum creatinine levels. FPG values were 168 ± 63 mg/dl in the DM group, 94 ± 10mg/dl in the AGT group, and 88 ± 7mg/dl in the NGT group, while HbA1c values were 8.0% ± 1.4%, 5.7% ± 0.3%, and 5.5% ± 0.3%, respectively; both values were significantly higher in the DM group than in the other two groups (*P*< 0.05).

Table 3: Results of the 75g OGTT

	AGT group (n=29)	NGT group (n=32)	*P* value
Fasting plasma glucose (mg/dl)	93.9 ± 10.1	88.3 ± 7.4	0.02
Fasting plasma insulin (mg/dl)	8.4 ± 3.5	6.8 ± 3.6	0.09
Glucose value (30 min)	167.9 ± 30.3	151.4 ± 24.7	0.02
Insulin value (30 min)	70.5 ± 74.2	78.4 ± 47.1	0.62
Glucose value (60 min)	189.6 ± 36.3	157.5 ± 34.4	<0.01
Insulin value (60 min)	91.3 ± 52.9	108.4 ± 64.3	0.26
Glucose value (120 min)	177.4 ± 28.6	111.0 ± 18.6	<0.01
Insulin value (120 min)	115.8 ± 65.6	61.8 ± 28.6	<0.01
ΣPG	628.7 ± 73.0	505.2 ± 61.3	<0.01
ΣIRI	286.0 ± 157.5	255.4 ± 113.0	0.38

Values are expressed as mean ± SD.

[ab]Cells with same superscripts within row do not differ (*P*>0.05).

OGTT: Oral Glucose Tolerance Test, AGT: Abnormal Glucose Tolerance, NGT: Normal Glucose Tolerance

ΣPG: Total Plasma Glucose (fasting, 30 min, 60 min, 120 min)

ΣIRI: Total Immunoreactive Insulin (fasting, 30 min, 60 min, 120 min)

Table 4: QCA and IVUS data

	DM group (n=35)	AGT group (n=29)	NGT group (n=32)	*P* value
Vessel diameter (QCA)	3.3 ± 0.7	3.2 ± 0.7	3.4 ± 0.6	0.58
IVUS analysis				
External elastic membrane area (mm^2)	14.7 ± 3.9	16.5 ± 4.2	14.9 ± 4.5	0.21
Lumen cross-sectional area (mm^2)	7.4 ± 2.8[a]	8.4 ± 2.3[ab]	9.2 ± 3.3[b]	0.047
Plaque cross-sectional area (mm^2)	7.3 ± 1.9[a]	8.1 ± 3.4[a]	5.7 ± 2.6[b]	<0.01
Plaque burden (%)	50.3 ± 9.4[a]	47.9 ± 12.7[a]	38.3 ± 12.4[b]	<0.01

Values are expressed as mean ± SD.

[ab]Cells with same superscripts within row do not differ (*P*>0.05).

DM: Diabetes Mellitus, AGT: Abnormal Glucose Tolerance, NGT: Normal Glucose Tolerance, QCA: Quantitative Coronary Angiography, IVUS: Intravascular Ultrasound

Table 5: Results of Multivariable linear regression analysis

	Standard regression coefficient
Body Mass Index	0.049
Glucose 120min	0.041
Insulin 120min*	0.460
Multiple correlation coefficient	0.508
Coefficient of determination	0.258

* p<0.01

QCA and IVUS findings

Vessel diameters on QCA were 3.3 ± 0.7mm, 3.2 ± 0.7mm, and3.4 ± 0.6mm in the DM, AGT, and NGT groups, respectively, while EEM values were 14.7 ± 3.9mm^2, 16.5 ± 4.2mm^2, and 14.9 ± 4.5mm^2, respectively; there were no significant differences among the three groups in both parameters. The lumen CSA measured 7.4 ± 2.8mm^2 in the DM group, 8.4 ± 2.3mm^2 in the AGT group, and 9.2 ± 3.3mm^2 in the NGT group, indicating that the lumen CSA was significantly smaller in the DM group than in the NGT group (*P*=0.0140; Figure 4A). The plaque CSA measured 7.3 ± 1.9mm^2, 8.1 ± 3.4mm^2, and 5.7 ± 2.6mm^2 (Figure 4B), while the plaque burden was 50.3% ± 9.4%, 47.9% ± 12.7%, and 38.3% ± 12.4% in the DM, AGT, and NGT groups, respectively (Figure 4C); plaque CSA and plaque burden were significantly greater in the DM and AGT groups than in the NGT group (*P*<0.05), with no significant differences between the DM and AGT groups (Table 4).

Correlation of plaque CSA with insulin levels (fasting, 30 min, 60 min, 120 min, total), and glucose levels

The correlation of plaque CSA with insulin levels and glucose levels based on the 75g OGTT was evaluated. Insulin values at 120

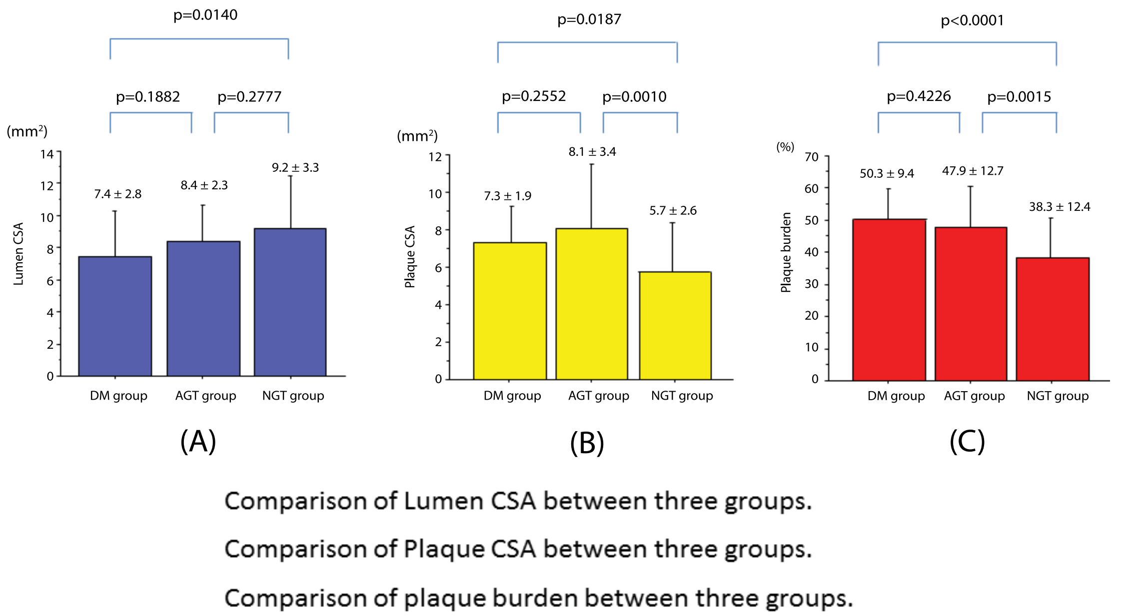

Figure 4: Intravascular ultrasound (IVUS) parameters

4A: Comparison of the lumen cross-sectional area (CSA) among the three groups. The lumen CSA was significantly smaller in the DM group than in the NGT group (*P*=0.0140).

4B: Comparison of plaque CSA among the three groups. Plaque CSA was significantly greater in the DM and AGT groups than in the NGT group (*P*=0.0187, *P*=0.0010, respectively). There was no significant difference between the DM and IGT groups.

4C: Comparison of plaque burden among the three groups. Plaque burden was significantly greater in the DM and AGT groups than in the NGT group (*P*<0.0001, *P*=0.0015, respectively). There was no significant difference between the DM and AGT groups.

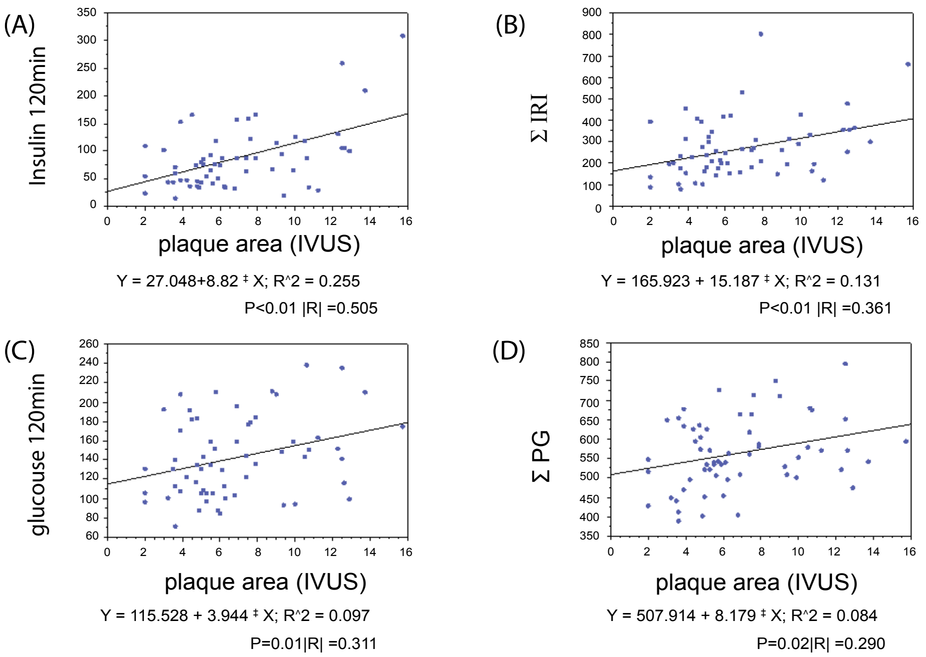

Figure 5: Correlations of insulin and glucose levels with the plaque cross-sectional area (CSA)

5A: Insulin levels at 120 min are highly correlated with the plaque CSA

5B: Glucose levels at 120 min and plaque CSA also correlate, albeit less strongly than insulin levels at 120 min and plaque CSA.

5C: Total immunoreactive insulin (ΣIRI) and plaque CSA show a significant but relatively weak correlation.

5D: Total plasma glucose (ΣPG) and plaque CSA show a significant but relatively weak correlation.

min after the glucose challenge showed the strongest correlation with plaque CSA (R=0.505, *P*<0.01; Figure 5A). Total insulin values after the glucose challenge (Figure 5B), glucose values at 120 min after the challenge (Figure 5C), and total glucose values after the challenge (Figure 5D) correlated with plaque CSA.

Multivariable liner regression analysis found Insulin 120 min as the independent predictor of increasing Plaque CSA (Table 5).

Discussion

This study evaluated IVUS findings and revealed that the plaque

CSA was significantly greater in patients with AGT than in those with NGT, that there was no significant difference in the plaque CSA between patients with AGT and those with DM, and that insulin levels at 120 min after the 75-g OGTT correlated with plaque CSA in patients with AGT and NGT.

Atherosclerosis at the time of IGT and newly diagnosed DM

The most common cause of cardiovascular events represented by acute coronary syndrome is thrombus formation due to rupture or erosion of coronary artery plaque [17,18]. Existence of coronary plaque, regardless of the presence or absence of significant stenosis, is a risk factor for all-cause mortality and cardiovascular events [19,20]. It has been reported that DM has a strong relationship with the amount of coronary plaque as evaluated by IVUS or coronary computed tomography angiography [21-23] and that atherosclerosis initiates before DM development [5].

It has also been reported that carotid artery intimal and medial thickness is strongly correlated with postprandial glucose and is increased in the pre-diabetes stage [24,25]. These findings are consistent with the contention that atherosclerosis initiates before DM development, and they support the concept that atherosclerosis is not only a focal disease but also a systemic disease. Despite these findings, investigations of coronary artery plaque at various stages of IGT and the early phase of DM remain scarce. Therefore, we assessed coronary plaque in LAD proximal to the lesion, which appeared normal on CAG, using IVUS and revealed that the plaque CSA was significantly greater in the AGT group than in the NGT group and not significantly different in the DM group. These results strongly suggest that silent coronary atherosclerosis initiates and progresses during AGT.

Importance of coronary plaque during newly diagnosed DM and IGT

Many trials have demonstrated that the control of hypercholesterolemia [26-28] and hypertension [29,30] results in the prevention of cardiovascular events by control of cholesterol and blood pressure, regardless of the presence of DM. In contrast, intensive medical treatment targeted at HbA1c failed to demonstrate clinical benefits with regard to mortality [31-34].

However, it seems reasonable to expect that glucose control will contribute to the prevention of cardiovascular disease. In fact, meta-analysis of recent trials involving intensive DM control revealed that this strategy decreased the risk of myocardial infarction and cardiovascular death [35].

In addition, it was reported that diabetic intervention therapy at the stage of IGT and newly diagnosed DM is effective for the prevention of macrovascular disease [10-12,36]. Furthermore, establishment of diabetic intervention therapy at the time of DM diagnosis is useful for the prevention of macrovascular disease, and these effects have been documented to last for >10 years [37].

Our study demonstrated that coronary plaque in patients with AGT is similar to that in patients with DM and that insulin levels at 120 min after the glucose challenge were significantly associated with the quantity of coronary plaque. These findings strongly suggest the clinical benefits of glucose control in the initial stages of AGT. Furthermore, it may be reasonable to consider that the treatment of hyperinsulinemia during IGT or early-phase DM is essential for the prevention of macrovascular disease.

Study Limitations

This study had some limitations. First, it was a retrospective, single-center study; therefore, selection bias cannot be entirely ruled out. Second, cases of in-hospital death, cardiogenic shock, hemodialysis, and left main and LAD proximal lesions were excluded. These are usually severe cases, and most had DM. The possibility that these exclusions may have affected the results cannot be denied. We used 2D gray scale IVUS in this study; however, gray-scale IVUS has significant limitations with regard to the quality assessment of plaque [38].

Currently, the quantity of coronary artery plaque can be measured using three-dimensional IVUS or coronary computed tomography angiography, while the quality of plaque can be evaluated using coronary computed tomography angiography, virtual histology-IVUS, and iMap-IVUS [39-41].

Future studies should assess both the quality and quantity of plaque using the available technology.

Conclusions

Coronary plaque in patients with AGT was identified to be similar to that in patients with DM, and it was correlated with insulin levels at 120 min after a 75g OGTT. These results suggest that the progression of atherosclerosis occurs in the AGT phase and that the prevention of atherosclerosis should be given more careful consideration at the time of AGT or newly diagnosed DM.

Author Declaration

These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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