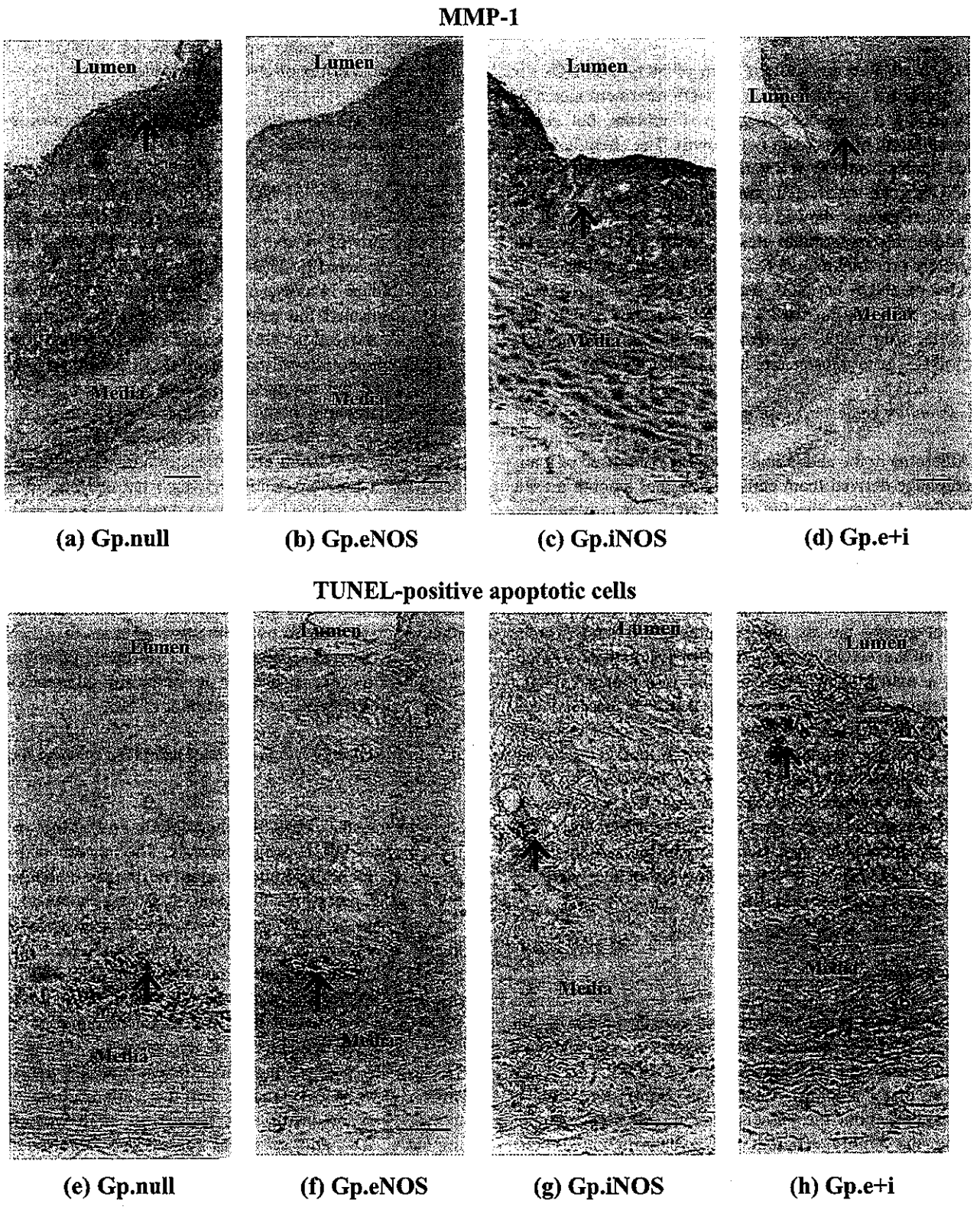

Fig. 6. Upper: expression of MMP-1-positive cells (arrow). (a) Gp null, Ad.null. (b) Gp eNOS, Ad.eNOS. (c) Gp iNOS, Ad.iNOS. (d) Gp e+i, Ad.eNOS plus Ad.iNOS. Strong expression of MMP-1 was observed in the lesions of Gps null, iNOS, and e+i. The expression was decreased in Gp eNOS. Original magnification, × 100. Lower: expression of TUNEL-positive apoptotic cells (arrow). (e) Gp null. (f) Gp eNOS. (g) Gp iNOS. (h) Gp e+i. Apoptotic cells were detected in Gps null, iNOS and e+i. However, apoptotic cells were rare in Gp eNOS. The scale bar represents 50 μm.

3.7. Nitrite and nitrate (NO_2^-/NO_3^-) and detection of aortic superoxide generation

Levels of NOx in medium (sum of NO_2^- and NO_3^-) in each group are shown in Table 1. iNOS treatment increased NOx in the regular control group of rabbits, but not in atherosclerotic rabbits (data not shown). The chemiluminescence signals from O_2^- production were greater in the aortae of iNOS gene-transfected groups, and the eNOS gene-transfected groups showed a slight decrease (Table 1). As an additional experiment described in Section 2.2, we separately prepared rabbits fed with a regular diet, and gene transfer of eNOS or iNOS was performed using dispatch catheter. NOx was increased, and O_2^- was not increased in the aortae from eNOS gene transfer rabbit as well as those from iNOS gene transfer rabbits (data not shown).

3.8. Immunocytochemical analysis

Atheroma in the abdominal aorta was composed of many macrophage-derived foam cells and intimal smooth muscle cells (Fig. 5). Gene transfer of Ad.eNOS not only reduced the area of atherosclerosis, but also decreased the area stained by the macrophage antibody and the areas positive for $ONOO^-$ established by nitrotyrosine staining (Fig. 5). The area stained by the smooth muscle cell actin was not different among the six groups, although it tended to be higher in the eNOS groups. MMP-1 (interstitial collagenase), a matrix metalloproteinase that initiates collagen degradation, was localized predominantly in macrophages. Although the difference did not reach the level of statistical significance, the expression of MMP-1 tended to be decreased in vessels of Gp eNOS and Gp heNOS (Fig. 6). A TUNEL-positive area was observed around a necrotic core in the atheroma as an apoptosis-susceptible area. The apoptosis-susceptible area seemed to be decreased in Gp eNOS and Gp heNOS; however, these differences were not statistically significant (Fig. 6).

4. Discussion

In the present study, in vivo gene transfer of eNOS, but not that of iNOS, resulted in a regression of advanced atherosclerosis and an improvement of EDR. This study has four major findings. First, NOS expression was increased throughout the vessels after transfection, demonstrating the highly efficient adenovirus-mediated gene transfer into severely atherosclerotic arteries. Second, adenovirus-mediated transfer of the eNOS gene alone restored EDR in atherosclerotic vessels. Third, eNOS gene transfer regressed atherosclerosis, and this effect appeared to have been due to a decrease of tissue lipids, although apoptosis or a decrease of extracellular matrix components may also have played a role. Finally, transfection with the iNOS gene failed to improve EDR and did not regress atherosclerosis. Further, simultaneous transfection of both the eNOS and iNOS genes also failed to improve EDR and did not regress atherosclerosis. In other words, transfection of iNOS blocked the beneficial effect of eNOS transfection.

4.1. Highly efficient adenovirus-mediated gene transfer in severe atherosclerosis

Gene transfers of NOS isoforms have been reported previously [9–12,23–27]. However, there have been only a few reports of in vivo gene transfer in advanced atherosclerotic vessels [9]. These studies used a high-cholesterol diet to induce atherosclerosis, resulting in patchy lesions that complicated the evaluation of gene transfer. In this study, we induced severe atherosclerosis by balloon injury and a high-cholesterol diet, resulting in severe atherosclerosis around the whole luminal area of vessels. The successful expression of the transgene (eNOS or iNOS) was confirmed by immunohistochemistry and Western blotting. We employed a 3-min perfusion at 6 atm. This choice was based on a previous study in which the efficacy of gene transfer was enhanced at a pressure greater than 4 atm, and in which no change in efficacy occurred between 2 and 40 min of perfusion [24]. Thahlil et al. [25] reported that the transduction rate is lower in medial smooth muscle cells than in the neointima or endothelium. Our data are almost identical to theirs. We used the same volumes of Ad.eNOS and Ad.iNOS, and separately used a 10-times higher titer of Ad.eNOS to evaluate whether or not the anti-atherosclerotic effect was dependent on the amount of NO.

4.2. Restoration of NO function of advanced atherosclerosis by Ad.eNOS

Gene transfer of eNOS remarkably improved the severely impaired EDR in atherosclerosis. The amount of transgene used in our experiment cannot be directly compared to that in the report by Ooboshi et al. [9]; however, the improvement of EDR by in vivo eNOS gene transfer in the present study is comparable with their report. In the present study, the animals receiving a high eNOS transfection (Gp heNOS) did not show any remarkable change in EDR or in the area of atherosclerosis compared to those receiving a smaller amount of the transgene (Gp eNOS). This finding suggest that the efficiency of the transgene might not be dose-dependent, and that a high dose of gene transfer may be insufficient to achieve a restoration of impaired EDR and complete regression. Regarding the mechanism of EDR improvement, we first hypothesized that regression of atherosclerosis could improve EDR, as the severity of atherosclerosis is inversely correlated with the impairment of EDR [15]. However, in the present study, the EDR improvement was much larger than that of the atherosclerosis regression. We speculated that EDR improvement occurs when NO bioavailability improves as a result of eNOS gene transfer, in turn related to the regression of

atherosclerosis. In fact, basal NO (as evaluated by tone-related basal NO release, NOx from vessels, and tissue cGMP concentration) was increased by eNOS gene transfer, but not by iNOS gene transfer. In the present study, the decrease level of O_2^- due to eNOS gene transfer also increased NO bioavailability.

4.3. The mechanisms of regression of atherosclerosis in response to eNOS

The pathological findings in the abdominal aortae of the present study were similar to previous findings in coronary arteries; i.e., in both cases the vessels were rich in macrophage-derived foam cells and lipids [15]. In the present study, eNOS gene transfer facilitated a significant regression of lesions, as well as a decrease in macrophages, indicating that the atheroma was stabilized. We previously established that there is a significant inverse relation between basal NO and the severity of atherosclerosis [13,15], and our present data suggest that this relation is involved in the NO release after eNOS gene transfer. Although previous studies have investigated the possibility of the regression of atherosclerosis by in vivo gene transfer [9,26–28], this might be the first demonstration of regression in a model of severe atherosclerosis induced by balloon injury and a high-cholesterol diet. The regression may be caused by the absorption of tissue lipid, while a cell decrease due to apoptosis or a decrease of the extracellular matrix such as collagen fibers may be a concern (Table 1 and Fig. 6). Absorption of tissue lipid can be caused by NO released from transferred eNOS, and we can speculate that HDL may be partially related to this absorption through increased NO release [29]. The apoptosis-suspected area by Tunnel staining tended to be small in Gp eNOS and Gp heNOS. Because $ONOO^-$ has cytotoxicity and the decreased level of O_2^- by eNOS gene transfer may contribute to a reduction in the substrate of $ONOO^-$, it could contribute to apoptosis. We cannot fully rule out the possibility that cell death occurred before our observation, because the effect of adenovirus gene transfer has been reported to peak at 3 days after transfection [27]. The role of apoptosis in regression should be elucidated further. Quian et al. [28] reported that monocyte recruitment occurred fairly quickly—i.e., within 24 h—after Ad.nNOS gene transfer. We speculate that a similar mechanism might occur by Ad.eNOS treatment for advanced atherosclerosis. We cannot fully rule out the possibility that other mechanism is responsible for regression, since our examination was made 7 days, rather than 24 h, after gene transfer. The tendency of a decrease in the MMP1-positive area supports the hypothesis that eNOS gene transfer stabilized the atheroma. The ratio of SMCs in atheroma did not differ significantly among the different groups of rabbits, although it tended to be relatively high in the Ad.eNOS transferred groups. We speculated that this occurs due to more decrease in macrophages in eNOS gene transfer group. Preliminarily, we did immunohistochemistry using anti-proliferating cellul nuclear antigen (PCNA), and TUNEL positive area looks like larger than anti-PCNA positive area in atheroma of each group on 7 days after gene transfer. We speculate the decrement in monocyte adhesion and the lipid in atheroma may be one of the possible mechanisms of regression, although other mechanisms may play a role. Further studies will be needed to establish the mechanism by which eNOS gene transfer regresses atherosclerosis.

4.4. Failure to improve impaired EDR and regression of severe atherosclerosis in response to Ad.iNOS, or Ad.eNOS plus iNOS

Neither gene transfer of iNOS nor that of eNOS plus iNOS improved EDR (Fig. 3). Transfection of empty vector with or without Ad.eNOS or Ad.iNOS did not affect EDR or the area of atherosclerosis compared to that of Gp eNOS, Gp iNOS, or Gp cont, indicating that the iNOS transgene not only impairs the improvement of EDR but also impairs the regression effect of eNOS. These data are somewhat contrary that iNOS is effective for improving vascular function, such as in the spastic arteries of various animal models [11,26,30]. As for the cause of the discrepant effects between previous and present studies, we speculate that the difference of enzyme activity of transferred gene between eNOS and iNOS, and the presence of intrinsic iNOS and O_2^- releasing enzymes in advanced atherosclerosis are important, although iNOS was transferred into iNOS-poor areas in previous studies [11,26,30]. In fact, the release of O_2^- was not increased, and that of NO was increased after iNOS gene transfer into normal aorta (3.5). The NO release from the Ad.eNOS-transfected atherosclerotic vessel was different from the Ad.iNOS-transfected vessel (Table 1). Both genes have the component of L-arginine (as substrate) binding site and BH4 (as cofactor) binding site. Ca^{2+}/calmodulin binding site is located in eNOS gene; however, it is already incorporated in iNOS gene. It is speculated that intracellular Ca^{2+} concentrations, even with transferred status, regulate NO release from eNOS and that iNOS is characterized by a greater specific activity, producing much larger quantities of NO in a calcium- and agonist-independent fashion [31]. eNOS releases O_2^- under conditions of depleted substrates or cofactors [32]. Large amount of transferred eNOS gene (Gp heNOS) may not be able to release NO by relative depletion of L-arginine or BH4. Intrinsic iNOS in atheroma is distributed in deep areas of atherosclerotic plaque (Fig. 2). These areas tend to be hypoxic with a relatively limited supply of arginine from the vasa vasorum or lumen [33,34]. The transferred iNOS was also distributed in all other components of blood vessels as well as in deep areas of the atherosclerosis. We suggest that iNOS releases O_2^- as well as NO, since iNOS is known to release O_2^- under conditions that deplete substrates, such as hypoxia, or that deplete arginine [35]. The report by Gunnett [12] may support our data. Macrophages or other inflammatory cells release O_2^- from NADPH oxidase or xanthine/xanthine

oxidase when stimulated by cytokines such as interferon γ, which also induce iNOS and co-localize in atheroma (data not shown). Nitrotyrosine, a marker of $ONOO^-$, was observed in the atherosclerotic regions, and its density was much greater in vessels transfected with iNOS and eNOS plus iNOS (Fig. 5). The response of O_2^- to a large amount of NO from transferred iNOS may have caused greater quantities of $ONOO^-$ and blocked the beneficial effect of NO from transferred eNOS. These differential effects between transgenes are interesting and important in gene therapy. As there are many O_2^- releasing enzymes such as NADPH oxidase and xanthine/xanthine oxidase as well as eNOS or iNOS, further studies like the experiment of iNOS gene transfer with or without antioxidant supplementation is necessary to elucidate the mechanisms.

4.5. Clinical significance of the present study

These findings may be relevant for improving blood flow and preventing thrombosis in advanced atherosclerotic arteries. The results of this study indicate that eNOS gene transfer should be clinically applied not only for prevention of atherogenesis, but also for the regression of advanced atherosclerosis. Because human atherosclerotic lesions, including intimal thickening, begin as early as childhood and by middle age are often quite prominent in the aorta and coronary arteries, hence regression is an important treatment tool. Regression and stabilization of atheroma is the main objective in the management of atherosclerotic lesions in humans. In the future, we expect that such clinical regression will be applicable for unstable angina or acute coronary syndrome. Although we must continue to work for a means of complete regression, the present results showed that eNOS gene transfer clearly improved the endothelial function and induced a regression of advanced atherosclerosis.

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Low Well-Being Is an Independent Predictor for Stroke in Elderly Patients with Diabetes Mellitus

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OBJECTIVES: To examine whether psychological factors are risk factors for the development of stroke in elderly diabetic patients.

DESIGN: Prospective cohort study.

SETTING: Outpatient clinic.

PARTICIPANTS: Three hundred seventy-six diabetic outpatients free of stroke; mean age 75.

METHODS: Well-being and diabetes-specific burden were assessed at baseline using the Philadelphia Geriatric Center morale scale and the Elderly Diabetes Burden Scale (EDBS), respectively. Symptomatic stroke was defined as a focal neurological deficit with rapid onset that persists for more than 24 hours, supported by brain computed tomography or magnetic resonance imaging.

RESULTS: During the 3-year follow-up period, 25 symptomatic strokes (24 ischemic strokes and 1 cerebral hemorrhage) occurred. Low scores on the morale scale (≤ 7) were significant predictors for stroke after adjustment for age; sex; body mass index; hemoglobin A_{1c} level; systolic blood pressure; serum levels of total cholesterol, triglycerides, and high-density lipoprotein cholesterol; smoking; and previous ischemic heart disease (IHD) (hazard ratio (HR) = 3.0, 95% confidence interval (CI) = 1.2–7.3, $P = .017$). The relationship between low morale scores and future stroke remained significant after adjusting for socioeconomic factors and microalbuminuria. Increased symptom burden and social burden, but not dietary restrictions, worry about diabetes mellitus (DM), treatment satisfaction, and burden by tablets or insulin of EDBS, were also significant predictors for stroke after adjustment for age, sex, duration of DM, previous IHD, and microalbuminuria (HR = 2.6, 95% CI = 1.1–6.5, $P = .039$).

CONCLUSION: Low well-being and symptom burden were predictors of stroke in elderly patients with diabetes mellitus (DM), although the causal relationship remains unknown. J Am Geriatr Soc 52:205–210, 2004.

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Key words: well-being; diabetes burden; stroke; diabetes mellitus; risk factors

Diabetic patients have a variety of psychological problems, such as depression, low well-being, loneliness, and emotional distress.[1–4] The psychological aspects of the diabetic population are assessed using scales of depression; subjective well-being, which includes positive and negative feelings about life experiences; and diabetes-specific burden, which is caused by diabetes-related symptoms, the effect of diabetes mellitus (DM) on social life, treatment of DM, fear of hypoglycemia, worry about DM, and treatment dissatisfaction.[1–3,5–7]

Diabetic complications, treatment of DM, comorbidity, and socioeconomic conditions affect the psychological state of people with DM. Depressive symptoms in elderly diabetic patients are associated with disabilities in activities of daily living (ADLs), visual impairment, urinary incontinence, presence of diabetic micro- and macrovascular complications or other chronic illnesses, lack of health service, and poorer well-being.[1,2] Reduced well-being in older diabetic people is reported to be associated with ADL disabilities, insulin treatment, dietary restrictions, high negative social support, and low satisfaction with economic status in elderly diabetic patients.[3,6,7] A previous cross-sectional study showed that diabetes-specific burden was associated with ADL disabilities, hyperglycemia, insulin treatment, low positive support, high negative social support, and low satisfaction with economic status.[6] Diabetes-specific burden and diabetes-related distress may affect blood glucose control and adherence to self-care behaviors.[4,7]

Although DM is frequently associated with atherosclerotic disease, conventional risk factors such as hyperglycemia, hypertension, and hyperlipidemia cannot fully explain the increased risk of stroke in diabetic patients.[8] It has been suggested that psychological factors, including depression,[9,10] low vitality,[11] low contentment (discontent),[11,12] and Type A behavior,[13] are independent risk factors for atherosclerotic disease in nondiabetic populations. Because older diabetic patients often have low well-being,

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depression, and diabetes-specific burden,[1–3,6] it was postulated that psychological factors such as low well-being or diabetes-specific burden might affect the risk for development of stroke. Therefore, this 3-year longitudinal study investigated whether low well-being or diabetes-specific burden is a predictor for the development of stroke in elderly diabetic patients. The study also examined whether the association between low well-being or diabetes-specific burden and the risk of stroke is independent of conventional risk factors.

METHODS

Three hundred seventy-six elderly (≥65) diabetic outpatients free of clinical stroke were recruited from 463 participants of The Study of Quality of Life in Elderly Diabetics in the Tokyo Metropolitan Geriatric Medical Center. Participants were consecutively registered at the diabetes clinic of the Department of Endocrinology in the Tokyo Metropolitan Geriatric Medical Center unless they had severe dementia or aphasia. They were asked to complete questionnaires about their quality of life and to participate in a prospective study on the relationship between several measures of quality of life (ADLs, cognitive function, well-being, diabetic burden, visual acuity, and socioeconomic aspects) and the subsequent prognosis, including mortality, morbidity of diabetic complications, and macrovascular disease. Five of these participants were excluded for one of the following reasons: chronic renal failure with a serum creatinine level greater than 2.0 mg/dL, other endocrine disease, and hormone replacement therapy. At baseline, 82 patients who had neurological deficits or a history of stroke were excluded from this study. Three hundred seventy-six elderly diabetic patients (124 men, 252 women) free of previous symptomatic stroke participated in this study. The participants had a shorter mean duration ± standard deviation (SD) of DM (13.7 ± 8.3 years vs 16.8 ± 9.5 years, $P<.01$) and higher mean ADL scores (11.3 ± 2.6 vs 9.9 ± 3.7, $P<.001$) than nonparticipants, although ages (75.2 ± 5.9 vs 75.5 ± 6.3) were similar in the two groups.

Psychological Assessment

At baseline, a professional interviewer (FF) interviewed the participants for about 30 to 60 minutes, and participants answered questionnaires about diabetes-specific and nonspecific quality of life, including the Philadelphia Geriatric Center (PGC) morale scale (Japanese version),[14] the Elderly Diabetes Burden Scale (EDBS),[5] an ADL scale (the Tokyo Metropolitan Institute of Gerontology Index of Competence), social support, economic status (annual income and satisfaction with economic status), and family members with whom they lived.

The PGC morale scale is used to assess subjective well-being of elderly people.[14] Morale refers to future-oriented optimism or pessimism regarding problems associated with living and aging. Different from depression, the concept of morale includes positive feeling of happiness, life satisfaction, and acceptance of aging, as well as negative affects or depressive symptoms. It consists of three components: agitation, attitude toward own aging, and loneliness and dissatisfaction with life.[14] Based on the lowest 20th percentile of the distribution of the PGC moral scale, low morale was defined as a score of seven and under. The Pearson correlation coefficient (r) of the test-retest of the morale scale at 7-day intervals was 0.990 ($P<.0001$).

The EDBS was used to assess diabetes-specific burden and worry in elderly diabetic individuals. The EDBS is a short, revised version of the elderly diabetes impact scale, as previously reported.[4] The EDBS consists of six subscales: symptom burden (four items), social burden (five items), diet restrictions (four items), worry about DM (four items), treatment satisfaction (three items), and burden by tablets or insulin (three items). Symptom burden represents burden due to edema of the lower extremities, polyuria, paresthesia, or visual disturbance. Social burden represents burden imposed on relationships with family and friends, leisure activities, social activities, and social life due to DM. Dietary restriction refers to burden associated with caloric restriction, eating a well-balanced diet, restrictions on many favorite foods, and dietary management. Medication burden is the burden of taking pills for DM or injecting insulin, fear of hypoglycemia, and worry about a sick day. Worry about DM represents anxiety about living with DM, diabetic complications, and burdensome treatment in the future due to DM. Treatment satisfaction refers to satisfaction with results of DM treatment, blood glucose levels, and all aspects of DM. Each item of EDBS (23 items) was rated on a four-point multiple-choice scale. EDBS was calculated by reversing the scores of the treatment satisfaction subscale, summing the scores of six subscales.

The EDBS had good test-retest reliability, construct validity, and convergent validity and internal consistency of satisfactory magnitude.[4,8] The internal consistencies (Cronbach α) of symptom burden, social burden, diet restrictions, worry about DM, treatment satisfaction, burden by tablets or insulin, and EDBS scales were 0.55, 0.88, 0.89, 0.85, 0.85, 0.78, and 0.89, respectively. Nineteen patients took the second EDBS within 5 to 8 days of the first EDBS. The results of test-retest showed that the r of the two measurements of symptom burden, social burden, diet restrictions, worry about DM, treatment satisfaction, and total EDBS at 7-day intervals were 0.998, 1.000, 0.957, 0.994, 0.937, 0.984, and 0.995 (all $P<.001$). The PGC morale scale in the elderly patients correlated significantly with the subscales of EDBS: symptom burden ($r=-0.44$, $P<.001$), social burden ($r=-0.35$, $P<.001$), diet restrictions ($r=-0.31$, $P<.001$), treatment dissatisfaction ($r=-0.21$, $P<.001$), burden by tablets or insulin ($r=-0.25$, $P<.001$), and worry about DM ($r=-0.45$, $P<.001$).

Socioeconomic Factors

Years of education, family status, and living situation (whether subject lived alone) were recorded. The annual household income of the subjects was rated using a six-point multiple-choice scale from less than $8,000 through more than $40,000. Satisfaction with economic status was assessed using a five-point multiple-choice scale.

Blood pressure was measured using a mercury sphygmomanometer with a cuff of appropriate size. Diastolic blood pressure was determined as Korotkoff phase V. Body mass index (BMI) was calculated as weight in kilograms/height in meters squared. Venous blood was drawn to

determine blood glucose and serum concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides according to established methods.

Experienced ophthalmologists performed funduscopic examinations through dilated pupils using direct ophthalmoscopy. Retinopathy was classified into three categories: no retinopathy, background retinopathy, and proliferative retinopathy. Urinary albumin was measured using immunological assay. Diabetic nephropathy was classified according to mean urinary albumin-to-creatinine ratio (ACR) in two or three successive urinalyses as no nephropathy (ACR <30 mg/gCr), microalbuminuria (30 ACR <300 mg/gCr), or persistent proteinuria (ACR 300 mg/gCr or urinary protein 30 mg/dL). Diabetic neuropathy was defined as loss of Achilles tendon reflexes and diminished vibration sensation or neuropathic symptoms including paresthesia. Ischemic heart disease (IHD) was considered to be present when diabetic patients had one of the following: (1) a history of myocardial infarction characterized by a typical clinical picture (chest pain, chest oppression, syncope, pulmonary edema), typical electrocardiogram (ECG) alteration with occurrence of pathological Q waves or localized ST variations, and typical enzymatic changes in creatine phosphokinase (CPK) and CPK-myocardial band (MB) or (2) a history of angina pectoris, positive postload ECG findings, and positive postload cardiac scintigram findings confirmed by coronary angiography.

Assessment of End Points

The DM patients were followed between March 1, 1997, and October 15, 2000. After follow-up of 3 years, 305 (81.1%) of 376 elderly diabetic patients were alive, 25 (6.6%) had died, and 44 (11.7%) had moved to other hospitals or long-term care facilities. The follow-up rate for this study was 87.7%. All patients except those who died or moved visited the DM clinic every 1 to 2 months to check conventional risk factors (body weight, hemoglobin A_{1c} (HbA1c), blood pressure, and serum lipids). Microalbuminuria was checked at least twice a year. Funduscopic examinations were conducted at least once a year. Physicians blind to psychological status at baseline followed the patients. Every year, the medical records, including admission records of all the patients, were intensively reviewed in a similar fashion to examine the development and progression of retinopathy, nephropathy, stroke, IHD, and peripheral vascular disease. Two physicians blind to the identity of the patients independently coded all the events. The development of symptomatic stroke during the follow-up period was defined as hospitalization for this diagnosis (clinical sign of a focal neurological deficit with rapid onset that persists for longer than 24 hours). A neurologist made the diagnosis of symptomatic stroke, which was confirmed by the findings of brain computed tomography (CT) (15%) or magnetic resonance imaging (MRI) (85%) in all cases. Thus, transient ischemic attack was not included. Acute onset of cerebral infarction was verified with the diffusion-weighted MRI or repeated examination of CT or MRI. Silent cerebral infarction on the MRI and insidious onset of nonspecific symptoms were excluded from the diagnosis of symptomatic stroke.

At the second examination, in 1998, a representative sample (about 75%) of the patients underwent brain MRI scans to examine the relationship between asymptomatic cerebral infarction on brain MRI and psychological findings at baseline or the subsequent development of symptomatic stroke. Brain MRI was performed using a 1.5-T apparatus. T2-weighted images (Fast Spin Echo: repetition time = 3000 ms; echo time = 100 ms) were obtained in the transverse plane, and T1-weighted images (Spin Echo; repetition time = 540 ms; echo time = 9 ms) were obtained as transverse slices at 6.5-mm intervals. Twenty slices of each type of image were obtained. Asymptomatic cerebral infarction was defined as a focal-positive T2 high-intensity lesion larger than 3 mm correlative to T1 low-intensity lesion on brain MRI in those who had neither focal neurological deficits nor history of stroke. An experienced radiologist (YM) assessed the brain MRIs.

Statistical Analysis

In univariate analysis, unpaired *t* and chi-square tests were used to compare clinical characteristics at baseline of those who developed subsequent stroke and those who did not in the 3-year follow-up period. The correlation between two variables was assessed using Spearman *r*. Cox proportional hazards regression analyses were used to estimate the association between clinical features at baseline and hazard ratios (HRs) for stroke, controlling for potential confounders and explanatory factors. Patients who died or moved to other facilities during the follow-up period were censored. To examine whether the relationship between low morale (score ≤ 7), increased symptom burden, and development of stroke was independent, Cox proportional hazards regression analyses were performed using the variables of age and sex or nine conventional risk factors (age, sex, BMI, HbA1c, systolic blood pressure, total cholesterol, triglycerides, HDL-C, and previous IHD). Cox proportional hazards regression was also used to evaluate the association between low morale and future stroke after adjustment for age, sex, duration of DM, microalbuminuria, and previous IHD. At final analysis, Cox proportional hazards model was used, controlling for age, sex, and socioeconomic variables (years of education, income, satisfaction with economic status, and living situation). Results are presented as means ± SD. $P<.05$ was regarded as statistically significant. Statistical analyses were performed using SPSS for Windows, version 11.0 (SPSS, Inc., Chicago, IL).

RESULTS

During a 3-year follow-up period, 25 of 376 patients (6.7%) developed symptomatic stroke; neurologists diagnosed all of them based on neurological deficits and brain CT or MRI. Twenty-four of 25 patients (96%) had cerebral infarction (22 nonfatal, two fatal), and one had cerebral hemorrhage. The diagnosis of the two fatal cerebral infarctions was confirmed by autopsy.

Clinical characteristics at baseline for the patients with and without stroke during the follow-up period are given in Table 1. Sociodemographic variables, including age, sex, BMI, years of education, living situation, and annual household income were similar between the two groups.

Table 1. Clinical Characteristics of Elderly Diabetic Patients at Baseline

Characteristic	Patients with Stroke During Follow-Up (n = 25)	Patients Without Stroke During Follow-Up (n = 351)
Sociodemographic variables		
Age, mean ± SD	75.0 ± 5.4	75.2 ± 5.9
Men, %	46	32
Body mass index, kg/m^2, mean ± SD	23.0 ± 2.7	23.0 ± 3.4
Years of education, mean ± SD	10.5 ± 3.2	9.7 ± 3.2
Living alone, %	12	15
Annual household income (<$8,000:$8,000–23,000: $24,000–39,000: ≥$40,000), %	14:27:27:32	10:46:29:15
DM variables		
Duration of DM, year, mean ± SD	16.9 ± 7.7*	13.5 ± 8.4
Treatment of DM (diet:tablet:insulin), %	23:69:8	32:55:13
Hemoglobin A_{1C}, %, mean ± SD	7.7 ± 1.7	7.7 ± 1.4
Retinopathy (none:background:proliferative), %	44:39:17	64:24:12
Nephropathy (none:microalbuminuria:persistent proteinuria), %	42:27:31	51:25:24
Neuropathy, %	65	53
Risk factors for atherosclerotic disease		
Systolic blood pressure, mmHg, mean ± SD	142 ± 17	142 ± 19
Diastolic blood pressure, mmHg, mean ± SD	75 ± 11	74 ± 11
Hypertension (drug-treated), %	50	55
Total cholesterol, mg/dL, mean ± SD	199 ± 40	204 ± 37
Triglycerides, mg/dL, mean ± SD	128 ± 72	124 ± 65
HDL cholesterol, mg/dL, mean ± SD	53 ± 15	49 ± 14
Hyperlipidemia, drug-treated, %	23	28
Current smoker, %	17	14
Ischemic heart disease (none:angina pectoris:myocardial infarction), %	92:4:4	86:10:4

*$P < .05$ vs patients without stroke during the follow-up period.
SD = standard deviation; DM = diabetes mellitus.

Patients who experienced stroke during follow-up had a significantly longer duration of DM, but there were no significant differences in HbA1c; blood pressure; serum levels of cholesterol, triglycerides, and HDL-C; and prevalence of smoking, use of antihypertensive medications, and diabetic complications between the two groups. Usage of calcium blockers and angiotensin-converting enzyme inhibitors was similar in both groups (42% vs 42% and 27% vs 17%, respectively). The prevalence of atrial fibrillation was also similar in patients with and without stroke (4.2% vs 4.8%).

PGC Morale and Risk of Stroke

Patients who developed stroke had significantly lower PGC morale scale scores at baseline than those who did not (Table 2). In the Cox regression analysis, low morale score (≤7) was a significant predictor of stroke during the follow-up period after adjustment for age and sex (HR = 2.5, 95% confidence interval (CI) = 1.1–5.6, $P = .035$). Even after adjustment for nine conventional risk factors for atherosclerosis (age; sex; BMI; HbA_{1c}; serum levels of total cholesterol, triglycerides, and HDL-C; smoking; and previous IHD), the relationship between low morale at baseline and the incidence of stroke during the follow-up remained significant (HR = 3.0, 95% CI = 1.2–7.3, $P = .017$). When the risk for stroke in the subscales of morale was analyzed, only absence of positive attitude toward aging was a significant predictor for stroke after the nine conventional risk factors for atherosclerotic disease (HR = 3.0, 95% CI = 1.3–7.2, $P = .012$). In contrast, neither agitation nor loneliness and dissatisfaction with life affected the risk of stroke (HR = 2.3, 95% CI = 0.81–6.5, $P = .118$ and HR = 2.1, 95% CI = 0.74–6.1, $P = .162$).

EDBS and Risk of Stroke

In univariate analyses using the unpaired t test, patients who developed stroke tended to have higher symptom burden and social burden of EDBS scores (Table 2), but the scores of the other subscales of EDBS (diet restrictions, worry about DM, treatment dissatisfaction, and burden by tablets or insulin) were similar between the two groups. In multivariate analyses using the Cox proportional hazards regression analyses, the symptom burden (score ≥9) and social burden (score ≥13) subscales of EDBS were significant predictors for stroke after adjustment for age; sex; BMI; HbA_{1c}; serum levels of total cholesterol, triglycerides, and HDL-C; smoking; and previous IHD (HR = 3.2, 95% CI = 1.3 = 7.8, $P = .012$ and HR = 2.7, 95% CI = 1.1–6.6, $P = .035$, respectively), but dietary restrictions, worry about DM, treatment dissatisfaction, and burden by tablets or insulin did not affect the risk of stroke after adjustment for the nine conventional risk factors.

Table 2. Well-Being and Diabetes Mellitus Burden at Baseline in Those with and without Stroke

Variable	Patients with Stroke During Follow-Up (n = 25)	Patients without Stroke During Follow-Up (n = 351)	Difference (95% Confidence Interval)
	Mean ± Standard Deviation		
Well-being (Philadelphia Geriatric Center morale scale)	9.8 ± 4.4*	11.5 ± 4.0	−1.7 (−3.3 to −0.1)
Agitation	4.8 ± 2.5	5.6 ± 2.3	−0.8 (−1.7–0.1)
Attitude toward own aging	2.8 ± 1.8*	3.5 ± 1.7	−0.8 (−1.5 to −0.1)
Lonely dissatisfaction	2.3 ± 0.9	2.4 ± 0.8	−0.1 (−0.5–0.2)
Elderly diabetes burden scale	48.2 ± 14.5	44.5 ± 12.1	3.7 (−1.2–8.6)
Symptom burden	5.7 ± 4.5*	4.3 ± 3.5	1.4 (0.02–2.9)
Social burden	10.0 ± 3.7	8.7 ± 3.4	1.3 (−0.1–2.6)
Diet restrictions	10.5 ± 3.6	10.0 ± 3.3	0.6 (−0.8–1.9)
Worry about diabetes	10.7 ± 3.3	10.1 ± 3.2	0.5 (−0.8–1.8)
Treatment dissatisfaction	6.2 ± 2.1	6.5 ± 2.0	−0.2 (−1.0–0.6)
Burden by tablets or insulin	5.1 ± 2.3	5.1 ± 2.0	0.1 (−0.8–0.9)

* $P < .05$ vs patients without stroke during the follow-up period.

When the PGC morale scale and symptom burden were entered simultaneously into the Cox regression model, the significant associations between low morale or symptom burden and development of stroke disappeared because of high correlations between the two variables, but there was no interaction between low well-being and symptom burden on the risk of stroke.

Effects of Diabetic Nephropathy and Asymptomatic Stroke

Microalbuminuria or proteinuria has been reported to be an independent predictor for stroke.[15,16] To exclude the potential effect of diabetic renal complications, Cox regression analysis was performed using the covariates age, sex, duration of DM, previous IHD, and microalbuminuria. Controlling for the covariates attenuated the association between social burden at baseline and the development of stroke (HR = 2.1, 95% CI = 0.85–4.7, $P = .110$), possibly because of the relatively strong correlation between social burden and nephropathy, but after adjustment for the covariates, including microalbuminuria, the relationship between low morale or symptom burden at baseline and future stroke remained significant (HR = 2.6, 95% CI = 1.1–6.3, $P = .029$ and HR = 2.6, 95% CI = 1.1–6.5, $P = .039$, respectively). Similarly, neither persistent proteinuria nor retinopathy affected the significant associations between low morale or symptom burden and the incidence of stroke during the follow-up period (data not shown).

A significant difference was not observed between those with low morale (score ≤ 7) and those with high morale (score ≥ 8) (37.0% vs 39.3%) in the prevalence of asymptomatic cerebral infarction on brain MRI. In those who developed symptomatic stroke, morale score was similar in those with asymptomatic cerebral infarction and those without (10.3±4.0 vs 9.6±5.6).

Confounding Effects of Socioeconomic Factors

To investigate the confounding effects of socioeconomic factors on the relationship between psychological variables at baseline and subsequent stroke, years of education, annual household income, satisfaction with economic status, and living situation were assessed. The relationship between low morale score, symptom burden, and social burden and future stroke remained significant after adjustment for age, sex, education, income, satisfaction with economic status, and living situation (HR = 2.7, 95% CI = 1.1–6.8, $P = .028$, HR = 3.1, 95% CI = 1.2–7.8, $P = .015$, and HR = 2.9, 95% CI = 1.1–7.2, $P = .025$, respectively).

DISCUSSION

The major finding of this prospective study was that low well-being, measured using the PGC morale scale was an independent predictor for the development of stroke over a 3-year follow-up of 376 elderly diabetic patients free of clinical stroke. The relationship between reduced well-being and future stroke was independent of conventional risk factors for atherosclerotic disease or socioeconomic factors. The results on the relationship between lack of positive well-being and risk of stroke are inconsistent with reports on the independent association between depression,[9,10] low vitality,[11] or discontentment[11] and future stroke in nondiabetic population. The current study is the first to show that the absence of positive attitudes toward aging was a risk factor for stroke in diabetic patients, but agitation and loneliness and dissatisfaction with life were not.

The study also showed that diabetes-specific symptom burden and social burden, but not diet restrictions, worry about DM, treatment dissatisfaction, or medication burden of EDBS, were predictors for stroke in diabetic people after adjustment for conventional risk factors. Symptom burden may be a somatic reflection of low well-being, because symptom burden was highly correlated with low morale scale sores in elderly diabetic patients. The link between social burden and stroke is inconsistent with a report demonstrating that social effect of DM was associated with increased risk of mortality in patients with type 2 DM.[17]

The reason for the association between low morale or symptom burden of EDBS and subsequent development of stroke remains unknown. First, the state of low well-being,

similar to depression, might induce activation of platelet activity, which would lead to the development of cerebral infarction. Depressed patients have showed an increase in platelet activity.[18,19] In contrast, antidepressant agents, such as selective serotonin reuptake inhibitors, inhibited the activation of platelets in patients with depression.[19] Increased expression of inflammatory markers associated with depression might be involved in the pathogenesis of atherosclerotic disease.[20]

Second, psychosocial stress, as reflected by low well-being or diabetes-specific burden may play an important role for the development of stroke due to high sympathetic nerve activity. In experimental studies, psychosocial stress accelerated endothelial dysfunction and arteriosclerosis in monkeys.[21,22] In contrast, β-adrenergic blockers inhibited coronary atherosclerosis in monkeys exposed to psychosocial stress.[23]

Third, it might be argued that diabetic complications at baseline may be related to reduced well-being or increased DM burden and to increased risk of future stroke, but the relationship between low well-being or symptom burden and future stroke remained significant after adjustment for previous IHD and microalbuminuria, proteinuria, or retinopathy. Thus, it seems unlikely that the association between low well-being and future stroke is simply a direct result of the severity of microvascular and cardiovascular complications.

Finally, diabetic patients with low morale might have asymptomatic cerebral infarction apparent on brain MRI at baseline, which would lead to the development of clinical symptomatic stroke during follow-up. Vascular depression due to cerebral infarction is not uncommon in elderly people,[24] but no significant associations were observed between the presence of asymptomatic cerebral infarction and morale score in the patients who developed symptomatic stroke. Therefore, the contribution of asymptomatic cerebral infarction to the development of symptomatic stroke in patients with low morale appears to be small.

There are some limitations to the present study. First, the small number of stroke events in this study might have limited the power to determine the presence of multiple independent predictors of stroke that would emerge if the sample size of the study were larger or the study had been extended for a longer length of time. Second, because subjects were recruited from outpatient clinics, some selection bias might have affected the results. The results should be verified on other diabetic populations.

In conclusion, reduced well-being and increased symptom burden were independent predictors for stroke during a 3-year follow-up period of elderly diabetic patients. Further studies are necessary to understand the mechanism for the association between low well-being and risk of stroke. To improve low well-being in elderly diabetic patients, psychosocial interventions,[25] such as counseling, group therapy, antidepressant medication, family and social support, and exercise training,[26] may be necessary. At present, it remains unknown whether psychological intervention can prevent the development of stroke in elderly diabetic patients. If the future intervention produces favorable effects on the incidence of stroke, the results of this study would lead to development of new treatment strategies to prevent stroke in elderly patients with DM.

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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

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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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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%,

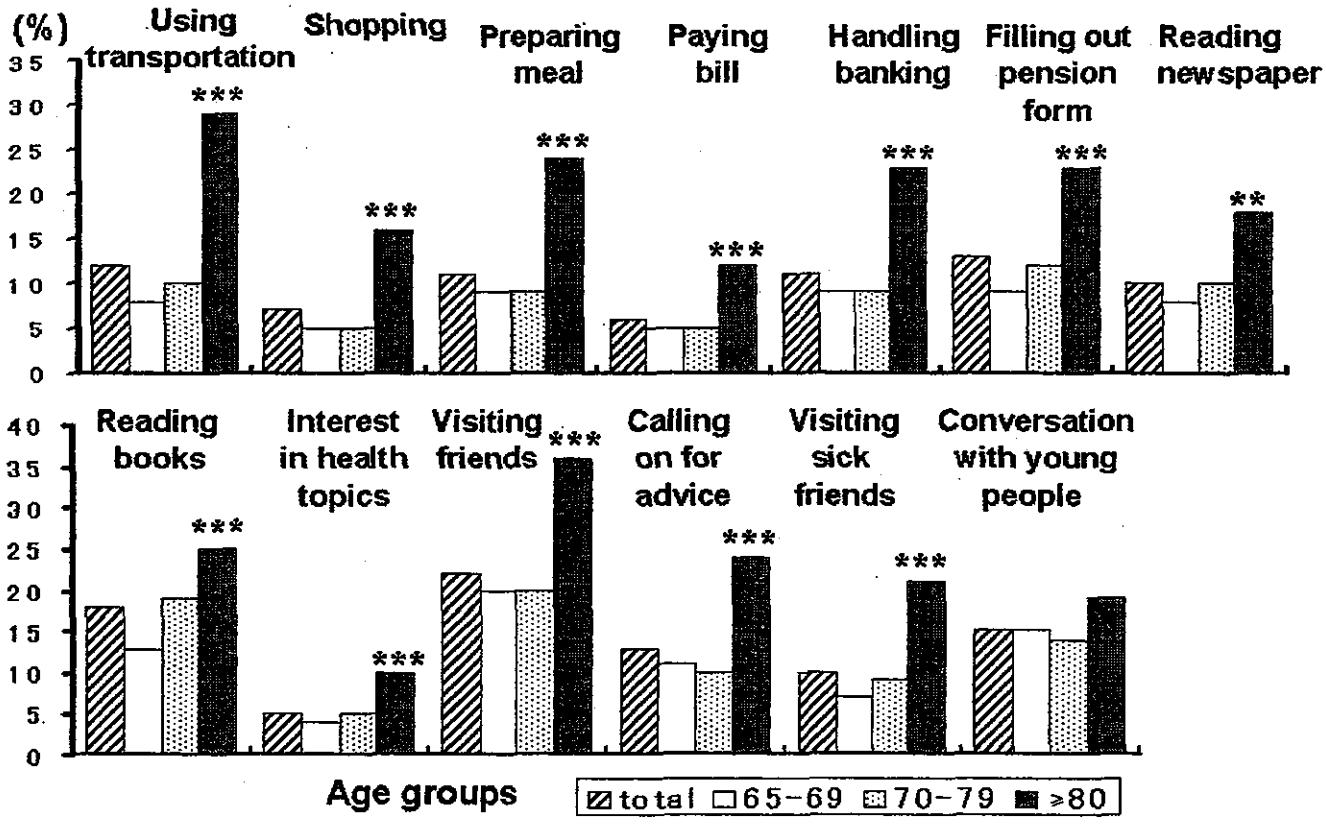

Figure 1 The relationship between aging and functional disabilities in elderly patients with diabetes mellitus (**$P < 0.01$, ***$P < 0.001$ *versus* the youngest group [65–69 years old]; $n = 1135$).

$P < 0.001$) 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,

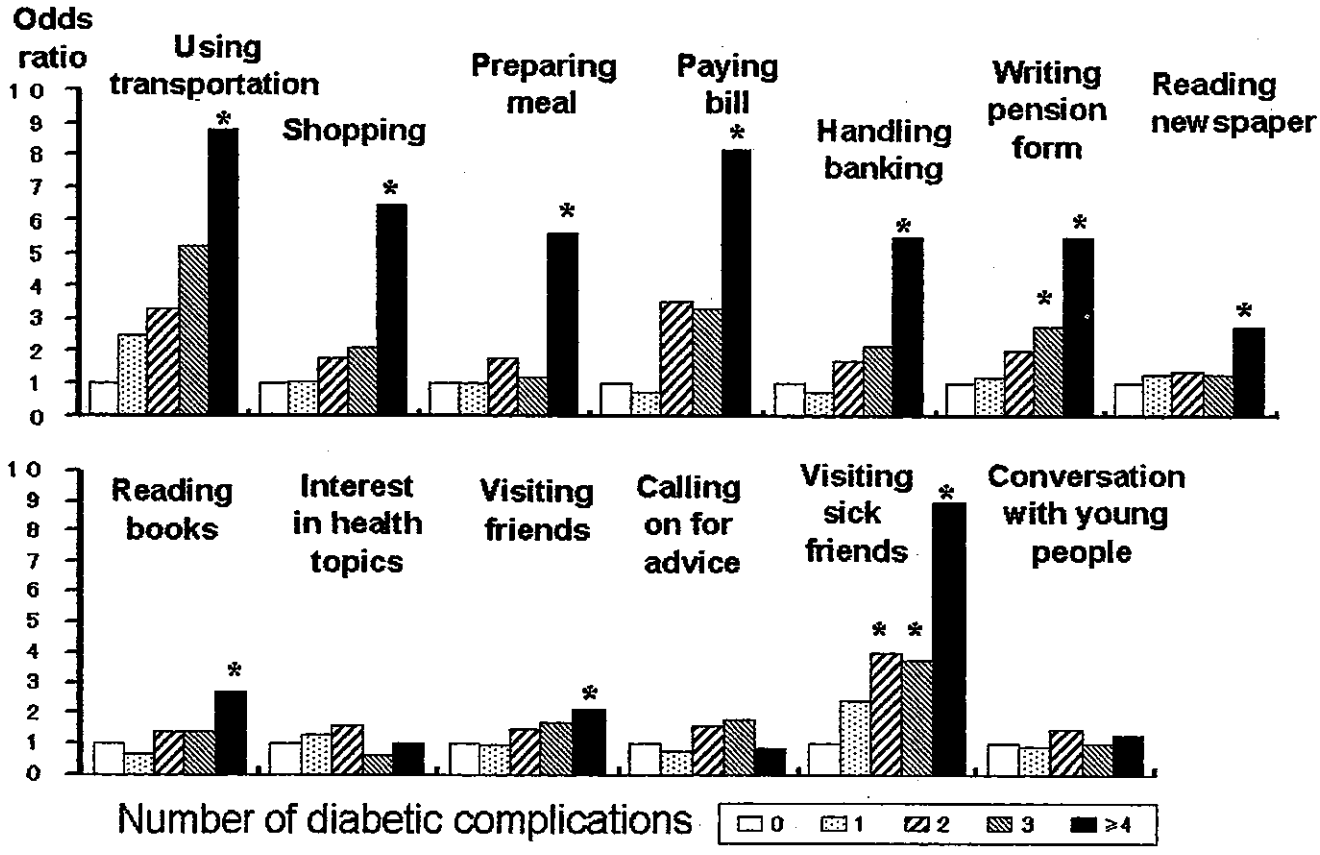

Figure 2 The relationship between the number of complications and functional disabilities in elderly patients with diabetes mellitus. (*$P < 0.05$ *versus* diabetic patients without any complications. Odds ratios were calculated with multiple logistic regression analysis after adjustment for age, gender, 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.

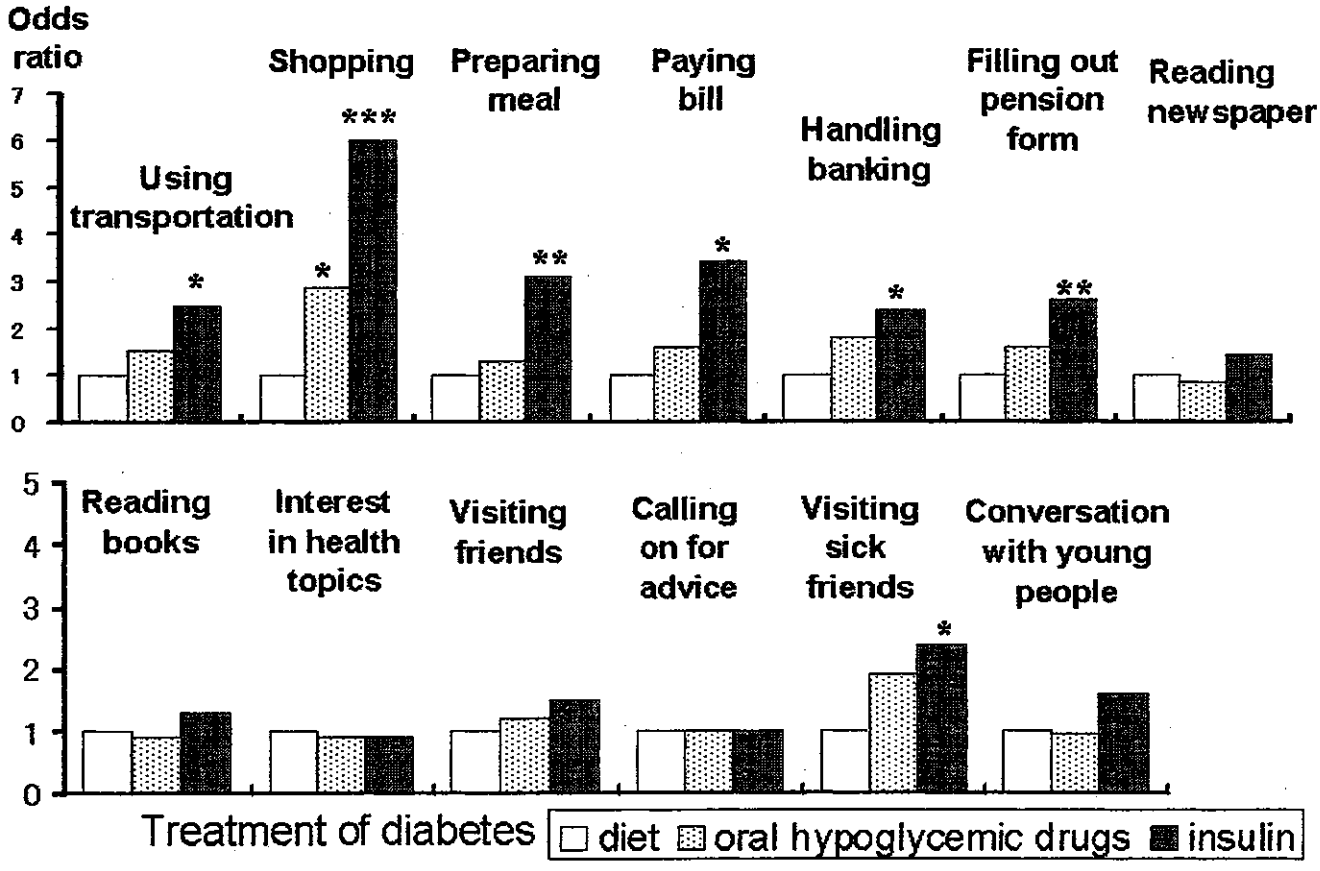

Figure 3 The relationship between treatment of diabetes and functional disabilities in elderly patients with diabetes. (Odds ratios were calculated with multiple logistic regression analysis after adjustment for age, gender, duration of diabetes, body mass index, HbA1c, microangiopathy, macroangiopathy, 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]