obesity if accompanied by clustering of metabolic disorders, and (4) AHA/NHLBI-MetS, comprising both abdominal obese and non-abdominal obese metabolic factor clustering cases, was the most useful for prediction of cardiovascular disease in diabetic elderly.

The incidence of MetS in the general population reportedly differs widely among ethnic groups and according to the definition of MetS [13, 33–38]. It has also been reported that the prevalence of MetS increases with age [39, 40]. However, the prevalence of MetS-type risk factor clustering among patients with known diabetes is consistently high regardless of ethnicity or definition [6–13, 30, 33, 41–48]. In the Japan Diabetes Complications Studies (JDCS), which was concerned with relatively younger diabetic patients aged 40–70 years, the prevalence of IDF-MetS risk factor clustering was 32% for men and 9.2% for women [47]. Although the inclusion criteria of JDCS and JEDIT were not the same, it seems likely that prevalence of MetS-type risk factor clustering in Japanese patients with type 2 diabetes increases with age, at least until the age of 80. To our knowledge, there are no epidemiological data of MetS-type risk factor clustering of diabetic elderly in the other ethnic groups.

Although we did not measure insulin resistance directly in this study, HOMA-IR has been shown to correlate well with direct methods in subjects with various degrees of glucose tolerance, including patients who have already developed diabetes [27]. The averages of HOMA-IR of younger diabetic subjects have been reported as 2.9–3.3 [28, 30]. In our diabetic elderly, insulin resistance was evidently high (4.2 ± 5.0), which may be due to the diabetic state itself and/or age-associated changes in body composition such as increases in fat mass and decreases in fat-free mass [16]. We therefore expected that the correlation of insulin resistance with abdominal obesity might become weaker in diabetic elderly, but there was in fact a significant linear association of insulin resistance with waist circumference, and the former was found to be higher in JSIM-MetS and IDF-MetS. In this respect, it should be pointed out that insulin resistance also increased moderately in MetS-type risk factor clustering without abdominal obesity, so that the mechanism for the increase in insulin resistance associated with non-obese type metabolic factor clustering remains to be clarified [40].

Evidence is accumulating that MetS is clinically relevant for the prediction of cardiovascular disease in non-diabetic elderly [49–51]. Our study is the first to demonstrate that AHA/NHLBI-MetS correlates independently with cardiovascular disease in diabetic elderly after adjustment for the other risk factors for atherosclerotic disease. It seems plausible that non-obese metabolic factor clustering together with increased insulin resistance has a major impact on the risk of cardiovascular diseases of diabetic elderly, because MetS with abdominal obesity does not always appear to be associated with cardiovascular diseases [10, 52–54]. Definitions of MetS-type risk factor clustering that specify abdominal obesity have not yet been developed for Asian (Japanese) diabetic elderly. Other studies have also identified the usefulness of the National Cholesterol Education Program (NCEP)-MetS and AHA/NHLBI-MetS for the prediction of cardiovascular disease in younger subjects with type 2 diabetes [9–10, 13]. On the other hand, Sone et al. [30] have demonstrated that NCEP-MetS has limited clinical usefulness as a predictor for Asian diabetic patients. Further prospective analyses are thus needed to investigate the clinical significance of MetS-type risk factor clustering without abdominal obesity for diabetic elderly.

There are certain limitations to our study. First, we performed a cross-sectional evaluation and our results are therefore subject to survival bias. Second, our study subjects were hospital-based patients with diabetes of relatively long duration, so that any inferences are of necessity limited to similar patient groups. On the other hand, this population sample represents the real-world scenario of type 2 diabetes in Japan.

In conclusion, abdominal obesity and insulin resistance were found to increase with age, at least until the age of 80, in Asian diabetic elderly, and a relationship between waist circumference and HOMA-IR was demonstrated. An important finding was that MetS-type metabolic factor clustering without abdominal obesity also showed elevated insulin resistance. AHA/NHLBI-MetS, comprising both obese and non-obese metabolic disease clustering, was found to be the most effective for the prediction of cardiovascular disease, whilst the significance of MetS with abdominal obesity in this respect remains unclear. An on-going prospective study of J-EDIT may help to clarify the pathophysiology of metabolic disease clustering and its association with cardiovascular disease and geriatric syndromes of diabetic elderly.

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Short Report

Amyloid-β neurotoxicity restricts glucose window for neuronal survival in rat hippocampal slice cultures

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ABSTRACT

Diabetes may increase the risk of Alzheimer's disease (AD). However, a preventive strategy to combat cognitive decline in diabetic elderly with preexisting AD has remained unknown. The aim of this study was to determine the effects of metabolic perturbation on amyloid-β (Aβ) neurotoxicity and the optimal glucose range for improved neuronal survival, which is referred to as the "glucose window". Organotypic hippocampal slice cultures were incubated in either normoglycemic or hyperglycemic medium for 48 h, and subsequently treated in experimental media containing 0–30 mM glucose, with and without $A\beta_{25-35}$. Neuronal survival was evaluated by the propidium iodide method. Aβ neurotoxicity was exacerbated during hypoglycemia/hyperglycemia (≦2 mM/≧30 mM) without Aβ and ≦3 mM/≧20 mM with Aβ. ROS elevated in the respective glucose ranges and supplementation of ROS scavengers effectively improved neuronal survival. Interestingly, a sharp and sudden drop in glucose levels from preceding hyperglycemia further increased Aβ neurotoxicity. Supplementation of pyruvate protected exacerbated Aβ neurotoxicity. These results indicate that increased oxidative stress during severe hypoglycemia, hyperglycemia and fluctuation of blood glucose enhances neuronal cell death, resulting in the extremely limited glucose window, and therefore suggest that careful management of glucose avoiding hypoglycemia is needed to prevent brain degeneration in diabetic patients with AD.

1. Introduction

Diabetes and dementia are two of the most common and devastating health problems of the elderly. A systematic review of population-based studies has provided accumulated evidence that diabetes is associated with cognitive decline and increases the risk of developing Alzheimer's disease (AD) in people who do not have dementia [1].

It has been postulated that diabetes and AD share a number of features. Although the exact pathogenesis remains somewhat unclear, several mechanisms through which diabetes may affect the brain have been identified [1]. First, the relationship between diabetes and AD can be explained by diabetic vasculopathy and its sequelae. Second, toxic effects of hyperglycemia are thought to be involved in the development of diabetic end-organ damage to the brain. An increase in advanced glycation end products, disturbances of intracellular second messenger pathways, and an imbalance in the generation and scavenging of reactive oxygen species (ROS) would be crucial in the pathogenesis of AD [2,3]. Third, iatrogenic hypoglycemia during aggressive treatment of diabetes is considered to have a specific impact on cognitive function [4]. Finally, deficits in brain insulin signaling have been recently postulated in AD pathogenesis [5].

To date, an effect of diabetes on the rate of cognitive decline in patients with preexisting AD is unclear. A previous study found no difference in the rate of cognitive decline of the Mini-mental state examination (MMSE) score in patients with and without diabetes [6]. Another studies found an unexpected slower rate of cognitive decline of the MMSE in patients with a history of diabetes with AD [7,8], while a history of diabetes was associated with faster annual cognitive decline in patients with incident AD [9]. This controversial result could be result from the age of patients and/or the difference in treatment and metabolic abnormalities of diabetes [7].

A preventive strategy to combat cognitive decline in diabetic elderly with preexisting AD has remained a matter of debate. In healthy subjects, fasting glucose and 2 h postglucose levels are less than 5.5 mM and 7.8 mM, respectively, while fasting glucose ≧7.0 mM or 2 h postloaded glucose ≧11.1 mM in diabetic patients [10]. Several studies have suggested that blood glucose levels should be normalized for better cognitive function, but special attention is needed to avoid hypoglycemia [4,11]. The lower and upper limits of blood glucose levels required to avoid irreversible neuronal degeneration remain unclear. Moreover, there is little information on the molecular basis of metabolic perturbation in diabetes that could influence AD pathology.

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To address these matters, we performed in-vitro experiments to identify the optimal glucose range, which is referred to as the "glucose window", for improved neuronal survival. We hypothesized that amyloid-β (Aβ) neurotoxicity is exacerbated during both hypoglycemia and hyperglycemia. The goals of our study were thus 1) identification of the glucose window in the presence and absence of Aβ, 2) to clarify the underlying mechanism of exacerbated Aβ-neurotoxicity during glucose metabolism abnormalities, and 3) to identify substrates for enlargement of the glucose window to improve neuronal survival in the presence of Aβ.

2. Materials and methods

2.1. Preparation of organotypic hippocampal slice cultures (OHCs)

All animals were treated according to the guidelines for animal experimentation of the Kobe University School of Medicine. OHCs were prepared from 9-to-11-day-old Wistar rats (SLC Japan, Hamamatsu, Japan) using a standard method [12] and incubated in the medium containing 36 mM glucose before the 12th day of culture (Fig. 2A). Then, OHCs were incubated in either normoglycemic (10 mM) or hyperglycemic (20 mM) medium for 48 h, and subsequently treated for another 48 h in various experimental media containing 0–30 mM glucose, with and without Aβ, trolox (1 mM) or sodium pyruvate (10 mM).

2.2. Preparation of $A\beta_{25-35}$

$A\beta_{25-35}$ is a short synthetic peptide and suitable for studying Aβ neurotoxicity. $A\beta_{25-35}$ and $A\beta_{1-42}$ oligomers have been shown to induce neuronal damage through similar mechanisms [13]. Since the effect of $A\beta_{25-35}$ at 50 μM on neuronal survival was found to be equivalent to that of $A\beta_{1-42}$ oligomer at 1 μM (data not shown), $A\beta_{25-35}$ was used at a concentration of 50 μM in all subsequent experiments.

2.3. Measurement of neuronal death and ROS

The propidium iodide (PI) method, was used for the assessment of neuronal death in the CA1 region of OHCs [12]. 4.6 μg/ml PI (Sigma, St. Louis, USA) was added to the wells of the culture microplates. After obtaining PI images after 48 h treatment in the conditioning mediums, all living neurons were killed by adding 10 μM N-methyl-D-aspartic acid. Final PI fluorescence intensity was adjusted to 100%, which is equivalent to total neuronal cell death, and cell death observed at 48 h was expressed as a percentage of the maximum fluorescence.

ROS levels were measured by using a non-fluorescent compound, 2′,7′-dichlorodihydrofluorescein diacetate (H_2DCF-DA, Invitrogen, USA), following procedures previously utilized to estimate β-amyloid-induced ROS production in neurons [14]. Because ROS levels significantly increased after 1–3 h treatment with $A\beta_{25-35}$, but not after 6 h (data not shown), we measured ROS contents 3 h after each experimental treatment.

2.4. Statistical analysis

Data analysis was conducted using the ANOVA and Tukey statistics (SPSS 15.0 J). A value of $P<0.05$ was considered statistically significant.

3. Results

3.1. Exacerbation of Aβ neurotoxicity during hypoglycemia/hyperglycemia

First, the effects of a variety of extracellular glucose concentrations on neuronal survival were tested in the absence of $A\beta_{25-35}$. In comparison with control (10 mM glucose), neuronal survival was not affected when the medium glucose concentration was 3–25 mM, while severe hypoglycemia (≦2 mM) and hyperglycemia (≧30 mM) caused neuronal death (Fig. 1A and B). Impairment of neuronal survival during hyperglycemia was not due to elevated osmolarity, because adjustment of osmolarity with sucrose to make it equivalent to glucose concentration did not affect neuronal survival at any glucose concentration (data not shown). Compared to control, neuronal death in the presence of $A\beta_{25-35}$ increased when medium glucose concentration was ≦3 mM and ≧20 mM.

Because our slice culture was a static system without dynamic flow of medium, we measured glucose concentrations at the termination of experiments ($n=4$) and found that glucose concentrations were reduced to approximate 60–70% of the original concentrations. Mean glucose concentrations during 48 h observation were 0.2, 1.7, 2.3, 4.1, 8.6, 12.7, 17.4, and 28.9 (mM) in media containing 0, 2, 3, 5, 10, 15, 20, and 30 (mM) glucose at start of experiments, respectively. These findings demonstrate that hyperglycemia as well as hypoglycemia had adverse effects on neuronal survival and exacerbated Aβ neurotoxicity during hypoglycemia/hypoglycemia, resulting in a restricted glucose window (5–15 mM).

3.2. Effect of oxidative stress on Aβ neurotoxicity elicited during hypoglycemia and hyperglycemia

The contribution of Aβ-induced oxidative stress on neuronal death during hypoglycemia/hyperglycemia was examined. When the medium glucose concentration was ≦2 mM and ≧30 mM, ROS concentration in the OHCs without Aβ increased compared with control (Fig. 1C). In the presence of $A\beta_{25-35}$, ROS levels were further elevated when glucose concentration was ≦3 mM and ≧20 mM. Supplementation of trolox, an ROS scavenger, partially reversed the increment in ROS as a result of glucose deprivation, as well as improved neuronal survival (Fig. 1D). Trolox completely eliminated hyperglycemia-induced ROS accumulation accompanied by a recovery of neuronal survival to control levels. In the presence of $A\beta_{25-35}$, trolox also reduced ROS accumulation and reversed neuronal death during hypoglycemia/hyperglycemia, suggesting that oxidative stress plays a pivotal role in the increase in Aβ neurotoxicity elicited during hypoglycemia/hyperglycemia.

3.3. Sharp and sudden drop in glucose levels from preceding hyperglycemia further increases Aβ neurotoxicity

Finally, the effects of fluctuations in glucose levels on neuronal survival were investigated (Fig. 2A). In the absence of $A\beta_{25-35}$, reduction of glucose to 3–10 mM from preceding hyperglycemia (20 mM) did not cause any apparent changes in neuronal survival, but severe hypoglycemia (2 mM) after hyperglycemia exacerbated neuronal death (Fig. 2B). In the presence of $A\beta_{25-35}$, a sharp and sudden drop in glucose caused deterioration in neuronal damage (Fig. 2C). Reduction of glucose to 5 mM, which is equivalent to the physiological concentration of glucose, caused significant neuronal death in association with elevated levels of ROS (Fig. 2C and D). Severe hypoglycemia (2–3 mM) induced an increase in neuronal death after the drop in glucose from previous hyperglycemia.

Supplementation with trolox and pyruvate diminished Aβ neurotoxicity (Fig. 2D and E), to enlarge the restricted glucose window. Several beneficial effects of pyruvate on neuronal survival have been reported, including its function as an antioxidants and an energy substrate [12,15]. Protective effect of pyruvate was more pronounced than that of trolox ($P=0.003$ at 2 mM glucose). Our findings indicated that Aβ neurotoxicity was exacerbated after the drop in glucose level from the preceding hyperglycemia accompanied by an increase in ROS accumulation. It is of note that the glucose window was 10–15 mM for this preparation.

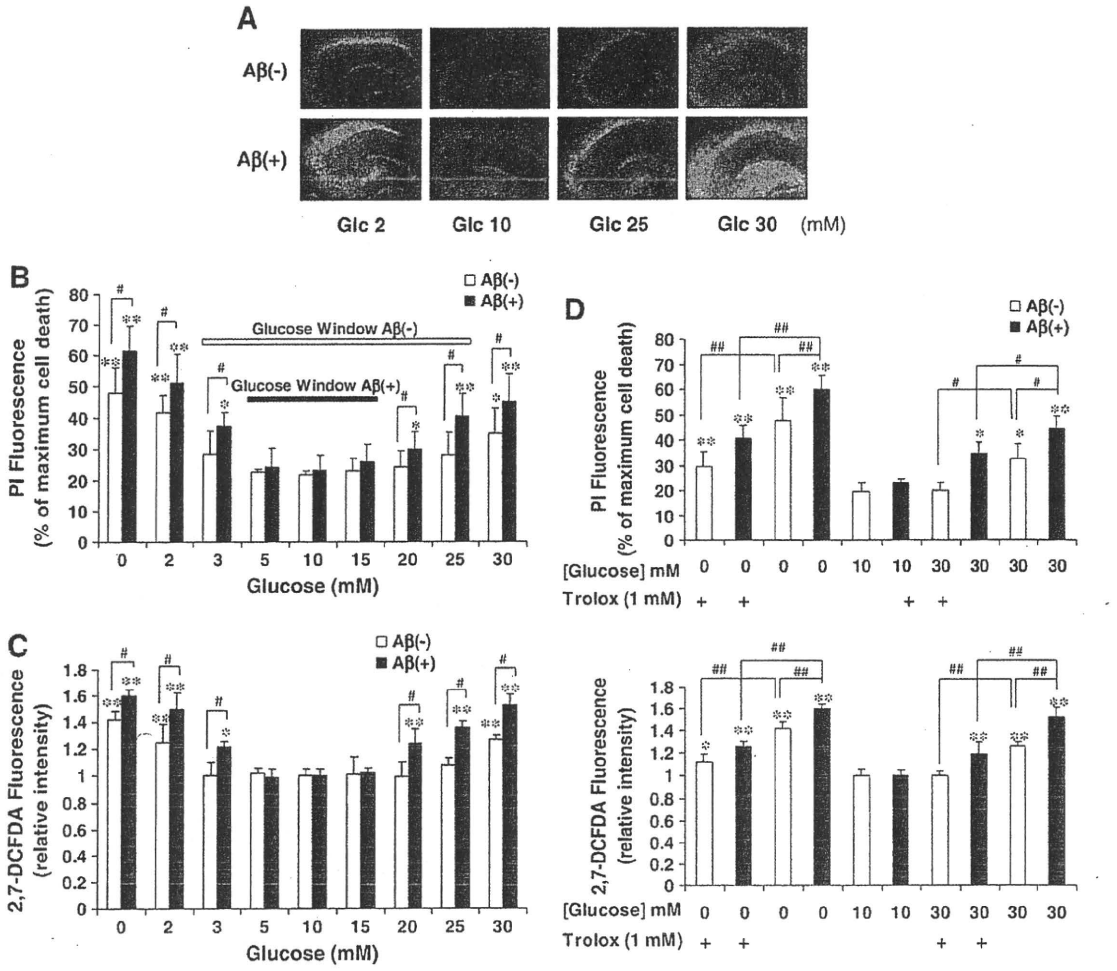

Fig. 1. Effects of glucose concentrations on neuronal death in the presence and absence of amyloid-β (Aβ) in organotypic hippocampal slice cultures (OHCs) (A) Representative images of propidium iodide (PI) fluorescence in OHCs at various glucose concentrations, with and without $Aβ_{25–35}$. (B) Neuronal death with and without Aβ at a variety of glucose concentrations. After 12 days in culture, OHCs were incubated for 48 h in a medium containing 10 mM glucose, and subsequently treated in various experimental media containing 0–30 mM glucose with and without 50 μM $Aβ_{25–35}$ (black and white bars, respectively). Neuronal survival was affected in severe hypoglycemia/hyperglycemia (≦2 mM/≧30 mM) without Aβ, while neuronal death increased when glucose concentration was ≦3 mM/≧20 mM in the presence of $Aβ_{25–35}$. Normal glucose window (3–25 mM) was seriously restricted in the presence of Aβ (5–15 mM). Data are presented as averages and SEMs (vertical bars) ($n=12$). Asterisks indicate significant differences from control (10 mM glucose) for each group (ANOVA followed by Tukey post-hot test; $^{*}p<0.05$, $^{**}p<0.01$). $^{\#}p<0.05$ denotes the difference between the findings in the presence and absence of Aβ for the various glucose concentrations. (C) Changes in reactive oxygen species (ROS) contents of OHCs during hypoglycemia/hyperglycemia with and without Aβ. OHCs were exposed to conditioned media for 3 h and ROS levels were measured with an H_2DCFDA assay. Data are expressed as fold increases over control (10 mM glucose) in the presence and absence of Aβ (black and white bars, respectively) ($n=12$). Asterisks indicate significant differences from control ($^{*}p<0.05$, $^{**}p<0.01$). $^{\#}p<0.05$ denotes the difference between the findings in the presence and absence of Aβ for the various glucose concentrations. (D) Protective effects of trolox (1 mM), a vitamin E analogue, on neuronal death (upper panel) and ROS levels (lower panel) during glucose deprivation and hyperglycemia (30 mM glucose) with (black bars) and without (white bars) $Aβ_{25–35}$. Asterisks indicate significant differences from control (10 mM glucose) in the presence and absence of Aβ ($^{*}p<0.05$, $^{**}p<0.01$) ($n=12$). $^{\#}p<0.05$ and $^{\#\#}p<0.01$ denote differences among the four subgroups (Aβ +/− and trolox +/−) in glucose-free and 30 mM glucose medium.

4. Discussion

The primary conclusions of this study are that: (1) optimal glucose concentration for neuronal survival in OHCs was found to be 3–25 mM, and a glucose window of 5–15 mM in the presence of Aβ; (2) Aβ and hypoglycemia/hyperglycemia additively increased oxidative stress, resulting in an increase in neuronal death; (3) a drop in glucose from preceding hyperglycemia further exacerbated neuronal death with Aβ; (4) pyruvate was capable of restoring Aβ neurotoxicity and to enlarge the glucose window. These results provide evidence that the glucose window resistant to Aβ neurotoxicity is extremely restricted and metabolic substrates such as pyruvate reverse the glucose window in OHCs model of AD.

This study clearly demonstrates that hyperglycemia can cause neuronal damage in hippocampal neurons through an ROS-mediated mechanism. Impaired metabolic glucose pathways have been implicated in the pathogenesis of diabetic complications, which results in an increase in cellular oxidative stress [2]. Recently, Suh et al. [16] identify glucose as the requisite electron donor for reperfusion-induced neuronal superoxide production in stroke. Furthermore, the association of ROS accumulation with hypoglycemia-induced neuronal death was also demonstrated in our study. Hypoglycemia-induced brain degeneration is not the result of fuel deprivation per se. It has been recently postulated that hypoglycemia triggers a cascade of events in vulnerable neurons, including free radical generation [15,17]. Because Aβ links to the production of oxidative stress in AD pathogenesis [13], it seems likely that Aβ-induced free radical production during hypoglycemia/hyperglycemia can easily overcome the antioxidant defense system in OHCs.

Surprisingly, hippocampal neuronal cells were seen to be extremely vulnerable to acute glucose reduction from preceding hyperglycemia with Aβ. It is plausible that even moderate hypoglycemia after

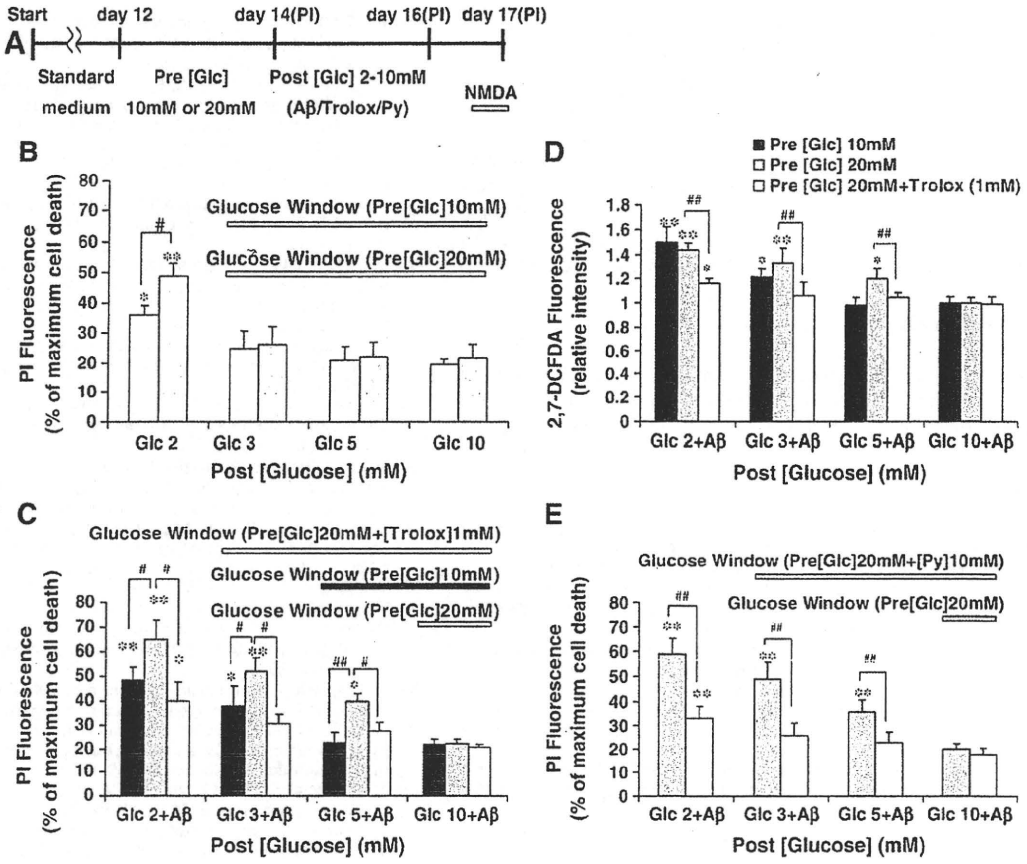

Fig. 2. Exacerbated Aβ neurotoxicity after a sharp and sudden drop in glucose level following hyperglycemia. (A) Schematic presentation of experimental protocols for acute glucose reduction from preceding hyperglycemia. On day 12, OHCs were incubated in normoglycemic or hyperglycemic medium for 48 h (Pre [Glc] 10 mM or 20 mM). On day 14, OHCs were treated with experimental media containing various concentrations of glucose (Post [Glc] 2–10 mM), with and without Aβ, trolox and sodium pyruvate (Py). PI fluorescence images were obtained on days 14, 16 and 17. (B) Neuronal death after acute changes in glucose following hyperglycemia without Aβ. Reduction of glucose to 3–10 mM did not cause any apparent changes in neuronal survival between Pre [Glc] 10 mM and Pre [Glc] 20 mM (white and gray bars, respectively) ($n = 12$). However, severe hypoglycemia (2 mM glucose) after previous hyperglycemia exacerbated neuronal death compared with control (10 mM glucose) ($^{**}p<0.01$), and a significant difference was observed between the groups ($^{\#\#}p<0.01$). (C) Exacerbation of neuronal damage after acute glucose reduction from hyperglycemia in the presence of 50 μM $A\beta_{25-35}$. A sharp and sudden reduction in glucose level from 20 mM to less than 5 mM caused significant neuronal death (gray bars) compared with identical hypoglycemia following Pre [Glc] 10 mM (black bars). The glucose window was 10–15 mM for this preparation. Supplementation with trolox (1 mM) reversed the exacerbation of Aβ neurotoxicity (white bars) ($^{*}p<0.05$, $^{**}p<0.01$ compared with 10 mM glucose; $n = 12$). $^{\#}p<0.05$ and $^{\#\#}p<0.01$ denote significant differences among the three subgroups for each of the glucose concentrations. (D) Oxidative stress after acute glucose reduction from hyperglycemia with Aβ. The acute drop in glucose to 2 mM and 5 mM from previous hyperglycemia apparently increased ROS accumulation in OHCs in the presence of $A\beta_{25-35}$ (gray bars) compared with the 10 mM glucose level ($^{*}p<0.05$, $^{**}p<0.01$, $n = 12$). Supplementation with trolox effectively reversed ROS accumulation (white bars) ($^{\#\#}p<0.01$). (E) Beneficial effects of pyruvate on exacerbated Aβ neurotoxicity after acute glucose reduction from hyperglycemia. Administration of pyruvate (10 mM) appeared to improve Aβ neurotoxicity after an acute drop in glucose from hyperglycemia (white bars), resulting in an enlarged glucose window ($^{**}p<0.01$ compared with control). $^{\#\#}p<0.01$ represents a difference between the presence and absence of pyruvate at each of the glucose concentrations ($n = 12$).

prolonged hyperglycemia may cause irreversible neurological changes in the presence of Aβ, thus endorsing the need for gradual and moderate normalization of hyperglycemia. In this connection, Suh et al. [18] provided evidence that hypoglycemic neuronal death is increased during glucose reperfusion as a result of elevated superoxide production through NADPH-oxidase activation. This implies that the adverse effects of fluctuations in glucose levels from hyperglycemia to hypoglycemia and vice versa should be stressed in the management of diabetes.

Finally, our results have raised the question concerning what is the optimal glucose ranges for neuronal survival in the pathological conditions? A substantial body of evidence supports the benefits of strict glucose management with insulin therapy in general critical practice [19]. However, the effects of intensive insulin therapy on the outcome of critically ill neurologic patients have not been fully investigated [20,21]. Recent report involving the human brain suggests that tight systemic glucose control (4.4–6.7 mM) is associated with reduced cerebral glucose availability and increased prevalence of brain energy crisis, which in turn correlates with increased mortality in patients with severe brain injury, when compared with intermediate glucose range (6.8–10.0 mM) [22]. Based on these investigations, optimal glucose utilization for better neuronal survival and neurological outcomes appears to vary in pathological conditions.

Our experiments clearly indicated that hippocampal neurons were particularly sensitive to metabolic perturbation in diabetes, which exacerbates Aβ neurotoxicity, leading to the restricted glucose window. This study examines disease propagation, rather than incidence of AD, and therefore suggests that hypoglycemia and hyperglycemia, as well as fluctuation of blood glucose should be avoided for better neuronal survival. It may be the case in the human brain with Aβ pathology. In this context, a protective effect of pyruvate against Aβ neurotoxicity seems fascinating as an available and economical tool to enlarge the restricted glucose window, because it is usually difficult to control diabetes in such restricted glucose ranges in the demented elderly.

It is noted that higher concentration of Aβ (50 μM) was used in this study. Most estimates for the concentration of the human brain have been in the low nanomolar range [23]. To span this large concentration gap, several potential mechanisms have been proposed. Recently, Hu et al. [24] reported that Aβ at low physiologically relevant concentrations

of extracellualr Aβ can be taken up by neurons, and then concentrated into endosomes/lysosomes (≥2.5 μM). Our experiments might accelerate this process using higher concentrations of Aβ, leading to increased Aβ neurotoxicity. However, detailed studies are needed to reveal mechanism of Aβ induced neuronal degeneration.

In summary, increased oxidative stress during hypoglycemia, hyperglycemia and/or fluctuation of blood glucose induce the greater rate of Aβ-induced neuronal damage of the cultured hippocampal slices. Multifactorial impacts of metabolic abnormalities in diabetes on neuronal survival have to be examined in further experiments.

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Geriatr Gerontol Int 2011; **11:** *114–118*

CASE REPORT

Usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography for diagnosis of asymptomatic giant cell arteritis in a patient with Alzheimer's disease

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It is often difficult to diagnose disease in elderly patients, in particular those with dementia, who do not present with typical symptoms. This report describes our experience of an elderly patient (an 83-year-old woman) who presented with a chief complaint of memory loss, showed a marked inflammatory response, and was diagnosed with large-vessel giant cell arteritis (GCA) on the basis of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) findings. She had no symptoms typical of GCA including jaw claudication, visual field defect and heavy headed feeling. Corticosteroid therapy resulted in a trend toward improvement in the inflammatory response and then she first recognized that she might have experienced slight dull headache before treatment of GCA. This was probably because this patient had large-vessel GCA, which produces a few symptoms in the head and neck, and because she had Alzheimer's disease and could not accurately describe her symptoms. Our experience suggests the usefulness of FDG-PET for the diagnosis of GCA, particularly in elderly patients without typical symptoms. **Geriatr Gerontol Int 2011; 11: 114–118.**

Keywords: Alzheimer's disease, arteritis, inflammation, positron emission tomography.

Introduction

In daily clinical practice, physicians sometimes encounter elderly patients who do not have typical symptoms of a disease as young patients do. Elderly patients with dementia cannot describe their symptoms accurately, which often makes diagnosis more difficult. Patients with giant cell arteritis (GCA) are characterized by jaw claudication, diplopia and headache,[1] but elderly patients often do not have these symptoms. It is reported that ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is effective for the diagnosis of systemic inflammatory disease.[2,3] Here, we report our

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Author contribution: substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data by S. K., T. A. and T. S.; drafting the article or revising it critically for important intellectual content by S. K., T. A. and T. S.; and final approval of the version to be published by all authors.

Table 1 Blood data on admission

Parameter	Value	Parameter	Value	Parameter	Value
WBC	5400/μL	γ-GTP	22 IU/L	Fe	13 μg/dL
RBC	336 × 10^4/μL	CK	29 IU/L	UIBC	193 μg/dL
Hb	8.7 g/dL	ChE	162 IU/L	Ferritin	107 ng/mL
Ht	28.0%	AMY	111 IU/L	IgG	2200 mg/dL
MCV	83 fL	Lipase	33 IU/L	IgA	382 mg/dL
MCH	25.9 pg	BUN	12 mg/dL	IgM	81 mg/dL
MCHC	31.1%	Cre	0.69 mg/dL	TSH	0.419 μU/mL
Plt	53 × 10^4/μL	UA	4.3 mg/dL	fT3	2.2 pg/mL
Reticulocytes	0.7%	Na	139 mEq/L	fT4	1.27 ng/dL
PT%	76.5%	K	3.9 mEq/L	Vitamin B_1	55 ng/mL
TP	7.5 g/dL	Cl	104 mEq/L	Vitamin B_{12}	>1500 pg/mL
T-Bil	0.5 mg/dL	Ca	8.3 mg/dL	Folic acid	6.8 ng/mL
AST	15 IU/L	P	3.4 mg/dL	CRP	7.30 mg/dL
ALT	8 IU/L	Glu	170 mg/dL	ESR	>100 mm/h
ALP	255 IU/L	TG	47 mg/dL	HBsAg	(–)
LDH	139 IU/L	HDL-C	42 mg/dL	HCV-Ab	(–)
		LDL-C	56 mg/dL		

ALP, alkaline phosphatase; ALT, alanine transaminase; AMY, amylase; AST, aspartate transaminase; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; ChE, choline esterase; Cre, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Fe, iron; fT3, free triiodothyronine; fT4, free thyroxine; Glu, glucose; Hb, hemoglobin; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HDL-C, high-density lipoprotein cholesterol; Ht, hematocrit; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; K, potassium; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; P, phosphorus; Plt, platelet count; PT, prothrombin time; RBC, red blood cell count; γ-GTP, γ-glutamyl transpeptidase; T-Bil, total bilirubin; TG, triglyceride; TP, total protein; UA, uric acid; UIBC, unsaturated iron binding capacity; WBC, white blood cell count.

experience in a patient with GCA who showed a marked inflammatory response during tests for cognitive function, in whom the cause of inflammation was effectively diagnosed by FDG-PET.

Case report

An 83-year-old woman attended the outpatient department of our hospital with a chief complaint of memory loss. Her memory impairment had begun 1 year earlier and slowly progressed. From 4 months earlier, she had refused to take a bath occasionally. From 3 months earlier, she had begun to say or ask the same thing many times, and forgot appointments to meet her friends more frequently. She was aware of her memory loss. She could no longer manage money and began to dislike going shopping in the neighborhood. During the course of observation, she did not have such symptoms as jaw claudication, visual field defect, headache or numbness of the upper limbs. She had lost 3 kg in 1 month prior to admission, and was found to have a significant inflammatory response on blood tests, and was admitted to our department for further evaluation of cognitive impairment in June 2008.

She had no particular medical history. Her sister had a history of pituitary adenoma without neurological disorder or dementia. She had no family history of collagen disease. She did not smoke, and drank alcohol only on social occasions. She had no history of allergy and had never been abroad. She had been educated for 8 years. She had worked as an accountant until the age of 60 years. She lived with her daughter's family.

She was 146.0 cm tall and weighed 39.8 kg, with a body mass index of 17.3 kg/m^2. Temperature was 37.1°C, and pulse was regular (89 b.p.m.). Blood pressure was 96/56 mmHg (left upper limb) and 108/56 mmHg (right upper limb). She had clear consciousness. No arterial bruit was heard in the carotid arteries. The temporal arteries were non-tender on palpation. The palpebral conjunctivae were pale, but the bulbar conjunctivae were not icteric. Funduscopic findings were normal. Superficial lymph nodes were not palpable and the thyroid gland was not enlarged. There were no abnormal findings in the thoracoabdominal region. Examination of the skin revealed no redness or rash. The limbs were not edematous. There was no arthralgia. Neurological findings were normal.

Blood data are presented in Table 1. Urine was negative for occult blood and protein, and many white cells were observed in the urinary sediment. Chest radiograph and electrocardiogram were normal.

Neuropsychological tests showed cognitive deterioration, with a Mini-Mental State Examination (MMSE) score of 20 points, and a revised Hasegawa Dementia Scale (HDS-R) score of 16 points. Specifically, she did not score high in delayed recall, calculation, orientation and verbal recall. The 10-word recall test and the Rey–Osterrieth complex figure test also indicated a significant decline in delayed recall. She was able to recall 5 digits in the same order as they had been presented and 3 digits in the reverse order. She took 210 s to finish the trail making test part A (mean: 151 s in healthy persons), and part B was discontinued because she did not understand the task. She was thus found to have reduced overall cognitive function with memory impairment and disturbance of attention.

Cranial magnetic resonance imaging (MRI) showed diffuse cerebral atrophy on T_1-weighted images; particularly, the Sylvian fissure and the inferior horns of the lateral ventricles were dilated, while there was marked atrophy in the medial parietal and temporal lobes. T_2-weighted images and fluid-attenuated inversion recovery images showed lesions deep in the white matter and a high-signal-intensity area in the paralateral ventricles, appropriate for her age. Brain perfusion scintigraphy (^{123}I-iodoamphetamine single photon emission computed tomography) showed reduced blood flow in the medial temporal lobes, parietal-temporal association area and precuneus. Cerebrospinal fluid was colorless and transparent and showed a slightly increased protein level (65 mg/dL), with no increase in cell count (1/μL) and a normal glucose level (63 mg/dL) and blood glucose level (94 mg/dL). There was no obvious inflammatory response, with immunoglobulin (Ig)G index of 0.05 and negative test results for anti-herpes IgM and IgG antibodies. Phosphorylated tau protein level was 50.03 pg/mL (reference value: ≤31.3 pg/mL), and amyloid β1-42 level was 254.31 pg/mL (reference value: ≥1005 pg/mL), supporting the diagnosis of Alzheimer's disease.

With regard to inflammatory responses, the patient had a persistent slight fever after admission, but did not experience any obvious symptoms including apparent appetite loss. She had lost approximately 3 kg during 1 month before admission. She had shown a prolonged inflammatory response since attendance at our outpatient department, and had normocytic normochromic anemia, decreased Fe, and increased ferritin, suggesting chronic inflammation. The patient also underwent investigation for systemic diseases, including infections, malignant diseases and collagen diseases.

Urinalysis on admission showed pyuria, and she was treated with 200 mg/day of levofloxacin under a diagnosis of urinary tract infection. The urinary findings improved, while the inflammatory response did not. Plain computed tomography (CT) of the chest and abdomen, upper and lower gastrointestinal endoscopy, and transthoracic echocardiography were performed to search for the site of inflammation, but failed to detect any obvious findings. Blood cultures were negative.

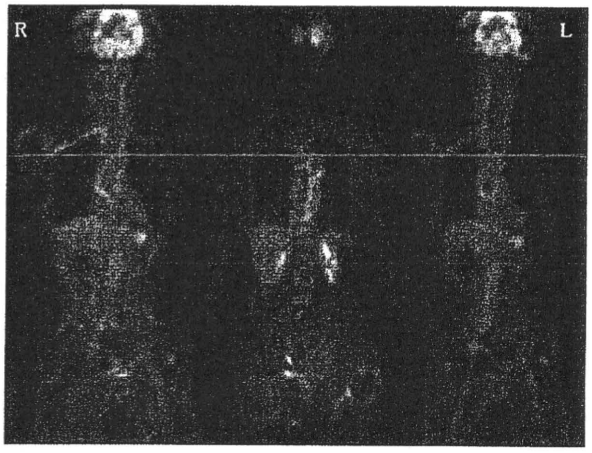

Figure 1 ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrated increased glucose uptake in the ascending aorta, both carotid arteries, both subclavian arteries, and from the descending aorta to both common iliac arteries.

To search for collagen diseases, blood tests were performed and showed an elevated rheumatoid factor titer of 1:25 and an increased anti-cyclic citrullinated peptide antibody level of 277.0 U/mL. Early rheumatoid arthritis was suspected, but the patient did not have any joint symptoms, and radiography of the joints of the whole body did not show any findings suggestive of rheumatism.

Therefore, FDG-PET (Fig. 1) was performed to identify the site of inflammation. This examination showed increased glucose uptake in the ascending aorta, both carotid arteries, both subclavian arteries, and from the descending aorta to both common iliac arteries, raising the suspicion of aortitis syndrome. Contrast-enhanced CT of the chest and abdomen (Fig. 2) showed thickening of the wall of the thoracoabdominal aorta and delayed contrast enhancement of this part of the aorta. Ultrasonography of the superficial temporal arteries revealed a halo in both superficial temporal arteries and stenosis/occlusion of both frontal branches and both occipital branches. Biopsy of the left superficial temporal artery showed giant cell and lymphocytic infiltration of the arterial wall, leading to the diagnosis of GCA (Fig. 3).

Although the patient had extensive vasculitis, treatment was initiated with 20 mg of oral prednisolone because she did not have any lesions in the ocular fundi, and taking her age into consideration. Because she had a reduced bone mass (59% and 84% of that of the young adult mean measured in the forearm and a lumbar vertebra, respectively), oral bisphosphonate was also administrated for the prevention of steroid-induced osteoporosis. Corticosteroid therapy resulted in a trend

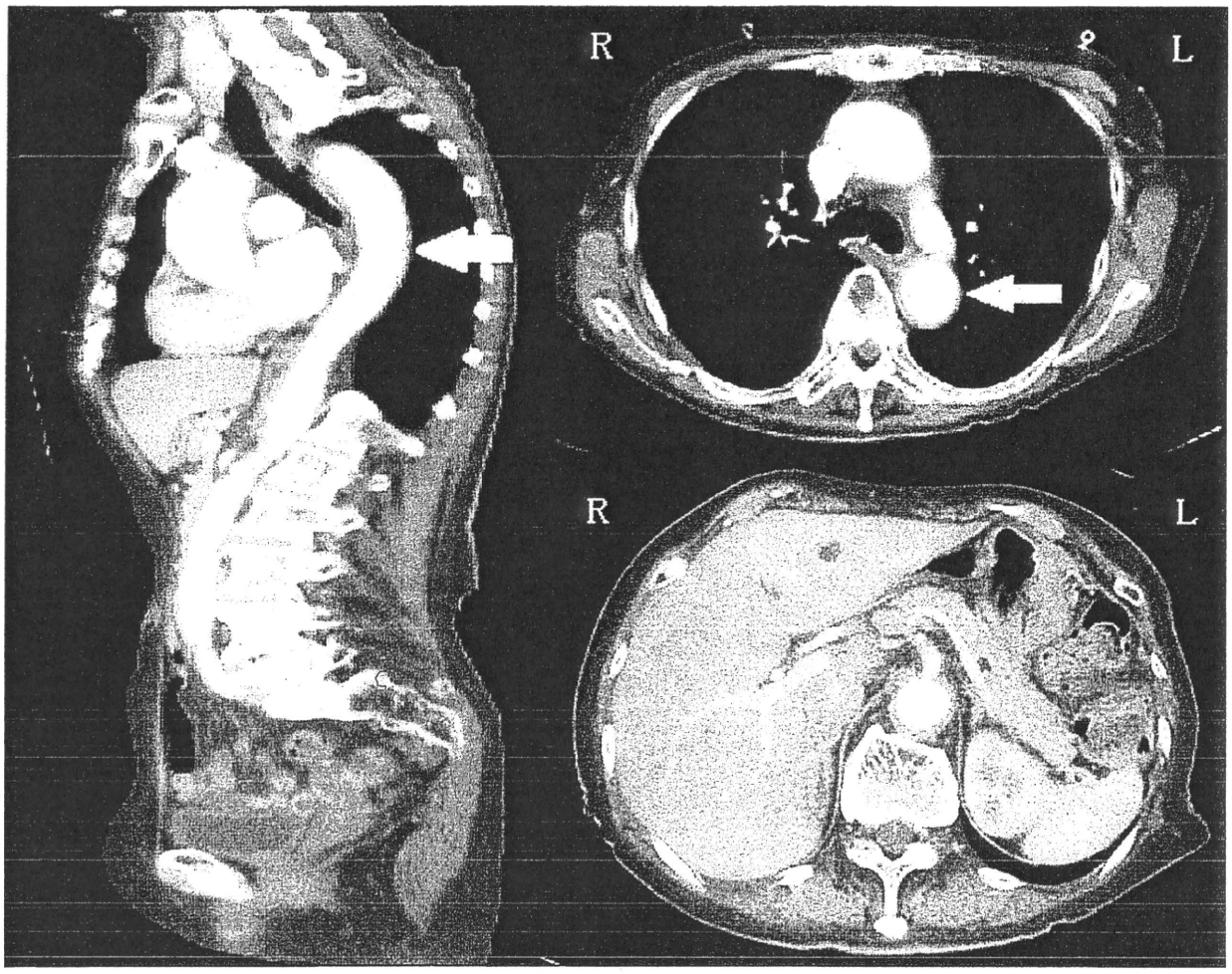

Figure 2 Contrast-enhanced computed tomography (CT) image. Contrast-enhanced CT of the chest and abdomen showed thickening of the wall of the thoracic descending aorta to the abdominal aorta and both common iliac arteries, and delayed contrast enhancement of these arteries. None of the aortic branches was stenosed.

toward improvement in the inflammatory response. The patient did not complain of her heavy headed feeling or any similar symptoms before treatment, but after successful treatment of GCA, she first recognized that she might have experienced slight dull headache. On day 29 of corticosteroid therapy, blood tests indicated improvement of the inflammatory response, with a negative result for C-reactive protein and an erythrocyte sedimentation rate of 21 mm after 30 min and 52 mm after 60 min. Accordingly, the dose of prednisolone was reduced to 18 mg. On day 32 of corticosteroid therapy, contrast-enhanced CT demonstrated reduced thickening of the aortic wall and reduced contrast enhancement. Neuropsychological tests were performed again on days 10 and 29 after initiation of oral corticosteroid therapy, but revealed no improvement (day 10: MMSE, 21 points; HDS-R, 13 points. Day 29: MMSE, 17 points; HDS-R, 12 points). The patient subsequently made favorable progress and was discharged.

Discussion

Giant cell arteritis normally occurs in patients aged 50 years or older. It is a granulomatous angiitis involving the aorta and its major branches. According to the classification proposed by the American College of Rheumatology,[4] GCA should be diagnosed if at least three of the following five criteria are present: (i) age at disease onset of 50 years or more; (ii) new onset of localized headache; (iii) temporal artery tenderness to palpation or decreased pulsation; (iv) elevated erythrocyte sedimentation rate (≥50 mm/h); and (v) biopsy specimen with an artery showing necrotizing vasculitis characterized by a predominance of monocytes, or granulomatous change with multinucleated giant cells.

Because our patient did not complain of headache at first, FDG-PET, which was performed to identify the site of inflammation, played an important role in diagnosis.

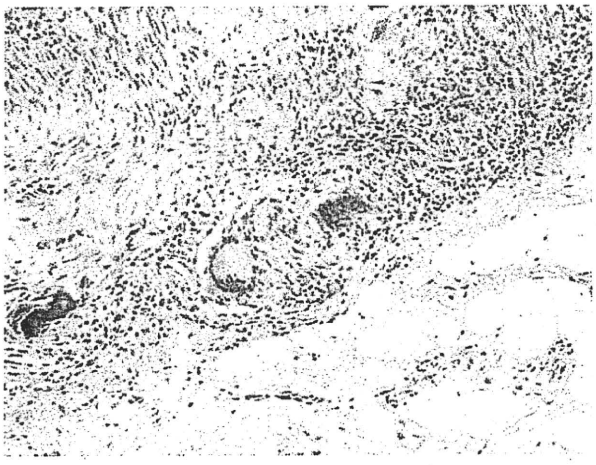

Figure 3 Histological findings of temporal artery. Biopsy of the left superficial temporal artery showed multinucleated giant cell and lymphocytic infiltration of the internal elastic lamina of the arterial wall (hematoxylin–eosin, original magnification ×200).

Brack *et al.* reported that GCA can be divided into two groups: classic cranial GCA and large-vessel GCA. They mentioned that headache was the most frequent symptom for cranial GCA (42%), but not for large-vessel GCA.[5] According to them, vasculitis is present around the aorta in large-vessel GCA. Temporal artery biopsy findings were negative in 42% of patients with large-vessel GCA, and many patients had ischemic disorders of the upper limbs (arterial bruit, 80%; pain on movement, 78%; difference in blood pressure measured in both arms, 58%) as initial symptoms, while only 10% of patients had headache as an initial symptom. They also reported that the time from disease onset to diagnosis was significantly longer in patients with vasculitis only involving the cranial arteries.[5] Although there has been a report of a patient without headache in whom GCA was diagnosed on the basis of elevated glucose uptake in the aorta detected by FDG-PET, as was the case in our patient,[6] thickening of the vessel wall shown by CT or MRI is also known to be a useful finding.[7,8] The clinical course in our patient was consistent with that of large-vessel GCA, and she may have had fewer symptoms in the head and neck compared to those in the trunk and upper limbs. In addition, she may not have been able to accurately express her symptoms because of Alzheimer's disease.

Some patients with GCA also have cerebral infarction or transient cerebral ischemia resulting from vasculitis. In one study, 3% of patients with GCA had psychiatric symptoms, including depression,[9] but it is not clear whether ischemia was involved in the mechanism. While there is a report of GCA in a patient with cognitive impairment that was improved by corticosteroid therapy,[10] our patient did not show any change in cognitive function after initiation of corticosteroid therapy, and thus there seems to be no relation between GCA and cognitive impairment. The decline of the score of MMSE was considered that it might be the effect of corticosteroids or hospitalization or progression of Alzheimer's disease. Our patient's course was also consistent with the diagnosis of Alzheimer's disease.

As detailed above, GCA should be positively differentiated when elderly patients have an inflammatory response, even if they do not have typical symptoms such as headache. In our patient, GCA was effectively diagnosed by evaluation of blood vessels by imaging, including FDG-PET and contrast-enhanced CT. Because of its high sensitivity in an active inflammatory state,[2] FDG-PET might become a powerful diagnostic tool in the management of large-vessel inflammation.

Acknowledgments

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ORIGINAL ARTICLE

Causes of decreased activity of daily life in elderly patients who need daily living care

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Aim: The causes of decreased activity of daily life (ADL) in elderly patients include cerebrovascular diseases, bone fracture by falls, and dementia. The present study was conducted among elderly patients with decreased ADL who were hospitalized in nursing wards in order to investigate the causes of becoming early bedridden and to determine precautionary measures against decreased ADL.

Methods: The study subjects were 224 elderly patients with decreased ADL (mean age: 83.3 ± 8.0 years) and 49 outpatients without decreased ADL (mean age: 76.8 ± 5.3 years). Current age, age at the start of ADL decrease, medical history and history of smoking were investigated.

Results: In the groups with decreased ADL, current age and the age of becoming bedridden in non-diabetic versus diabetic groups were 84.7 ± 7.9 versus 80.3 ± 7.5 and 82.7 ± 8.3 versus 77.6 ± 8.0 years, respectively, both showing significantly lower values in the diabetic group ($P < 0.05$). Multiple regression analysis revealed that sex difference and diabetes were the factors determining the age of becoming early bedridden. Diabetic patients with smoking habit were significantly younger than diabetic and non-diabetic patients without smoking habit.

Conclusion: Sex difference, smoking habit and presence of diabetes mellitus are independent risk factors of becoming early bedridden. Therefore, the major targets of medical care among elderly should be diabetic men with a smoking habit to lower the risks of decreased ADL. **Geriatr Gerontol Int 2011; 11: ••–••.**

Keywords: activity of daily life, bedridden, diabetes mellitus, elderly, smoking habit.

Introduction

In our country, an aging population is already prominent and we will face further increase in the elderly population who need daily living care. The financial and psychological burden of families as well as the rise of medical expenditure in the national budget have become serious social problems demanding urgent countermeasures.

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The causes of decreased activities of daily living (ADL) of Japanese elderly include cerebrovascular diseases (27.7%), bone fracture by falls (11.8%) and dementia (10.7%), all of which result from complicated or overlapped lifestyle diseases.[1]

On the other hand, the incidence of metabolic syndrome, which is a combination of lifestyle diseases, has continued to increase with age in Japan, with high rates among men (29.7%) and women (19.3%) alike after 70 years of age.[2] Failure to intervene in metabolic syndrome is usually followed by the onset of type 2 diabetes mellitus in a short time. It has been reported that, once the diagnosis of diabetes mellitus is made, overall life expectancy is shortened by approximately 7 years.[3]

In older populations, failure of independent living or self-support increases with disturbed ADL or cognitive functions due to major and minor vascular diseases.

Because these conditions significantly compromise quality of life (QOL), early and vigorous control of lifestyle diseases is required to maintain QOL among the elderly.

According to the World Health Organization, the health age, which refers to the age without decreased ADL, of the Japanese is 74.1 years, while the average life expectancy is approximately 80 years (men 78.6, women 85.6 years).[4] In particular, falls among the elderly is one of the important causes of decreased ADL, which is experienced by 30% of the US population aged 75 years or older.[5,6] Investigation on the risk factors of falls, therefore, would be helpful in reducing mortality and morbidity in this age group. The National Service Framework for the elderly also emphasizes the prevention of falls, especially in the high-risk group.[7–10]

However, comprehensive studies have rarely been conducted on the causes of decreased ADL such as nutritional status and atherosclerotic conditions as well as the presence of lifestyle diseases including type 2 diabetes among the elderly. It is well-known that patients with diabetes mellitus develop complications such as retinopathy at late stage, neuropathy and nephropathy, which may lead to decreased ADL. Therefore, we hypothesized that age of becoming bedridden in diabetic patients is younger than non-diabetic patients.

Consequently, this study was conducted on elderly patients with decreased ADL who were hospitalized in nursing wards in order to investigate the causes of decreased ADL, to evaluate nutritional status and atherosclerotic conditions, and to determine precautionary measures against decreased ADL.

Methods

The study subjects consisted of 224 elderly patients (mean age: 83.3 ± 8.0 years) with decreased ADL who were hospitalized in Inamino Hospital, Hyogo, Japan (Table 1). A total of 155 patients were non-diabetic (113 female) and 69 patients had diabetes mellitus (47 female). Sixty non-diabetic and 29 diabetic patients with decreased ADL were excluded from the analysis of age of decreased ADL, because of the lack of exact information concerning the age at decreased ADL from their families.

On the other hand, 49 outpatients (mean age: 76.8 ± 5.3 years) at Kobe University Hospital with favorable ADL were enrolled as the control group, of which 22 patients were non-diabetic (15 female) and 27 patients had diabetes mellitus (10 female). Informed consent was signed by the families of all hospitalized

Table 1 Characteristics of 2 study groups

	Decreased ADL (n = 224)	Favorable ADL (n = 49)
Age (years)	83.3 ± 8.0	76.8 ± 5.3
Age of decreased ADL (years)	81.2 ± 8.5 (n = 135)	
BMI (kg/m^2)	18.4 ± 3.4	21.0 ± 2.9
Alb (g/dL)	3.4 ± 0.4	4.1 ± 0.3
TC (mg/dL)	171.3 ± 37.6	202.4 ± 34.6
TG (mg/dL)	90.5 ± 40.9	126.8 ± 70.1
HDL-C (mg/dL)	53.0 ± 16.9	64.4 ± 21.6
LDL-C (mg/dL)	99.9 ± 30.7	113.9 ± 27.8
SBP (mmHg)	122.2 ± 20.6	131.7 ± 17.4
DBP (mmHg)	67.2 ± 11.8	67.4 ± 11.0
IMT (mm)	1.2 ± 0.5 (n = 112)	
HDS-R	10.8 ± 8.1 (n = 117)	
CVD	39.2% (n = 135:yes 53, no 82)	
Fall fracture	24.4% (n = 135:yes 33, no 102)	
Dementia	9.6% (n = 135:yes 13, no 122)	
Infection	9.6% (n = 135:yes 13, no 122)	
Smoking	24.0% (n = 104:yes 25, no 79)	

ADL, activity of daily life; Alb, serum albumin; BMI, body mass index; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HDS-R, Hasegawa dementia scale – Revised; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; NDM, non-diabetic; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

patients and by the outpatients themselves. This study was approved by each local ethics committee. This study was performed from April 2005 to March 2008.

With regard to independent living of the disabled, we used the classification of the Japanese long-term care insurance, patients were classified as chair-bound (B) (39.3%) and the others were classified as bed-bound (C) (60.7%).[11]

According to medical record information provided by the families, the causes of decreased ADL were categorized into cerebrovascular diseases, bone fracture by fall, dementia, infection and others. Current age, age at the start of ADL decrease, intima-media thickness (IMT) measured by carotid artery ultrasonography, medical history, body mass index (BMI), blood pressure, blood glucose, HbA1c, lipid profiles (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], small dense LDL cholesterol [sLDL-C], triglyceride [TG]) and serum albumin were investigated. History of cigarette smoking was also taken. The definition of "smoking habit" indicates patients who had experienced smoking. All patients with impaired ADL were not current smokers because smoking was prohibited in the hospital.

The severity of dementia was evaluated using the Hasegawa Dementia Scale – Revised (HDS-R). Blood sugar, HbA1c, lipid profiles and sLDL-C were measured using the hydrogen peroxide electrode method, high-performance liquid chromatography, an automated lipid analyzer and the method reported by Hirano *et al.*,[12] respectively.

Simple regression analysis for age at the start of ADL reduction was performed with respective risk factors as independent variables (sex, diabetes mellitus, BMI, cerebrovascular diseases and serum albumin levels). Thereafter, multivariate regression analysis was performed using StatView ver. 5.0 for Windows in order to find the independent association of lifestyle risk factors with the age of becoming bedridden. Hypertension and dyslipidemia were entered as covariates besides variables that were shown to have significant simple correlation with the age at the start of ADL reduction. ANOVA followed by Scheffe's multiple comparison test was used for analysis between four study groups. The χ^2-test was also employed for comparison of frequency of bone fracture between the non-diabetic and diabetic groups of decreased ADL. Data were expressed as mean ± standard deviation.

Results

In the groups with decreased ADL, current age and the age at the start of ADL decrease of the diabetic group were lower than non-diabetic patients ($P < 0.05$ by ANOVA, Table 2). BMI and serum albumin tended to be higher in diabetic patients with decreased ADL. The levels of LDL-C and TG were higher in groups with favorable ADL and without diabetes mellitus. Blood pressure was not significantly different between any group. In the decreased ADL group, lipid parameters (except for TG) and IMT on carotid artery ultrasonography did not show any significant differences between

Table 2 Characteristics of four study groups

	Decreased ADL		Favorable ADL	
	Non-diabetics ($n = 155$)	Diabetics ($n = 69$)	Non-diabetics ($n = 22$)	Diabetics ($n = 27$)
Age (years)	84.7 ± 7.9†	80.3 ± 7.5‡	77.0 ± 5.9‡	76.7 ± 4.9‡
Age of decreased ADL (years)	82.7 ± 8.3† ($n = 95$)	77.6 ± 8.0‡ ($n = 40$)		
BMI (kg/m^2)	17.9 ± 3.3†	19.6 ± 3.2‡	20.5 ± 3.0‡	21.4 ± 2.8‡
Alb (g/dL)	3.3 ± 0.4†	3.5 ± 0.4‡	4.1 ± 0.3§	4.1 ± 0.3§
HbA1c (%)		6.4 ± 1.1		7.2 ± 1.2
TC (mg/dL)	170.1 ± 37.0†	174.1 ± 37.4†	212.8 ± 39.5‡	193.9 ± 27.9‡
TG (mg/dL)	88.0 ± 41.0†	95.9 ± 40.6‡	133.5 ± 64.0§	121.4 ± 75.5§
HDL-C (mg/dL)	54.6 ± 17.2†	52.3 ± 16.2†	70.0 ± 17.1‡	60.1 ± 14.0§
LDL-C (mg/dL)	99.1 ± 30.7†	102.6 ± 31.3†	119.3 ± 31.6‡	110.0 ± 23.9‡
SBP (mmHg)	120.5 ± 20.5†	125.7 ± 20.3†	133.6 ± 19.3†	130.2 ± 16.0†
DBP (mmHg)	67.6 ± 12.0†	66.4 ± 11.4†	65.3 ± 12.5†	69.1 ± 9.6†
IMT (mm)	1.2 ± 0.3†	1.2 ± 0.6†		
HDS-R	9.8 ± 7.6† ($n = 66$)	12.2 ± 8.6‡ ($n = 51$)		

†‡§There are significant differences between the groups not sharing the same symbol by ANOVA ($P < 0.05$). ADL, activity of daily living; Alb, serum albumin; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HDS-R, Hasegawa Dementia Scale – Revised; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; NDM, non-diabetic; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 3 Simple regression analysis to explore the determinant of disabled age of decreased ADL patients

	Regression coefficient	95% CI, upper	95% CI, lower	*P*-value
Sex (M 1, F 0)	−4.78	−1.33	−8.22	<0.05
BMI	−0.54	−0.12	−0.96	<0.05
Alb	−5.13	−1.89	−8.36	<0.05
DM (yes 1, no 0)	−5.19	−2.13	−8.25	<0.05
CVD (yes 1, no 0)	−3.16	−0.23	−6.09	<0.05
Fall fracture (yes 1, no 0)	1.72	5.24	−1.80	<0.05
Smoking (yes 1, no 0)	−0.01	−0.001	−0.02	0.07
HT (yes 1, no 0)	1.78	4.68	−1.12	0.23
DL (yes 1, no 0)	−1.84	−1.41	−5.09	0.26

ADL, activities of daily living; Alb, serum albumin; BMI, body mass index; CI, confidence interval; CVD, cerebral vascular disease; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension.

non-diabetic and diabetic groups (Table 1). sLDL-C level was measured in 24 non-diabetic and 18 diabetic patients, which were significantly higher in the diabetic group (16.7 ± 11.2 vs 26.2 ± 15.5 mg/dL, $P < 0.05$). Cognitive function was evaluated by HDS-R in 66 of 155 (42.5%) and 51 of 69 (73.9%) patients in non-diabetic and diabetic patients of the decreased ADL group, respectively, which is significantly higher in the diabetic patients of the decreased ADL group. However, the scores were 9.8 ± 7.6 and 12.2 ± 8.6, respectively, and the difference was not significant.

In the group with decreased ADL, 95 (20 male, 75 female) and 40 (11 male, 29 female) patients were non-diabetic and diabetic, respectively, at the age of becoming bedridden, while 22 patients were non-diabetic (seven male, 15 female) and 27 patients had diabetes mellitus (17 male, 10 female) in the favorable ADL group.

In the decreased ADL group, the coronary risk levels were categorized according to the number of risk factors (hypertension, dyslipidemia, diabetes mellitus) into three groups: the group with three risk factors, the group with two risk factors, the group with a single risk factor and the group with no risk factor. The age at the start of ADL decrease of the group with three risk factors was 77.2 ± 10.5 years, the group with two risk factors, with a single risk factor and with no risk factor were 80.5 ± 8.6, 81.3 ± 9.0 and 82.5 ± 7.3 years, respectively.

Causes of decreased ADL were clarified in 95 non-diabetic and 40 diabetic patients. The incidence of cerebrovascular diseases was 47.5% and 35.5% in diabetic and non-diabetic participants, respectively, and diabetic bedridden patients after cerebrovascular diseases were younger than non-diabetic individuals (75.1 ± 8.0 vs 82.0 ± 10.0 years, $P < 0.05$). The frequency of patients with bone fracture by fall in the diabetic group was higher than in the non-diabetic (32.5% vs. 21.1%) but the difference was not significant by the χ^2-test. The prevalence of dementia as a reason for ADL reduction was 7.5% and 16.1% in the diabetic and non-diabetic groups, respectively. While 10.5% of non-diabetic patients were bedridden after some serious infection such as pneumonia, no bedridden case after infection was found in the diabetic group.

Simple regression analysis for the age at the start of ADL reduction were performed with respective risk factors as independent variables. Male sex ($P = 0.01$), presence of diabetes mellitus ($P = 0.01$), higher BMI ($P = 0.01$), cerebrovascular diseases ($P = 0.03$) and higher levels of serum albumin ($P = 0.002$) were significantly associated with younger age of becoming bedridden (Table 3). To find the independent association of lifestyle risk factors with the age of becoming bedridden, hypertension and dyslipidemia were entered as covariates besides variables that were shown to have significant correlation ($P < 0.05$) in subsequent multivariate regression analysis. As a result, male sex, higher BMI, higher levels of serum albumin and presence of diabetes mellitus were the independent factors determining the age of becoming bedridden, while hypertension and dyslipidemia were not selected as an independent determinant (Table 4). These results showed the pronounced effects of diabetes on the severe impairment of ADL.

Because smoking habit seemed to have a substantial impact on the age at the start of ADL reduction, we further compared the additive effects of diabetes and smoking on the age of becoming bedridden. As shown in Figure 1, diabetic patients with smoking habit were significantly younger than diabetic and non-diabetic patients without smoking habit.

Discussion

As already mentioned, the population requiring daily living care in Japan has been steadily increasing. The

Table 4 Multiple regression analysis to explore the determinant of disabled age of decreased ADL patients

	Regression coefficient	95% CI, upper	95% CI, lower	*P*-value
Sex (M 1, F 0)	−4.40	−1.10	−7.69	<0.05
BMI	−0.43	−0.02	−0.84	<0.05
Alb	−4.16	−1.05	−7.27	<0.05
DM (yes 1, no 0)	−3.69	−0.68	−6.70	<0.05
CVD (yes 1, no 0)	−2.00	−0.86	−4.86	0.17
HT (yes 1 no 0)	2.00	4.64	−0.72	0.15
DL (yes 1, no 0)	−0.05	3.12	−3.22	0.98

ADL, activities of daily living; Alb, serum albumin; BMI, body mass index; CI, confidence interval; CVD, cerebrovascular disease; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension.

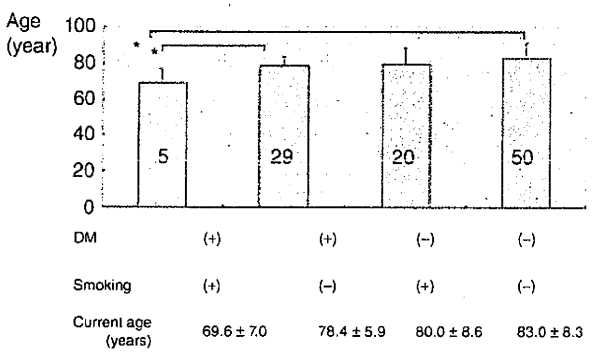

Figure 1 Mean age of bedridden of diabetic and non-diabetic patients with and without smoking habit. The number in the column represents the number in each group. *There are significant differences between each group by ANOVA ($P < 0.05$). DM, diabetes mellitus.

causes of this status are considered to include stroke, dementia and bone fracture by falls, all of which are closely associated with the progression of cerebral atherosclerosis. We conducted this study to investigate the causes of decreased ADL and the bedridden status, as well as to determine precautionary measures for shortening the bedridden period.

In the two groups with decreased ADL, the mean ages of the diabetic group were significantly younger than those of the non-diabetic groups. In other words, elderly diabetics will reach bedridden status approximately 5 years earlier than non-diabetics. Indeed, it is obvious that aging is one of the most important factors for decreased ADL. However, another group of old outpatients with comparable age to that of the decreased ADL group was not available. this time. The diabetic patients with impaired ADL were under strict energy control in the hospital. On the other hand, the diabetic patients without impaired ADL were all outpatients and therefore they had free access to any food. Thus, diabetic patients without impaired ADL showed a higher HbA1c level than that of those with impaired ADL.

Roliz-Cruz *et al.* have reported that metabolic syndrome carries a 2.2-times higher risk for decreased ADL than the non-metabolic elderly population.[13] Because hyperglycemia is a major component of metabolic syndrome, the results of our study support this estimate.

The numbers of patients who were able to be evaluated using HDS-R were 51 of 69 (73.9%) and 66 of 155 (42.5%), which was obviously higher in the diabetic group. Furthermore, the mean HDS-R score did not differ between the two groups. It was suggested that the diabetic group was younger and the their periods after becoming bedridden were shorter than the non-diabetic group, and consequently, patients with more severe dementia were fewer in the diabetic group. The frequency of cerebrovascular diseases in the diabetic group was higher than that of the non-diabetic group. Also, diabetic patients who had decreased ADL by cerebrovascular disease were significantly younger than non-diabetics. From these results, it can be concluded that diabetics have a higher risk of becoming bedridden due to stroke. In support of this, it has been widely reported that diabetics have a higher mortality, with cerebrovascular diseases being an independent risk factor.[14–18]

Dementia is known to be one of the complications of the cerebrovascular disease. According to the Copenhagen Stroke Study, it was proven that the mean age of patients with cerebrovascular disease complications was younger in the diabetic group than in the non-diabetic group by 3.2 years.[16] On the other hand, in this study the frequency of dementia was not higher in the diabetic group than the non-diabetic group. The influence of older mean age in the non-diabetic group than in the diabetic group was suggested with regard to dementia.

A recent Taiwanese study on diabetes mellitus and bone fracture has reported a higher risk of femoral fracture in diabetic patients.[19] Functional impairment of osteoblasts[20] and apoptosis of osteoblasts induced by enhanced gluconeogenesis[21] have been suggested as the underlying mechanisms. Menz *et al.* have reported that diabetic individuals with peripheral neuropathy had

impaired peripheral sensation and reaction time, and had impaired ability to stabilize their body when walking on irregular surfaces.[22] They also had reduced walking speed and step length, and less rhythmic acceleration patterns at the head and pelvis compared with controls.[23] In this study, the experience of bone fracture in diabetic subjects with decreased ADL was more frequent than that of non-diabetics, but the difference was not significant. Further study will contribute to better understanding of the influence of bone fracture on decreased ADL of diabetic patients.

Infection was considered to be the cause of decreased ADL in 12.9% and 0% of the patients in the non-diabetic and diabetic groups, respectively. This is contrary to the fact that the defense mechanism against infection is weakened in diabetics. We believe that further research is needed to clarify this finding. With regard to sex, men showed an odds ratio of 2.11 on diabetes and fracture, which are both associated with decreased ADL.[24] Furthermore, because increased BMI may lead to failure of independent living, men over 50 years should particularly be paid attention to in this index.[25]

In this study, the levels of sLDL-C were significantly higher in the diabetic group than in the non-diabetic group (17.0 ± 11.4 vs 25.2 ± 10.6 mg/dL; $P < 0.05$ by ANOVA). The atherogenic phenotype, which refers to a tendency to demonstrate a predominant sLDL-C, has been reported to have a higher risk of myocardial infarction.[26] Increased sLDL-C has also been reported in diabetics.[27] Increased sLDL-C in the diabetic group suggests susceptibility to cerebrovascular diseases in elderly diabetics, and consequently, lower age at becoming bedridden than in the non-diabetic group.

In spite of the overt higher risk in diabetics, plaque scores on carotid artery ultrasonography were not significantly different between the two groups. This may be due to the younger mean age of patients in the diabetic group.

Simple regression analysis on age of becoming bedridden suggested a correlation with sex, BMI, diabetes mellitus and serum albumin. Multiple regression analysis revealed that sex, BMI, serum albumin and the presence of diabetes mellitus were the factors determining the age of becoming bedridden. However, because BMI scores used in this study were determined from weights measured during the observation period, which might differ from those measured at hospitalization from decreased ADL, BMI cannot be considered as one of the causes of the bedridden status. In addition, multiple regression analysis using age at the bedridden status as a dependent variable and the presence of diabetes mellitus and smoking history as independent variables suggested that both diabetes mellitus and smoking history were correlated with the age of becoming bedridden. Therefore, it can be concluded that diabetic men with a smoking history among the elderly become bedridden at the youngest age.

The limitations of the present study are as follows: First, because this investigation is a cross-sectional study of a number of severely demented patients with a mean HDS-R score of 10.8, the causes of decreased ADL were estimated from medical records instead of being directly obtained from the patients. Second, because the range of the subjects examined was limited to patients hospitalized in a nursing ward, it was difficult to compare the examined groups to a healthy elderly group. Third, with regard to diabetes mellitus, interpretation was not performed regarding types (two type I vs 67 type II patients) and treatments (32% with insulin vs 36% with oral hypoglycemic agents). Fourth, the number of bedridden diabetics with smoking habit was only five. Because this patient group was very young, it is possible that many of them might have been dead earlier in a nursing ward. This conjecture warrants retrospective analysis using deceased patient records. Fifth, complications of diabetes mellitus, especially retinopathy, were not considered as a significant factor. Because complications of diabetes mellitus such as visual disturbance, peripheral neuropathy and nephropathy have been reported to be risk factors of falls in the elderly,[28] this area needs further studies. Finally, causes of dependence should be multi-factorial and heterogeneous. However, undernutrition cannot be the main cause of dependence in our wards although undernutrition can be the results of bedridden status.

In conclusion, among diabetes mellitus, hypertension and dyslipidemia, this study showed that diabetes mellitus is an independent risk factor of becoming bedridden. In the diabetic groups, cerebrovascular diseases were the major causes of becoming bedridden at a younger age. Also smoking habit was an independent determinant of becoming bedridden at a younger age. Therefore, the major targets of medical care among elderly should be diabetic male patients with a smoking habit in order to lower the risk of becoming bedridden at a younger age.

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