ORIGINAL ARTICLE

B-type natriuretic peptide is predictive of hospitalization in community-dwelling elderly without heart diseases

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Aim: To examine prospectively the relationship between plasma B-type natriuretic peptide (BNP) levels in community-dwelling elderly and their hospitalization.

Methods: A total number of 644 subjects aged 65 years or older were recruited from the annual community health examinations. Those with a history of stroke or neurological findings were not included. After excluding those with old myocardial infarction, left ventricular dysfunction, moderate or severe valvular disorders, atrial fibrillation, renal insufficiency, and history of hospitalization within 1 year, 602 participants (226 men, 376 women; mean age, 80.3 ± 6.2 years) remained eligible for this study. Antihypertensive medications, activities of daily living (ADL) score and history of hospitalization were assessed by annual interview. Measurement of casual blood pressure, Mini-Mental State Examination, electrocardiography and echocardiography were performed. Plasma BNP, serum creatinine, total cholesterol, albumin and hemoglobin A1c levels were also examined. A follow-up survey was performed for the occurrence and reasons for hospitalization.

Results: During a median follow up of 37 months, 112 subjects were hospitalized. After adjustment for conventional risk factors of hospitalization using the Cox proportional hazard model, each increment of 1 standard deviation in log BNP levels was associated with a 36% increase in the risk of hospitalization ($P = 0.02$). Plasma BNP levels were significantly higher in the hospitalized subjects due to stroke, heart diseases, dementia, pneumonia and also difficulty to live alone than those of the subjects without hospitalization.

Conclusion: Plasma BNP level is a very useful biochemical marker predictive of future hospitalization in community-dwelling independent elderly people without apparent heart diseases.

Keywords: B-type natriuretic peptide, community-dwelling elderly, hospitalization.

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Introduction

In our rapidly aging societies, it is very important to take preventive intervention for elderly people requiring care and medical treatment to reduce the numbers of frail elderly.[1] There have been many approaches to predict the risk of care-requiring, frail conditions based on the actual status of activities of daily living (ADL) of the elderly. However, there are few biochemical markers that represent frailty of the elderly, except for markers of poor nutrition, such as serum total cholesterol and albumin,[2,3] or electrolyte.[4]

B-type natriuretic peptide (BNP) is a member of the natriuretic peptide family;[5] biosynthesis of BNP is known to increase in the presence of cardiac failure.[6] Recent reports have suggested that elevated plasma BNP level is related to the development of stroke and transient cerebral ischemic attack.[7,8] A relationship between plasma BNP level and mortality was also reported in the elderly.[9] However, many of these reports are either limited to the very elderly accommodated in nursing homes[10,11] or the functionally-impaired elderly,[12] or have focused on the elderly with heart diseases.[13,14]

Thus, in the elderly living independently in the community, the clinico-epidemiological relevance of elevated plasma BNP level is unclear. We have therefore examined plasma BNP level in community-dwelling elderly people without apparent heart diseases, and discuss its usefulness as a marker of future hospitalization which can be thought as one of the events representing frailty of the elderly.

Methods

Subjects

A total of 644 independent subjects aged 65 years or older had been recruited from the annual community health examination between 2000 and 2003. The end of follow-up survey was 2004. By definition, those with a history of stroke and those with neurological findings were not included in this study. The patients had consented that the results of their health examinations be used. The study was performed in "K town", in a rural area of Japan, in which subjects older than 65 years account for 37% of the total population. We excluded 32 subjects who had been diagnosed with old myocardial infarction, moderate to severe mitral or aortic valvular disorders, or moderate to severe left ventricular dysfunction with fractional shortening of less than 20%, on first health examinations. Three subjects whose serum creatinine levels exceeded 2.0 mg/dL, and seven subjects who were diagnosed with atrial fibrillation were also excluded. Thus, 602 subjects (226 men, 376 women; mean age, 80.3 ± 6.2 years) remained eligible for this study.

Parameters

All subjects completed questionnaires regarding current ADL and antihypertensive medications. When the subjects had a history of brain magnetic resonance imaging (MRI) examination, a questionnaire regarding asymptomatic findings of MRI including lacunae and white matter lesions was also obtained. Seven items of ADL were assessed; namely, walking, ascending and descending stairs, feeding, dressing, toileting, and bathing, noting the help required on a 4-point scale as our previous study:[15] 3, completely independent; 2, need some help; 1, need much help; 0, completely dependent. The Barthel index[16] adjusted for Japanese lifestyle was also assessed. Cognitive function was evaluated by Mini-Mental State Examination (MMSE). Casual blood pressure with the average value of two readings at rest in sitting position was measured. All subjects had blood drawn when they participated in their first health examination. These blood samples were placed in cold storage immediately after collection and were measured within 48 h. As blood biochemical examination, plasma BNP, serum creatinine, total cholesterol, albumin and hemoglobin A1c (HbA1c) levels were determined. Plasma BNP was measured using a radioimmunoassay method with Sionoria (Shionogi, Tokyo, Japan). Electrocardiography was also performed. To examine the left ventricular systolic function and valvular disorder, echocardiography was performed by cardiologists.

Follow-up survey

We had followed up all of the subjects concerning hospitalization and evaluated the reasons for hospitalization following the first health examination till 2004. The district nurses confirmed the reasons for hospitalization. The median follow-up period was 37 months (range, 2–48 months). Concerning 112 subjects who were hospitalized, duration to hospitalization was also analyzed; the median duration to hospitalization was 22 months (range, 2–48 months). Six of the 602 subjects moved out of the community over the course of the investigation and were treated as censored data.

Statistical analysis

Hospitalized subjects were compared with those without hospitalization, according to demographic characteristics, age, sex, serum creatinine, total cholesterol, albumin, plasma BNP and HbA1c levels, systolic blood pressure, MMSE score, ADL score and antihypertensive medications.

Then, to confirm the usefulness of plasma BNP level as a predictive marker for hospitalization, we used age, sex, serum creatinine, total cholesterol, albumin and

plasma BNP levels and asymptomatic brain MRI findings as covariates with the Cox proportional hazard model. In this analysis, log-transformed plasma BNP level was used for analysis because log plasma BNP exhibited a normal distribution.

Results

Characteristics of the study population

A total of 112 subjects were hospitalized during the follow up: 47 subjects died during hospitalization and 65 subjects survived. There were 490 healthy subjects who survived without hospitalization (Fig. 1). As shown in Table 1, compared with subjects without hospitalization, hospitalized subjects were older ($P < 0.001$) and included more men ($P = 0.02$). They had significantly higher plasma log BNP levels ($P < 0.001$). They also had higher serum creatinine levels ($P < 0.001$), lower serum total cholesterol levels ($P = 0.008$), lower serum albumin levels ($P = 0.003$), lower MMSE scores ($P < 0.001$) and lower ADL scores ($P < 0.001$). They had higher prevalence of asymptomatic brain MRI findings ($P < 0.001$) (Table 1).

Factors related to hospitalization

Plasma BNP level, ADL score, and asymptomatic brain MRI findings remained as factors significantly related to hospitalization, after analysis with the Cox proportional hazard model using age, sex, serum creatinine, serum total cholesterol, serum albumin and plasma BNP levels, MMSE score, ADL score and asymptomatic brain MRI findings as covariates. The adjusted hazard ratio of 1 standard deviation (SD) increment of log plasma BNP level was 1.36 (95% confidence interval [CI], 1.05–1.75; $P = 0.02$). That of one point decrement in ADL score was 1.23 (95% CI, 1.08–1.40; $P = 0.001$), and that for asymptomatic brain MRI findings was 3.24 (95% CI, 1.96–5.36; $P < 0.001$). Age, sex, serum creatinine, total cholesterol and albumin levels were not independently related to hospitalization (Table 2). The area under the receiver–operator curve (ROC) for plasma BNP and hospitalization was 0.620 (95% CI, 0.557–0.682).

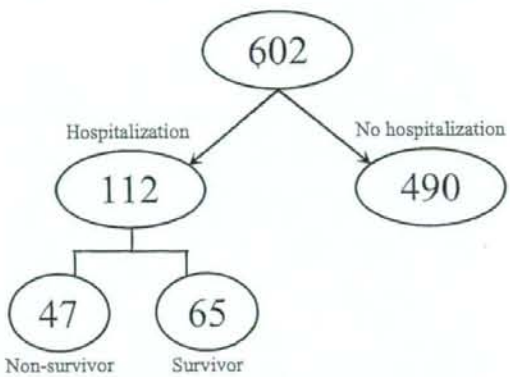

Figure 1 Study subjects and clinical course. Six hundred and two subjects were eligible for this study. A total of 112 subjects were hospitalized. A total of 47 subjects died during follow up. There were 65 subjects who were hospitalized but survived. There were 490 healthy subjects who survived without hospitalization.

Table 1 Baseline characteristics

Characteristics	Hospitalized subjects ($n = 112$)	Subjects without hospitalization ($n = 490$)	*P*-value*
Age (years)	83.2 ± 6.3	79.6 ± 5.9	<0.001
Men (%)	52/112 (46.4%)	174/490 (35.6%)	0.02
Creatinine (mg/dL)	0.86 ± 0.25	0.78 ± 0.18	0.001
Total cholesterol (mg/dL)	189 ± 39	199 ± 32	0.008
Albumin (mg/dL)	4.18 ± 0.36	4.26 ± 0.25	0.003
Log BNP (pg/mL)	1.75 ± 0.42	1.58 ± 0.34	<0.001
Hemoglobin A1c (%)	5.38 ± 0.64	5.46 ± 0.86	0.33
Casual systolic blood pressure (mmHg)	143 ± 21	143 ± 24	0.85
MMSE	25.9 ± 3.8	27.0 ± 2.8	0.005
ADL score (range 0–21)	20.2 ± 1.9	20.7 ± 1.1	<0.001
Asymptomatic brain MRI findings (%)	25/109 (22.9%)	39/486 (8.0%)	<0.001
Antihypertensive medications (%)	44/105 (41.9%)	176/445 (39.6%)	0.69

*P-value was computed using two-sample Student's t-test (when continuous) or Fisher's exact test (when dichotomous). ADL, activities of daily living; BNP, B-type natriuretic peptide; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

Table 2 Hazard ratios for hospitalization

Characteristics	Hazard ratios (95% CI)	*P*-value§
Age	1.03 (0.99–1.07)*	0.20
Men	1.48 (0.87–2.49)	0.14
Creatinine	1.11 (0.88–1.41)†	0.38
Total cholesterol	0.82 (0.64–1.04)†	0.10
Albumin	0.97 (0.77–1.23)†	0.81
Log BNP	1.36 (1.05–1.75)†	0.02
MMSE	1.05 (0.98–1.12)‡	0.15
ADL score	1.23 (1.08–1.40)‡	0.001
Asymptomatic brain MRI findings	3.24 (1.96–5.36)	<0.001

*1 year older. †1 standard deviation increment. ‡1 point decrement. §*P*-value was computed using the Cox proportional hazard model. ADL, activities of daily living; BNP, B-type natriuretic peptide; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

With an alternative analysis using tertiles of the BNP level, the accumulated rate of hospitalization was significantly higher in subjects with highest plasma BNP levels (27.5%) than those with middle (14.4%) and lowest plasma BNP levels (13.4%) ($P < 0.001$). The difference of those with middle and lowest plasma BNP level was not significant. The odds ratio of highest tertile compared with lowest tertile as a risk for hospitalization was 2.07 (95% CI, 1.32–3.25; $P = 0.002$). Thus, there was no linear relationship between plasma BNP and hospitalization. The risk of hospitalization seemed to be drastically elevated in those with highest plasma BNP levels.

Reasons for hospitalization

Among the 112 subjects with hospitalization, malignancy was the most common reason for hospitalization ($n = 18$, 16.1%), followed by difficulty to live alone due to decline in ADL or cognitive function ($n = 13$, 11.6%), stroke ($n = 12$, 10.7%), heart diseases ($n = 11$, 9.8%), orthopedic problems ($n = 10$, 8.9%), dementia ($n = 9$, 8.0%), pneumonia ($n = 6$, 5.4%), renal failure ($n = 4$, 3.6%) and other causes ($n = 16$, 14.3%). The reason for hospitalization of 13 subjects (11.6%) could not be specified (Table 3).

The common reasons for hospitalization among 47 non-survivors were malignancy, heart diseases, stroke and pneumonia. On the other side, the common reasons for hospitalization among 65 survivors were difficulty to live alone, stroke, orthopedic problems and dementia. These conditions accorded well with the diseases ranked highly among the reasons for hospitalization in Japan according to past statistics.[1]

Table 3 Reasons for hospitalization

Reasons	*n*
Malignancy	18 (16.1%)
Difficulty to live alone	13 (11.6%)
Stroke	12 (10.7%)
Heart diseases	11 (9.8%)
Orthopedic problems	10 (8.9%)
Dementia	9 (8.0%)
Pneumonia	6 (5.4%)
Chronic kidney disease	4 (3.6%)
Sepsis	2 (1.8%)
Liver failure	2 (1.8%)
Gallstone	2 (1.8%)
Asthma	2 (1.8%)
Others*	8 (7.1%)
Unknown causes	13 (11.6%)
Total	112 (100%)

*Bowel obstruction, diabetes mellitus, old tuberculosis, cataract, anorexia, pacemaker generator exchange, senile decay and accident.

Plasma BNP levels of subjects according to reasons for hospitalization

We compared plasma BNP levels of hospitalized subjects to those of subjects without hospitalization according to the reasons for hospitalizations (Table 4). Plasma BNP levels of hospitalized subjects due to difficulty to live alone, heart diseases, stroke, dementia and pneumonia were significantly higher than those of the subjects without hospitalization. When heart disease and stroke were considered as cardiovascular disease, the adjusted hazard ratio of 1 SD increment of log plasma BNP level was 2.59 (95% CI, 1.53–4.40; $P < 0.001$). Plasma BNP levels of hospitalized subjects probably due to non-cardiovascular diseases including malignancy and orthopedic problems were not significantly different when compared with subjects without hospitalization (Table 4).

Discussion

Heart diseases and plasma BNP level

High plasma BNP level was an independent risk factor for future hospitalization in community-dwelling elderly without apparent heart diseases, even after adjustment for several confounding factors, including age, sex, serum creatinine, total cholesterol and albumin levels, MMSE score, ADL score and asymptomatic brain MRI findings. Thus, plasma BNP level can be considered as an independent predictive biomarker for hospitalization. As far as we know, no previous studies have shown a relationship between plasma BNP level and hospitalization of the community-dwelling

Table 4 Plasma BNP levels according to reasons for hospitalization

Reasons (*n*)	Log BNP (pg/mL)	*P*-value‡
Malignancy (18)	1.66 ± 0.35	0.3
Difficulty to live alone (13)	1.82 ± 0.43	0.01
Stroke (12)	1.85 ± 0.45	0.006
Heart diseases (11)	1.84 ± 0.40	0.01
Orthopedic problems (10)	1.59 ± 0.37	0.86
Dementia (9)	1.94 ± 0.41	0.001
Pneumonia (6)	1.96 ± 0.40	0.006
Chronic kidney disease (4)	1.80 ± 0.39	0.17
Others (29)*	1.65 ± 0.40	0.26

*Including unknown cause. ‡*P*-value was computed using two-sample Student's *t*-test vs subjects without hospitalization. BNP, B-type natriuretic peptide.

independent elderly. Measurement of plasma BNP level at health examination could be a simple and useful means of prediction for future hospitalization in the community-dwelling healthy elderly.

Plasma BNP level is elevated due to biosynthesis under conditions of heart failure. Many cardiac conditions, including systolic dysfunction,[17] diastolic dysfunction,[18,19] mitral regurgitation,[20] aortic stenosis,[21,22] pulmonary hypertension,[23] cardiomyopathy[24] and senile cardiac enlargement,[25] are associated with increase in BNP. In the present study, despite the fact that subjects with moderate to severe valvular disorders, old myocardial infarction and moderate to severe left ventricular systolic dysfunction were excluded, there were 11 subjects who were hospitalized because of newly developed conditions such as heart failure. Because plasma BNP is known to be useful to detect preclinical ventricular systolic and diastolic dysfunction,[26] it may also be useful for community-dwelling elderly who are at high risk of future hospitalization due to preclinical cardiac dysfunction.

Stroke and plasma BNP level

Among hospitalized subjects, there were 12 subjects who developed stroke and nine subjects with dementia. There have been several reports indicating a correlation between the occurrence of stroke and high plasma BNP level.[7,27-29] Relation of plasma BNP level and cognitive function was also reported.[30] Although the mechanism of these relationships remains unresolved, the elderly at high risk of stroke and dementia may show the elevation of plasma BNP level as seen in our study subjects.

There were 13 subjects who were hospitalized because of difficulty to live alone that was suggestive of decline in ADL by dementia and stroke. In fact, seven of these 13 subjects had asymptomatic brain MRI findings. The plasma BNP levels of these hospitalized subjects because of difficulty to live alone were significantly higher than that of subjects without hospitalization.

There were 10 hospitalized subjects with orthopedic problems with fracture and lower back pain. Although this can potentially be explained by the fact that decline in ADL due to stroke results in falls and fractures, plasma BNP levels in these subjects were not significantly increased. There are no clinical reports concerning the relationships among BNP level, bone fracture and osteoporosis. Further investigation of these relationships is required.

Chronic kidney disease and plasma BNP level

There were four subjects who were hospitalized due to chronic kidney disease. Plasma BNP level was elevated in these four subjects although it was not statistically significant. A correlation between chronic kidney disease and BNP elevation has been reported previously.[31,32] Many elderly subjects with normal creatinine may have impaired kidney function.[33] In addition, mild chronic kidney disease has been recently reported to be associated with the likelihood of decline in ADL and walking speed.[34] Further investigation regarding chronic kidney disease, BNP elevation and hospitalization may be warranted.

Study limitations

In this study, although district nurses conducted a follow-up survey of the diseases that caused hospitalization, the precision of the data can be challenged. For example, although subjects who were diagnosed with atrial fibrillation at the health examinations were excluded, those with paroxysmal atrial fibrillation might have been included. Also, it is possible that asymptomatic mild systolic and diastolic dysfunction might have been included.

Conclusion

High plasma BNP level was found in the community-dwelling elderly subjects who were later hospitalized

because of heart diseases, stroke and chronic kidney disease, which were known to be closely related to the frail elderly. Thus, plasma BNP level is a very useful serological biomarker for future hospitalization in apparently healthy elderly people living in the community.

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COMMUNITY-DWELLING ELDERLY FALLERS IN JAPAN ARE OLDER, MORE DISABLED, AND MORE DEPRESSED THAN NONFALLERS

To the Editor: We read with interest the article published by Somadder et al.[1] The authors document a correlation between depressive symptoms and self-reported numbers of falls in older subjects attending a day hospital in the United Kingdom. They reported that there were no significant differences in age, comorbidities, or performance on activities of daily living (ADLs) between fallers and infrequent fallers in their small population. We reexamined this important issue in community-dwelling elderly people in Japan and found findings different from those of Somadder et al.

The study population consisted of 1,261 people aged 65 and older (men 529, women 732, mean age 75.4 ± 7.2) living in T town, Kochi Prefecture, Japan. Fallers were screened using self-reported questionnaires, along with additional tests of ADLs and subjective quality of life (QOL) for community-dwelling older people in 2006. The question "Do you have any history of a fall within the past year?" was used for detecting fallers. Subjects who answered yes to the question were considered to be fallers. For the assessment of basic ADLs, the scores for seven items (walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, and grooming) were summed using a rating scale from 0 (completely dependent) to 3 (completely independent) to obtain a basic ADL score (0–21). For advanced ADLs, the Tokyo Metropolitan Institute of Gerontology index of competence rating scale of 0 to 13 was used.[2] This scale includes instrumental self-maintenance (0–5), intellectual activity (0–4), and social role (0–4). Five indicators of QOL (sense of subjective health, relationship with family, relationship with friends, financial satisfaction, and subjective happiness) were rated on a 100-mm visual analogue scale (worst QOL on the left end of the scale, best to the right).[3,4] The 15-item Geriatric Depression Scale (GDS-15)[5] was used for the assessment of depression; a score of 10 or more was considered to indicate depression. A fall risk index[6,7] with a score ranging from 0 (low risk of fall) to 21 (high risk of fall) was added to those and used for the assessment of risk of falls. Statview version 5.0 (SAS Institute, Inc., Cary, NC) was used for calculating chi-square tests for categorical variables, unpaired *t*-test for continuous variables, and Spearman correlation (r_s) between number of falls and GDS-15 and between fall risk index and GDS-15.

The proportion of fallers was 31.6% in this population. Fallers were significantly older (76.9 vs 74.7) and had significantly lower scores for each item of the ADLs and QOLs than nonfallers, even after the adjustment for age (Table 1). The proportion of subjects with depression was significantly

Table 1. Comparison of Activities of Daily Living (ADLs), 15-Item Geriatric Depression Scale (GDS-15) and Quality of Life (QOL) Scores of Fallers and Nonfallers

Characteristic	Fallers n = 399 (31.6%)	Nonfallers n = 862 (68.4%)	*P*-Value
Age, mean ± SD	76.9 ± 7.5	74.7 ± 6.9	<.001
Male, %	40.2	42.6	.40
Basic ADLs score, mean ± SD	19.1 ± 3.5	20.2 ± 2.6	<.001
Tokyo Metropolitan Institute of Gerontology index of competence (range 0–13), mean ± SD	9.3 ± 3.8	10.7 ± 3.2	<.001
Self-maintenance (range 0–5), mean ± SD	4.0 ± 1.6	4.4 ± 1.3	<.001
Intellectual activity (range 0–4), mean ± SD	2.7 ± 1.3	3.2 ± 1.1	<.001
Social role (range 0–4), mean ± SD	2.6 ± 1.4	3.2 ± 1.2	<.001
GDS-15 score			
Mean ± SD	6.5 ± 4.1	4.3 ± 3.7	<.001
>10, %	26.8	11.6	<.001
Fall risk index (range 0–21), mean ± SD	11.8 ± 3.8	7.0 ± 3.9	<.001
QOL score, mean ± SD			
Sense of subjective health	47.7 ± 21.8	56.7 ± 20.9	<.001
Relationship with family	72.3 ± 21.7	76.9 ± 20.3	<.001
Relationship with friends	69.5 ± 23.1	74.3 ± 20.7	<.001
Financial satisfaction	43.8 ± 24.9	51.2 ± 23.8	<.001
Subjective happiness	54.8 ± 22.0	62.0 ± 21.5	<.001

Unpaired *t*-test for continuous variables, chi square test for categorical variables.
Variables were adjusted for age when they were significantly correlated with age.
SD = standard deviation.

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higher in fallers (26.8% vs 11.6%, $P<.001$). Although only 59.6% of the fallers answered the numbers of falls, there was weak but significant correlation between number of falls and GDS-15 scores in those who had fallen ($r_s = 0.17$, $P = .002$). The mean fall risk index score was significantly higher in fallers than nonfallers, and there was significant correlation between fall risk index and GDS-15 ($r_s = 0.53$, $P<.001$) in fallers.

We confirmed the higher prevalence of depression in fallers than nonfallers, and there was a significant correlation between the number of falls and GDS-15, as Somadder et al. reported. However, unlike with the findings of Somadder et al., community-dwelling elderly fallers in Japan were significantly older and had lower quantitative ADL and QOL scores, as well as higher GDS-15 scores than nonfallers, even after adjustment for age.

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SUBJECTIVE SLEEP DISTURBANCES WERE CLOSELY ASSOCIATED WITH COMPREHENSIVE GERIATRIC FUNCTIONS IN DOSE-RESPONSIVE MANNER IN THE COMMUNITY-DWELLING ELDERLY PEOPLE IN JAPAN

To the Editor: Sleep disturbance and insomnia increase greatly with age. Because of its multifactorial origins, sleep disturbance should be regarded as a geriatric syndrome and a comprehensive geriatric assessment should be performed for its improvement.[1,2] The association between sleep satisfaction and activities of daily living (ADLs), depression, and qualities of life (QOL) was assessed in community-dwelling elderly people in Japan. Elderly people with poor and moderate sleep satisfaction had lower comprehensive geriatric function (CGF) scores than those with good sleep satisfaction.

The study population consisted of 1,432 subjects aged 65 and older (male:female 594:838, mean age 75.6 ± 7.2) living in a rural Japanese town, Tosa, in Kochi prefecture. Sleep satisfaction was assessed using a self-reported questionnaire, and subjects were classified into three classes using a sleep satisfaction scale; each subject was asked, "Do you sleep well?" Possible answers were good, moderate, and poor. Seven basic ADL items (walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, grooming) were assessed, each on a 4-level scale, with 3 = completely independent, 2 = needs some help, 1 = needs much help, and 0 = completely dependent. Scores for each item were summed to generate a total basic ADL score ranging from 0 to 21.[3] Higher-level daily activities were assessed using the Tokyo Metropolitan Institute of

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Stress-induced blood pressure elevation in subjects with mild cognitive impairment: Effects of the dual-type calcium channel blocker, cilnidipine

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Aim: We investigated whether mental stress-induced blood pressure elevation was related to cognitive function in the elderly, and further examined the effects of the dual-type calcium channel blocker, cilnidipine, on stress induced hypertension in subjects with mild cognitive impairment.

Methods: In study I, 39 consecutive outpatients (mean age ± standard deviation, 77 ± 8 years), who were referred to our memory clinic and were not taking any medications, were studied. They were divided into three groups according to cognitive function on the Hasegawa Dementia Scale-Revised (HDSR): group 1 ($n = 8$), 28 points or more; group 2 ($n = 18$), 21–27 points; and group 3 ($n = 13$), 20 points or less. In study II, 14 outpatients with hypertension and mild cognitive impairment (aged 79 ± 8 years; HDSR score, 24 ± 4) were assigned to receive cilnidipine (10–20 mg/day). The control group ($n = 10$) matched for age, HDSR and blood pressure was followed without cilnidipine.

Results: In study I, although age and basal blood pressure were similar among the three groups, the blood pressure response to a mental arithmetic test was twice as large in group 2 (26 ± 12 mmHg in systolic pressure and 11 ± 8 mmHg in diastolic pressure) as those in groups 1 and 3. In study II, after 4 weeks, cilnidipine treatment significantly decreased the blood pressure responses to the mental arithmetic test compared to the baseline as well as to those of the control group.

Conclusions: Stress-induced blood pressure elevations are exaggerated in subjects with mild cognitive impairment. Cilnidipine may have inhibitory effects on stress-induced hypertension.

Keywords: calcium antagonists, dementia, hypertension, mental stress.

Introduction

Mental stress-induced increases in blood pressure (BP) and heart rate are often experienced during daily living. Psychophysiological cardiovascular reactivity is caused by autonomic nervous system activation via the hypothalamus–pituitary–adrenal axis,[1–3] and is

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modulated by individual characteristics, environmental exposures, interpersonal and social contexts and genetic factors.[4–7] It has been reported that the subjects with exaggerated cardiovascular reactivity to mental stress are predisposed to hypertension,[8,9] atherosclerosis[10–12] and cerebrovascular disease such as stroke and silent cerebral infarction.[13,14]

Although the central nervous system plays an important role in mental stress-induced cardiovascular reactivity,[1–3] little is known about the relationship between the reactivity and cognitive function or dementia. Association of increased short-time BP variability with cognitive impairment[15] suggests but does not directly demonstrate the link between BP responses to mental stress and cognitive function. Because the patients with cognitive impairment cannot easily perform cognitive tasks, we hypothesized that exaggerated mental stress responses would result in BP elevation in such patients.

To test this hypothesis, we conducted a cross-sectional study examining the relationship between cognitive function and BP responses to a mental arithmetic test using the subjects who were referred to our memory clinic and not taking any medications. Furthermore, we examined the effects of cilnidipine, an N- and L-type calcium channel blocker, on BP responses to a mental arithmetic test in hypertensive patients with mild cognitive impairment.

Methods

Subjects

The subjects who were referred to our memory clinic and were suspected to have hypertension on the first visit were enrolled. Depressive patients (15-item Geriatric Depression Scale score of ≥10 points) and post-stroke patients were excluded from the study. Each subject gave written informed consent before enrollment in this study. The study protocol was approved by the ethics committee of Kyorin University School of Medicine.

In study I, 39 consecutive patients (20 men and 19 women, aged 77 ± 8 years), who showed high-normal or higher BP (>130 mmHg in systolic or >85 mmHg in diastolic) and were not taking any medications, were enrolled. They underwent mental stress tests and were divided into three groups according to cognitive function on the Hasegawa Dementia Scale-Revised (HDSR): group 1 ($n = 8$), 28 points or more; group 2 ($n = 18$), 21–27 points; and group 3 ($n = 13$), 20 points or less. All the patients in group 3 and five patients in group 2 were clinically diagnosed to have Alzheimer's disease, but none were so in group 1.

In study II, 14 patients with hypertension (>140 mmHg in systolic or 90 mmHg in diastolic BP, or taking antihypertensive agents) and mild cognitive impairment (aged 79 ± 8 years; HDSR score, 24 ± 4 points; HDSR range, 21–27) were assigned to receive cilnidipine. Nine patients of group 2 in study I, who showed more than 140 mmHg in systolic or 90 mmHg in diastolic BP, were included in study II. Fifteen treated ($n = 11$) or untreated ($n = 4$) hypertensive patients were additionally included in study II. The dose of cilnidipine was initiated at 10 mg/day, and was increased to 20 mg/day if systolic BP was more than 150 mmHg or diastolic BP was more than 90 mmHg 2 weeks later. The patients were followed for an additional 2 weeks. Separately, the control group ($n = 10$) matched for age, HDSR and baseline BP were followed for 4 weeks. Mental stress tests were performed before and after the 4-week study period. Any medications except for cilnidipine were not changed throughout the study period.

Mental arithmetic test

After resting for 5 min in a quiet room, baseline BP and pulse rate (PR) were measured using an automated, digital electro sphygmomanometer (HEM-727IC; Omron Healthcare, Kyoto, Japan) on the non-dominant arm in the sitting position. Then, each subject was instructed to continuously subtract 7 from 213 as accurately as possible. BP and PR were measured again after 1 min of subtraction to evaluate the response to mental arithmetic. Measurements of BP and PR were repeated twice at each step, and the average values were used in the analyses. This test was modified for patients with cognitive impairment from the original version.[16] The correlation coefficients between the two repeated measurements of a 4-week interval were 0.971 for systolic BP and 0.850 for diastolic BP ($n = 15$, $P < 0.01$) after mental arithmetic.

Data analysis

The values are expressed as mean ± standard deviation in the text, tables and figures unless otherwise specified. Differences between the groups were analyzed using one-factor ANOVA, followed by a Newman–Keuls test. Changes in BP and PR during the study period were analyzed using a paired Student's t-test. $P < 0.05$ was considered statistically significant.

Results

Study I: Stress-induced BP elevation in the subjects as categorized by cognitive function

The characteristics of the subjects in the three groups are shown in Table 1. There were no significant differences

Table 1 Characteristics of subjects in study I

	Group 1 (HDSR, ≥28 points)	Group 2 (HDSR, 21–27 points)	Group 3 (HDSR, ≤20 points)
No. of subjects (men/women)	8 (4/4)	18 (10/8)	13 (6/7)
HDSR, points	29.0 ± 1.0	24.6 ± 1.9[§]	14.7 ± 3.8[†]
Age, years	75 ± 8	78 ± 7	78 ± 7
SBP, mmHg	150 ± 14	148 ± 20	145 ± 20
DBP, mmHg	84 ± 12	77 ± 10	74 ± 11
Pulse rate (b.p.m.)	71 ± 11	73 ± 11	73 ± 11

Values are expressed as mean ± standard deviation. [§]$P < 0.01$ vs group 1; [†]$P < 0.01$ vs group 2. All other variables are not significantly different among the groups. DBP, diastolic blood pressure; HDSR, Hasegawa Dementia Scale-Revised; SBP, systolic blood pressure.

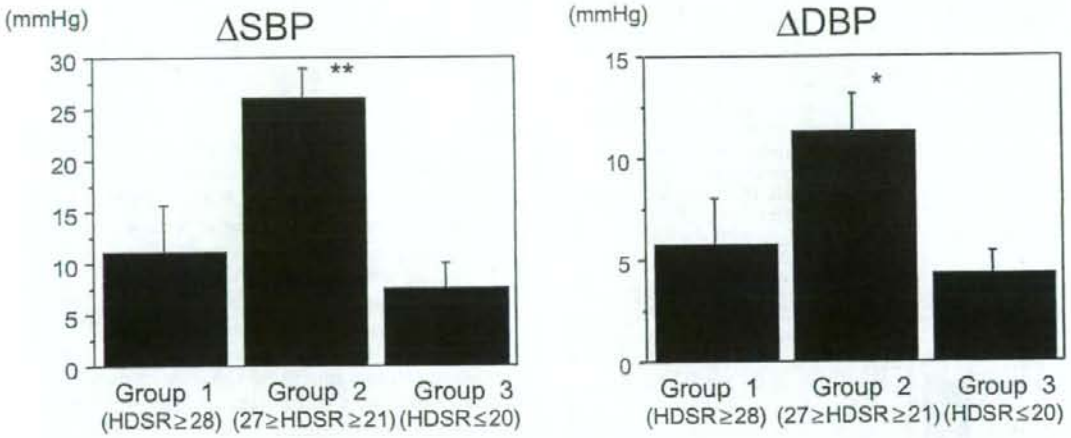

Figure 1 Influence of cognitive function on stress-induced blood pressure elevation. The changes of systolic (SBP) and diastolic blood pressure (DBP) during the mental arithmetic test in study I are shown. Values are expressed as mean ± standard error of the mean. Group 1, Hasegawa Dementia Scale-Revised (HDSR) score of ≥28 points; group 2, 21–27 points; and group 3, ≤20 points. *$P < 0.05$, **$P < 0.01$ vs groups 1 and 3.

in sex, age and baseline BP between the groups. As shown in Figure 1, the responses of both systolic and diastolic BP to the mental arithmetic test were twice as large in group 2 as those in groups 1 and 3.

Study II: Effects of cilnidipine on stress-induced BP elevation

All the subjects completed the protocol of study II. The characteristics of the subjects are shown in Table 2. The average dose of cilnidipine used in the cilnidipine group was 13 ± 5 mg/day. There were no significant differences in cognitive function, age and resting BP between the control group and the cilnidipine group, although resting systolic and diastolic BP fell significantly by the treatment with cilnidipine for 4 weeks. Figure 2 shows the BP responses to the mental arithmetic test. In the control group, BP responses did not change during the study period. In the cilnidipine group, however, BP responses to the mental arithmetic test were significantly decreased after 4 weeks. As a result, there were significant differences in the responses of systolic and diastolic BP to the mental arithmetic test between the control group and the cilnidipine group at the end of the study. We attempted to calibrate the reactivity by baseline BP. The percent changes of systolic BP during the mental arithmetic test were significantly smaller in the cilnidipine group than in the control group after treatment (12 ± 5% cilnidipine vs 18 ± 6% control, $P < 0.05$), although they were comparable in both groups before treatment (18 ± 6% cilnidipine vs 20 ± 9% control).

Table 2 Characteristics of subjects in study II

	Control	Cilnidipine
No. of subjects (men/women)	10 (5/5)	14 (6/8)
HDSR, points	26.0 ± 3.0	25.0 ± 4.0
Age, years	81 ± 8	79 ± 8
Pretreatment drugs		
ACEI/ARB, *n* (%)	3 (30%)	3 (21%)
CCB, *n* (%)	3 (30%)	3 (21%)
Before treatment		
SBP, mmHg	153 ± 17	161 ± 20
DBP, mmHg	80 ± 7	85 ± 11
Pulse rate, b.p.m.	75 ± 9	74 ± 13
4 weeks after treatment		
SBP, mmHg	151 ± 18	144 ± 16†
DBP, mmHg	79 ± 7	76 ± 9†
Pulse rate, bpm	75 ± 8	77 ± 13

Values are expressed as mean ± standard deviation. †$P < 0.01$ vs baseline. No significant differences were found between the control and cilnidipine groups. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB, L-type calcium channel blocker; DBP, diastolic blood pressure; HDSR, Hasegawa Dementia Scale-Revised; SBP, systolic blood pressure.

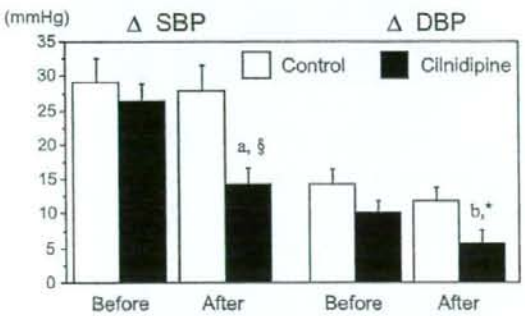

Figure 2 Effects of cilnidipine on stress-induced blood pressure elevation in elderly hypertensives with mild cognitive impairment. The changes of systolic (SBP) and diastolic blood pressure (DBP) during the mental arithmetic test before and after the treatment in study II are shown. Values are expressed as mean ± standard error of the mean. a$P < 0.01$, b$P < 0.05$ vs before treatment. §$P < 0.01$, *$P < 0.05$ vs control.

Discussion

In study I, we investigated whether mental stress-induced BP elevation was related to cognitive function in the elderly who were referred to our memory clinic. A few studies have shown the relationship between mental stress-induced BP responses and cognitive function. Pierce *et al.*[17] have reported that BP responses during neuropsychological testing were unrelated to cognitive performance in college-aged subjects. Alternatively, Waldstein *et al.*[18] have reported that higher stress-induced BP reactivity is associated with poorer performance on tests of cognitive function in stroke- and dementia-free middle-aged and older adults (ages 54–79 years). In the present study, using older subjects with or without cognitive impairment, we found that the relation between mental stress-induced BP elevation and cognitive function was inverted U-shaped, and that stress-induced BP elevations were exaggerated in subjects with mild cognitive impairment.

Subjects with mild cognitive impairment can recognize their cognitive decline,[19] thus anxiety and irritation during the mental arithmetic test may arouse the accelerated BP response. By contrast, the mental arithmetic test is not likely to impose a heavy burden on demented subjects, because they display deficits in executive function,[20] often associated with depression and apathy.[21] Recently, greater variability in BP on 24-h ambulatory monitoring has been associated with poorer cognitive performance or cognitive impairment in samples of older adults.[15,22] Murakami *et al.*[23] investigated the relation between pressor responses to mental arithmetic tests and 24-h BP variability in normotensive subjects and hypertensive patients. They reported that the pressor response during the mental arithmetic test was significantly correlated with the value of 24-h BP variability in both subjects. Taken together, it is possible that mental stress-induced BP elevation in daily life is a strong determinant of BP variability in subjects with mild cognitive impairment.

In study II, we found that cilnidipine had inhibitory effects on stress-induced BP elevation in subjects with hypertension and mild cognitive impairment. Cilnidipine is a 1,4-dihydropyridine derivative calcium antagonist with potent inhibitory actions against not only L-type but also N-type voltage-dependent calcium channels.[24] Fujita *et al.*[25] have recently reported that cilnidipine is superior to amlodipine in preventing the progression of proteinuria in hypertensive patients with chronic kidney disease. The N-type voltage-dependent calcium channel plays an important role in sympathetic neurotransmission and regulates the release of norepinephrine from sympathetic nerve endings.[26] Accordingly, several studies have reported the inhibitory effects of cilnidipine on ambulatory BP and "white coat effect" in patients with essential hypertension.[27–30] The present results found in elderly hypertensives with mild cognitive impairment are consistent with these studies, and may provide a therapeutic implication in elderly hypertension.

Controversy exists as to prognostic significance of stress-induced BP elevation, typically known as the white coat effect, clinic-ambulatory BP difference.[31]

Verdecchia *et al.*[32] reported that white coat effect does not predict cardiovascular morbidity and mortality in subjects with essential hypertension. Also, Khattar *et al.*[33] reported that white coat hypertensives had a significantly lower incidence of cardiovascular events than sustained hypertensives. In contrast, Mulè *et al.*[34] reported that left ventricular mass was greater in the group with higher systolic and diastolic white coat effect, suggesting an end-organ damage in white coat hypertension. Amado *et al.*[35] reported that elderly hypertensives with white coat effect have more previous history of ischemic cardiovascular or cerebrovascular disease than those with no white coat effect. Other numerous studies also found a considerable association between the white coat effect[36,37] or the exaggerated cardiovascular reactivity to mental stress[8–14] and cardiovascular mortality or target organ damage. Recent studies suggest that hypertension is associated with the onset and exacerbation of Alzheimer's disease.[38–42] Thus, the control of stress-induced hypertension may be a therapeutic target in the management of elderly hypertensives.

This study has some limitations. First, the number of subjects examined was small, and, therefore, the results of the present study should be carefully interpreted and be confirmed in large-scale studies. Second, we studied only the response to a mental stress. BP is influenced by all kinds of stress associated with daily activities, such as mental stress, static exercise, dynamic exercise and temperature variation.[23] We also assessed the responses to hand grip exercise and found similar results to the mental arithmetic test, but did not show the data because of low reproducibility of the responses to the modified and weakened hand grip load. Third, significant increases in PR in response to the mental arithmetic test were not observed in this study. It has been known, however, that the heart rate reactivity to mental stress was attenuated in older adults compared to younger adults and children.[43–45] This phenomenon is attributable, at least in part, to the age-related decline of β-adrenergic sensitivity.[46] Consequently, it is not surprising that PR reactivity was dissociated from BP reactivity in elderly subjects in the present study. Fourth, we only measured BP and PR as physiological responses to stress. There are many indicators of the quantity of stress received, such as BP, heart rate, sympathetic activity, and catecholamine and cortisol levels.[47–49] Particularly, many investigators evaluated plasma norepinephrine and epinephrine concentrations together with BP and heart rate.[50,51] The lack of PR responses to the mental arithmetic test in the present study may have been recompensed if we had measured plasma catecholamine.

In summary, stress-induced BP elevations were exaggerated in elderly subjects with mild cognitive impairment. Cilnidipine decreased the BP responses to the mental arithmetic test in elderly hypertensives with mild cognitive impairment. These findings may provide insight into the mechanistic link between hypertension and cognitive impairment, and therapeutic implication on the management of elderly patients.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Switch to oral hypoglycemic agent therapy from insulin injection in patients with type 2 diabetes

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Aim: We aimed to determine the feasibility of substituting thiazolidinedione-based therapy for insulin injection therapy in patients with type 2 diabetes.

Methods: Thirty-six subjects (17 men and 19 women) aged 67.8 ± 11.3 years with an average insulin dose of 0.46 ± 0.17 U/kg bodyweight, a duration of insulin therapy of 6.1 ± 8.2 years and an average hemoglobin A1c (HbA1c) of 6.8 ± 1.3% were switched from insulin injection therapy to pioglitazone, glimepiride and voglibose combination therapy.

Results: The number of subjects achieving HbA1c levels of less than 7% at 4 months was 30. The success rate of switch therapy was 83% (30/36). HbA1c was significantly reduced from 6.7 ± 1.3% to 5.9 ± 0.7% at 4 months after the switch ($P < 0.01$) in 32 patients who completed the planned 4-month study. No adverse effects including heart failure, liver dysfunction or severe hypoglycemia were observed. The insulin dose and the maximum blood glucose on the switch day were significantly lower and the age was significantly higher in the subjects who achieved HbA1c less than 7% at 4 months compared to those who did not ($P < 0.05$).

Conclusion: Thiazolidinedione-based oral combination therapy may efficiently and safely substitute relatively high-dose insulin injection therapy in patients with type 2 diabetes.

Keywords: insulin injection, oral hypoglycemic agent, switch therapy.

Introduction

As the population with diabetes increases, those receiving insulin injections increase in number proportionally. Insulin injection treatment is associated with pain and puts a heavy physical, mental and financial burden on patients. The occurrence of hypoglycemia is relatively high in those having multiple insulin injections,[1] which causes deterioration of cognitive function and thus induces dementia.[2]

In this study, we aimed to develop a method to change the route of administration of hypoglycemic agents from needle-mediated to oral, thereby enabling patients, especially elderly patients, with diabetes to have a more comfortable life by being liberated from painful procedures and recurrent insulin-induced hypoglycemic incidents. Although reports on this area are scarce, one study showed a success rate of switching from insulin injection to oral agents of approximately 50% in those who had maintained insulin therapy for a relatively long period of time with an insulin dose of less than 0.3 U/kg

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bodyweight.[3] As the average insulin dose used in general is approximately 0.4–0.5 U/kg bodyweight,[1,4] a more sophisticated method is needed to enable a successful switch from insulin injections to oral agent treatment.

Pioglitazone is a newly available agent that improves insulin resistance,[5,6] a core defect in type 2 diabetes.[7] Pioglitazone for the first time among hypoglycemic agents including insulin and sulphonylureas, significantly reduced the composite of mortality, stroke and myocardial infarction.[8]

Because pioglitazone has not been used as a major agent for switching, this study used this agent together with a sulphonylurea, glimepiride that improves insulin resistance[9] and has a less marked effect on bodyweight gain[10,11] and an α-glucosidase inhibitor, voglibose, that is effective for blood glucose control with a sulphonylurea[12] and pioglitazone[13] to develop a new approach for the substitution of insulin therapy.

Because insulin injection per se may exacerbate insulin resistance, we completely stopped insulin injections before the switch and then immediately began administration of oral agents in patients under long-term insulin injection in order to maximize the insulin-sensitizing capacity of pioglitazone.

Methods

A total of 38 type 2 diabetes patients on insulin injection therapy were recruited from our internal medicine division from May 2005 to December 2006. Type 2 diabetes was diagnosed according to World Health Organization criteria, by a 2-h post-load venous full blood glucose value of more than 10.0 mmol/L.[14]

This study protocol was approved by the local ethics committee, and all participants gave written informed consent before inclusion in the study.

Patient eligibility

Inclusion criteria were as follows: (i) aged 40–86 years; (ii) insulin dosage of more than 10 units/24 h; (iii) insulin injection duration of more than 3 months; (iii) C-peptide in 24-h urine of more than 10 μg; and (iv) fasting C-peptide immunoreactivity (CPR) of more than 0.5 ng/mL.

Exclusion criteria were as follows: (i) positive for glutamine acid decarboxylase antibody; (ii) alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) more than threefold the upper limit of normal; (iii) currently and/or previously suffering from heart failure; (iv) ejection fraction assessed by echocardiography of less than 40%; (v) malignancy on active therapeutic regimen or without complete remission or cure; (vi) concomitantly suffering from infection; (vii) planning to have surgery; (viii) more than 50% positivity for insulin antibody; (ix) diagnosis of type I diabetes; (x) pregnancy or breast feeding; (xi) under dialysis; (xii) concomitantly using pioglitazone; and (xiii) hemoglobin A1c (HbA1c) of 10% or more.

Two patients were excluded from the study, one because of heart failure and the other because of colon cancer. Thirty-six patients were enrolled in the study (Fig. 1).

Switch from insulin therapy to oral agents

On the day when insulin injection therapy was completely withdrawn together with concomitantly used oral hypoglycemic agents, combination therapy was initiated. Medication other than hypoglycemic agents was continued after the switch. Because the proposed switch therapy was not a generally accepted approach, in order to ensure careful monitoring of blood glucose and to take immediate actions against hypoglycemia, all the enrolled patients were hospitalized.

Pioglitazone was started at a dose of 15–30 mg, glimepiride at 1–3 mg and voglibose at 0.9 mg. The maximum dose of pioglitazone was 45 mg, and that of glimepiride was 4 mg. If fasting plasma glucose was less than 5.55 mmol/L and/or hypoglycemia developed, glimepiride was first reduced in dose and then pioglitazone.

In patients more than 65 years of age and in female cases, pioglitazone was initially used at 15 mg in order to avoid the development of heart failure.

When the post-prandial blood glucose level was less than 16.7 mmol/L, the patient was discharged and followed in the outpatient clinic on a monthly basis for 4 months.

Definition of success, failure and dropout in the study

Success was defined as HbA1c at 4 months after the switch of less than 7.0%. Failure was defined as: (i) on the switch day and the following days before discharge, blood glucose level reached more than 22.2 mmol/L at any point of the day; (ii) after discharge, the blood glucose level was more than 11.1 mmol/L in the fasting state or 16.6 mmol/L in the post-prandial state; (iii) heart failure developed; (iv) AST/ALT reached more than threefold the upper limit of normal. Countermeasures were taken to alleviate the conditions defined as failure. First, combined oral hypoglycemic agents were immediately stopped and the original therapy including insulin injection was reinitiated. Second, for the conditions (iii) and (iv), patients were referred to expert cardiovascular and hepatology clinicians.

Dropout was defined as: (i) insulin injection treatment was mandatory because of surgical operation, treatment of infectious disease or initiation of anticancer chemotherapy; (ii) the patient voluntarily returned

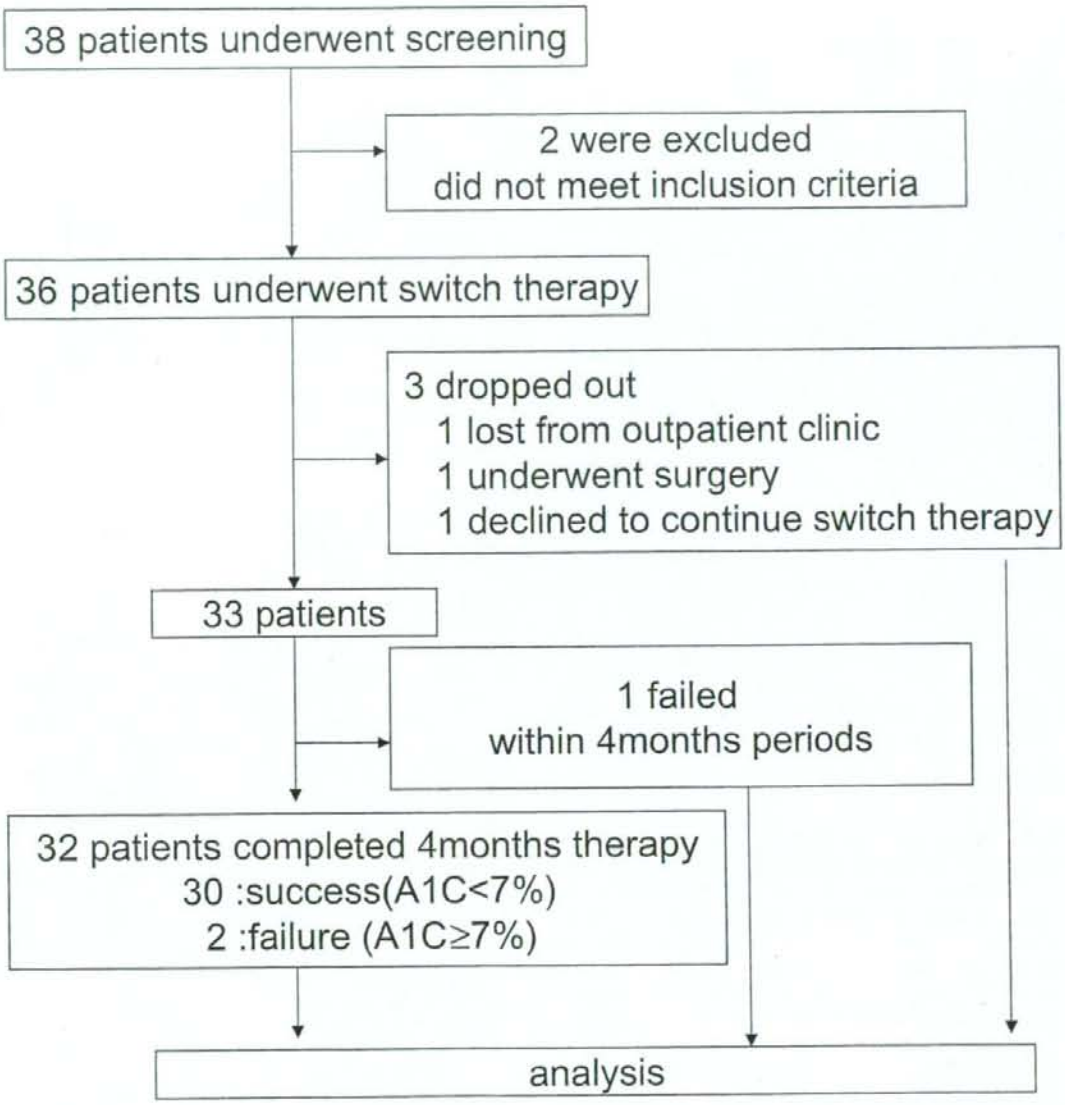

Figure 1 Enrollment and outcomes. A1c, hemoglobin A1c.

to insulin therapy; or (iii) the patient did not attend the outpatient clinic after the switch.

Laboratory studies

Concentrations of overnight fasting plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by enzyme methods, insulin, C-peptide and antibodies against glutamine acid decarboxylase and insulin by radioimmunoassay, glycosylated HbA1c by high-performance liquid chromatography, creatinine by the modified Jaffe method, blood urea nitrogen by urease indophenol method, albumin by the bacille Calmette–Guerin method, hematocrit by the erythrocyte pulse wave method, and alkaline phosphatase, AST and ALT by the JCCLS-SOP methods (Kishimoto Clinical Laboratory, Hokkaido, Japan).

Analysis of data

The primary outcome measure was the rate of success in the study. The secondary outcome measure was the difference in mean HbA1c from the baseline to the 4-month time point. Differences among values of serum lipid concentrations, blood pressure, bodyweight, hematocrit, albumin, blood urea nitrogen, creatinine, AST and ALT were assessed at months 0 and 4. Severe hypoglycemia was defined as an episode requiring intervention and either a blood glucose level of less than 36 mg/dL or the use of countermeasures. Differences among values of age, body mass index, weight, diabetes duration, insulin duration, insulin dosage, fasting blood glucose, initial HbA1c, fasting immunoreactive insulin, fasting plasma C-peptide, urinary C-peptide excretion, and maximum blood glucose on the switch day were assessed in subjects who achieved HbA1c levels of less than 7% and those who did not at the end of the study. Maximum blood glucose was defined as the highest postprandial 2-h blood glucose level on the day of the switch. First, dropouts were included in the analysis by adopting an intention-to-treat concept. Second, the datasets were compared between data including dropouts and data excluding dropouts.

Data are presented as mean ± standard deviation. Data were compared between two groups by the Student's *t*-test, and among more than two groups by one-way ANOVA followed by Bonferroni's test. $P < 0.05$ was considered significant.

Results

Of the 36 patients enrolled in the study, three patients dropped after the switch (Fig. 1). The first dropout case, aged 67 years, did not attend the outpatient clinic 2 months after the switch; the second case, aged 54 years, returned to insulin therapy in order to undergo thyroid resection surgery 2 months after the switch; and the third case, aged 55 years, voluntarily returned to insulin treatment 3 days after the switch.

Patient profile

The patient profiles of all 36 patients who underwent switch therapy are summarized in Table 1 (left column). The mean age was 67.8 years. The average diabetes duration was 15.7 years. The average insulin dose was 27.6 U/24 h (12–64 units) and 0.46 U/kg bodyweight per 24 h for an average duration of 6.1 years. HbA1c and fasting plasma glucose immediately before the switch were 6.8% and 7.1 mmol/L, respectively. The average C-peptide level was 1.97 ng/mL, with urinary C-peptide excretion per day of 48.4 μg.

The level of HbA1c within 2 months before the switch was 7.0 ± 1.2%, which was not statistically significantly different from that immediately before the switch ($P = 0.50$). These data indicate that the patients in the study maintained stable blood glucose control before the switch.

α-Glucosidase inhibitors and/or biguanides were used concomitantly with insulin before the switch in 18 and two patients, respectively.

Of patients aged more than 60 years, the mean age was 73.3 ± 7.5 years ($n = 26$, 11 men and 15 women). The average diabetes duration was 17.4 ± 12.6 years. The average insulin dosage was 24.9 ± 8.9 U/24 h and 0.42 ± 0.15 U/kg bodyweight per 24 h for an average duration of 6.1 ± 9.3 years. HbA1c and fasting plasma glucose immediately before the switch were 6.5 ± 0.9% and 6.9 ± 1.5 mmol/L, respectively. The average C-peptide level was 1.82 ± 0.59 ng/mL, with urinary C-peptide excretion/day of 45.7 ± 24.9 μg.

Outcome measures

As fasting plasma glucose reached more than 11.1 mmol/L 1 month after the switch in one male case aged 54 years with a daily insulin dose of 54 U, this case was determined to be a failure (Fig. 1).

The remaining 32 cases completed the planned 4-month study after the switch. Of these 32 cases, 30 achieved HbA1c of less than 7.0%. The primary outcome measure – the proportion of patients who achieved HbA1c of less than 7.0% at 4 months – was 83.3% (30/36). The average insulin dosage was 0.43 ± 0.17 U/kg bodyweight per 24 h and 25.7 ± 11.4 U/24 h for an average insulin therapy duration of 5.9 ± 8.2 years in these 30 patients. The results indicate a high rate of success in switching from insulin therapy to oral agents.

The baseline profiles of these 32 patients who maintained the switch therapy for 4 months are shown in Table 1 (right column). No data were statistically significantly different between all the enrolled patients (left column in Table 1) and those who completed 4 months of switch therapy (right column in Table 1). These results indicate that these 32 patients had similar baseline characteristics to those of all the enrolled patients.

In these 32 patients, HbA1c gradually decreased every month after the switch (before switch, 6.7 ± 1.3%; after switch, 1 month, 6.4 ± 1.1%; 2 months, 6.4 ± 1.0%; 3 months, 6.2 ± 0.8%; 4 months, 5.9 ± 0.7%). The average HbA1c at 4 months after the switch was significantly lower than that before the switch ($P < 0.01$) and that 1 month after the switch ($P < 0.05$). HbA1c was also significantly lower at 3 months ($P < 0.05$) compared to the baseline value. The results showed that the switch therapy provided significantly better blood sugar control.

The average maintenance dose of pioglitazone was 26.4 ± 12.4 mg, that of glimepiride was 2.3 ± 1.2 mg, and that of voglibose was 0.84 ± 0.22 mg.

Table 1 Baseline characteristics of 36 patients who underwent switch therapy (left column) and 33 patients except for drop-outs (right column)

Age (years)		67.8 ± 11.3	68.6 ± 11.4
Male/female number		17/19	15/18
Weight (kg)		60.8 ± 10.7	60.9 ± 10.8
Body mass index (kg/m^2)		24.2 ± 3.8	24.6 ± 3.8
Diabetes duration (years)		15.7 ± 11.8	14.9 ± 11.7
Insulin treatment duration (years)		6.1 ± 8.2	6.4 ± 8.5
Insulin dosage (U/24 h)		27.6 ± 11.5	27.2 ± 12.4
Insulin dosage (U/kg per 24 h)		0.46 ± 0.17	0.45 ± 0.18
Fasting plasma glucose (mmol/L)		7.1 ± 1.9	7.0 ± 1.9
A1C (%)		6.8 ± 1.3	6.7 ± 1.3
Fasting IRI (μU/mL)		23.5 ± 23.4	21.9 ± 20.3
Fasting plasma C-peptide (ng/mL)		1.97 ± 0.76	1.95 ± 0.75
Urinary C-peptide excretion (μg/24 h)		48.4 ± 26.7	47.9 ± 27.2
Systolic blood pressure (mmHg)		121.8 ± 13.8	122.9 ± 13.8
Diastolic blood pressure (mmHg)		69.0 ± 10.6	69.3 ± 11.0
Triglyceride (mg/dL)		131.8 ± 56.1	132.2 ± 56.1
Creatinine (mg/dL)		1.1 ± 0.4	1.0 ± 0.3
Albumin (g/dL)		4.1 ± 0.4	4.1 ± 0.4
Blood urea nitrogen (mg/dL)		18.3 ± 6.7	18.1 ± 6.6
Total cholesterol (mg/dL)		185.1 ± 37.4	181.0 ± 33.3
LDL cholesterol (mg/dL)		110.5 ± 33.2	107.3 ± 29.1
HDL cholesterol (mg/dL)		46.6 ± 15.1	44.7 ± 13.0
Risk factor	Hypertension	24 (66.7)	22 (66.7)
	Hyperlipidemia	22 (61.1)	20 (60.6)
	Smoking	7 (19.4)	7 (21.2)
Complications	Retinopathy	20 (55.5)	19 (57.6)
	Nephropathy	22 (61.1)	19 (57.6)
	Neuropathy	22 (61.1)	20 (60.6)
	Cerebrovascular disease	5 (13.9)	5 (15.2)
	Ischemic heart disease	4 (11.1)	4 (12.1)
Treatments	Beta-blockers	2 (5.5)	2 (6.1)
	ACE inhibitors	7 (19.4)	7 (21.2)
	Angiotensin receptor blocker	11 (30.5)	11 (33.3)
	Statins	19 (52.7)	18 (54.5)
	α-Glycosidase	18 (50.0)	18 (54.5)
	Biganide	2 (5.6)	2 (6.1)

Data are mean ± standard deviation (SD) or *n* (%). A1c, hemoglobin A1c; ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; IRI, immunoreactive insulin; LDL, low-density lipoprotein.

Of the 26 patients aged more than 60 years, the remaining 25 subjects completed the planned 4-month study after the switch. Of these 25 cases, 24 achieved HbA1c of less than 7.0%. The primary outcome measure – the proportion of patients who achieved HbA1c of less than 7.0% at 4 months – was 92.3% (24/26). The results indicate a high rate of success in switching from insulin therapy to oral agents, even in elderly patients. In these 25 patients who completed the 4-month study, the average HbA1c at 4 months after the switch was 5.8 ± 0.8%. The value was significantly lower than that before the switch ($P < 0.01$). The results showed that the switch therapy provided significantly better blood sugar control also in elderly patients.

Safety measures

Bodyweight was not significantly different before and after the switch (Table 2). No cases were diagnosed as having heart failure or drug-induced liver dysfunction. All the other parameters were not statistically significantly different before and after the switch. Hematocrit significantly decreased after the switch.