Diagnosis of Coronary Artery Disease in Patients with Abnormal Glucose Metabolism at a Private Practitioner's Office in Collaboration with a Hospital Laboratory Using a Multi-slice CT Scan

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Abstract

Private practitioners are not adequately staffed or equipped to handle such medical emergencies as acute myocardial infarction at their offices. Diabetic patients with hypertension and/or lipid abnormalities are known to be at a high risk of developing myocardial infarction.

At the private clinic of Dr. Sassa, 183 patients with abnormal blood glucose metabolism, accompanied by hypertension and/or lipid abnormalities, thus having an increased risk of developing myocardial infarction, were identified. These patients were referred to and underwent 64-slice multidetector computed tomography (MDCT) at the Osaka Hospital of Japan Seafarers Relief Association in order to study whether clinically significant coronary artery disease was present.

Among 183 study patients, coronary stenosis was frequently detected: 25% stenosis in 60 patients, 50% stenosis in 32 patients, and 75% or more in 46 patients. Furthermore, 14 patients were identified as having asymptomatic myocardial ischemia, all successfully undergoing percutaneous transluminal coronary artery dilatation. Each of these 14 asymptomatic patients was demonstrated to have a 75% or more stenosis with vulnerable plaque in their proximal coronary arteries.

These results suggest the utility of performing the test of 64-slice multidetector computed tomography in abnormal blood glucose metabolism patients with hypertension and/or lipid abnormalities in early stage in order to detect clinically significant coronary artery stenosis, requiring coronary intervention procedures.

Key words Abnormal glucose metabolism, Asymptomatic myocardial ischemia, Hospital-clinic collaboration, 64-slice multidetector computed tomography scan

Introduction

Currently private medical practitioners cannot adequately treat medical emergencies occurring in their clinics, including in the case of acute myocardial infarction. However, private practitioners are blessed with opportunities for treating diabetes, which is a representative disease in which onset of acute myocardial infarction is common. The vast majority of diabetic patients treated by private practitioners have Type 2 diabetes, and the majority of these also have hypertension and/or dyslipidemia. However, because clinical symptoms rarely appear even when glycemic control is poor, patients frequently ignore physicians' instructions and may in some not uncommon cases discontinue treatment. Consequently, patients and their families tend to mistakenly

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believe that acute ischemic heart diseases suddenly developed.

Amongst diabetic patients, ischemic heart diseases often manifest as asymptomatic myocardial ischemia, which is often accompanied by cardiac failure due to a high incidence of diffuse multivessel disease. Therefore, the concept of Type 2 diabetes as a "cardiovascular disease accompanying high blood glucose" is gradually spreading, but the track record for coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) for myocardial infarctions in diabetic patients is poor.[1] Here the author, with the collaboration of the Cardiovascular Internal Medicine Department of the Osaka Hospital of Japan Seafarers Relief Association, examined the coronary arteries of patients of the Sassa Clinic with abnormal glucose metabolism believed to be at high risk for acute myocardial infarction using 64-multidetector computed tomography (MDCT). This is a report of these examinations and knowledge gained from these results as well as observations.

Method

Subjects were 183 patients of the Sassa Clinic who were treated for abnormal glucose metabolism combined with either hypertension or dyslipidemia or both between August 2006 and December 2007 (94 male and 89 female; average age: 66 ± 9). Abnormal glucose metabolism was combined with hypertension in 26 cases, with dyslipidemia in 41 cases, and with both in 116 cases.

Diabetes mellitus (DM) in this study was defined as either having a fasting blood glucose of 126 mg/dl or above, a blood glucose of 200 mg/dl or above at 2 hours after ingestion of 75 g glucose, or several random glucose levels of 200 mg/dl or above. With regard to patients diagnosed with impaired glucose tolerance (IGT), 75 g oral glucose tolerance test (OGTT) was not necessarily carried out in all cases, and the diagnosis included those patients with a fasting blood glucose level of less than 126 mg/dl and a 2-hour postprandial or random blood glucose reading of between 160 mg/dl and 200 mg/dl. Hypertension was defined as systolic blood pressure of 140 mmHg or above and diastolic blood pressure of 90 mmHg or above; dyslipidemia was defined as LDL cholesterol of 140 mg/dl or above and serum triglyceride levels of 150 mg/dl or above.

Two subjects who experienced chest pain while waiting to undergo 64-MDCT scanning were found to have electrocardiographic abnormalities and immediately underwent coronary angiography testing, so their data were not included in this report as they did not undergo 64-MDCT scanning. Moreover, as a general rule, patients with a serum creatinine level of 1.8 mg/dl or above, who were aged 85 years or above, who could not hold their breath for 10 seconds, or those who were allergic to contrast dye were excluded from 64-MDCT scanning.

All coronary artery imaging using 64-MDCT scanning was performed at the Osaka Hospital of Japan Seafarers Relief Association. All subjects were orally administered with bisoprolol fumarate (5 mg of Maintate®) 1 hour prior to the procedure. The amount of contrast dye injected was increased or decreased according to the subject's weight and administered at a speed of 3.5–4.5 ml/sec. for 20 seconds via intravenous drip infusion. As a result, evaluable images were obtained for all subjects tested. Two subjects became unwell due to allergic reactions to the contrast dye but recovered after rest. No subjects were observed to have serum creatinine level increases of twice or more after one month of testing.

Results

No stenosis of coronary arteries was observed in 45 cases (24.6%). The results of visual classification of stenosis level were: 25% stenosis in 60 cases, 50% stenosis in 32 cases, 75% stenosis in 30 cases, 90% stenosis in 9 cases, 99% stenosis in 1 case, and 100% stenosis in 6 cases.

Of the 46 cases with significant stenosis (75% or above), 18 (39.1%) had single-vessel pathological abnormalities, 15 (32.6%) had double-vessel abnormalities, and 13 (28.3%) had triple-vessel abnormalities. Moreover, 3 of the 32 subjects (9.4%) with 50% stenosis and 14 of the 46 subjects (30.4%) with 75% or above stenosis—a total of 17 cases—had experienced chest pain in the past. In 6 of these 17 cases, the chest pain had not been recent and they were thought to have stable angina; no electrocardiographic abnormalities were observed. The 11 other subjects with 50% to 75% or above stenosis who had experienced chest pain and the 14 subjects who had asymptomatic coronary artery disease with

Table 1 Classification of stenosis rates

Stenosis rate (%)	Number of cases (chest pain)	Number of cases in which PCI was carried out
0	45 (0)	0
25	60 (0)	0
50	32 (3)	0
75	30 (6)	13 (+CABG 1) {9: Asymptomatic 4: Chest pain
90	9 (5)	8
99	1 (1)	1
100	6 (2)	3 (2: Asymptomatic)
Total	183 (17)	25

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.
Proportion of asymptomatic cases: 90.6% of cases with 50% stenosis; 69.6% of cases with 75% or above stenosis.

Table 2 Pathological condition of PCI cases

Case	Abnormal glucose metabolism	BMI	IVUS-MLA (mm^2)	Hypertension	Lipid abnormalities	Chest pain
1	DM	25.1	Not measured	(−)	(+)	(+)
2	DM	28.1	Not measured	(+)	(+)	(−)
3	IGT	31.9	Not measured	(−)	(+)	(+)
4	DM	25.7	Not measured	(+)	(+)	(+)
5	DM	29.8	Not measured	(+)	(+)	(+)
6	IGT	24.1	Not measured	(+)	(+)	(−)
7	DM	23.9	1.2	(+)	(+)	(+)
8	IGT	23.6	1.3	(+)	(+)	(+)
9	IGT	24.5	1.4	(+)	(+)	(+)
10	DM	24.3	1.7	(+)	(+)	(+)
11	DM	23.7	1.8	(+)	(−)	(−)
12	DM	21.5	2.1	(−)	(+)	(−)
13	DM	25.0	2.2	(+)	(+)	(−)
14	IGT	23.9	2.4	(+)	(+)	(−)
15	DM	20.2	2.5	(−)	(+)	(−)
16	DM	25.2	2.5	(+)	(+)	(−)
17	IGT	25.6	2.5	(+)	(+)	(+)
18	IFG	23.7	2.5	(+)	(+)	(+)
19	IGT	25.3	2.5	(+)	(+)	(−)
20	DM	23.6	2.8	(−)	(+)	(−)
21	DM	24.7	2.9	(+)	(−)	(+)
22	DM	29.4	2.9	(+)	(−)	(−)
23	IGT	30.2	3.0	(+)	(+)	(−)
24	DM	29.0	3.1	(+)	(+)	(−)
25	DM	22.1	3.3	(+)	(+)	(−)

BMI: body mass index; IVUS: intravascular ultrasound; MLA: minimum lumen area; DM: diabetes mellitus; IGT: impaired glucose tolerance; IFG: impaired fasting glucose.

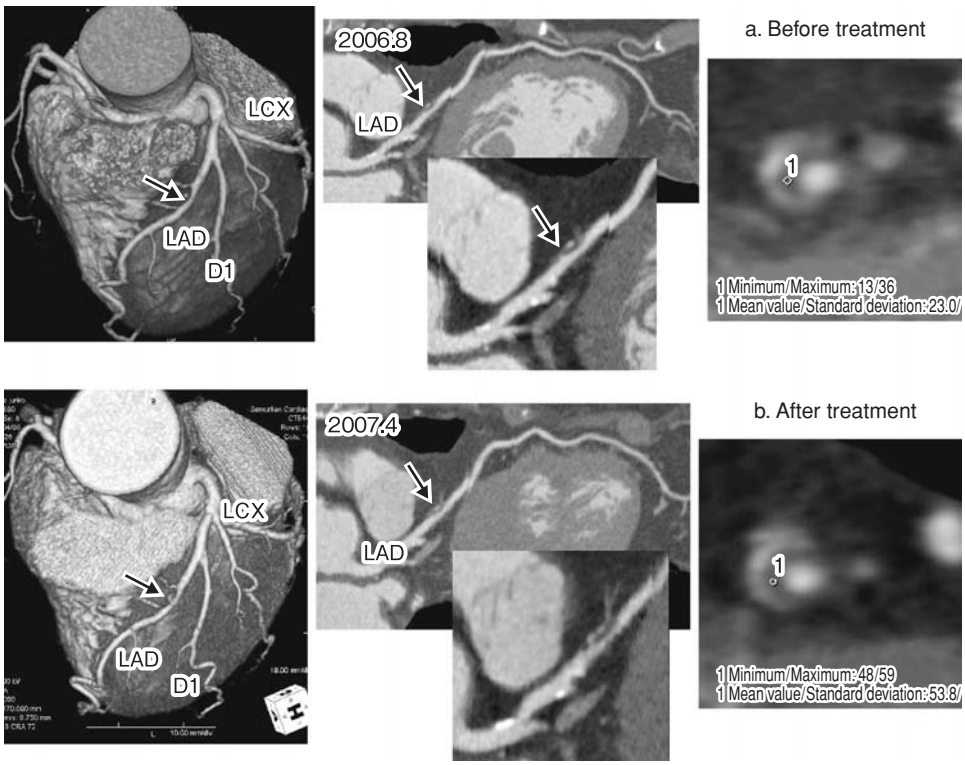

Fig. 1 A patient with asymptomatic single-vessel pathological abnormality

Prior to commencement of oral treatment, vulnerable plaque with a CT value of 23.0 HU was confirmed in left anterior descending artery (LAD) #7 using MDCT (a). Since the stenosis level was 25–50%, oral treatment was begun and lifestyle intervention intensified, and a follow-up examination of the same area using MDCT was performed 8 months later. The CT value had risen to 53.8 HU and plaque stability was confirmed (b). There was no significant abnormality in the CT for the MLA (4 mm^2). LCX: left circumflex coronary artery; D1: first diagonal branch. The circle at 1 indicates region of interest (ROI).

proximal pathological abnormalities—a total of 25 cases—underwent PCI, and another subject who had experienced chest pain (triple vessel disease) underwent CABG. Of the 25 cases that underwent PCI, 3 cases had single-vessel pathological abnormalities (2 cases with 75% stenosis, and 1 case with 90% stenosis), all of which were asymptomatic. With regard to the 11 patients with existing chest pain who underwent PCI, in the case discovered to have 99% stenosis in the left anterior descendingartery (LAD) #7, inversion of the T wave in precordial leads was observed that had not been detected on an electrocardiogram 1 month previously to the 64-MDCT scan. This subject was thought to have unstable angina, and in the other 10 cases no obvious ischemia was detected on an electrocardiogram.

Table 1 shows classification of stenosis rates, the relationship between existence of chest pain and performance of PCI, and the proportion of asymptomatic cases with 50% or 75% or above stenosis. Of the cases that underwent PCI, in 4 cases minimum lumen area (MLA) could not be measured because intravascular ultrasound (IVUS) could not be performed, and in 2 cases IVUS could not be performed due to 100% stenosis. In the other 19 cases, the MLA was 1.2–3.3 mm^2.

Table 2 shows classification of abnormal glucose metabolism, body mass index (BMI), MLA, existence of accompanying hypertension and/or dyslipidemia, and existence of chest pain for subjects who underwent PCI. The subjects who underwent PCI include 8 subjects with IGT and 1 case with impaired fasting glucose (IFG). The subjects who did not undergo PCI despite having vulnerable plaque were treated orally (statin, antiplatelet agents, pioglitazone hydrochloride,

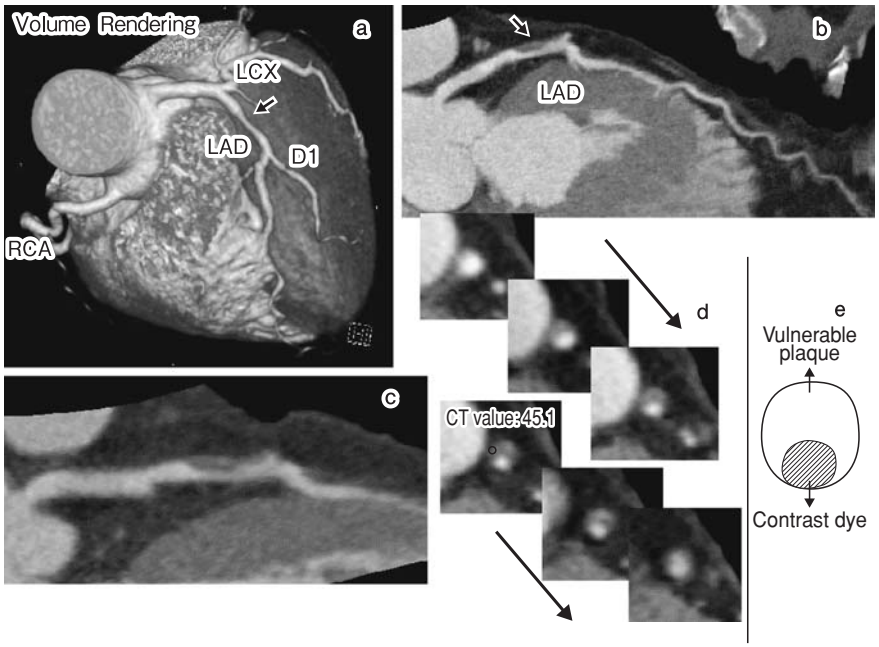

Fig. 2 A patient with asymptomatic single-vessel pathological abnormality

Vulnerable plaque with 75% stenosis was confirmed in LAD#7 using MDCT (a–c). Positive remodeling of the stenosis area can also be observed with a short axis view. The pathological abnormality continues from the upper arrow to the lower arrow, from proximal to distal sites (d), which schematic diagram is shown in (e). The CT value for the plaque was a low 45.1 HU. LCX: left circumflex coronary artery; D1: first diagonal branch; RCA: right coronary artery.

etc.) to stabilize the plaque and thorough lifestyle intervention begun.

The first subject treated orally had a fasting blood glucose level of 102 mg/dl, a 75 g OGTT 2-hour postprandial blood glucose reading of 200 mg/dl, blood pressure of 190/100 mmHg, LDL cholesterol of 120 mg/dl, and serum triglyceride level of 75 mg/dl; 25–50% stenosis was discovered in LAD #7. After 8 months of treatment, plaque stabilization was confirmed with plaque CT values measured using 64-MDCT scanning. The CT values express the rate of absorption of x-rays, with the CT value of water, 0 HU, used as the standard. Within the plaque several regions of interest (ROI) were set and the average values for these were calculated by computer; the smaller the CT value, the softer and more unstable the plaque. In the case of the first subject treated orally, the average plaque CT value prior to treatment was 23.0 HU, and this had risen to a high 53.8 HU after 8 months of treatment, indicating that the plaque had stabilized (**Fig. 1**). **Figures 2** and **3** show an asymptomatic

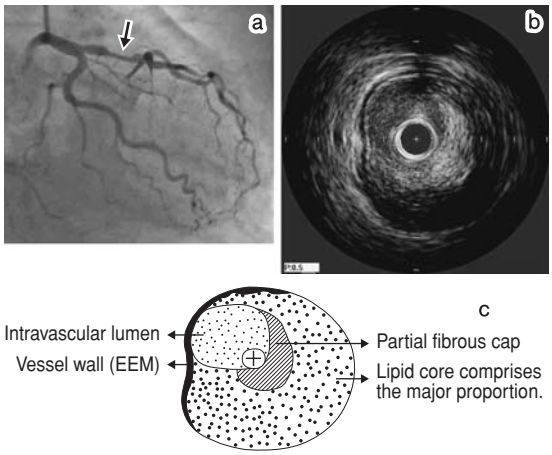

Fig. 3 Coronary angiography and IVUS findings for the same case as in Fig. 2.

Coronary angiography showed 50% stenosis for the same region (a), but intravascular ultrasound (IVUS) showed 80% stenosis, enabling observation of vulnerable plaque with low eccentric ultrasound levels (b). The schematic diagram of b is shown in (c).

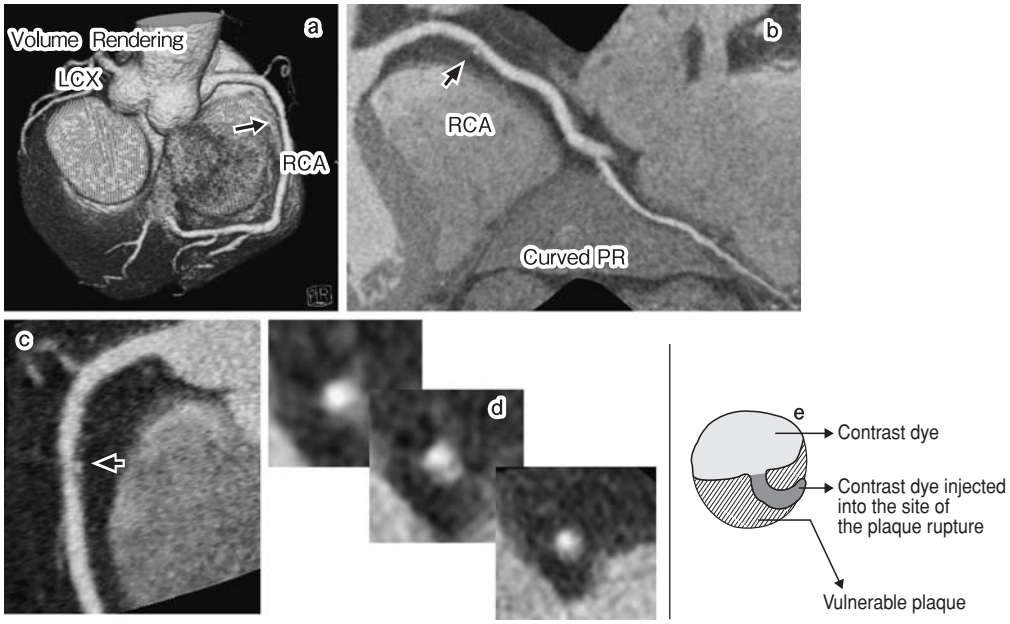

Fig. 4 A patient with asymptomatic multiple-vessel pathological abnormality

In (a), 25% stenosis of the right coronary artery (RCA) #2 was observed, but in (b) and (c) stenosis was observed to be protruding from the lumen (arrows). An ulcer-like lesion passing through the lumen was observed with a short axis view, and this was thought to be a plaque rupture (d). The schematic diagram of d is shown in (e). LCX: left circumflex coronary artery; PR: planar reconstruction.

case in which the CT value was a low 45.1 HU for LAD #7 and that had 75% stenosis due to plaque. PCI was consequently performed and the MLA was 3.3 mm^2.

Figure 4 shows a case with 25% stenosis in the right coronary artery (RCA) #2 in which images of plaque rupturing could be observed. Since the patient had no subjective symptoms, this was thought to have been a case of asymptomatic plaque rupture. In this case, angiography was performed after 2 weeks of the 64-MDCT scan and the plaque rupture observed using IVUS (**Fig. 5**). However, when normal saline solution was injected into the lumen, the solution did not flow into the area where the plaque rupture had been. Accordingly, **Figs. 4 and 5** are thought to show the process of plaque rupture repair.

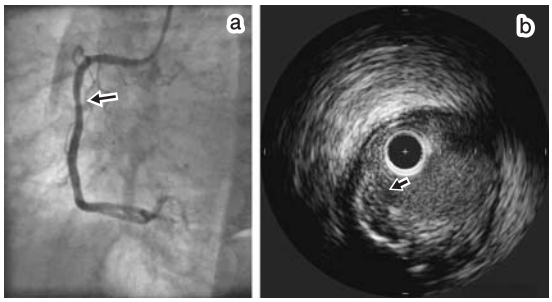

Fig. 5 Coronary angiography and IVUS findings for the same case as in Fig. 4.

Stenosis was thought to be 25% (a). IVUS showed rupturing of vulnerable plaque (b, arrow).

Discussion

Recently IGT, or pre-diabetes, has become regarded as a problem. Moreover, there are clinical conditions which are diagnosed as postprandial hyperglycemia because postprandial blood glucose levels are high even when fasting blood glucose levels are normal, and both IGT and postprandial hyperglycemia are defined as having a genetic factor, poor initial insulin secretion. However, even without genetic factors, there is also an increasing incidence of Type 2 Diabetes triggered by metabolic syndrome with sustained insulin resistance.

It has recently become clear that the risk of developing cardiovascular disorders exists even from such mild diabetes stages that private medical practitioners frequently encounter. Diagnosis is not made unless acute myocardial infarction occurs. Moreover, because this is a serious disease that frequently becomes fatal, it is extremely helpful to have forewarning if possible.

Diagnostic imaging has recently advanced, and the accuracy of coronary arteries stenosis diagnosis using 64-MDCT scanning is particularly high. Less invasive than coronary angiography testing, 64-MDCT scanning enables diagnosis of not only stenosis but also plaque characteristics by thinly slicing stenotic vessel images into horizontal and vertical cross-sections.

It is said that until coronary arteries stenosis progresses such that the external elastic membrane (EEM) area occupied by plaque reaches 40%, the diameter of coronary arteries expands to compensate in so-called "positive remodeling," and intravascular lumen stenosis does not progress. However, as plaque volume increases, so does the risk of rupture.[2,3] Amongst the cases treated at the Clinic, too, a typical example of this was observed using 64-MDCT scanning (**Fig. 2d**). One method for knowing the disease status is IVUS which, although invasive, is the best method at this stage. (**Fig. 3b**).

When a case of asymptomatic plaque rupture as shown in **Figs. 4 and 5** is thought to exist, the author believes that aggressive lipid-lowering therapy to stabilize the plaque and rigorous blood glucose control and blood pressure management are necessary. The same can be said when there is a high risk of plaque rupture indicating a lipid-rich vulnerable plaque with thin capsules even if the stenosis level is below 75%, now that the characteristics of plaque can be diagnosed using 64-MDCT scanning. Incidentally, when 64-MDCT scan observations are compared with IVUS observations, if CT values are 50 HU or above, plaque is regarded as being stable or fibrous, but in future positive examination of multiple cases is required.[4,5] In cases where load testing found the existence of myocardial ischemia or 64-MDCT scanning found strong proximal coronary artery stenosis, even if the patient was asymptomatic, cardiac catheterization was performed and patients with an MLA of 4 mm^2 or less were diagnosed with asymptomatic coronary artery disease and subjected to PCI because of the amount of stenosis was thought to be sufficient to cause ischemia.[6,7]

The diagnostic rate of coronary artery abnormalities using dobutamine stress echocardiography testing is virtually the same as that for myocardial scintigraphy, with 82% sensitivity, 84% specificity, and 83% correct diagnosis.[8] However, in a case where dobutamine stress echocardiography testing found no myocardial ischemia despite observation of 75% stenosis of LAD #6, PCI was performed because the patient developed chest pain after a short time, and the patient went into remission afterward. In this case, fasting blood glucose levels ranged widely between 102 and 144 mg/dl; postprandial glucose level was 110 mg/dl, fasting serum insulin level was 3 μU/ml, 90-minute postprandial serum C peptide level was 5.6 ng/ml, and HbA1c was 5.4%. The case was therefore diagnosed as IFG but was complicated by hypertension and dyslipidemia. In this way, myocardial ischemia is not diagnosed 100% with dobutamine stress echocardiography testing, and so it is thought that PCI should be considered in cases where stenosis is 75% or above, particularly in proximal sites, even if the patient is asymptomatic.

A relationship between diabetic peripheral neuropathy, especially dysautonomia, and asymptomatic myocardial ischemia in diabetes has been found by O'Sullivan et al.,[9] but Airaksinen has disagreed with this, claiming the clinical and epidemiological evidence[10] is unconvincing. Recently, Wackers et al. affirmed this relationship in the DIAD study, reporting that myocardial ischemia in diabetic patients is frequently asymptomatic and increases particularly amongst cases of advanced diabetes.[11] Faerman et al. reported observing typical diabetic neuropathy in intramyocardial sympathetic nerves and parasympathetic nerve fibers in multiple cases of autopsies on diabetic patients who had died of painless myocardial infarction.[12] Currently the dominant opinion is that the reason myocardial infarction and myocardial ischemia in diabetes are painless and asymptomatic is that diabetic autonomic neuropathy involves the nerves responsible for providing the heart with sensation.

As shown in **Table 2**, our observations also found that amongst the asymptomatic patients who underwent PCI, 4 were IGT cases but 10 were diabetes cases. A co-existence of abnormal glucose metabolism, hypertension and/or dyslipi-

demia is an ominous combination, indicating the presence of clinically significant coronary artery disease and furthermore premature death,[13] and this is also shown in **Table 2**. Accordingly, it is thought that in routine examinations of diabetes complicated by hypertension and/or dyslipidemia, the possible existence of asymptomatic coronary artery disease must be considered, even if the patient has experienced no chest pain or autonomic disorder and stress electrocardiography shows no abnormalities.

However, there are limitations to MDCT. Moreover, the coronary arteries of diabetic patients are frequently associated with calcification, and in such cases evaluation of intravascular lumen using 64-MDCT is often difficult. In such cases, calcification scores can be measured using simple CT. If the calcification score is too high, application of coronary angiography should be considered at that stage.[14] Although there were limits to evaluation of the presence of coronary arteries stenosis using MDCT for cases of cardiac dysrhythmia such as atrial fibrillation, we are moving toward resolution of this problem with the increase of detector rows. Currently 320-row MDCT scanning is used clinically. Increasing row number is said to reduce motion artifacts and decrease x-ray exposure amounts by approximately one half. Further developments in this field are greatly expected in the future.

Conclusion

In cases of patients with abnormal glucose metabolism combined with hypertension and/or dyslipidemia, early observation of the coronary arteries using 64-MDCT scanning is recommended to enable identification of patients at high risk for developing acute coronary syndromes, even if the patient is asymptomatic.

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