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ORIGINAL ARTICLE

Low well-being, cognitive impairment and visual impairment associated with functional disabilities in elderly Japanese patients with diabetes mellitus

Atsushi Araki,[1] Tadasumi Nakano,[2] Kenzo Oba,[3] Chikako Ito,[4] Seijiro Mori,[5] Shun Ishibashi,[6] Fumio Umeda,[7] Ryuzo Abe,[8]* Hideto Kojima,[9] Ryuichi Kikkawa,[9] Ryuzo Kawamori[10] and Hideki Ito[2]

[1]Department of Endocrinology, Tokyo Metropolitan Geriatric Medical Center and [2]Tokyo Metropolitan Tama Geriatric Medical Center Division of Geriatric Medicine, [3]Nippon Medical School, [4]Hiroshima A-Bomb Casualty Council Health Management Center, [5]2nd Department of Internal Medicine, Chiba University, [6]3rdDepartment of Internal Medicine, Tokyo University, [7]3rd Department of Internal Medicine, Kyushu University, [8]Ohta General Hospital, [9]3rd Department of Internal Medicine, Shiga Medical University, [10]Department of Medicine, Metabolism and Endocrinology, Juntendo University, Japan

Background: The objective of this study is to examine the important factors associated with functional disabilities in elderly patients with diabetes mellitus.

Methods: This was a multicenter cross-sectional study. A total of 1135 elderly diabetic outpatients aged over 65 years in 10 hospitals participated in our study. Functional disabilities were assessed with questionnaires on the instrumental activity of daily livings (IADL), intellectual activity and social role using the Tokyo Metropolitan Institute of Gerontology Index of Competence. Cognitive function and well-being were assessed by the mini-mental state examination and morale scale, respectively.

Results: The patients were divided into three age groups. The oldest (≥ 80 years) group reported significant high prevalence of functional disabilities (10% to 36%) compared to the youngest (65–69 years) group (4% to 20%). The number of vascular complications (≥ 4) was associated with a 5.5–8.8 fold increased risk of disabilities relating to the tasks on IADL (using public transportation, shopping, preparing meals and paying bills). Using multiple logistic regression analyses, low scores of morale scales (≤ 7) and mini-mental state examination (≤ 23) were significantly associated with disabilities on the IADL, intellectual activity and social role after adjustment for age, gender, BMI, duration of diabetes, HbA1c, insulin treatment, microangiopathy and macroangiopathy. Insulin treatment and low visual acuity were also associated with the IADL after adjustment for the other variables.

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Correspondence: Dr Atsushi Araki, MD, PhD, Department of Endocrinology, Tokyo Metropolitan Geriatric Medical Center, 35–2 Sakae-cho, Tokyo 173–0015, Japan. Email: fwic3817@mb.infoweb.ne.jp

*Deceased

Conclusions: Older age, insulin treatment, low well-being, cognitive impairment, and visual impairment were independently associated with the functional disabilities of elderly patients with diabetes mellitus.

Keywords: cognition, diabetes mellitus, functional disabilities, visual impairment, well-being.

Introduction

The prevalence of diabetes increases with age and about 15% of the elderly general population aged 65 years or older have diabetes mellitus in Japan.[1] Even elderly diabetic patients often suffer from diabetic microvascular and macrovascular complications. The goal of treatment in the elderly diabetic population is to maintain functional abilities and quality of life (QOL) as well as to prevent diabetic complications.

Functional abilities in the elderly population are assessed by various indices of activities of daily living (ADL), such as basic ADL, instrumental ADL (IADL), and the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence.[2–4] The IADL are activities reflecting abilities to adapt to one's social life and to maintain an independent life in the community.[3,4] The TMIG Index of Competence, consisting of the three subscales, IADL, intellectual activity and social role, has been developed to assess higher levels of competence.[5]

Diabetes in the elderly has been reported to have a two- to three-fold increased risk for functional disabilities.[6,7] Few studies have demonstrated what factors have important associations with functional disabilities in elderly diabetes mellitus.[6,7] Gregg *et al.* reported that older age, obesity, coronary artery disease, arthritis, physical inactivity and visual impairment were independently associated with disabilities in elderly diabetic women.[6] In our previous study, age, retinopathy, neuropathy and cerebrovascular disease were independent determinants of the functional disabilities as assessed with the TMIG Index of Competence.[8] Although elderly patients with diabetes often have cognitive impairment,[9] and low well-being,[8] it remains unknown whether cognitive impairment and well-being are independently associated with functional disabilities in elderly diabetic populations.

Therefore, we have conducted a cross-sectional study of 1135 elderly diabetic outpatients in 10 institutions in Japan to examine the prevalence of functional disabilities and to explore the independent factors associated with functional disabilities in elderly diabetic patients.

Subjects and methods

The Elderly Diabetes Quality of Life Study (EDQOLS) was conducted to investigate the cross-sectional or prospective relationship between several types of measures of quality of life such as activities of daily living (ADL), visual acuity, cognitive function, psychological aspects, socioeconomic aspects, and the subsequent prognosis including mortality and morbidity of diabetic complications in elderly patients with diabetes. The participants were aged 65–90 years and recruited from diabetic outpatients in 10 representative hospitals in Japan between February and April 1997. A total of 1187 diabetic outpatients aged over 65 years were registered. Those with severe dementia, aphasia or acute or severe illness were excluded.

All subjects were asked to complete comprehensive questionnaires about QOL and functional abilities, the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence,[5] the Philadelphia Geriatric Center (PGC) morale scale (Japanese version),[10] the Folsteine's Mini-mental state examination (MMSE),[11] social support scales (positive and negative), economic status and family members with whom they lived. Forty-three and nine patients respectively were excluded from our analyses because of complete and partial missing data on the TMIG Index of Competence. Finally, a total of 1135 elderly diabetic patients (95.6%) completed the questionnaires on functional abilities.

At baseline, we assessed functional disabilities using the TMIG Index of Competence. The TMIG Index of Competence has 13 items and consists of three subscales: IADL, intellectual activity and social role.[5] The IADL of the TMIG index of Competence were assessed by questions regarding abilities to perform the tasks involved in using public transportation, shopping for daily necessities, preparing meals, paying bills and handling one's own banking. The intellectual activity reflects the abilities to fill out the pension form, to read newspapers, books or magazines, and to be interested in new stories or programs dealing with health, while the social role refers to the abilities to visit the homes of friends or sick people, to be called on for advice and to initiate conversation with young people. The index was well-validated and has been widely used for measuring the extent of functional abilities in the community-dwelling or institutionalized elderly.[2]

General well-being in elderly diabetic patients was evaluated using the PGC morale scale (Japanese version).[10] The morale refers to a future-oriented optimism or pessimism regarding the problems associated with

living and aging. It consists of three components: agitation, attitude toward own aging and lonely dissatisfaction. Low well-being was defined as a morale score of seven points and under. The low score of morale scale suggests that one has a low well-being. The Pearson's correlation coefficients (r) of the test-retest of the morale scale between 7 days were 0.990 ($P < 0.0001$).

To assess comprehensive cognitive function including orientation, memory recall and calculation ability, the Folsteine's MMSE was performed.[11] Cognitive impairment was defined as a MMSE score of 23 points and under.

According to the corrected visual acuity of their worst eye, the subjects were divided into three groups: normal group (≥ 0.7), moderately impaired group (0.6–0.2), and severely impaired group (≤ 0.1).

Blood pressure was measured with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic blood pressure was determined as Korotkoff phase V. Body mass index was calculated as weight (kilograms)/height (meters).[2] Venous blood was drawn for the determination of blood glucose, HbA1c and serum concentrations of total cholesterol, HDL cholesterol, triglycerides and creatinine according to established methods.

Microangiopathy (retinopathy, nephropathy and neuropathy) were assessed at baseline. Fundoscopic examinations were performed through dilated pupils by experienced ophthalmologists using direct ophthalmoscopy. The status of retinopathy was classified into three categories: no retinopathy, background retinopathy and proliferative retinopathy. Urinary albumin was measured by immunological assay. According to the mean urinary albumin-to-creatinine ratio (ACR: μg/mg creatinine) in two or three successive urinalyses, diabetic nephropathy was classified as no nephropathy (ACR < 30), microalbuminuria (30 ≤ ACR < 300) and persistent proteinuria (ACR ≥ 300 or urinary protein ≥ 30 mg/dL). Diabetic neuropathy was defined as loss of Achilles tendon reflexes and diminished vibration sensation, and/or neuropathic symptoms including paresthesia.

Information about the subjects' histories of macroangiopathy (ischemic heart disease, stroke and peripheral vascular disease) was obtained from medical records. Ischemic heart disease (IHD) was considered to be present when diabetic patients had at least one of the following: (i) a history of myocardial infarction characterized by a typical clinical picture (chest pain, chest oppression, dyspnea), typical ECG alteration with occurrence of pathological Q waves and/or localized ST variations), and typical enzymatic changes (CPK, CPK-MB); (ii) a history of angina pectoris, and positive treadmill ECG test or positive post-load cardiac scintigram findings, and confirmed by coronary angiography. Stroke was defined as clinical signs of a focal neurological deficit with rapid onset that persists ≥ 24 h, confirmed by the findings of either brain computed tomography or magnetic resonance (MR) imaging. Peripheral vascular disease (PVD) was defined as both the absence of dorsal pedal artery or posterior tibial artery pulsation and ankle-brachial index < 0.8 or the presence of foot gangrene or ulcers.

The number of vascular complications was counted by summing up the incidence of retinopathy, nephropathy, neuropathy, IHD, stroke, and PVD.

Statistical analysis

In univariate analysis, we used the unpaired t and χ^2-tests to compare clinical characteristics at baseline among the age groups or treatment groups. The correlation between two variables was assessed with Spearman's correlation coefficients. To examine independent factors associated with functional disabilities we performed multiple logistic regression analyses using the 10 variables: age, gender, BMI, duration of diabetes, HbA1c, insulin treatment, microangiopathy, macroangiopathy, morale scales and MMSE scores. Using logistic regression analyses, odds ratio (OR) and 95% CI (confidence interval) were estimated. As final analysis, we used multiple logistic regression analyses to evaluate the association between visual impairment and functional disabilities after adjustment for the other 10 variables. Results are presented as means ± SD. $P < 0.05$ was regarded as statistically significant. Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences, Inc., Chicago, IL, USA) for Windows (version 11.0).

Results

We divided 1135 elderly diabetic patients into the three groups by age. The oldest (≥ 80 years) group had significantly more women and less insulin-users, high prevalence of hypertension, persistent proteinuria, neuropathy, low well-being, cognitive impairment, and visual impairment compared with the youngest (65–69 years) group (Table 1). However, BMI, blood pressure, levels of HbA1c, serum total cholesterol, triglycerides and HDL-cholesterol, and the prevalence of retinopathy, stroke, and IHD were similar among the three groups.

The oldest group reported a significantly higher prevalence of disabilities on tasks for IADL and intellectual activity as compared with the youngest group: using public transportation (29% versus 8%, $P < 0.001$), shopping (16% versus 5%, $P < 0.001$), preparing meals (24% versus 9%, $P < 0.001$), paying bills (12% versus 5%, $P < 0.001$), managing one's own banking (23% versus 9%, $P < 0.001$), filling out pension forms (23% versus 9%, $P < 0.001$), reading newspapers (18% versus 8%, $P < 0.01$), reading books or magazine (25% versus

Table 1 Clinical characteristics of elderly patients with diabetes mellitus

	Age groups			Total
	65–69 (n = 349)	70–79 (n = 604)	≥ 80 (n = 182)	(n = 1135)
Age (years)	67.1 ± 1.4	73.0 ± 2.8	83.0 ± 3.1	73.3 ± 5.8
Gender (women, %)	43	58	68*	55
Body mass index (kg/m^2)	23.2 ± 3.3	23.1 ± 3.5	22.8 ± 3.2	23.1 ± 3.4
Duration of diabetes (year)	12.0 ± 8.5	13.9 ± 9.0	14.9 ± 9.0	16.5 ± 9.3
Treatment of diabetes (diet : OHA : insulin)	33 : 42 : 24	31 : 52 : 17	28 : 58 : 14**	31 : 50 : 19
HbA1c (%)	7.2 ± 1.3	7.5 ± 1.5	7.4 ± 1.3	7.4 ± 1.4
Systolic BP (mmHg)	140 ± 18	140 ± 19	141 ± 19	140 ± 18
Diastolic BP (mmHg)	78 ± 10	75 ± 11	72 ± 11	76 ± 11
Hypertension (%)	48	55	61**	54
Total cholesterol (mg/dL)	205 ± 44	204 ± 36	201 ± 36	204 ± 38
Triglycerides (mg/dL)	127 ± 93	121 ± 63	118 ± 58	122 ± 73
HDL cholesterol (mg/dL)	54 ± 16	53 ± 15	52 ± 14	53 ± 15
Retinopathy (%; none : background : proliferative)	63 : 38 : 9	59 : 31 : 10	58 : 31 : 11	60 : 30 : 10
Nephropathy (%; no : microalubuminuria : persistent proteinuria)	63 : 18 : 20	55 : 25 : 20	50 : 25 : 25*	57 : 23 : 21
Neuropathy (%)	27	46	50*	44
Stroke (%)	13	16	17	15
Ischemic heart disease (%)	12	15	16	14
Peripheral vascular disease (%)	3	5	5	5
Low well-being (score ≤ 7%)	16	15	25*	17
Mini-mental state examination (score ≤ 23%)	15	25	41***	25
Visual impairment (≤ 0.1%)	11	19	26***	18

*P < 0.05, **P < 0.01, ***P < 0.001 *versus* the younger group (65–69 year).
OHA, oral hypoglycemic agents.

13%, P < 0.001) and being interested in health topics (10% versus 4%, P < 0.001)(Fig. 1). The prevalence of disabilities on tasks for social role, except the conversation with young people (19% versus 15%, not significant), was significantly higher in the oldest group than in the youngest group: visiting friends (36% versus 20%, P < 0.001), being called on for advice (24% versus 11%, P < 0.001) and visiting sick people (21% versus 7%, P < 0.001). The prevalence of disability on at least one item of the TMIG Index of Competence in the diabetic population was about 45%. Disability on at least one item of the TMIG Index of Competence was more prevalent in the oldest group than the youngest group (63% versus 40%, P < 0.001).

Using multiple logistic regression analyses, we examined the relationship between functional disabilities and the presence of diabetic complication after adjustment for age, gender, duration of diabetes, BMI, HbA1c, insulin treatment, morale scale, MMSE and other complications. The inability to use public transportation, to prepare meals, and to pay bills were significantly associated with the presence of retinopathy (OR 2.6 [1.5–4.6], P < 0.001, OR 2.4 [1.3–4.4], P < 0.01 and OR 2.7 [1.2–5.9], P < 0.05, respectively) and stroke (OR 2.5 [1.4–4.5], P < 0.01, OR 2.2 [1.2–3.9], P < 0.05 and OR 2.3 [1.1–4.8], P < 0.05, respectively). The presence of retinopathy led to difficulties in shopping for daily necessities (OR 3.0 [1.4–6.2], P < 0.01), handling own banking (OR 3.0 [1.7–5.2], P < 0.001), filling out pension forms (OR 1.9 [1.1–3.3], P < 0.05) and reading books or magazines (OR 2.0 [1.3–3.2], P < 0.01). The presence of neuropathy also affected the ability to use public transportation (OR 2.1 [1.2–3.7], P < 0.01) and to visit sick friends (OR 2.0 [1.1–3.7], P < 0.05). The presence of PVD was significantly associated with the inability to prepare meals (OR 3.2 [1.2–8.7], P < 0.05). Unexpectedly, the ability to initiate conversation with young people was preserved in diabetic patients with IHD (OR 0.32 [0.15–0.66], P < 0.01).

Of the diabetic patients, only 26% had no vascular complications. Of the remainder, 25% had one, 24% had two, 17% had three and 9% had four to six complications. The large number (≥ 4) of vascular complications was associated with functional disabilities except the inabilities to be interested in new stories or programs dealing with health, to being called on for advice, and to initiate conversation with young people (Fig. 2).

Disability on at least one item of the TMIG Index of Competence was more prevalent in the insulin-treated group than in the diet-treated group (61% versus 41%,

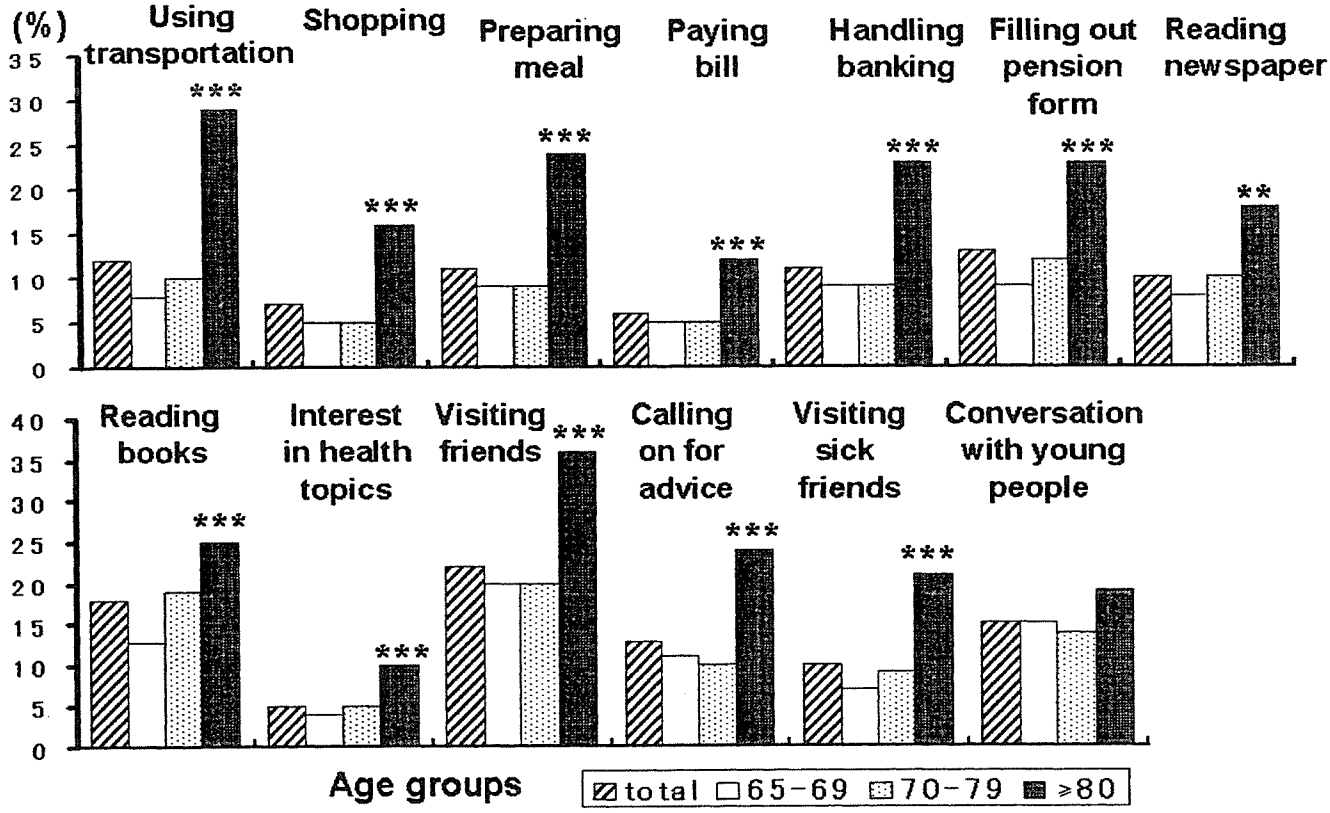

Figure 1 The relationship between aging and functional disabilities in elderly patients with diabetes mellitus (**$P < 0.01$, ***$P < 0.001$ *versus* the youngest group [65–69 years old]; $n = 1135$).

$P < 0.001$) or the group treated with *oral* hypoglycemic agents (61% versus 41%, $P < 0.001$). After adjustment for age, gender, duration of diabetes, BMI, HbA1c, microangiopathy, macroangiopathy, morale scale and MMSE, insulin treatment significantly increased the risk of disability in the use of public transportation (OR 2.5 [1.2–5.1], $P < 0.05$), shopping (OR 6.0 [2.2–16.7], $P < 0.001$), preparing meals (OR 3.1 [1.5–6.2], $P < 0.01$), paying bills (OR 3.4 [1.3–9.4], $P < 0.05$), handling banking (OR 2.4 [1.1–4.9], $P < 0.05$), filling out pension forms (OR 2.6 [1.3–5.2], $P < 0.01$) and visiting sick friends (OR 2.4 [1.1–5.3], $P < 0.05$) as compared to diet therapy (Fig. 3). Neither the times nor doses of insulin were associated with the disabilities in the insulin-treated patients.

Self-reported frequency of hypoglycemia was significantly associated with the disabilities in using public transportation, shopping, filling out pension forms, reading newspapers, and being called on for advice in univariate analysis. However, after controlling for the 10 variables (age, gender, duration of diabetes, BMI, HbA1c, microangiopathy, macroangiopathy, morale scale, MMSE, and insulin treatment) in multivariate analysis, only the association between increased frequency of hypoglycemia (at least once a month) and the disabilities in reading newspapers (OR 4.0 [1.0–10.2], $P < 0.05$) or being called on for advice (OR 4.0 [1.1–14.4], $P < 0.05$) persisted.

The effects of well-being and cognitive function on functional disabilities were examined in 973 elderly patients with diabetes mellitus using multiple logistic regression analyses (Table 2). Low well-being (defined as the morale score ≤ 7) was significantly associated with inability to do almost all the tasks of the TMIG Index of Competence after controlling for the other 9 covariables. The ORs of the disabilities to conduct the tasks of the social role (visiting friends or sick friends, being called on for advice and conversation with young people) for the low morale group compared to the high morale group (≥ 11) were relatively high and ranged from 2.3 to 4.6. After adjustment for the other 9 covariables, cognitive impairment, defined as the MMSE score ≤ 23 was independently associated with inability to do the tasks of the instrumental ADL as well as the intellectual activity (Table 3).

Visual acuity was assessed in 797 diabetic patients. According to the corrected visual acuities in the worst eye, we divided the patients into three groups: normal (≥ 0.7), moderate impairment (0.2–0.6), and severe impairment groups (≤ 0.1). Severe visual impairment was associated with inability to do all the tasks in the TMIG Index of Competence after adjustment for age,

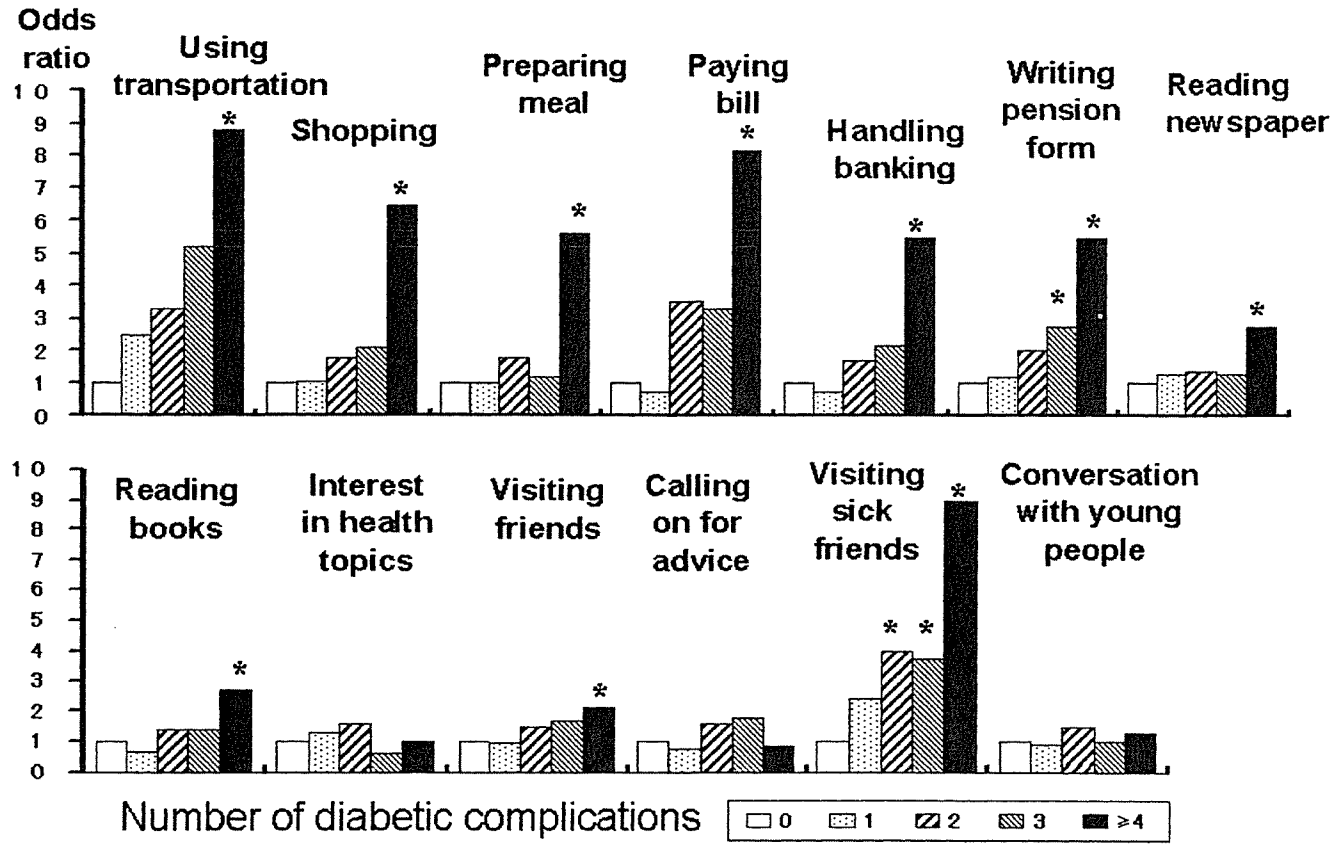

Figure 2 The relationship between the number of complications and functional disabilities in elderly patients with diabetes mellitus. (*$P < 0.05$ *versus* diabetic patients without any complications. Odds ratios were calculated with multiple logistic regression analysis after adjustment for age, gender, duration of diabetes, body mass index, HbA1c, morale scale, Folsteine's mini-mental state examination and insulin treatment; $n = 774$.)

Table 2 Odds ratios (OR) of disabilities according to well-being (morale) in diabetic patients ($n = 973$)

	Morale		
	≥ 11	8–10	≤ 7
Using public transportation	1	2.2 (1.3–3.6)**	1.6 (0.91–2.7)
Shopping	1	1.8 (0.32–3.5)	1.7 (0.87–3.2)
Preparing meals	1	2.2 (1.3–2.3)**	2.0 (1.2–3.5)*
Paying bills	1	1.8 (0.86–3.8)	2.4 (1.4–5.4)**
Handling banking	1	1.6 (0.92–2.7)	2.4 (1.4–3.9)***
Filling out pension forms	1	2.4 (1.5–4.1)***	2.9 (1.8–4.8)***
Reading newspapers	1	2.2 (1.3–3.8)**	2.5 (1.5–4.2)***
Reading books	1	2.8 (1.8–4.3)***	2.6 (1.7–4.1)***
Interest in health topics	1	3.5 (1.8–6.7)***	1.7 (0.73–3.8)
Visiting friends	1	2.3 (1.5–3.4)***	2.3 (1.5–3.5)***
Being called on for advice	1	3.0 (1.8–4.8)***	3.2 (2.0–5.3)***
Visiting sick friends	1	2.0 (1.1–3.5)*	3.6 (2.1–6.0)***
Conversation with young people	1	4.4 (2.8–6.9)***	4.6 (2.9–7.2)***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
ORs were calculated using multiple logistic regression analysis after adjustment for age, gender, duration of diabetes, body mass index, HbA1c, insulin treatment, microangiopathy, macroangiopathy and mini-mental state examination.

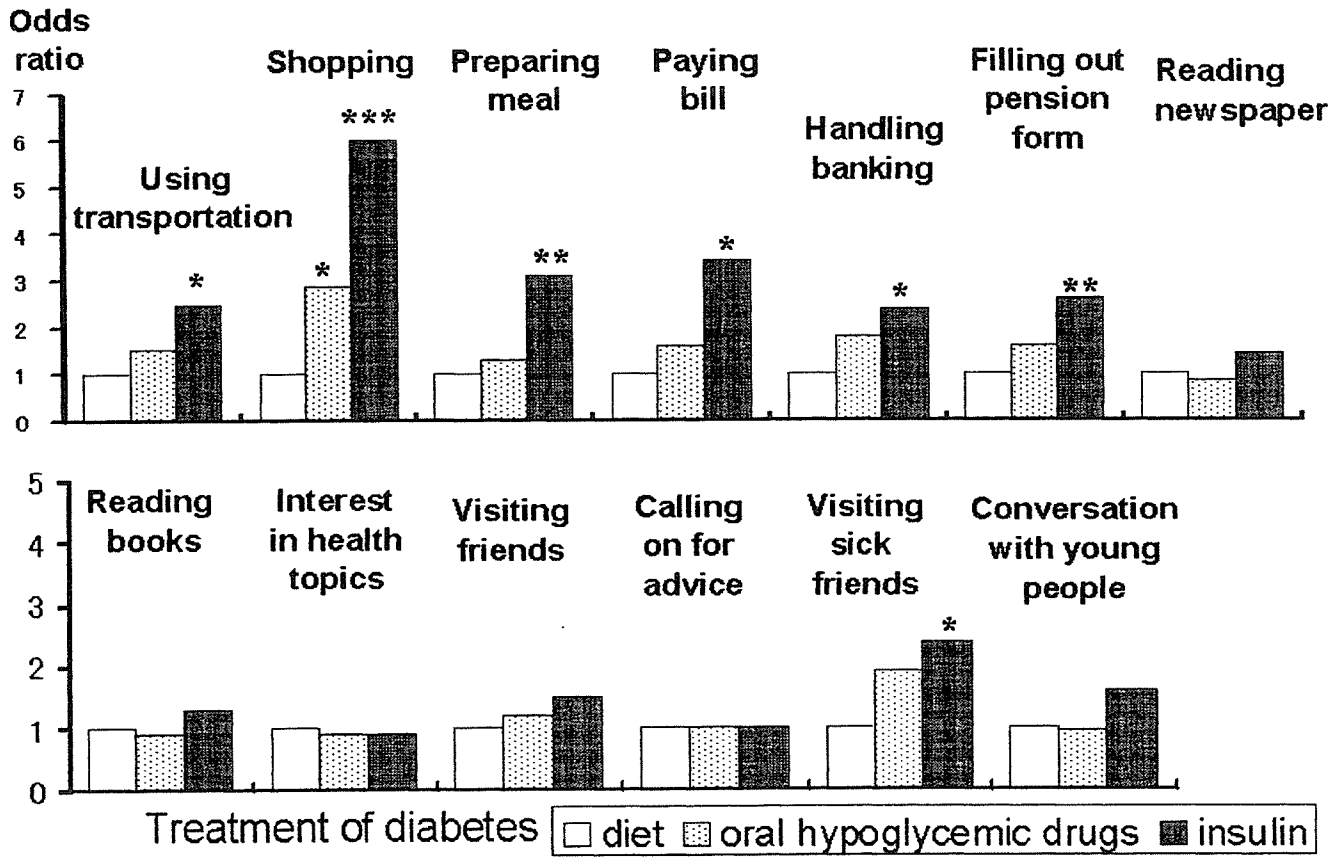

Figure 3 The relationship between treatment of diabetes and functional disabilities in elderly patients with diabetes. (Odds ratios were calculated with multiple logistic regression analysis after adjustment for age, gender, duration of diabetes, body mass index, HbA1c, microangiopathy, macroangiopathy, morale scale, and Folsteine's mini-mental state examination; $n = 973$.)

Table 3 Odds ratios (OR) of disabilities according to the cognition (mini-mental state examination) in diabetic patients ($n = 973$)

	Mini-menal state examination		
	≥ 27	24–26	≤ 23
Using public transportation	1	1.4 (0.81–2.3)	2.6 (1.5–4.4)***
Shopping	1	1.3 (0.69–2.6)	2.2 (1.1–4.2)*
Preparing meals	1	1.3 (0.76–2.2)	2.9 (1.7–5.0)***
Paying bills	1	0.96 (0.46–2.0)	1.8 (0.89–3.6)
Handling banking	1	1.2 (0.72–2.1)	3.6 (2.2–6.0)***
Filling out pension forms	1	1.4 (0.85–2.4)	3.6 (2.1–5.9)***
Reading newspapers	1	2.2 (1.3–3.8)**	3.4 (1.9–5.9)***
Reading books	1	1.8 (1.2–2.8)**	2.9 (1.9–4.6)***
Interest in health topics	1	0.48 (0.20–1.2)	2.4 (1.2–4.7)*
Visiting friends	1	1.1 (0.73–1.6)	1.5 (0.97–2.3)
Being called on for advice	1	1.4 (0.81–2.3)	3.9 (2.4–6.4)***
Visiting sick friends	1	1.4 (0.79–2.4)	2.0 (1.1–3.5)*
Conversation with young people	1	1.2 (0.80–1.9)	1.3 (0.76–2.1)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
ORs were calculated using multiple logistic regression analysis after adjustment for age, gender, duration of diabetes, body mass index, HbA1c, insulin treatment, microangiopathy, macroangiopathy and morale scale.

Table 4 Odds ratios (ORs) of disabilities according to visual acuity in diabetic patients (n = 797)

	Visual acuity		
	≥ 0.7	0.2–0.6	≤ 0.1
Using public transportation	1	2.4 (1.3–4.4)**	4.4 (2.3–8.3)***
Shopping	1	3.7 (1.4–9.7)**	7.1 (2.7–19.0)***
Preparing meals	1	1.3 (0.72–2.3)	3.2 (1.7–6.0)***
Paying bills	1	1.9 (0.72–4.9)	5.8 (2.2–14.8)***
Handling banking	1	2.9 (1.5–5.4)***	6.5 (2.2–6.0)***
Filling out pension forms	1	2.7 (1.4–5.0)**	6.0 (3.1–11.6)***
Reading newspapers	1	1.7 (0.9–3.3)	4.0 (2.1–7.9)***
Reading books	1	1.9 (1.1–3.0)*	3.6 (2.1–6.1)***
Interest in health topics	1	1.5 (0.67–3.4)	3.0 (1.2–7.3)*
Visiting friends	1	1.5 (0.99–2.2)	2.4 (1.4–3.8)***
Being called on for advice	1	1.5 (0.89–2.7)	2.9 (1.6–5.3)***
Visiting sick friends	1	1.7 (0.91–3.2)	2.3 (1.1–4.5)*
Conversation with young people	1	1.6 (1.01–2.6)*	1.7 (0.95–3.0)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
ORs were calculated using multiple logistic regression analysis after adjustment for age, gender, duration of diabetes, body mass index, HbA1c, insulin treatment, microangiopathy, macroangiopathy, morale scale, and mini-mental state examination.

gender, duration of diabetes, BMI, HbA1c, microangiopathy, macroangiopathy, MMSE, and the morale scale (Table 3). The moderate visual impairment group was unable to perform the tasks of using transportation, shopping, handling banking, filling out pension forms, reading books or magazines or conversing with young people.

Discussion

In this study, we have shown that the prevalence of functional disabilities in 1135 elderly patients with diabetes mellitus aged over 65 years in 10 representative institutions in Japan ranged from 5% in getting interested in healthy topics to 22% in visiting friends. The prevalence of disabilities in the diabetic patients are slightly lower or comparable to those of disabilities in 7735 elderly residents living in an urban Japanese community (using public transportation, 12% versus 14%; shopping, 7% versus 11%; preparing meals, 11% versus 16%; handling banking, 11% versus 14%).[12] In the present study, the prevalence of disability on at least one item of the TMIG Index of Competence in the diabetic population was about 45%. However, Gregg *et al.* reported that 63% of older diabetic women have difficulty in performing daily physical tasks such as walking up or down 10 steps, doing housework, shopping and cooking meals.[6] The Assets and Health Dynamics among the Oldest Old (AHEAD) study showed that 72% of diabetic people living in the community in the United State (US) had at least one IADL/ADL disability as compared to 58% of non-diabetic people.[14] The lower prevalence of disabilities in Japan than in US could be explained by differences in the prevalence and severity of diabetic complications or the method of assessment of functional disabilities. The higher prevalence of obesity, arthritis, visual impairment and heart disease are likely to contribute to relatively higher prevalence of disabilities in western diabetic patients.[6,13,14] For instance, the prevalence (32% to 43%) of IHD in US elderly diabetic populations was twice or three times as many as that of the present study (14%).[6,14]

Alternatively, the relatively well-controlled metabolic status of lipid profile, blood pressure, and glucose in outpatients of university hospitals or professional centers, might have favorable effects on disabilities in our study because of a low prevalence of severe diabetic complications. About half of the elderly patients in our study had two or more vascular complications, indicating that our study population had more complications than the other study (20%).[13] However, the result would not have lead to the increase in disabilities in the present study because the greater number of complications may be due to the inclusion of complications at an earlier stage (microalbuminuria and asymptomatic neuropathy).

The disabilities increased with advancing age and the prevalence of disabilities of diabetic patients aged over 80 years was about twice to three times those of those aged 65–69 years, suggesting increased need for help in those aged over 80 years.

The presence of diabetic complications affected functional disabilities in the elderly even after controlling for gender, duration of diabetes, BMI, HbA1c, insulin treatment, morale scale and MMSE. Retinopathy affected instrumental ADL and intellectual activity, while stroke impaired the abilities regarding social roles (visiting sick friends and conversation with young people) as well as

instrumental ADL. Nephropathy did not affect disabilities in the patients possibly be due to the exclusion of patients with chronic renal failure or those who were receiving hemodialysis. These results agree with the previous reports showing that retinopathy, neuropathy and stroke were independent determinants of the TMIG Index of Competence.[6,8] In this study, the greater number of complications also disturbed the functional abilities of elderly patients with diabetes mellitus.

Interestingly, insulin-treated patients had more functional disabilities on the instrumental ADL than those who treated with diet therapy alone after adjustment for age, gender, duration of diabetes, HbA1c, micro- and macrovascular complications, morale scale and MMSE. The finding is consistent with the data on the relationship between insulin treatment and impaired physical function in type 2 diabetic patients.[15,16] Although the cause of the association between insulin treatment and functional disability is unknown, psychological burden or worry other than low morale might have led to lower functional capacity in diabetic patients.

Functional disabilities in diabetic patients were associated with low well-being as assessed with the PGC morale scale after adjustment for age, gender, duration of diabetes, HbA1c, micro- and macrovascular complications and MMSE. The result is consistent with previous reports on the relationship between low morale and low TMIG Index of Competence or between depression and physical function.[8,15] In the present study, moderately (morale score; 8–10) or severely (morale score ≤ 7) reduced well-being was associated with almost all disabilities on social role, intellectual activity and instrumental ADL.

We previously reported that cognitive function in elderly patients with diabetes was more impaired compared with non-diabetic controls and that cognitive impairment was associated with age, poor glycemic control and the presence of cerebral infarction on brain MR imaging.[9] In the present study, cognitive impairment (MMSE score ≤ 23), was independently associated with the difficulties in performing tasks of the instrumental ADL as well as intellectual activity in the TMIG Index of Competence. This is in agreement with the other report showing that a low MMSE score was also significantly associated with reduced ADL and poorer ability in diabetes self-care in elderly subjects with type 2 diabetes mellitus.[17] Nourhashemi *et al.* also reported that cognitive impairment as assessed by the Pfeiffer test was associated with disabilities on the instrumental ADL in community-dwelling women aged over 75 years.[18] These results suggest that the preservation of cognitive and psychological functions is very important for the maintenance of functional capacity in elderly patients with diabetes mellitus.

In this study, severe visual impairment was associated with all the disabilities on the instrumental ADL, intellectual activity and social role. Moderate visual impairment was also associated with difficulties in performing the tasks of using transportation, shopping, handling banking, filling out pension forms, reading books or magazines and conversing with young people. These results are in agreement with the other report showing that visual acuity was related to the physical function scale of SF-36 scale score in diabetic patients.[19] Although the main cause of visual impairment is unknown in this study, the four most prevalent age-related ocular diseases (cataract, macular degeneration, open-angle glaucoma and diabetic retinopathy) would lead to visual impairment in elderly diabetic patients.[20] Rudberg *et al.* reported that visual impairment by itself is an independent risk factor for future four-year disabilities in basic ADL in the Longitudinal Study of Aging.[21] Ophthalmic evaluation and treatment at an earlier stage may be of great importance in the maintenance of functional activities even in elderly patients with diabetes mellitus. These results also suggest that standard clinical visual assessment as well as the information provided by functioning and well-being measures is necessary in comprehensive geriatric assessment of elderly people with diabetes mellitus.

The strength of our study was to have assessed simultaneously physical, visual, psychological and cognitive functioning of a large multicentered sample of elderly diabetic patients and to have found independent associations between functional disabilities and low morale, low MMSE and low visual acuity in diabetic patients.

There are some limitations to the present study. First, since this study is cross-sectional, the cause–effect relationship between low functional disability and reduced well-being or cognitive function remains unknown. The impairment of psychological and cognitive function might directly cause functional disability and decline. Wang *et al.* reported that depression was associated with increased functional decline in non-demented community-dwelling elderly people.[22] We have recently found that low well-being was an independent predictor for stroke in elderly patients with diabetes that would lead to functional disabilities.[23] On the other hand, functional disabilities might cause low well-being and cognitive impairment. To clarify this issue, further prospective intervention studies are necessary. Second, our study was not a population-based, but multicenter study of 10 representative professional hospitals in Japan. Selection bias might have affected some favorable results on metabolic controls, complications and disabilities. Third, the other factors that we did not assess may have affected functional activities in this study. Disease other than diabetic complications,[15] poor nutritional status,[16] lack of social support and social networks and poor home environment may be important factors in affecting functional disabilities in the elderly.[8,24]

In conclusion, older age, insulin treatment, low well-being, cognitive impairment and visual impairment were independently associated with functional disabilities of elderly patients with diabetes mellitus. At present, it is unknown whether psychological intervention and rehabilitation of physical, cognitive and visual impairment prevent functional decline or not. However, further growing understanding of underlying processes of functional disabilities could provide a basis to design effective strategies to delay functional decline in elderly patients with diabetes mellitus.

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Increased Risk for Cardiovascular Outcomes and Effect of Cholesterol-Lowering Pravastatin Therapy in Patients with Diabetes Mellitus in the Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE)

Toshitsugu Ishikawa, MD, PhD,[1] Hideki Ito, MD, PhD,[2] Yasuyoshi Ouchi, MD, PhD,[3] Yasuo Ohashi, PhD,[4] Yasushi Saito, MD, PhD,[5] Haruo Nakamura, MD, PhD,[6] and Hajime Orimo, MD, PhD,[7] for the PATE Investigators*

[1]Wellness Center, Sony Corporation, Tokyo, Japan; [2]Tokyo Metropolitan Tama Geriatric Hospital, Tokyo, Japan; [3]Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; [4]Department of Biostatistics/ Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan; [5]Department of Clinical Cell Biology, Graduate School of Medicine, Chiba University, Chiba, Japan; [6]Mitsukoshi Health and Welfare Foundation, Tokyo, Japan; and [7]Health Science University, Yamanashi, Japan

ABSTRACT

Background: The Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE) was the first large-scale, prospective clinical trial to show that cholesterol-lowering therapy with pravastatin is effective in reducing the risk for cardiovascular events (CVEs) in elderly (aged ≥60 years) patients with hypercholesterolemia. PATE also included a subgroup of patients with diabetes mellitus (DM).

Objective: The aim of this post hoc analysis was to assess the effects of long-term pravastatin therapy on cardiovascular outcomes in the subgroup of patients with DM compared with a subgroup without it.

Methods: PATE was conducted at 50 hospitals, universities, and clinics across Japan. Patients were randomly allocated to 1 of 2 treatment groups: low-dose pravastatin (5 mg PO QD; L group) or standard-dose pravastatin (in Japan, 10 mg PO QD; S group). Treatment was given for 3 to 5 years. Serum cholesterol levels were measured and the prevalence of CVEs was determined. The primary end point of the study was the S:L risk ratio for fatal or nonfatal CVEs. The secondary end point was the effect of diabetic patients' glycemic control on CVEs.

Results: A total of 665 patients (527 women, 138 men; mean [SD] age, 72.8 [5.7] years) were followed up for a mean of 3.9 years (range, 3–5 years). Among these, 199 patients had DM; 104 patients with DM were allocated to the L group and

*The PATE Investigators are listed in **Appendix I**.

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95 to the S group. Four hundred sixty-six patients did not have DM (L group, 230 patients; S group, 236 patients). Overall, between 3 months and 3 years after the initiation of treatment, patients in the L group (mean dose, 4.5 mg/d) experienced reductions from baseline total cholesterol level of 11% to 13%. Those in the S group (mean dose, 8.3 mg/d) experienced reductions from baseline of 15% to 17%. Decreases in low-density lipoprotein cholesterol (LDL-C) levels were 17% to 20% and 23% to 26% in the L and S groups, respectively. Statistically similar reductions were noted between patients with DM and those without it in response to either dose. The DM subgroup experienced 32 CVEs (L group, 17; S group, 15) compared with 39 CVEs (L group, 25; S group, 14) in the subgroup without DM. The S:L CVE risk ratio (primary end point) was 0.94 (95% CI, 0.46–1.92) in patients with DM and 0.54 (95% CI, 0.28–1.05) in those without DM; the differences between the treatment groups were not statistically significant. The risk for CVEs in patients with DM whose glycosylated hemoglobin concentrations were <8.0% and ≥8.0% were, respectively, 1.87-fold (95% CI, 1.09–3.20; $P = 0.02$) and 3.79-fold (95% CI, 1.92–7.48; $P < 0.01$) higher than that in patients without DM.

Conclusions: In this post hoc analysis of the effects of long-term cholesterol-lowering therapy (low- and standard-dose pravastatin) on cardiovascular outcomes in elderly patients with DM, dose had no effect on the risk for CVEs in these patients as it did in those without DM. Poorer glycemic control in patients with DM was related to a higher risk for CVEs. The lack of pravastatin efficacy found in the subgroup with DM may have been attributable to the small differences in LDL-C levels found between the 2 treatment groups and/or the small sample size of the study. (*Curr Ther Res Clin Exp.* 2005;66:48–65)

Key words: PATE study, elderly patients, pravastatin, hyperlipidemia, diabetes mellitus, prospective interventional trial.

INTRODUCTION

The Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE)[1] was the first large-scale, prospective clinical trial specifically designed to investigate the effects of lowering serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) on the risk for cardiovascular events (CVEs) in elderly patients with hypercholesterolemia. Based on a MEDLINE search (key terms: *hypercholesterolemia, intervention*, and *elderly people*; years, 1980–2000), PATE was the first such study.

Briefly, the study included male and female Japanese patients aged ≥60 years with and without cardiovascular disease (CVD) and with hypercholesterolemia. Patients were randomly allocated to 1 of 2 treatment groups: low-dose pravastatin (5 mg PO QD; L group) or standard-dose pravastatin (in Japan, 10 mg PO QD; S group). Treatment was given for 3 to 5 years. The primary end point of PATE was the prevalence of CVEs, including ischemic heart disease, cerebrovascular disease, peripheral vascular disorder, and sudden cardiac death.

Because all of the patients in the study were at risk for CVEs due to their age and TC levels, no placebo group was included. The hypothesis of the study was that pravastatin would lower patients' TC and LDL-C levels. Because elderly patients commonly have reduced drug tolerance and their physicians often prescribe lower drug doses compared with younger patients, the rationale behind the study design was assessment of the effects of low- versus standard-dose therapy on clinical outcome.

A total of 665 patients were enrolled (527 women, 138 men; mean [SD] age, 72.8 [5.7] years; mean [SD] serum TC level, 253 [15] mg/dL; mean [SD] serum LDL-C level, 165 [24] mg/dL; L group, 334 patients; S group, 331 patients). Mean follow-up was 3.9 years. The mean pravastatin doses in the L and S groups were 4.5 and 8.3 mg/d, respectively.

Overall, between 3 months and 3 years after the initiation of treatment, the mean (SD) serum TC levels decreased 11% to 13% (from 253 [15] to 218 [28] mg/dL) in the L group and 15% to 17% (from 253 [15] to 211 [27] mg/dL) in the S group (both, $P < 0.01$). In the same period, the mean (SD) LDL-C levels decreased 17% to 20% (from 164 [23] to 131 [27] mg/dL) in the L group and 23% to 26% (from 166 [25] to 127 [27] mg/dL) in the S group (both, $P < 0.01$). Forty-two CVEs occurred in the L group and 29 in the S group; the difference was statistically significant ($P = 0.046$).

In addition to cholesterol lowering in reducing cardiovascular risk, evidence shows that diabetes mellitus (DM) may be associated with a markedly increased risk for CVEs,[2–6] and it is widely recognized that established risk factors for CVEs (eg, dyslipidemia, hypertension, obesity) are common in patients with DM.[7] Diabetic dyslipidemia in particular appears to be strongly linked to CVD.[8] Impaired glucose tolerance—an independent risk factor for CVD and an intermediate stage in the pathogenesis of type 2 DM[9,10]—has been associated with the insulin resistance syndrome, which includes hypertension, a low high-density lipoprotein cholesterol (HDL-C) level, and an elevated serum triglyceride (TG) level.[11,12] An elevated TG level has been shown to decrease LDL-C particle size[13] (which, in turn, has been shown to increase the atherogenicity of LDL-C[14,15]) and to increase platelet release of plasminogen activator inhibitor 1[16] (which has been shown to contribute to enhanced thrombosis[17]). Thus, it is of considerable interest to ascertain the effects of lowering TC and LDL-C on the occurrence of macrovascular abnormalities in DM.

In a subanalysis[18] of 586 patients aged 21 to 75 years with DM and impaired glucose tolerance included in the Cholesterol and Recurrent Events (CARE) trial,[19] pravastatin therapy was associated with a lower prevalence of recurrent CVEs after myocardial infarction (MI) in this population compared with placebo ($P = 0.05$). The Scandinavian Simvastatin Survival Study (4S)[20] showed a similarly reduced risk in patients with elevated fasting plasma glucose levels or DM after cholesterol-lowering therapy in the setting of secondary prevention compared with placebo ($P < 0.01$).[21] The Heart Protection Study[22] also showed a decreased prevalence of CVEs in patients with DM with and without a history

of coronary heart disease or MI after cholesterol-lowering therapy with simvastatin compared with placebo ($P < 0.05$).

PATE included 199 patients with DM. The present report is a post hoc analysis of the effects of long-term (at least 3 years) pravastatin therapy on cardiovascular outcomes in this subgroup of patients compared with a subgroup without it.

PATIENTS AND METHODS

Study Design

The design and major findings of PATE have been reported elsewhere.[1] PATE was conducted at 50 hospitals, universities, and clinics across Japan. Patients were randomly allocated to the L or S group using an adaptive balancing method (biased coin minimization). History of CVD (MI, angina pectoris [AP], cerebrovascular disease, or arteriosclerosis obliterans), TC level, and study site were balancing factors.

Because the study was conducted before the International Conference on Harmonisation, Good Clinical Practice guidelines were established, verbal informed consent was obtained from eligible patients and was recorded in the medical records, and institutional review board approval of the study protocol was not sought at all of the study sites. However, the ethical aspects of the study were continually examined by the Monitoring Committee of the PATE Investigators. Although this trial was open-label, assessment of the end points was performed under investigator-blinded conditions.

Patients with familial or secondary hypercholesterolemia and/or malignant neoplasia were excluded from the study.

Patients who had confirmed DM or were receiving antidiabetic drugs at enrollment constituted the subgroup with DM; DM was diagnosed according to the criteria of the Japan Diabetes Society (**Appendix II**[23]). Primary care physicians' patient interviews and clinical examination of results were used to determine whether the patients met the criteria for inclusion in the DM subgroup. All other patients recruited in PATE constituted the subgroup without DM. Registration forms and records from follow-up indicated that patients with types 1 and 2 DM were included in the study, although all but 3 of these patients had type 2 DM.

All antihyperlipidemic drugs, except for the study agent, were to be discontinued at least 3 months before the study. Other concomitant drugs (eg, antidiabetic drugs) were allowed. Twelve-hour fasting serum lipid levels (TC, HDL-C, and TG), blood pressure, and body weight were measured at baseline (month 0); at 1, 3, and 6 months of pravastatin therapy; and every 6 months thereafter until study end. LDL-C levels were calculated using the Friedewald formula[24] unless the TG level was ≥400 mg/dL. *Hypertension* was defined as systolic/diastolic blood pressure ≥160/≥90 mm Hg[25] and/or the use of antihypertensive drugs. Routine physical examinations and laboratory analyses, including peripheral blood cell count, and biochemistry (including hepatic and renal func-

tion tests and creatine kinase activity), were conducted by primary care physicians at intervals of no more than 6 months.

During the follow-up period, physicians contacted patients by mail every 3 months to determine compliance with pravastatin therapy. If a patient had discontinued therapy, his or her physician was to record the discontinuation date and the reason(s) for it.

Primary care physicians provided general instructions for diet and exercise before the study. However, no further detailed instructions were given after the start of the study, and patients' diet and exercise habits were not investigated.

The primary end point of PATE was the S:L risk ratio for fatal or nonfatal CVEs, including cerebrovascular disease, ischemic heart disease, peripheral vascular disease, and sudden cardiac death. Cerebrovascular disease included cerebral infarction, cerebral hemorrhage, transient ischemic attack, and subarachnoid hemorrhage. Ischemic heart disease included MI, AP, congestive heart failure due to ischemic heart disease, and arrhythmia requiring pharmacologic treatment. A patient was diagnosed with AP if he or she had chest pain or discomfort with all of the following characteristics: (1) it included any level of the sternum; (2) it occurred during exertion or stress and usually lasted at least 30 seconds; (3) on most occasions it resolved within 10 minutes of stopping or decreasing the intensity of exertion; and (4) it was usually relieved within 2 to 5 minutes after receiving nitroglycerine, if nitroglycerine was used. All outcome variables were assessed based on the end point defined in the appendix of the original PATE study.[1]

The effect of the extent of glycemic control on the risk for CVEs (secondary end point) was assessed by measuring the prevalence of CVEs in patients with DM whose glycosylated hemoglobin (HbA_{1c}) concentration was ≥8.0% versus that in patients whose concentration was <8.0%. HbA_{1c} concentration 8.0% was selected as the cutoff point because it is generally considered indicative of uncontrolled DM.

Potential end points were reviewed and classified by the members of a Case/Event Evaluation Committee of the study investigators. Members of this committee were blinded to the identities and treatment assignments of the patients. In cases in which the first reporting by the physicians of a CVE was inadequate, additional information required to determine whether an event was a CVE (eg, electrocardiography, brain computed tomography, coronary angiography) was requested by the Case/Event Evaluation Committee.

Statistical Analysis

Analyses were performed on an intent-to-treat basis. Baseline characteristics were compared between groups using the Wilcoxon, Kruskal-Wallis, or chi-square test. Changes in serum lipid levels before and after the initiation of pravastatin therapy were assessed with the least squares means calculated using general linear models. Differences between patients with and without DM and between the 2 treatment groups were assessed using repeated-measures analysis of variance.

For the primary end point in patients with and without DM and overall, the Cox regression analysis was used to assess the effectiveness of standard-dose pravastatin compared with low-dose pravastatin adjusted for age, sex, DM, smoking history, hypertension, and history of CVD. Cardiovascular risk in patients with DM was also assessed using the Cox regression analysis adjusted for treatment group, age, sex, smoking history, hypertension, and history of CVD.

$P < 0.05$ (2-sided) was considered statistically significant. All statistical analyses were performed using SAS software version 6.12 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient Population

A total of 703 patients were enrolled in the original PATE.[1] After randomization, 38 patients were excluded for the following reasons: no attendance at hospital after registration (19 patients), withdrawal of informed consent (6), another cholesterol-lowering regimen in use at the start of pravastatin treatment (4), duplicate entry (3), active malignancy (3), familial hypercholesterolemia (2), and secondary hypercholesterolemia due to hypothyroidism (1). The remaining 665 patients (527 women, 138 men; mean [SD] age, 72.8 [5.7] years) were followed up (**Table I**). The L group contained 334 patients (104 with DM, 230 without it); the S group, 331 patients (95 with DM, 236 without it). The numbers of patients with and without DM were statistically similar between the 2 treatment groups.

No significant differences in age, HbA_{1c} concentration, or presence of cardiovascular risk factors (eg, hypertension, history of CVD, smoking) were found between the 2 treatment groups. Mean (SD) HbA_{1c} concentrations in the patients with DM were 6.9% (1.2%) (range, 4.8%–10.6%) in the L group and 6.9% (1.1%) (range, 5.1%–10.1%) in the S group. The percentages of patients with DM and a history of CVD were 26.9% (28/104) and 17.9% (17/95) in the L and S groups, respectively. The percentage of S-group female patients without DM was higher than those with DM ($P = 0.049$).

The clinical profile of the patients with DM (n = 199), including their concomitant drug regimens (eg, antihypertensive drugs, nitrites, antidiabetic drugs) is shown in **Table II**. Major DM complications present in these patients included diabetic nephropathy (L group, 1.9% [2/104]; S group, 2.1% [2/95]) and diabetic retinopathy (L group, 0; S group, 1.1% [1/95]). A total of 44.2% (46/104) of patients with DM in the L group and 45.1% (43/95) in the S group were receiving antihypertensive drugs. The numbers of patients receiving antihypertensive drugs were statistically similar between the L and S groups. The proportions of patients receiving hydrochlorothiazide were 1.9% (2/104) and 1.1% (1/95) in the L and S groups, respectively.

During the follow-up period, the mean pravastatin doses were 4.5 and 8.3 mg/d in the L and S groups, respectively. Patients who discontinued treatment were

Table I. Baseline demographic and clinical characteristics of patients in the Pravastatin Anti-atherosclerosis Trial in the Elderly.

Characteristic	Patients with DM		Patients Without DM		All Patients[1]	
	L Group (n = 104)	S Group (n = 95)	L Group (n = 230)	S Group (n = 236)	L Group (n = 334)	S Group (n = 331)
Demographic						
Age, mean (SD), y	72.5 (5.4)	72.5 (5.3)	72.6 (5.5)	73.2 (6.1)	72.6 (5.5)	73.0 (5.9)
Sex, no. (%)						
Female	76 (73.1)	73 (76.8)	178 (77.4)	200 (84.7)*	254 (76.0)	273 (82.5)
Male	28 (26.9)	22 (23.2)	52 (22.6)	36 (15.3)	80 (24.0)	58 (17.5)
Clinical						
BMI, mean (SD), kg/m^2	23.6 (3.1)	23.2 (2.9)	22.9 (3.2)	23.4 (3.3)	23.2 (3.2)	23.3 (3.2)
Lipid levels, mean (SD)						
TC, mg/dL	254 (16)	254 (15)	253 (15)	253 (16)	253 (15)	253 (15)
HDL-C, mg/dL	56 (15)	58 (15)	55 (16)	54 (14)	55 (15)	55 (15)
LDL-C, mg/dL	160 (24)	162 (25)	166 (23)	168 (25)	164 (23)	166 (25)
TG, mg/dL	161 (87)	147 (69)	149 (69)	155 (104)	153 (75)	152 (95)
HbA_{1c}, %	6.9 (1.2)	6.9 (1.1)	–	–	–	–
Risk factors						
HTN, no. (%)†	50 (48.1)	46 (48.4)	121 (52.6)	121 (51.3)	171 (51.2)	167 (50.5)
History of CVD, no. (%)	28 (26.9)	17 (17.9)	67 (29.1)	65 (27.5)	95 (28.4)	82 (24.8)
Smokers, no. (%)‡	12/104 (11.5)	6/95 (6.3)	21/226 (9.3)	18/234 (7.7)	33/330 (10.0)	24/329 (7.3)

DM = diabetes mellitus; L = low-dose pravastatin; S = standard-dose pravastatin; BMI = body mass index; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = glycosylated hemoglobin; HTN = hypertension; CVD = cardiovascular disease.

*$P < 0.05$ versus patients with DM.

†*Hypertension* was defined as systolic/diastolic blood pressure ≥160/≥90 mm Hg[25] and/or the use of antihypertensive drugs.

‡Data were unavailable in 12 patients.

Table II. Diabetes mellitus (DM) type, complications, and concomitant drug use in patients (no. [%]) in the Pravastatin Antiatherosclerosis Trial in the Elderly.*

Variable	L Group (n = 104)	S Group (n = 95)
DM type		
1	1 (1.0)	2 (2.1)
2	103 (99.0)	93 (97.9)
Complications		
Diabetic nephropathy	2 (1.9)	2 (2.1)
Diabetic retinopathy	0 (0.0)	1 (1.1)
Drug use		
Antihypertensive drugs		
CCB	34 (32.7)	36 (37.9)
ACEI	13 (12.5)	9 (9.5)
Beta-blocker	4 (3.8)	4 (4.2)
Hydrochlorothiazide	2 (1.9)	1 (1.1)
Alpha-blocker	1 (1.0)	5 (5.3)
Alpha- and beta-blocker	1 (1.0)	3 (3.2)
Sulfonylureas	45 (43.3)	35 (36.8)
Nitrites	4 (3.8)	1 (1.1)
Insulin	3 (2.9)	8 (8.4)

L = low-dose pravastatin; S = standard-dose pravastatin; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor.
*No significant between-group differences were found.

included in the calculation of the mean dose given in the S group (8.3 mg/d). The total discontinuation rate was 23.9% (L group, 21.3%; S group, 26.5%).

Total DM patients and total non-DM patients showed similar percent reductions in serum TC and LDL-C levels (**Figure 1A, B**). Furthermore, both DM and non-DM patients experienced similar reductions in TC and LDL-C in response to either low- or standard-dose pravastatin (**Figure 1C–F**). A significant difference ($P < 0.01$) between the L and S groups was seen in DM patients (**Figure 1C, D**) and non-DM patients (**Figure 1E, F**).

At the end of follow-up, in the L group of patients with DM, the mean (SD) serum TC level decreased from 254 (16) to 217 (27) mg/dL, and LDL-C from 160 (24) to 131 (26) mg/dL. In the S group, the mean (SD) TC level decreased from 254 (15) to 208 (28) mg/dL, and LDL-C from 162 (25) to 125 (25) mg/dL. LDL-C decreased to ≤100 mg/dL in 8.7% (9/104) of patients with DM receiving the low dose, and 13.7% (13/95) of patients with DM receiving the standard dose.

The subgroup with DM experienced 32 CVEs compared with 39 CVEs in the subgroup without DM. In the subgroup with DM, 17 CVEs occurred in patients receiving the low dose, and 15 CVEs in patients receiving the standard dose.

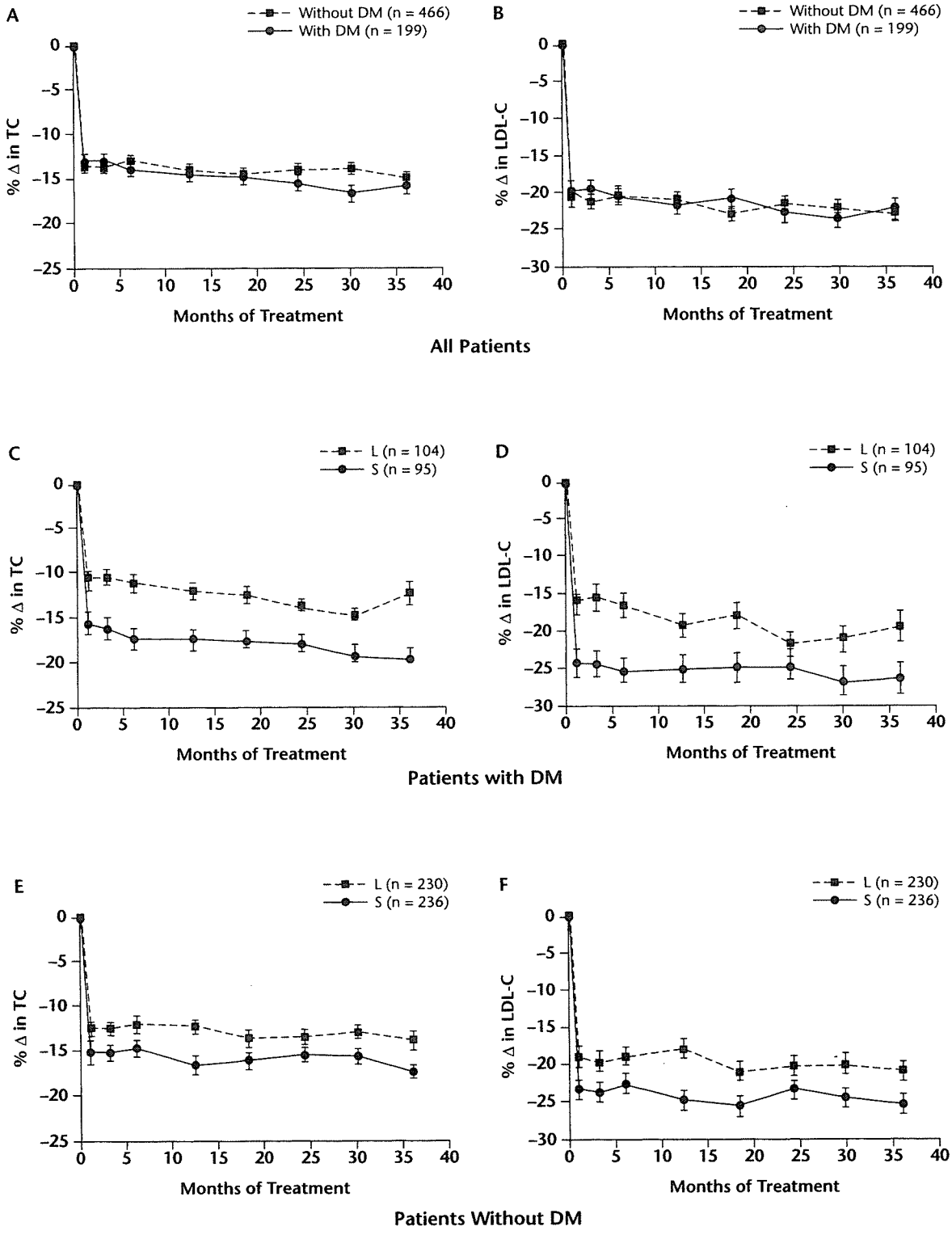

Figure 1. Least squares mean (SE) percentage changes in total cholesterol (TC) (A, C, E) and low-density lipoprotein cholesterol (LDL-C) (B, D, F) over time in patients in the Pravastatin Anti-atherosclerosis Trial in the Elderly.[1] DM = diabetes mellitus; L = low-dose pravastatin; S = standard-dose pravastatin. C–F, significant difference ($P < 0.01$) between the L and S groups.