PRINCIPAL OF MEDICAL MANAGEMENT OF ISCHEMIC HEART DISEASE IN DIABETIC PATIENTS*

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Abstract: The leading cause of death in patients with diabetes mellitus in the West is ischemic heart disease. Both in Japan and Asian countries, mortality due to ischemic heart diseases is on the rise and is most significant as the cause of death in diabetic patients. Ischemic heart disease seen in diabetic patients is associated with severe coronary artery lesions, with relatively few symptoms; and its discovery is often delayed. A acute myocardial infarction complicated by diabetes mellitus, when compared to a simple myocardial infarction, is associated with high mortality during the acute stage, an unsatisfactory outcome of coronary artery reconstruction, a high rate of recurrence, and poor prognosis. On the other hand, epidemiological surveys have established that diabetes mellitus is a significant risk factor for the development of ischemic heart disease. Recently, the results from a number of extensive clinical studies have been introduced on diabetic patients, in which the development of ischemic heart disease was used as the end point of the evaluation. These studies indicated that the control of blood pressure and lipid metabolism are more important than the management of blood sugar levels. With advances in diagnostic techniques, such as electron-beam computed tomography and transthoracic Doppler echocardiography, non-invasive detection of coronary artery lesions became possible. The principal means for managing ischemic heart diseases in diabetic patients are treatment based on scientific evidences obtained from clinical megatrials and early diagnosis by employing the latest non-invasive diagnostic procedures.

Key words: Megatrial; Insulin resistance; Early detection; Medical network

Introduction

The leading cause of death for patients with diabetes mellitus in the West is ischemic heart disease. Both in Japan and Asian countries, mortality due to ischemic heart diseases is on the rise and is most significant as the cause of death for diabetes mellitus. Ischemic heart disease seen in diabetic patients is associated with severe coronary artery lesions, with relatively few symptoms; and its discovery is often delayed.

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pared to a simple myocardial infarction, is associated with high mortality during
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high rate of recurrence, and poor prognosis. On the other hand, epidemiological
surveys have established that diabetes mellitus is a significant risk factor for the
development of ischemic heart disease. To improve the prognosis for diabetic
patients and prevent an increase in the incidence of ischemic heart diseases, it is
imperative that more precise diabetic control be implemented.

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have been introduced on diabetic patients, in which the development of ischemic
heart disease was used as the end point of the evaluation. These studies indicated
that the control of blood pressure and lipid metabolism are more important than
the management of blood glucose levels. With advances in diagnostic techniques,
non-invasive detection of coronary artery lesions became possible.

This report outlines the features of ischemic heart diseases in diabetic patients,
the key points in diabetic control, and early diagnosis based on large-scale clinical
trials.

**Characteristics of Ischemic Heart Disease in Patients with Diabetes Mellitus**

According to the results of a survey conducted by 1,000 physicians certified by
the Japanese Circulation Society and those certified by the Japan Diabetes Society,
the clinical features of ischemic heart diseases complicated by diabetes mellitus
include the involvement of multiple coronary branches, complex lesions, asymptom-
tomatic presentation, rapid progress, and severity.

1. **Subjective symptoms**

Patients with angina pectoris complicated with diabetes mellitus often do not
report typical anginal pain. Some do not experience any symptoms. The involve-
ment of diabetic neuropathy is suspected but details are not known.

2. **Coronary angiography**

Even when the anginal symptoms are mild, diabetic patients often exhibit
advanced stenosis or occlusion on coronary angiography. Coronary lesions are
characterized by accentuated calcification, complex morphology, extensive lesions,
involvement of multiple coronary branches, and diffuse lesions continuing to the
peripheral branches.

3. **Treatment and prognosis**

(1) **β-blockers**

Many clinical megatrials proved that β-blockers improve the prognosis for
patients with angina pectoris and old myocardial infarction. According to a recent
randomized control trial on diabetic patients, the effect of β-blockers was recog-
nized in preventing ischemic heart diseases. It was feared that β-blocker therapy
may delay correcting the hypoglycemic state or exacerbate diabetic control due to
deterioration of glucose tolerance; but no significant difference was found between
the β-blocker treated patients and the control in the management of hypoglycemia or diabetic control.

(2) Calcium antagonists
Calcium antagonists are the first choice among the therapeutic agents for the treatment of angina pectoris involving coronary vasospasm. The effect of these agents in preventing the onset of ischemic heart disease has not been established. It has been pointed out that short-acting calcium antagonists may increase the possibility of developing myocardial infarct.

(3) Angiotensin converting enzyme (ACE) inhibitors
The results of many clinical studies indicated that ACE inhibitors are effective in improving the prognosis of patients with ischemic heart diseases and compromised cardiac functions. A recent clinical intervention study on diabetic patients proved that ACE inhibitors prevent the onset of ischemic heart disease.

(4) Aspirin
In many clinical studies, it has been established that aspirin prevents the onset or recurrence of ischemic heart diseases and improves its prognosis. Diabetic patients are in a hypercoagulable state and it is anticipated that the clinical effects of antiplatelet agents will produce a favorable result. It has not been proven that administering aspirin to diabetic patients will result in the exacerbation of retinopathy. However, there have been no reports of clinical megatrials conducted on diabetic patients and the effects of aspirin in preventing ischemic heart disease in diabetic patients have not been proven.

(5) Coronary revascularization
The advances in coronary revascularization, such as percutaneous coronary angioplasty and coronary artery bypass, have markedly improved the quality of life of patients with angina pectoris. However, anginal patients with diabetes mellitus are known to suffer from high restenotic incidence and a poor long-term prognosis (Fig. 1).
Exercise therapy

Through an analysis of the results of an interventional blood sugar control trial on diabetic patients, it is intimated that an increase in body weight and a rise in their already high blood insulin level interfere with the preventive effect of blood sugar control on the development of ischemic heart disease. Appropriate exercise therapy is thought to be the best therapeutic modality to reduce body weight and improve insulin resistance. Recently, an improvement in the cardiac function of patients with heart diseases through rehabilitation therapy has been attracting attention. For patients with ischemic heart disease complicated with diabetes mellitus, exercise therapy must be prescribed more actively.

Diabetic Control to Prevent Ischemic Heart Disease

1. Blood sugar control

The results of clinical megatrials, such as UGDP (University Group Diabetes Program) of the 1970s and the more recent UKPDS (United Kingdom Prospective Diabetes Study) proved that blood glucose control is effective in preventing diabetic microangiopathy. However, the effect of blood glucose level reduction on averting ischemic heart diseases has not been substantiated (Table 1).

2. Reduction of blood lipid levels

Clinical application of potent hypolipemic agents that have been developed recently proved that lowering the blood lipid level prevents primary and secondary
ischemic heart diseases. The results of many clinical megatrials have established that the effect of hypolipemic therapy on diabetic patients is equal or greater than on non-diabetic patients (Table 2).

### 3. Hypotensive therapy

It has been noted that antihypertensive therapy for diabetic patients prevents ischemic heart diseases. Among the studies on this topic, the efficacy of ACE inhibitors has been reported by many reports (Table 3). ACE inhibitors, which have vasodilator and anti-arteriosclerotic effects, have been proven to improve the long-term prognosis for patients with heart failure. The use of these agents should be considered as a standard therapeutic modality for patients with ischemic heart diseases combined with diabetes mellitus who suffer from compromised cardiac functions.

#### Early Diagnosis of Ischemic Heart Disease

A characteristic of ischemic heart disease combined with diabetes mellitus is the presence of severe lesions in the coronary arteries in spite of a relatively asymptomatic state. However, it is hard to believe that these severe lesions existed from the onset: It is most likely that the disease progresses while diabetic patients undergo a long asymptomatic period. If the disease is detected during this stage, treatment will be effective and there will be significant improvement in the prognosis. With the development of ultra-fast CT and Doppler ultrasonic diagnosis with outstanding capacity, non-invasive detection of coronary lesions has become pos-
Table 3 Interventional Antihypertensive Trials on Diabetic Patients

<table>
<thead>
<tr>
<th>Name of trial</th>
<th>Number of subjects (males/females)</th>
<th>Period in years (mean observation period)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS Type 2 DM</td>
<td>(blood pressure over 160/94 mmHg) 1,148 (637/511)</td>
<td>1976–97 (8.4 years)</td>
<td>No significant difference in the incidence of cardiovascular diseases (trial to be continued for 5 more years)</td>
</tr>
<tr>
<td>ABCD Type 2 DM</td>
<td>(diastolic pressure over 80 mmHg) 470 (287/183)</td>
<td>1993–98 (5 years)</td>
<td>Enalapril reduced the incidence of myocardial infarction: Nisoldipine group, 11%; enalapril group, 2% (relative risk, 5.5)</td>
</tr>
<tr>
<td>FACET Type 2 DM</td>
<td>(blood pressure over 160/95 mmHg) 380 (152/228)</td>
<td>1994–98 (3.5 years)</td>
<td>Fosinopril reduced the incidence of cardiovascular events: Amlodipine group, 14%; fosinopril group, 7.4% (relative risk, 4.9)</td>
</tr>
<tr>
<td>HOT Type 2 DM</td>
<td>(diastolic pressure over 100 to 115 mmHg) 1,501</td>
<td>1992–97 (3.8 years)</td>
<td>Incidence of cardiovascular events reduced in the group with greater reduction in diastolic pressure: Significant difference between groups with different target diastolic pressures ((p = 0.005))</td>
</tr>
</tbody>
</table>

HOT: Hypertension Optimal Treatment Randomised Trial (Lancet 351: 1755–1762, 1998)

Table 4 Comparison of Non-invasive Methods to Detect Coronary Artery Diseases

<table>
<thead>
<tr>
<th>Methods</th>
<th>Sensitivity/ Specificity (%)</th>
<th>Time required</th>
<th>Cost (in yen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiography at rest</td>
<td>20%/?</td>
<td>10 minutes</td>
<td>1,500</td>
</tr>
<tr>
<td>Master’s exercise test</td>
<td>28–66%/70–85</td>
<td>30 minutes</td>
<td>3,500</td>
</tr>
<tr>
<td>Treadmill test</td>
<td>70–80%/82–97</td>
<td>30 minutes</td>
<td>7,000</td>
</tr>
<tr>
<td>Holter electrocardiography</td>
<td>30–40%/?</td>
<td>24 hours</td>
<td>15,000</td>
</tr>
<tr>
<td>Ultrafast CT</td>
<td>71–74%/70–90</td>
<td>10 minutes</td>
<td>13,840</td>
</tr>
<tr>
<td>Transthoracic Doppler echo cardiography (left anterior descending artery)</td>
<td>93/93</td>
<td>10 minutes</td>
<td>11,500</td>
</tr>
<tr>
<td>Exercise stress myocardial scintigraphy</td>
<td>80–90%/85–95</td>
<td>5 hours</td>
<td>104,210</td>
</tr>
</tbody>
</table>

sible.\(^6,7\) Because these diagnostic procedures are relatively inexpensive (in Japan) and can be conducted in a short time, they are applicable for routine diagnoses (Table 4).

Treatment at the Acute Stage and Relationship with Diagnosis

It has been reported that patients with acute myocardial infarction complicated with diabetes mellitus had few subjective symptoms. Because they often suffer from asymptomatic myocardial ischemia, hospitalization is delayed, which
results in a poor prognosis. An extended delay before hospital admission means missed opportunities for coronary angioplasty. Rapid diagnosis determines the prognosis. A well-organized medical network is important for rapid diagnosis before the condition becomes serious.

Conclusion

Diabetic patients are liable to develop ischemic heart diseases: yet they present few symptoms until the coronary lesions become severe, thus delaying detection of the condition and resulting in complications with cardiac failure, frequent recurrence of ischemia, and a poor prognosis. The “keys” to improve the prognosis for ischemic heart diseases in diabetic patients, the incidence of which is expected to increase in the future, are more precise and effective control of blood sugar, blood pressure, and blood lipid, early diagnosis during asymptomatic state, and correlation with the accurate determination of the disease condition during the acute stage.

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