individual difference of plasma NO_x levels by other factors such as severity of diseases [40,41]. These data are consistent with previous data, however, we should suppose the effect of aging on renal function, which increase NO_x levels. The number of participants is small and it should be elucidated more for larger participants in future.

Conclusively, this study first suggests the importance of the NO related responses in the prognosis of elderly, which is as strong as that of albumin, past well-known marker. Vascular factor might be important as much as nutritional factor in elderly.

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The New Worldwide Definition of Metabolic Syndrome Is Not a Better Diagnostic Predictor of Cardiovascular Disease in Japanese Diabetic Patients Than the Existing Definitions

Additional analysis from the Japan Diabetes Complications Study

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We previously reported (1) the limited clinical significance for Japanese diabetic patients of the widely used World Health Organization (WHO) (2) and National Cholesterol Education Program (NCEP) (3) definitions of metabolic syndrome and suggested that an international definition of metabolic syndrome that was applicable regardless of ethnicity was necessary (1).

Recently, the International Diabetes Federation published a long-awaited new worldwide definition of metabolic syndrome (4) that is intended to be applicable to various ethnic groups. The new definition is similar to the NCEP definition (3) but has several important differences. Notably, most components of the new definition now include subjects who are receiving specific treatments for the abnormalities that comprise metabolic syndrome. Also, central obesity (defined by waist circumference with ethnic modification in its thresholds) has become a mandatory component in the new definition. In this report, we evaluated the predictive power of the new international definition for cardiovascular disease (CVD), as compared with that of previous definitions, in Japanese diabetic patients.

RESEARCH DESIGN AND METHODS — The Japan Diabetes Complications Study (JDCS) has been described in detail elsewhere (1,5). The same dataset was used for evaluation so that the new definition of metabolic syndrome could be directly compared with the WHO and NCEP definitions (1–4). A total of 1,424 Japanese patients (771 men and 653 women, age 58.4 ± 7.4 years [means ± SD]) with previously diagnosed type 2 diabetes but without known CVD were followed for 8 years for coronary heart disease (CHD) and stroke events. Fatal and nonfatal CHD and stroke were defined as previously reported (1). The new International Diabetes Federation definition (4) was used with a recommended ethnic modification for Japanese subjects in relation to waist circumference (men ≥85 cm, women ≥90 cm). Since all of the subjects had diabetes, metabolic syndrome diagnosis was made in patients who met criteria for central obesity plus one or more of the following: increased triglycerides, increased blood pressure, or reduced HDL cholesterol (see Table 1 for detailed thresholds). Incidence rates in the two groups (with and without metabolic syndrome) were estimated under the Poisson assumption using person-year methods. Cox regression analysis was used to calculate the age-adjusted hazard ratio (HR) and 95% CI of metabolic syndrome risk factors with CHD, stroke, or both. The SAS software package (version 8.0; SAS Institute, Cary, NC) was used for all analyses. $P < 0.05$ was considered statistically significant.

RESULTS — At baseline, the prevalence of metabolic syndrome, using the new definition (Table 1), was notably lower, especially in female patients, than the prevalence under the WHO (2) and NCEP (3) definitions, which was ~50% on average (1). Diabetes duration in patients with (9.9 ± 6.9 years) or without (10.7 ± 7.3 years) metabolic syndrome did not differ significantly ($P = 0.07$). The proportion of patients that met the central obesity criterion (an essential component of the new definition) was 36.7% for men and 9.7% for women, such that 87% of men and 95% of women with central obesity had metabolic syndrome.

The incidence (per 1,000 patient-years) of CHD (13.5 [with metabolic syn-

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; JDCS, Japan Diabetes Complications Study; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient prevalence at baseline, age-adjusted HRs with 95% CIs, and incidence of CHD, stroke, or both in 1,424 Japanese patients with type 2 diabetes (771 men and 653 women) according to individual cardiovascular risk factors comprising the metabolic syndrome as defined by the International Diabetes Federation* (b, c, and d include specific treatment for each abnormality)

	Prevalence at baseline (%)		HR for CHD		HR for stroke		HR for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
a) Waist circumference ≥85 cm (men), ≥90 cm (women)	36.7	9.7	1.68 (0.92–3.08)	1.13 (0.26–4.86)	0.91 (0.44–1.86)	1.11 (0.31–4.05)	1.32 (0.83–2.10)	1.13 (0.43–2.97)
b) Triglycerides ≥150 mg/dl	26.5	23.4	2.93 (1.55–5.53)	2.03 (0.81–5.04)	1.10 (0.51–2.36)	0.59 (0.20–1.78)	1.96 (1.21–3.19)	1.13 (0.56–2.26)
c) HDL cholesterol <40 mg/dl (men), <50 mg/dl (women)	19.3	36.3	1.82 (0.94–3.54)	1.48 (0.63–3.49)	0.99 (0.41–2.40)	1.34 (0.61–2.94)	1.53 (0.90–2.61)	1.34 (0.74–2.40)
d) SBP ≥130 mmHg or DBP ≥85 mmHg	64.1	68.8	1.04 (0.53–2.01)	1.05 (0.39–2.84)	2.08 (0.90–4.82)	1.63 (0.60–4.37)	1.29 (0.77–2.17)	1.29 (0.64–2.59)
a plus one or more of *b*, *c*, or *d*	32.0	9.2	1.72 (0.94–3.15)	1.15 (0.27–4.90)	1.14 (0.56–2.34)	1.13 (0.31–4.11)	1.47 (0.91–2.35)	1.14 (0.44–3.01)

DBP, diastolic blood pressure; SBP, systolic blood pressure.

drome] vs. 8.1 [without metabolic syndrome] in men; 5.8 vs. 5.5 in women) or stroke (8.1 vs. 7.5 in men; 8.8 vs. 7.0 in women) did not differ significantly between subjects with or without metabolic syndrome. Age-adjusted HRs were calculated to determine whether the new metabolic syndrome definition or its components could predict cardiovascular events (Table 1). Patients diagnosed as having metabolic syndrome, even when subgrouped by therapeutic contents (oral hypoglycemic agents or insulin use), did not show significantly raised HRs for CHD, stroke, or both compared with subjects without metabolic syndrome. However, male patients with raised triglyceride levels and/or having specific treatment for this condition had a significantly increased risk of CHD (HR 2.93, $P < 0.001$) and combined CHD and stroke (1.96, $P = 0.006$), regardless of whether they had metabolic syndrome (Table 1).

CONCLUSIONS— Our previous analysis (1) showed that HRs for CVD in patients with WHO-defined metabolic syndrome were significantly elevated compared with HRs in subjects without metabolic syndrome (although the HR for CHD in male patients was not elevated). Diagnosis of metabolic syndrome by the NCEP definition was less predictive but still associated with a significantly elevated HR for CHD in male patients. However, metabolic syndrome diagnosis by the new definition was not predictive for CVD in either male or female patients in the same prospective setting. Therefore, the new definition did not improve the prediction of adverse cardiovascular events, and its clinical usefulness in Japanese diabetic patients is rather less than that of the existing definitions or of hypertriglyceridemia alone in male patients.

The indispensability of central obesity to the new definition was a major cause of the decrease in the prevalence of metabolic syndrome observed using the new definition. The fact that most patients with central obesity were classified as having metabolic syndrome revealed that metabolic syndrome diagnosis by the new definition was highly dependent on waist circumference when applied to Japanese diabetic subjects. It also denoted that most patients with central obesity had at least one other cardiovascular risk factor, suggesting a close relationship between central obesity and other cardiovascular risk factors. However, this combination was not necessarily associated with an increased risk of CVD in our patients. This latter observation led us to further evaluate the significance of waist circumference in our patients by modifying the threshold within the 65- and 105-cm range and recalculating the HRs. Interestingly, we could not find any thresholds associated with significantly elevated HRs for cardiovascular events in either male or female subjects (data not shown). Therefore, the new definition's lower prediction power for CVD seemed to be derived from the indispensability of the waist circumference component.

To date, prospective trials examining the significance of metabolic syndrome as a predictor of CVD in diabetic patients (1,6–9) have been inadequate (10,11). Many important issues remain to be resolved. *1*) Is the new definition of metabolic syndrome a good predictor of CVD in diabetic patients of differing ethnicities (12)? *2*) Are there any other combinations of components (or different thresholds) that are better predictors of CVD in Asian diabetic patients (13–15)? *3*) Is the concept of metabolic syndrome truly applicable or relevant to diabetic patients in general? Investigations of these issues would aid the screening of diabetic patients at especially high risk of CVD, as well as inform and direct ethnic group–specific management of diabetes (16–19).

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DIABETES/METABOLISM RESEARCH AND REVIEWS
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RESEARCH ARTICLE

Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT)

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Abstract

Background Type 2 diabetes is associated with cognitive dysfunction and increases the risk of dementia in the elderly. The aim of this study was to explore, by means of magnetic resonance (MR) imaging, possible relationships among clinical profiles of diabetes, cognitive function, white matter hyperintensities (WMHs) and subcortical brain atrophy.

Methods Data were obtained from 95 nondemented type 2 diabetic participants aged 65 years or over, enrolled in an intervention trial for Japanese elderly diabetic patients. Cognitive function was measured with neuropsychiatric tests, including mini-mental state examination (MMSE), verbal memory, digit symbol substitution and Stroop tests. Hyperintensity was classified into periventricular, deep white matter, thalamic and basal ganglia. Four ventricle-to-brain ratios were used to measure subcortical atrophy. To identify clinical features of diabetes, indices of glycemic control, lipid metabolism, blood pressure and complications were examined. Canonical correlation analysis and regression analysis were used to assess correlation.

Results Scores for digit symbol substitution and MMSE negatively correlated with WMHs in the parietal lobe and hyperintensities in the thalamus, respectively. Lower scores for memory and digit symbol substitution showed positive association with enlarged subcortical atrophy adjacent to lateral ventricles. There was no association between clinical pictures of diabetic patients with cognitive dysfunction and of those with morphological changes in the brain.

Conclusions Impaired cognitive domains of the speed of mental processes and memory were associated with WMHs and subcortical atrophy. Degenerative changes in the cerebral small vessels may constitute predictive factors for the rate of cognitive dysfunction in elderly diabetic patients.

Keywords type 2 diabetes mellitus; elderly; cognitive dysfunction; periventricular hyperintensity; white matter hyperintensities; subcortical atrophy

Introduction

Type 2 diabetes is an age-related disease with a prevalence in Japan estimated at more than 5% of the population [1]. For elderly diabetic patients, the

purpose of treatment is not only to control plasma glucose levels, but also to prevent diabetic complications. Prospective intervention studies have provided evidence that intensive glycemic control effectively slows the onset and progression of diabetic vascular complications associated with type 2 diabetes [2]. However, these epidemiological investigations did not consider the various aspects of the prevention of cognitive decline in elderly diabetic patients.

The influence of diabetes on brain function has been of interest for more than 80 years [3,4]. Subjects with type 2 diabetes initially manifest deficits in abstraction, problem solving, memory and the completion of tasks involving speed and complex perceptual-motor responses. Recently, several epidemiological studies have shown that diabetes increases the risk for the most common forms of dementia, Alzheimer's disease and vascular dementia [5–9]. Hence, the most critical issue is to identify the factors responsible for diabetic cognitive impairment that lead to severe cognitive decline in the elderly.

Diabetes-related brain disorders have been considered multifactorial and attributed to genetic predisposition, nutritional factors, cerebrovascular disorders and the neurotoxic effects of hypoglycemia and hyperglycemia [10]. The so-called Rotterdam study, which is one of the largest population-based cohort studies, demonstrated conclusively that diabetic subjects with cerebrovascular diseases and with insulin treatment are more prone to dementia [5]. Recent biological findings have supported the view that several risk factors could be linked to diabetes and cognitive dysfunction in the elderly [10,11]. However, clinical pictures of elderly diabetes are various and elderly diabetic patients may have coincident neuropsychiatric disorders, thus making it difficult to identify the factors specifically responsible for cognitive decline.

To address these controversies regarding cognitive decline in elderly diabetic patients, we conducted a large-scaled prospective study of the Japanese Elderly Diabetes Intervention Trial (J-EDIT). J-EDIT was a prospective intervention study designed to investigate and identify the clinical characteristics of nondemented diabetic elderly. In the report presented here, we have analyzed the baseline measures of cognitive dysfunction in nondemented elderly with type 2 diabetes. The aim of this study was to explore possible associations among diabetic cognitive dysfunction, brain morphological changes detected on magnetic resonance (MR) imaging, and diabetic clinical features. To analyze brain MR images, we focused on white matter hyperintensities (WMHs) and subcortical brain atrophy because subcortical structural changes have been associated with cognitive impairment in demented and nondemented elderly subjects [12,13]. We classified hyperintensities into periventricular, deep white matter, thalamic and basal ganglia. The research questions were: (1) What diabetic indices are associated with cognitive dysfunction? (2) Which WMHs influence specific cognitive domains of elderly diabetic patients? (3) Do brain structural changes on MR imaging correlate with clinical measurements of diabetes? To address these questions, we adopted the canonical correlation analysis and regression analysis.

Materials and methods

Participants

J-EDIT started in 2001 as a prospective intervention study of Japanese elderly with diabetes mellitus to prevent the several diabetic complications. The study involved 1173 diabetic subjects from 42 institutes and hospitals in Japan who were 65 years or older (mean age was 71.8 ± 4.6) and whose serum HbA_{1c} levels were $\geqq 7.0\%$. Written informed consent was obtained from all patients. From these subjects enrolled in the J-EDIT, we selected 95 subjects with type 2 diabetes [14], who were treated at Kobe University Hospital, Nagoya University Hospital, Chiaki Hospital, Aoki Memorial Hospital, Nagoya Kyoritsu Hospital and Tokyo Metropolitan Geriatric Hospital. The diabetic participants who had difficulties in communicating, or showed signs of speech disturbance, deafness, severe disturbance of visual acuity, dementia and serious deterioration of the activities of daily life were excluded from this study. Clinical diagnosis of dementia was established according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [15]. Subjects with chronic renal failure (serum creatinine >1.5 mg/dL), serious heart failure or symptomatic cerebral infarctions were also excluded from this study.

Assessment of diabetes mellitus, complications and comorbidities

The diagnosis and information of diabetes mellitus, blood examinations and complications were obtained from clinical charts [14]. Blood samples were obtained by vein puncture after overnight fasting to assess serum levels of glucose, HbA_{1c}, total cholesterol, triglyceride and HDL cholesterol. Serum insulin concentrations were measured in patients who were not receiving insulin therapy. Diabetic vascular complications were assessed for the coexistence of nephropathy, retinopathy, neuropathy and coronary diseases. Retinopathy was assessed fundoscopically through the dilated pupils by experienced ophthalmologists. The degree of retinopathy was classified into five categories; 0 (no retinopathy), 1 (intraretinal hemorrhages and hard exudates), 2 (soft exudates), 3 (intraretinal microvascular abnormalities, venous caliber abnormalities and venous beading), 4 (neovascularization of the disc or elsewhere in the retina, preretinal fibrous tissue proliferation, preretinal or vitreous hemorrhage and retinal detachment). Nephropathy was assessed in terms of the mean urinary albumin-to-creatinine ratio (ACR) and rated as 1 (no nephropathy: ACR <30 μg/mg), 2 (microalbuminuria: $30 \leqq$ ACR < 300 μg/mg), or 3

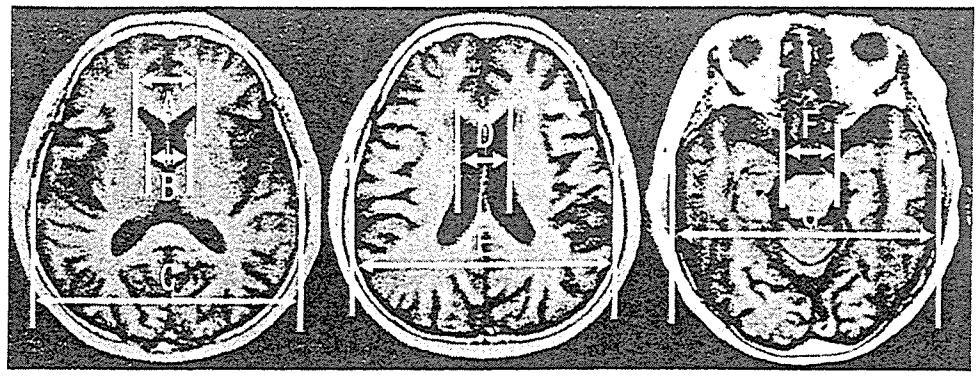

Figure 2. Measured portions on MR imaging. A, the maximum distance between the tips of the anterior horns; B, the width between the bilateral heads of the caudate nuclei; C, the maximum transverse inner diameter of the cranial space at the same MR section (left); D, the maximum width of the cella mediae; E, the maximum transverse inner diameter at the same section (center); F, the internal width between the bilateral temporal lobe at the level of basal cistern; G, the maximum transverse inner diameter at the same level (right). Evans ratio = A/C, caudate head index = B/C, inverse cella media index = D/E, basal cistern index = F/G

the neuropsychological tests of the National Center of Neurology and Psychiatry, Japan [26,27]. Finally, MMSE was used to measure global cognitive function [28].

Statistical analysis

To explore the association among cognitive profiles, clinical variables of diabetes, and morphological changes in MR imaging, we used canonical correlation analysis and regression analysis [29]. There were four sets of variables: seven cognitive tests, sixteen clinical variables of diabetes, eight brain WMH regions and four indices of brain atrophy. Since multiple test corrections would wipe out virtually any test significance, and variables within the same class often show a high degree of correlation, thus rendering the correlations redundant, we adopted the canonical correlation analysis to identify the direct relationship between two sets of variables. The fundamental principle behind canonical correlation analysis is the creation of a number of canonical solutions, each consisting of a linear combination of one set of variables, which has the form:

$$U_i = a_1(predictor_1) + a_2(predictor_2) + \cdots + a_m(predictor_m)$$

and a linear combination of the other set of variables, which has the form:

$$V_i = b_1(criterion_1) + b_2(criterion_2) + \cdots + b_n(criterion_n)$$

The purpose is to determine the coefficients (a's and b's) that maximize the correlation between canonical variates U_i and V_i. The first canonical correlation is the highest possible correlation between any linear combination of the variables in the predictor set and any linear combination of the variables in the criterion set.

A way of interpreting the canonical solutions is to look at the correlations between the canonical variates and the variables in each set. These correlations are called structure coefficients. The logic here is that variables that are highly correlated with a canonical variate have more in common with it and they should be considered more important when deriving a meaningful interpretation of the related canonical variates. As a substantial value of structure coefficients, an absolute value equal to or greater than 0.3 is often used [30,31].

For adjustment of confounders such as age and education, the correlation between cognitive function and MRI findings detected by the canonical correlations analysis was reanalyzed with multiple linear regression analysis. Statistical significance was defined as $p < 0.05$.

Results

Clinical characteristics of the 95 elderly diabetic patients are shown in Table 1. The mean age of the patients and duration of diabetes mellitus were 72.8 ± 0.5 years and 18.4 ± 1.2 years, respectively. Average HbA_{1c} was $7.9 \pm 0.1\%$, while other indices, such as blood pressure, serum cholesterol level and body mass index, were within reasonable limits. Eighteen diabetic subjects were receiving insulin therapy and 21 patients had hypoglycemic episodes. Because the number of patients in this study with insulin treatment or with hypoglycemic episodes was small, we could not analyze the effect of insulin therapy or hypoglycemia on cognitive dysfunction.

Canonical correlation analysis indicated a strong association of cognitive function with WMHs ($p = 0.004$) (Table 2). The canonical valuable of WMHs was contributed with the digit symbol substitution test, MMSE, immediate/delayed word-list recall, and Stroop tests (correlation of canonical variables: 0.76, 0.65, 0.33, 0.47, −0.41, respectively), and the canonical valuable of cognitive function was contributed with PVH and WMHs in the parietal, temporal and occipital lobes, total WMHs, and hyperintensities in the thalamus (correlation of canonical variables: −0.45, −0.33, −0.31, 0.33, −0.34, −0.39, respectively), but not with WMHs in frontal lobe. In other words, digit symbol substitution test, MMSE and immediate/delayed word-list recall had a negative

Table 4. Multivariate regression analysis for subcortical WMHs with adjustment for age, education and blood pressure

Digit symbol substitution test	*P*-value	95% CI
WMHs of frontal lobe	0.13	−0.0004–0.0033
WMHs of parietal lobe	<0.05	−0.0057–0.0002
WMHs of temporal lobe	0.99	−0.0039–0.0038
WMHs of occipital lobe	0.56	−0.0048–0.0087
Thalamus	0.34	−0.0187–0.0065
Basal ganglia	0.31	−0.0092–0.0030
Periventricular hyperintensity	0.54	−1.34–0.70
MMSE	*P*-value	95% CI
WMHs of frontal lobe	0.85	−0.0004–0.0005
WMHs of parietal lobe	0.10	−0.0012–0.0001
WMHs of temporal lobe	0.47	−0.0006–0.0012
WMHs of occipital lobe	0.18	−0.0005–0.0027
Thalamus	<0.05	−0.0062–0.0002
Basal ganglia	0.57	−0.0018–0.0010
Periventricular hyperintensity	0.93	−0.23–0.25

Each variable is adjusted for age, education, and systolic blood pressure. CI: confidence intervals

Table 5. Multivariate regression analysis for subcortical atrophy with adjustment for age, education, and blood pressure

Immediate word-list recall	*P-value*	95% CI
Evans ratio	0.50	−0.24–0.12
Caudate head index	<0.05	−0.33–0.02
Inverse cella media index	0.28	−0.22–0.07
Basal cistern index	0.77	−0.14–0.11
Digit symbol substitution test	*P*-value	95% CI
Evans ratio	0.87	−1.15–1.35
Caudate head index	1.00	−1.07–1.08
Inverse cella media index	<0.05	−2.07–0.08
Basal cistern index	0.13	−1.54–0.20

Each variable is adjusted for age, education, and systolic blood pressure CI: confidence intervals.

strongly correlate with several domains of diabetic cognitive impairment, such as impaired speed of cognitive processes and memory. Our study also indicates that the various and separate subcortical hyperintensities in the parietal lobes and in the thalamus, but not in the frontal lobe, are associated with diabetic cognitive impairment. However, we could not detect the diabetic factors responsible for cognitive dysfunction, nor for the morphological changes on MR images, in spite of our thorough investigation of the various diabetic indices, including diabetic control, complications and comorbidities. These findings were established with the canonical correlation analysis used for our study.

Previous studies have investigated the relationship between WMHs and cognitive decline in nondemented and demented elderly [18,34–38]. Cognitive test scores in older adults were found to be worse in the presence of severe WMHs, even after adjustments for age, gender and education [18]. PVH is more likely than subcortical WMHs to be associated with speed of cognitive processes and memory [18,34,35]. The white matter of the subcortical structure can be divided into the area just beneath the neocortex and the area surrounding the ventricles. The periventricular region contains many long association fibers that connect the cerebral cortex with subcortical nuclei such as those found in the striatum and in more distant cortical areas. On the other hand, the subcortical region close to the neocortex features a high density of short looped U-fibers connecting adjacent cortical areas [39]. Periventricular WMHs damage the long-tract white matter pathways connecting many cortical areas, which might explain their effects on multiple domains of cognition.

Impaired cognitive function in elderly diabetic patients was correlated with subcortical WMHs in the parietal lobe as well as hyperintensities in the thalamus in this study. The thalamus is recognized to be associated with cognitive functions such as learning, memory and executive function [32,40]. The parietal lobe constitutes association areas that are the sites of cortical integration for all behavior such as vision, body awareness and spatial orientation and for abstract and complex cognitive functions. Recent neuroradiological studies have demonstrated reduced regional cerebral blood flow and metabolism in Alzheimer's disease especially in the parieto-temporal cortical areas and correlated with the distribution of Alzheimer's pathological features, while the primary sensorimotor and visual cortical areas were relatively preserved [41,42]. Symptoms of early stage Alzheimer's disease originate from the impaired temporal and parietal lobe functions. Incidental onset of Alzheimer's disease in elderly diabetic patients can be expected to exacerbate the functional loss and clinical symptoms related to temporal and parietal lobes, as also observed in the case of diabetic cognitive dysfunction.

The pathophysiological origins of WMHs are still unclear, with vascular and nonvascular contributions likely to be causative factors. Subcortical WMHs on T2-weighted MR imaging correlate with several pathological changes such as myelin pallor, dilatation of the perivascular space, myelin or axonal loss, scattered cystic infarcts and angionecrosis. Periventricular hyperintensities on MR scans are associated with partial breakdown of the ependymal cell lining and subependymal gliosis in addition to the pathological changes of subcortical WMHs [43,44]. Although characteristic pathological features of the diabetic brain have yet not been identified, vascular compromise is common in the elderly and is accompanied by damage to white matter pathways [12,45]. Age and hypertension have been the most consistent predictors of WMHs [32,33,46,47], while some other studies have indicated that diabetes increases the risk of WMHs [13,36,48]. The increased WMHs in elderly diabetic patients, presumably accompanied by as yet unidentified clinical variables, may account, at least in part, for diabetic cognitive dysfunction.

To reduce the rate of dementia in elderly diabetic patients, it is crucial to identify the factors responsible for the progression toward severe cognitive decline. Degenerative changes in cerebral small vessels may affect diabetic cognitive dysfunction, while it seems likely that it is also influenced by diabetic metabolic abnormalities and complications with or without unidentified genetic susceptibility. However, the results of our study do not

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Outcome of One-year of Specialist Care of Patients with Type 2 Diabetes: A Multi-Center Prospective Survey (JDDM 2)

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Abstract

OBJECTIVE Specialist care is reportedly associated with favorable therapeutic results, although detailed outcomes of recent large-scale prospective surveys of specialist care have yet to be published. The goal of this study was to elucidate the effects of one year's specialist care on the management of type 2 diabetes.

PATIENTS AND METHODS A multi-centered, prospective observational study was undertaken. 754 type 2 diabetes patients, who made their first visit to one of eleven participating outpatient clinics specializing in diabetes care, were enrolled. Routine structured diabetes care according to established guideline, including diabetes self-management education, was provided to all patients at each clinic visit. Parameters relating to glycemic control, serum lipids, blood pressure, patient follow-up status and others were followed for twelve months.

RESULTS The HbA_{1C} level had improved significantly from 8.4±2.2% at baseline to 6.8±1.2% after six months and was 7.0±1.3% after twelve months (mean±SD). The higher the baseline HbA_{1C} level, the greater the subsequent improvement. Moreover, the most dramatic improvements in HbA_{1C} levels were seen within the first three months. The proportion of patients satisfying all of the therapeutic goals was extremely low at baseline and remained at less than 10% after twelve months of specialist care.

CONCLUSIONS Diabetic patients under specialist care experienced substantial improvement, especially in glycemic control, as early as a few months after the first visit. However, 35 percent of patients dropped out during the 12-month study period and this is one area that needs to be improved.

Key words: diabetes specialist, diabetes clinic, quality of care, diabetes self-management education (DSME), pharmacological therapy

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Introduction

Continuing medical care, including diabetes self-management education (DSME) provided by medical professionals with expertise in diabetes, is essential to minimize the risk of long-term complications in patients with diabetes (1-3). Specialist diabetes care has been shown to deliver a better glycemic control outcome than care provided by general practitioners (4-11). However, the outcome assessment of specialist routine care needs to be regularly updated to take into account the continual changes in modern diabetes care and pharmacotherapy (12). Other than a postal survey of secondary care services (13), very few large prospective surveys regarding the outcome of recent specialist care are available.

The Japan Diabetes Clinical Data Management Study Group (JDDM) is a large network of diabetes specialists in Japan. It consists of approximately seventy clinical diabetic specialists, most of whom are board certified and have their

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own clinics. The ultimate goal of the JDDM is to acquire clinical evidence that can be used to optimize diabetes care. To achieve this goal, the JDDM is developing a cohort of diabetic patients who are receiving care at the participating clinics, and by January 2005 approximately 60,000 patients were registered. Clinical and treatment information is stored on a standardized database system and from the cohort of the registered patients, we evaluated the clinical outcomes of new patients consecutively registered on the JDDM database during a particular period. The goal of this study was to elucidate the effects of one year of specialist care on the management of type 2 diabetes. Analyses based on prior treatment history and baseline glycemic status were also made.

Patients and Methods

Recruitment of patients

Eleven JDDM clinics throughout Japan (as listed in the appendix) that specialize in diabetes care voluntarily participated in this study. All type 2 diabetic patients who made their first visit to any of the participating clinics during the study period (January to June 2001) were consecutively recruited. A total of 754 patients entered the study, all of whom provided informed consent to participate. The protocol was consistent with the Japanese Government's "Ethical Guidelines Regarding Epidemiological Studies" and received ethical approval from the JDDM ethics committee. Patients were classified as having type 2 diabetes mellitus according to the Japan Diabetes Society (JDS) criteria (14) which are similar to the WHO criteria (15) in terms of glucose threshold levels. Patients with impaired glucose tolerance were not included in this study. The study follow-up period was 12 months from the patient's first visit.

Diabetes management and care

The patients took part in a comprehensive, structured program in accordance with JDS guidelines (16) and the care package included a comprehensive diabetes self-management education (DSME) program with an emphasis on the importance of lifestyle modifications which was conducted by Certified Diabetes Educators (CDE). Topics covered included good dietary habits, physical activities, treatment adherence, and standard medication including oral hypoglycemic agents and/or insulin. The therapeutic goals, mostly based on JDS guidelines at the time of the study, for the study participants were: a stable HbA_{1c} level <6.5%; a body mass index (BMI) $\leq$24 kg/m^2; blood pressure <130/85 mmHg; serum total cholesterol level <5.17 mmol/L (200 mg/dL); serum HDL cholesterol level $\geq$1.03 mmol/L (40 mg/dL); serum triglyceride level <1.68 mmol/L (150 mg/dL); smoking cessation; and, decreased alcohol consumption (16). Patients were requested to return to the clinic for follow-up care once a month (preferably) or at least once every two months. Changes in patient medication were made in an effort to reach the therapeutic goals outlined above on a treat to target basis. Standard JDS meal plans using diabetic food exchange lists (17) were used. Dieticians also provided individual nutritional guidance. All patients, except those with medical complications for whom a strenuous exercise regime was contraindicated, were encouraged to engage in physical exercise, for a minimum of 30 minutes at least three times a week, that was vigorous enough for them to work up a sweat. A diary to record the progress of laboratory and other data was distributed to the patients to provide feedback on the results of their therapy program.

Clinical and laboratory parameters

Body weight, blood pressure, HbA_{1c}, fasting plasma glucose, serum lipids/creatinine/urea nitrogen, and urine analysis results were obtained at scheduled clinic visits during the study period. Ophthalmological and neurological examinations were done at baseline. JDS guidelines were used to assess the development of microvascular complications. Neuropathy was defined as having three or more of the following: (i) absence of ankle tendon reflex; (ii) absence of knee tendon reflex; (iii) decreased vibration sensation; (iv) abnormal results for monofilament touch test (18); or (v) abnormal subjective symptoms. Nephropathy was defined as having an albumin excretion of more than 30 mg/g creatinine in two or more consecutive urine testings. Retinopathy was defined to involve simple, non-proliferative retinopathy. HbA_{1c} levels were determined by high-pressure liquid chromatography (HPLC) with 5.8% as the upper normal limit. Plasma glucose levels were determined by the glucose oxidase technique. All other laboratory tests were determined by standard methods.

Data processing and statistical analysis

Clinical data was input to a bespoke, standardized software system "CoDiC™" (19) which was distributed to each participating clinic. Data were collected from each institute on an anonymous basis and stored centrally for statistical analysis using SPSS, version 10.05 (SPSS Inc., Chicago, IL, USA). The F-test was used to determine whether the variance of each group was equivalent. Student's paired and unpaired t-tests, one-way ANOVA and a post hoc multiple comparison test (Dunnett) were used to compare continuous variables between groups. A P-value of less than 0.05 was considered significant. All values are presented as means ± standard deviations unless otherwise stated.

Results

Background characteristics and baseline analysis

Baseline measurements broken down according to prior or first time treatment are shown in Table 1. Of the previously treated patients, 93% were direct referrals from primary care physicians with the remainder discontinuing their previous medical care. Among the previously untreated patients, 62%

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Table 1. Patient characteristics at baseline and 12 months later. Baseline data of the patients that completed the 12-month study period are shown in [ ]

(Mean±S.D., n.a.; not applicable, n.d.; not done)

	Total		Newly treated patients		Previously treated patients	
	Baseline[a]	12th month[b]	Baseline[c]	12th month[d]	Baseline[e]	12th month[f]
Number of patients	754	491	341	194	413	297
Men/Women	496/258	311/180	241/100	134/60	255/158**	177/120
Age (yr.)	58.0±11.9 [58.8±11.6]	n.a.	56.2±11.1 [57.1±10.9]	n.a.	59.6±12.3*** [59.8±11.9]	n.a.
Diabetes duration (yr.)	9.1±8.8 [9.4±8.6]	n.a.	6.3±7.1 [6.7±7.5]	n.a.	10.7±9.3*** [10.6±8.8]	n.a.
BMI (kg/m2)	24.1±4.1 [24.2±4.4]	24.2±3.8*	24.7±4.2 [24.7±4.7]	24.4(3.9	23.7±4.1** [23.9±4.1]	24.1±3.7**
HbA1C (%)	8.4±2.2 [8.6±2.2]	7.0±1.3***	8.5±2.3 [9.0±2.4]	6.8(1.3***	8.4±2.1 [8.4±2.0]	7.2±1.3***+++
Systolic blood pressure (mmHg)	136.9±21.8 [136.9±21.3]	131.2±17.8***	136.8±21.2 [136.4±20.9]	130.4±17.1***	138.1±22.6 [137.2±21.7]	131.9±18.3***
Diastolic blood pressure (mmHg)	79.6±12.9 [79.5±12.5]	75.7±11.9***	81.4±12.8 [81.0±12.8]	76.3±12.7***	78.7±12.5** [78.4±12.2]	75.4±11.2***
Total cholesterol (mmol/l)	5.48±1.04 [5.37±1.00]	5.21±0.88***	5.61±0.98 [5.48±0.93]	5.23±0.80***	5.39±1.06 [5.31±1.05]	5.21±0.88**
HDL cholesterol (mmol/l)	1.41±0.39 [1.42±0.40]	1.40±0.36	1.42±0.37 [1.44±0.38]	1.40±0.31	1.41±0.39 [1.42±0.41]	1.40±0.36
Triglycerides (mmol/l)	1.72±1.24 [1.63±1.20]	1.73±1.63	1.80±1.39 [1.66±1.30]	1.41±0.82***	1.66±1.13 [1.60±1.12]	1.73±1.13++
Patients with retinopathy (%)	31.1 [34.0]	n.d.	20.0 [23.6]	n.d.	39.4 [40.7]	n.d.
Patients with nephropathy (%)	30.6 [31.2]	n.d.	21.1 [21.0]	n.d.	38.1 [37.9]	n.d.
Patients with neuropathy (%)	25.2 [25.8]	n.d.	17.6 [20.0]	n.d.	31.2 [29.7]	n.d.
Medication for hypertension (%)	17.4 [19.0]	33.8***	11.9 [13.8]	28.1***	21.7 [22.3]*	37.5***+
Medication for hyperlipidemia (%)	6.7 [6.9]	18.2***	3.5 [3.8]	13.8***	9.2 [8.8]*	21.0***+
Medications for both of the above (%)	3.4 [3.2]	8.7***	2.9 [2.9]	6.7***	3.8 [3.4]	10.1***
		*p<0.05, ***p<0.001 (a vs.b)		***p<0.001 (c vs.d)	*p<0.05, **p<0.01, ***p<0.001 (e vs.e)	**p<0.01, ***p<0.001 (e vs.f) +p<0.05, ++p<0.01, +++P<0.001 (d vs. f)

visited the clinics because of elevated FPG and/or HbA_{1c} levels found at a medical check-up, while 8% attended because of the development of diabetic symptoms. The remainder were referred from other speciality clinics or hospitals. Baseline HbA_{1c} was similar in patients with and without a previous history of diabetes care. However, the previously untreated patients were significantly younger with a shorter duration of diabetes and a lower BMI (Table 1).

Patient follow-up status and dropout

The proportions of patients making repeat clinic visits, sub-grouped according to whether they had received prior treatment for diabetes and by baseline HbA_{1c} levels, are shown in Fig. 1A and Fig. 1B, respectively. Approximately 35% of all participants defaulted from follow-up during the first year (Fig. 1A). At twelve months, patients with HbA_{1c}

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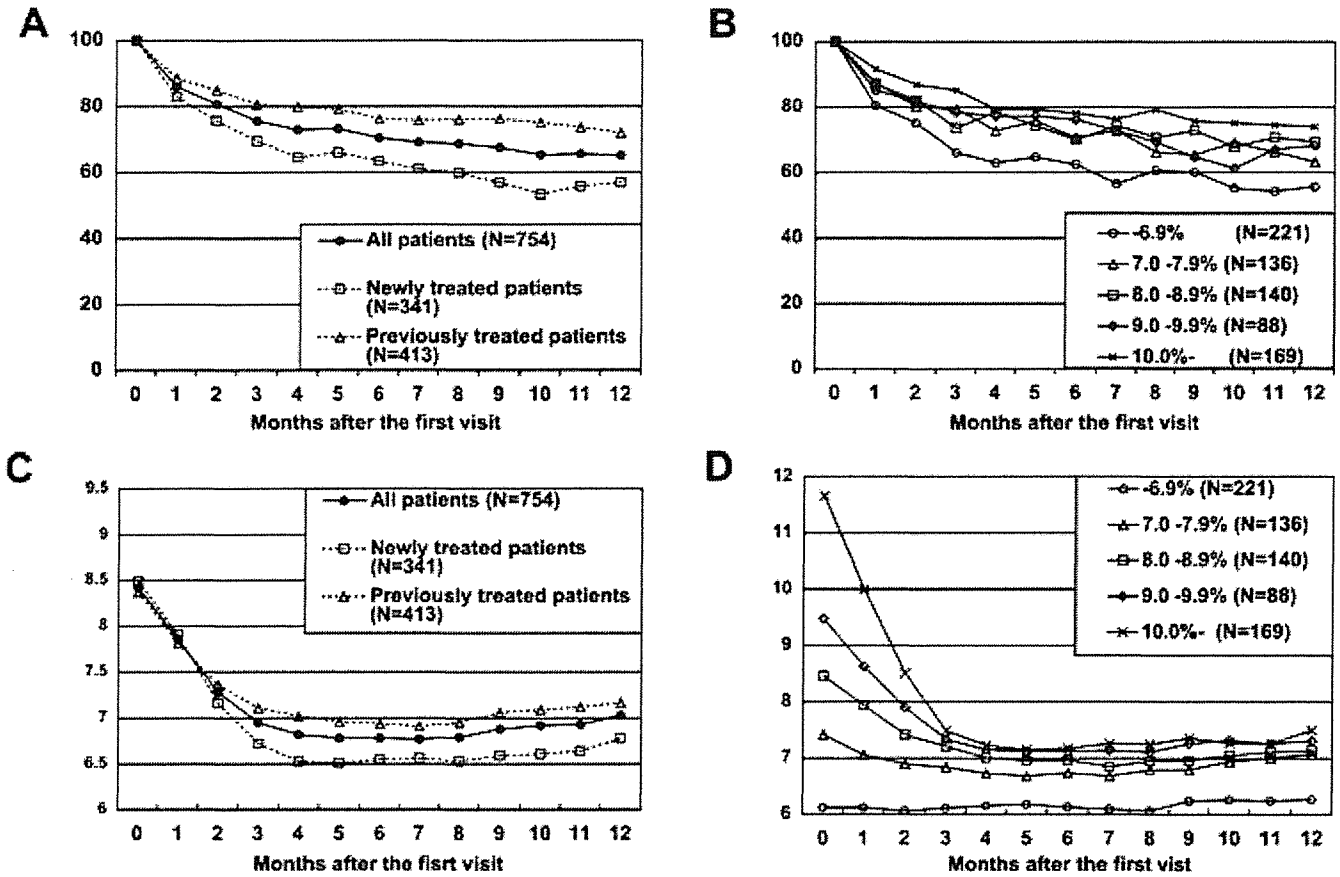

Figure 1. **Sequential changes in the proportion of patients under follow-up (A, B), and HbA_{1c} levels (C, D) during the twelve months following the first visit to a specialist clinic. The results were stratified according to the patients' previous follow-up status (A, C) or HbA_{1c} levels at baseline (B, D).**

levels of 6.9% or less had the greatest dropout rate (44.3%) while patients with levels of 10% or more had the lowest rate (26.0%) ($P<0.001$ between the two subgroups; Fig. 1B). A comparison of patient backgrounds at baseline between those who completed (N=491) and those who were lost to follow-up (N=263) showed that baseline HbA_{1c} levels were significantly lower ($P=0.039$) in those who dropped out (8.1±2.2%) than in those who completed treatment (8.6± 2.2%). However, there were no significant differences in age, gender, diabetes duration or baseline BMI between these two groups (data not shown). Patients being treated for diabetes for the first time had a significantly higher dropout rate (43%) than previously treated patients (28%) (Table 1 and Fig. 1A) ($P<0.001$). The reasons given for patient dropout included the pressure of official (28%) or private business (11%), misunderstanding regarding diabetes therapy (13%), moving out of town (11%), and economic reasons (6%).

Changes in glycemic and other control

The mean HbA_{1c} levels of all patients who completed 12-month follow-up improved significantly from 8.4±2.2% at baseline to 6.8±1.2% after six months, and 7.0±1.3% after twelve months (Fig. 1C). Newly treated patients showed significantly greater improvements in HbA_{1c} levels during the first year than the previously treated patients ($P<0.001$; Fig. 1C). As shown in Fig. 1D, the higher the initial HbA_{1c} level the greater the improvement that was seen. For patients with the highest baseline HbA_{1c} (10% or more), mean HbA_{1c} levels fell dramatically from 11.7±1.3% to 7.5±1.6% in the first three months and remained stable thereafter. Conversely, only very limited improvement was found in patients with HbA_{1c} levels of 7.9% or less. In general, decreases in HbA_{1c} levels were almost exclusively observed in the three months following the first visit. There was no significant correlation between the final HbA_{1c} levels and the frequency of DSME (data not shown). Total cholesterol and systolic/diastolic blood pressure significantly decreased regardless of treatment history, while HDL cholesterol did not show any significant changes during the 12-month study period. Significant improvement in triglycerides was seen only in newly treated patients (Table 1).

Pharmacological therapy and adherence to guidelines

The pharmacological therapy of patients is shown in

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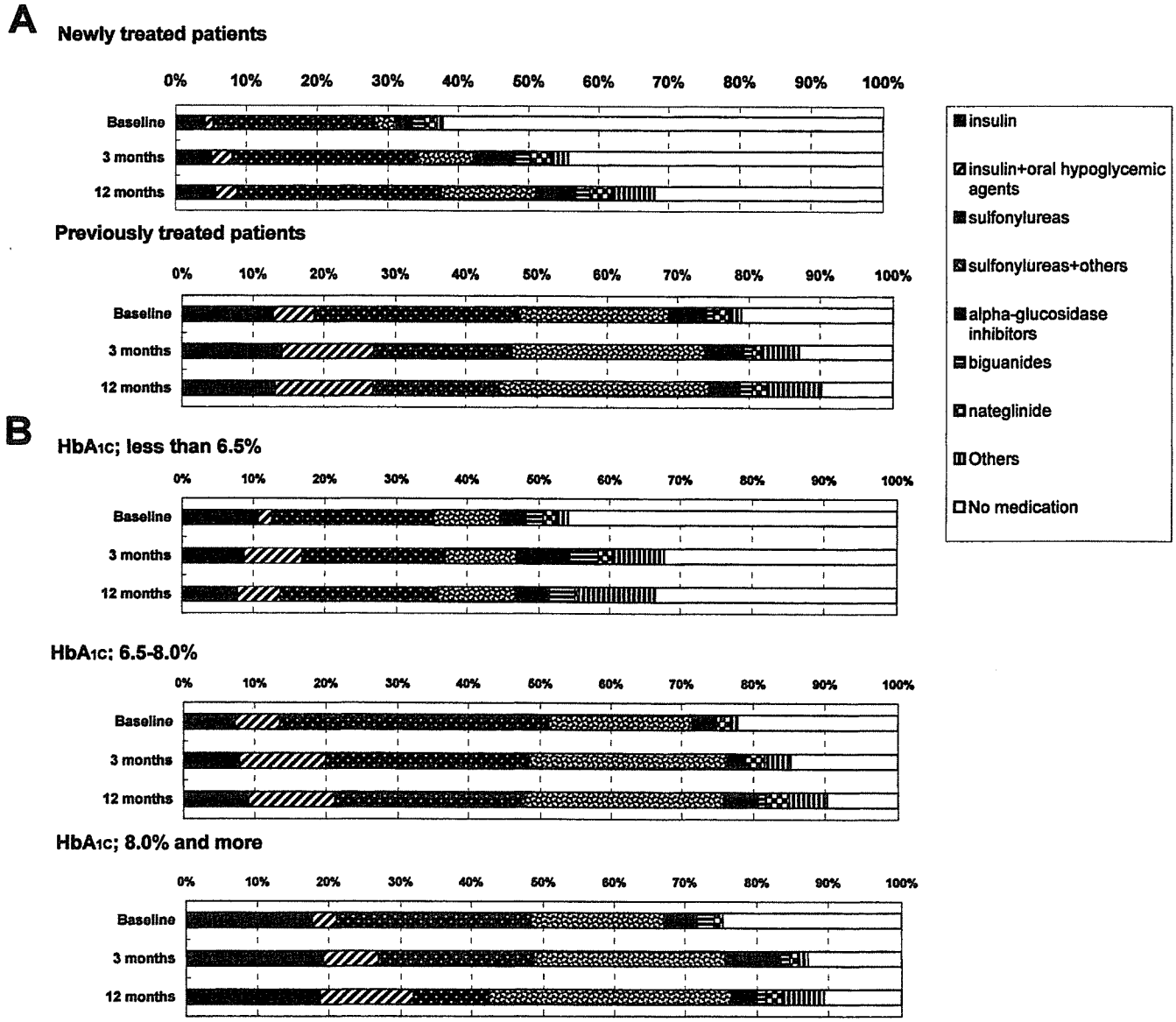

Figure 2. **Pharmacotherapeutic status of the patients at baseline, three months and twelve months after start of the study, stratified according to previous follow-up status (A) or HbA_{1c} levels at baseline (B).**

Fig. 2A and Fig. 2B, broken down according to previous treatment status or baseline HbA_{1c} level, respectively. The use of hypoglycemic agent, including insulin differ, according to a patient's prior treatment history. Patients who had been previously treated used more insulin than previously untreated patients and the proportion of patients using two or more agents was higher in previously treated patients (Fig. 2A). The proportion of patients using sulfonylureas was increased in patients with baseline HbA_{1c} levels of 6.5% or higher and insulin usage was higher in patients with initial HbA_{1c} levels of 8.0% and more than in the other subgroups (Fig. 2B). The proportion of patients taking medications for hypertension, hyperlipidemia, or both significantly increased two- or three-fold during the twelve months of study regardless of prior treatment history (Table 1). To investigate the adherence of each clinic to the guidelines, the HbA_{1c} levels used by clinics to trigger the start of medication were surveyed. The medication thresholds were as follows: 6.5% or more (2 clinics), 7.0% or more (2), 8.0% or more (3), 9.0% or more (1), and patient-by-patient assessment (3). The survey also revealed that clinic HbA_{1c} target levels were as follows: 5.8% or less (1 clinic), 6.5% or less (7) and 7.0% or less (3).

Therapeutic goal achievement rates

In assessing the proportions of patients who achieved either the individual or all of the therapeutic goals, comparisons were made at 12 months with two baseline groups; one containing all the patients who participated in the study, and the other containing only those patients who completed the 12-month study (Table 2). Of the patients who completed 12 months of follow-up, the proportion achieving the HbA_{1c}

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Table 2. **Proportion of patients satisfying the therapeutic goals (except smoking and drinking) at baseline and 12 months later. Baseline (1) includes all patients enrolled at registration, and baseline (2) includes only patients who remained until the end of the 12 month study. (P < 0.05*, 0.01**, 0.001*** Compared to the group of baseline (2) by McNeuar test)**

		Total (%)	Newly treated (%)	Previously treated (%)
HbA_{1C} < 6.5%	Baseline (1)	20.4	23.4	17.9
	Baseline (2)	16.5	17.9	15.7
	At 12th month	36.5 ***	46.9 ***	29.9 ***
HbA_{1C} < 7.0%	Baseline (1)	29.3	32.3	26.8
	Baseline (2)	24.6	25.1	24.2
	At 12th month	54.1 ***	63.1 ***	48.4 ***
BMI < 24 kg/m^2	Baseline (1)	55.7	49.5	60.7
	Baseline (2)	54.4	47.9	58.6
	At 12th month	51.3 *	49.1	52.7
Systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg	Baseline (1)	32.2	33.9	30.9
	Baseline (2)	33.3	34.3	32.5
	At 12th month	43.5 ***	44.8 *	42.6 *
Total cholesterol < 200 mg/dl	Baseline (1)	45.0	44.8	45.0
	Baseline (2)	38.5	37.1	39.5
	At 12th month	50.0 ***	51.7 **	48.9 *
HDL cholesterol > 40 mg/dl	Baseline (1)	86.6	86.5	86.6
	Baseline (2)	87.4	85.7	88.5
	At 12th month	88.3	89.3	87.6
Triglycerides < 150 mg/dl	Baseline (1)	67.8	67.7	67.9
	Baseline (2)	65.3	63.6	66.4
	At 12th month	69.4	74.1 *	66.4
All of the above (Regarding HbA_{1C}, goal of < 6.5% was adapted)	Baseline (1)	2.1	2.4	1.9
	Baseline (2)	1.2	1.0	1.3
	At 12th month	3.5	6.2	1.9
All of the above (Regarding HbA_{1C}, goal of < 7.0% was adapted)	Baseline (1)	2.5	2.4	2.5
	Baseline (2)	1.2	1.0	1.3
	At 12th month	4.7*	9.3**	1.9

goal of 6.5% or less increased significantly from 16.5% at baseline to 36.5% at 12 months. The improvement was particularly evident in newly-treated patients (from 17.9% at baseline to 46.9% at 12 months). The proportion of patients achieving the HbA_{1C} goal of 7.0% or less was 24.6% at baseline and 54.1% at 12 months. On the other hand, the proportion of patients who achieved the BMI goal ($\leq$24 kg/m^2) decreased significantly from 54.4% at baseline to 51.3% after 12 months. The proportions of patients achieving the blood pressure or total cholesterol goals increased significantly by approximately 10% during the 12-month period. Only newly-treated patients showed a significant improvement in achieving the triglyceride goal.

When adopting the HbA_{1C} goal of 6.5% for analysis, the proportion of patients satisfying all of the therapeutic goals (except smoking and alcohol drinking) at baseline was 2.1%, when all patients who participated in the study were included, and 1.2% when only patients who completed the 12-month follow-up were included. The proportion increased to 3.5% after 12 months but this increase was not statistically significant. However, when the HbA_{1C} goal of 7.0% was adopted for analysis, the proportion of patients satisfying all of the therapeutic goals increased significantly from 1.2% at baseline to 4.7% after 12 months.

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Discussion

Glycemic control and weight control

This prospective study highlights the current Japanese standards of diabetes management and care provided in specialist clinics and demonstrated, a reasonable improvement in the glycemic control of patients, especially in those with severe diabetes (Fig. 1). Most of the improvements in HbA_{1c} levels seen in the first year occured within the first three months of commencing management (Fig. 1C). It should be emphasized that even patients who had previously been treated in primary care settings showed improvement in HbA_{1c} levels. Of the patients receiving treatment for the first time, less than 40% started medication after their first visit, while at twelve months nearly 70% of those patients had been prescribed one or more medications (Fig. 2A). This probably accounts for the rapid improvement in HbA_{1c} in these patients (Fig. 1).

Several issues still remain concerning our care of glycemic control. The first is that the proportions of patients achieving the HbA_{1c} goals were still very low even after 12 months of care (Table 2). The second issue is that the improvement in HbA_{1c} was limited to patients with baseline HbA_{1c} levels of 8% or higher (Fig. 1D). The third issue is that the HbA_{1c} levels in patients with a baseline of 7.0% or more converged above the 7.0% level at the midpoint of the study and tended to increase (deteriorate) after that point (Fig. 1D). Finally, a slight but significant increase in BMI, which was possibly related to the effects of pharmacological therapy (20), was observed during the 12 months of care (Tables 1, 2). It is true that the mean BMI of Japanese patients with type 2 diabetes is much lower than that of the United Kingdom Prospective Diabetes Study (UKPDS) patients (21). However, the BMI cut-off for being overweight is now 23 kg/m^2 in Asian subjects (22), which is lower than the mean BMI of the present patients.

Other therapeutic goals

At baseline, the proportion of patients satisfying all of the therapeutic goals (except smoking and alcohol drinking) was only 2.5%, even when a HbA_{1c} goal of less than 7.0% was adopted (Table 2). Only 32.2% and 45.0% of the patients at baseline fulfilled the target goals for blood pressure and total cholesterol levels, respectively, which were lower than the proportions reported in the U.S. (35.8% for blood pressure and 51.8% for total cholesterol) (23), suggesting that under-treatment of cardiovascular risk factors in diabetic patients was common also in Japan.

After 12 months of specialist care, total cholesterol, HDL cholesterol, triglycerides and blood pressure, all critical factors associated with diabetic vascular complications (12, 24-26), were controlled at levels close to the treatment goals set by the JDS (Table 1). However, our results also demonstrated that, in spite of the dramatic increase in the proportion of patients taking medications for hypertension and/or hyperlipidemia (Table 1) only a small proportion of more patients achieved the treatment goals than at baseline, which was notably lower than the achievement rate for glycemic control noted above (Table 2). Although the prevalence of cardiovascular complications in Japanese patients with type 2 diabetes is known to be lower than in patients from other countries (27, 28), the incidences of cerebral infarction and coronary heart disease in Japanese patients with diabetes are both approximately three times higher than in non-diabetic subjects (29), suggesting that we also need to improve our management of hypertension and serum cholesterol in order to prevent macrovascular complications at the same time as we seek to control glycemia.

Effects of DSME

A recent meta-analysis (30) and the results of the JDCS, the largest and longest trial focusing on the effects of lifestyle intervention (31, 32), have demonstrated a moderate, beneficial impact of DSME. However, a meta-analysis of educational intervention on the management of diabetes (33) failed to show a significant correlation between management effects and the number of visits or education type. We could not find a significant correlation between the frequency of DSME and glycemic control results (data not shown). However, this does not necessarily refute the significance of DSME since the quality of the DSME cannot be represented as a frequency measure. DSME is inevitably involved in a specialist's routine care and it is difficult to extract the genuine effects of DSME (34). It is conceivable that the potent effects of pharmacological therapy on glycemic control in the first few months of the study period masked the moderate effects of DSME. As a matter of fact, even previously treated patients (mostly direct referrals from primary care physicians) who underwent only limited changes in pharmacotherapy after starting specialist care (Fig. 2A) showed significant improvement in HbA_{1c} levels (Table 1), suggesting that the DSME element of specialist care had some positive effects.

Issues regarding lost to follow-up

A common barrier to improved patient care is that a considerable proportion of patients are lost to follow-up (35-38) and these defaulting patients have poorer outcomes than patients who continue to attend clinics (2, 35, 39, 40). Our study demonstrated a dropout rate of 35% which was close to that observed in many other studies (35). Unlike the situation in many other countries, visiting a clinic every month or two is a common characteristic of the Japanese healthcare system and reflects the facts that the government-based health insurance covers all citizens and extra patient expenditure for specialist care is unnecessary. However, the health insurance system does not seem to contribute to an improvement in the patient dropout rate. The significant differences in baseline HbA_{1c} levels between the patients who dropped-out and those who completed the care program suggests that

patients with milder diabetes need to be encouraged not to abandon medical care.

Limitation of the study and future strategy

There are several important limitations in our study. First, this is only a one-year prospective study and longer-term results, including chronic complications, need to be evaluated, especially as there was a slight deterioration in HbA_{1c} during the last 6 months of the study period. A further study of the outcome of long-term care including actual changes in lifestyle parameters is necessary since only a few substantial studies lasting longer than two years (2, 41) are currently available. Second, the high dropout rate could affect the study result. Although those with lower HbA_{1c} showed the highest dropout rate, a rapid deterioration in their glycemic control cannot be ruled out. Third, individual compliance to the DSME was not monitored but should be investigated in relation to the therapeutic outcome of each patient. At the same time, an analysis of adherence to practice guidelines in each clinic and their patient outcomes should be analyzed in more detail. Fourth, differences in ethnic (21, 42-47), socioeconomic or cultural background need to be considered as a possible source of bias when applying these results to other regions. Finally, a control group of patients treated by primary care physicians was not available and the eleven clinics that participated did so voluntarily. Consequently, we cannot tell from this particular study whether specialist care is superior to that of primary care physicians, although patient selection bias was minimized by registering all newly visited patients consecutively.

In conclusion, enhanced management and care of patients, especially those with relatively mild hyperglycemia, and ongoing therapy for those with HbA_{1c} levels approaching 6.5%, together with continuing efforts to eliminate obesity and patient dropout, and to manage hypertension and dyslipidemia more carefully will probably result in an improved diabetes care outcome.

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Appendix: The following members of the JDDM group participated in this study (in alphabetical order); Dr. Hiroshi Hayashi (Matsuzaka), Dr. Koichi Hirao (Yokohama), Dr. Koichi Kawai (Tsukuba), Dr. Mikihiko Kudo (Aomori), Dr. Yoshio Kurihara (Sapporo), Dr. Mariko Oishi (Kyoto), Dr. Fuminobu Okuguchi (Sendai), Dr. Takeshi Osonoi (Naka), Dr. Hideo Sasaki (Niigata), Dr. Hiromichi Sugiyama (Shizuoka), Dr. Katsuya Yamazaki (Toyama). The JDDM consists of many investigators at participating institutes all over Japan.

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Angiotensin II type 1 receptor blocker telmisartan suppresses superoxide production and reduces atherosclerotic lesion formation in apolipoprotein E-deficient mice

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Abstract

Angiotensin II is involved in the process of atherosclerosis and stimulates superoxide production from cardiovascular cells. We examined the effect of telmisartan, an angiotensin II type 1 receptor blocker, on atherosclerosis. We chronically treated apolipoprotein E-deficient mice with two different doses of telmisartan dissolved in drinking water (0.3 and 3 mg/kg) starting from 4 weeks of age for 12 weeks. Lipid contents were not different in both telmisartan-treated groups compared with control group. Systolic blood pressure was significantly reduced with 3 mg/kg, but unchanged with 0.3 mg/kg. The total atherosclerotic lesion size at the aortic sinus was reduced with 0.3 mg/kg compared with control, and additional reduction was proved with 3 mg/kg. The fibrotic change was not different among three groups, but MOMA-2-, malondialdehyde-, 4-hydroxy-2-nonenal-immunostained areas were reduced by telmisartan. As the mechanism, we revealed that both doses of telmisartan markedly reduced superoxide production from in situ vessels assessed by lucigenin-enhanced chemiluminescence and dihydroethidium staining. And NAD(P)H dependent oxidase activity in vessels was reduced by telmisartan. Further, 8-*iso*-prostaglandin F2α level, a systemic oxidative stress marker, obtained from urine and plasma samples were significantly reduced by telmisartan. Telmisartan reduced atherosclerosis in apolipoprotein E-deficient mice at least partly via the suppression of oxidative stress.

Keywords: Angiotensin II type 1 receptor blocker; Atherosclerosis; Oxidative stress; Apolipoprotein E-deficient mouse

1. Introduction

The renin-angiotensin system (RAS) plays important roles in the regulation of not only blood pressure but also vascular structure. The main component of RAS is angiotensin II (Ang II), which is a potent vasoconstrictor and elevates blood pressure. Ang II generates aldosterone and activates sympathetic nervous system, leading to blood pressure elevation.

Besides its effect on blood pressure, a number of evidence revealed that Ang II is involved in atherogenesis. In animal models, chronic infusion of Ang II promotes atherosclerotic lesion formation [1]. It is shown that Ang II promotes atherogenesis via direct effects on vascular beds independent of hypertensive effects. Among them, the effect as the inducer of oxidative stress is recently attracting attention. In atherosclerosis, there is augmented production of reactive oxygen species (ROS) from various cell types including endothelial cells, vascular smooth muscle cells and monocytes/macrophages, and Ang II plays a pivotal role in their production [2–4]. There are increased expressions of angiotensin converting enzyme (ACE) and Ang II type 1 receptor in atherosclerotic arteries, indicating the presence of augmented local RAS activation [5,6]. Ang II increases superoxide production from vessel wall by activating NAD(P)H oxidase [7]. ROS are closely implicated

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