Lower body mass index is associated with orthostatic hypotension in Parkinson's disease

Tomohiko Nakamura [a, b,*], Masashi Suzuki[a], Miki Ueda[a], Masaaki Hirayama[c], Masahisa Katsuno [a, *]

[a] Department of Neurology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho Showa-ku Nagoya 466-8550, Japan

[b] Department of Laboratory Medicine, Nagoya University Hospital, 65 Tsurumai-cho Showa-ku Nagoya 466-8550, Japan

[c] Department of Pathophysiological Laboratory Sciences, Nagoya University Graduate School of Medicine, 1-1-20 Daiko-Minami, Higashi-ku, Nagoya 461-8673, Japan

*Address correspondence:

Tomohiko Nakamura, M.D., Ph.D.

Department of Neurology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho Showa-ku Nagoya 466-8550, Japan

Tel: +81-52-744-2391, Fax: +81-52-744-2393

E-mail: tomohiko@med.nagoya-u.ac.jp

or

Masahisa Katsuno, M.D., Ph.D.

Department of Neurology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho Showa-ku Nagoya 466-8550, Japan

Tel: +81-52-744-2385, Fax: +81-52-744-2384

E-mail:ka2no@med.nagoya-u.ac.jp

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Abstract

Introduction: Lower body mass index (BMI) is associated with orthostatic hypotension (OH) in the general population, especially in the elderly; however, no studies have addressed this issue in Parkinson's disease (PD).

Methods: We investigated the results of the head-up tilt test and BMI of patients with PD, and evaluated whether BMI is related to orthostatic systolic blood pressure (SBP) change during the head-up tilt test. PD patients were divided into male and female groups, and further divided into middle-aged (age <65 years) and elderly (age ≥65 years) subgroups in each sex.

Results: OH was observed in 13 of 64 male and 12 of 75 female patients with PD. BMI was lower in patients with OH than in those without, in both men and women. In the elderly group, a significant correlation between BMI and orthostatic SBP change was found (men, $r = 0.47$, $p = 0.006$; women, $r = 0.43$, $p = 0.005$), and a BMI below mean - 0.5 standard deviation increased OH odds (men: BMI < 20.5; odds ratio, 6.79; 95% CI, 1.06-43.36; women: BMI < 18.5; odds ratio, 5.11; 95% CI, 1.05-24.96).

Conclusion: Lower BMI is a predisposing factor of OH in elderly patients with PD.

1. Introduction

Orthostatic hypotension (OH) is one of the commonly occurring nonmotor symptoms in patients with Parkinson's disease (PD). Older age, male sex, advanced Hoehn-Yahr stage, longer disease duration, higher systolic blood pressure (SBP), and the use of dopaminergic drugs are predisposing factors [1, 2]. In the general population, multiple factors have been linked to OH, including bed rest, high blood pressure (BP), stroke, and medication, especially in elderly persons [3, 4]. In addition, lower body mass index (BMI) is reported to be associated with OH in elderly populations [4-6]. However, there have been no studies focusing on the association between OH and lower BMI in PD patients. Here, we examined whether BMI differs between PD patients with and without OH, and whether BMI is related to orthostatic BP change during the head-up tilt test. PD patients were divided into male and female groups, and further divided into middle-aged (age <65 years) and elderly (age ≥65 years) subgroups.

2. Methods

2.1 Subjects

We retrospectively investigated the medical charts of PD patients who underwent the head-up tilt test at Nagoya University Hospital from January 2007 to July 2015. PD was diagnosed according to the diagnostic criteria [7]. We excluded patients who matched the following criteria: (i) age <40 years; (ii) with severe obesity (BMI ≥35 kg/m^2); (iii) with diabetes mellitus; (iv) with a history of myocardial infarction; (v) with cardiac failure; (vi) with other known neurological disorders including suspicion for peripheral neuropathy; or (vii) taking vasopressor drugs, antihypertensive drugs, or selegiline.

The head-up tilt test was performed at 0900 h in a temperature controlled clinical laboratory (average temperature 25 ± 2°C) after an overnight fast. Any drugs that might influence the cardiovascular system, such as antiparkinsonian drugs, were discontinued at least 12 h before the examination. After resting for at least 5 min in a supine position, patients were tilted up to 60° in a stepwise manner (20° for 5 min, 40° for 5 min, and 60° for 5 min), as described in previous reports [8, 9]. BP and heart rate were measured with continuous non-invasive cardiovascular monitoring using the Task Force Monitor (CNSystems Medizintechnik AG, Austria). Electrocardiograms (ECG) were recorded continuously using four spot electrodes. Beat-to-beat BP measurements were obtained by finger plethysmography of the index finger on the right hand and continuously corrected to the BP of the brachial artery in the left arm obtained by oscillometric measurements. Baseline BP was defined as the last BP values in the supine position just before the tilt up. As OH may be observed after 3 min of orthostatic stress in autonomic failure, such as PD [10], OH was diagnosed as a reduction in SBP of at least 20 mmHg and/or diastolic BP of at least 10 mmHg at the 5 min mark in the 60° position compared to baseline [11]. If the subject reported presyncope symptoms (dizziness, feeling faint, or nausea) during the head-up tilt, and a progressively falling SBP (< 80 mmHg) was observed, the tilt table was returned to the horizontal position before the intended 5 min of head-up tilt were fulfilled; data from just before discontinuation were used for analysis. BMI was recorded at the time of the head-up tilt.

We identified 64 male PD patients (age 64 ± 9 years, disease duration 5.1 ± 4.7 years) and 75 female PD patients (age 64 ± 8 years, disease duration 4.8 ± 4.2 years). We then classified the PD patients into two groups according to the presence or absence of OH, and compared the measured variables including age, disease duration, levodopa equivalent dose [12], or BMI

between the groups. We also analyzed the correlation between orthostatic BP change during the head-up tilt test and the measured variables in the PD patients. There were no differences in age, disease duration, Hoehn- Yahr stage, or levodopa equivalent dose between genders; however, BMI differed between men and women (men 21.9 ± 2.7 kg/m^2, women 20.1 ± 3.1 kg/m^2, $p < 0.001$), and so we analyzed male and female data separately. Furthermore, as OH is reported to be associated with BMI in the elderly [4-6], we divided the patients into the middle-aged (age <65 years) and elderly (age ≥65 years) groups.

2.2 Ethics

This study adhered to the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Japanese government, and was approved by the Ethics Committee of Nagoya University. Written informed consent was waived because the study involved only a retrospective review of routine clinical tests and medical records. Instead, the study protocol was open to the public to assure the right to withdraw of patients.

2.3. Statistical analyses

SPSS software version 23 (SPSS, Chicago, IL, USA) was used for statistical analyses. Values are expressed as mean ± standard deviation (SD). Significant differences were defined as $p < 0.05$. Unpaired t-test or Mann–Whitney's U-test, depending on the data distribution, was used to compare the differences between two independent subgroups. To examine relationships, Pearson’s correlation coefficient was used. Multiple regression analysis was used to estimate the predictive factors of SBP changes during the head-up tilt test. The risk of OH associated with lower BMI was determined with odds ratios (OR) and 95% confidence

intervals (CI).

3. Results

3.1 Association with BMI and orthostatic BP change in the whole population

OH was observed in 13 of 64 male PD patients and 12 of 75 female PD patients. Among the 25 patients with OH, 6 patients discontinued the head-up tilt test due to the discontinuance criteria (5 patients felt faint at the 40° position of the head-up tilt test with a SBP of less than 80 mmHg, and 1 patient had nausea after 3 min at 60° with a SBP of less than 80 mmHg). The results of the comparison between PD patients with and without OH are shown in Table 1. BMI was significantly lower in PD patients with OH than in those without OH in both sexes.

The SBP change during the head-up tilt test did not correlate with age, disease duration, Hoehn–Yahr score, or levodopa equivalent dose in both male and female patients; however, it correlated with baseline SBP and BMI in both male (baseline SBP, $r = -0.35$, $p = 0.004$; BMI, $r = 0.32$, $p = 0.010$) and female (baseline SBP, $r = -0.37$, $p = 0.002$; BMI, $r = 0.33$, $p = 0.005$) groups. In addition, diastolic BP (DBP) change during the head-up tilt test also correlated with BMI in male patients ($r = 0.35$, $p = 0.005$) but not female patients ($r = 0.13$, $p = 0.33$).

We subsequently investigated the variables that were related to orthostatic SBP change. Stepwise regression analysis adjusted for age, disease duration, levodopa equivalent dose, baseline SBP, and BMI confirmed that baseline SBP and BMI were independently related to SBP changes during the head-up tilt test in both male ($R = 0.492$, $p < 0.001$) and female ($R = 0.457$, $p < 0.001$) PD patients.

In patients with a BMI < mean - 0.5 SD (men: BMI < 20.5, women: BMI < 18.5), the OR associated with OH was 3.20 in male patients (95% CI, 0.91 to 11.28) and 3.24 in female

patients (95% CI, 0.91 to 11.51), with a non-significant difference compared to patients with a BMI ≥ mean - 0.5 SD.

3.2 Association with BMI and orthostatic SBP change in middle-aged and elderly patients

The patients were further divided into the middle-aged and elderly groups. There were no differences in disease duration, Hoehn-Yahr score, levodopa equivalent dose, BMI, or BP and HR changes in the head-up tilt test between middle-aged and elderly patients irrespective of whether they were male or female patients. The results of this subgroup analysis demonstrated that in the middle-aged group (31 men and 34 women), SBP change during the head-up tilt test correlated with baseline SBP in men ($r = -0.42$, $p = 0.020$) and tended to be correlated with baseline SBP in women ($r = -0.34$, $p = 0.053$), but did not correlate with BMI in either men ($r = 0.13$, $p = 0.50$) or women ($r= 0.15$, $p = 0.39$) (Fig. 1). DBP change during the head-up tilt test also did not correlate with BMI in men ($r = 0.36$, $p = 0.06$) or women ($r= 0.13$, $p = 0.30$). Although OH was observed in six male and three female patients, BMI did not show a difference between PD patients with and without OH, regardless of sex (Table 2).

In this group, the OR associated with OH in patients with BMI < mean - 0.5 SD (men: BMI < 21.0, women: BMI < 18.9) did not change compared to patients with BMI ≥ mean - 0.5 SD (men: OR, 1.06; 95% CI, 0.16 to 7.06; women: OR, 1.05; 95% CI, 0.09 to 13.00).

On the other hand, in the elderly group (33 men and 41 women), orthostatic SBP change during the head-up tilt test correlated with BMI in both male ($r = 0.47$, $p = 0.006$) and female ($r = 0.43$, $p = 0.005$) patients (Fig. 1). It also correlated with baseline SBP in the female group ($r = -0.40$, $p = 0.011$) and tended to be correlated with baseline SBP in the male group ($r = -0.34$, $p = 0.057$). DBP change during the head-up tilt test correlated with BMI in men ($r = 0.36$, $p =$

0.04) but not in women (r= 0.26, p = 0.11).

In this elderly group, seven male and nine female patients showed OH, and BMI was significantly lower in patients with OH than in those without OH in both men and women (Table 2).

In addition, stepwise regression analysis adjusted for age, disease duration, levodopa equivalent dose, baseline SBP, and BMI confirmed that baseline SBP, and BMI were independently related to SBP changes during the head-up tilt test in both male (R = 0.565, p = 0.003) and female (R = 0.58, p < 0.001) PD patients of the elderly group.

Elderly patients with BMI < mean - 0.5 SD had increased OH odds compared to elderly patients with BMI ≥ mean - 0.5 SD in both men and women (men: BMI < 20.5, OR = 6.79, 95% CI 1.06 to 43.36; women: BMI < 18.5, OR = 5.11, 95% CI 1.05 to 24.96).

4. Discussion

In this study, we showed that there was a significant correlation between BMI and SBP change during the head-up tilt test in PD patients; furthermore, elderly PD patients with lower BMI had increased OH odds. Our results suggest that lower BMI is one of the major risk factors for OH in elderly PD patients.

The association between lower BMI and OH has been reported in general elderly populations [4-6]. However, the results are conflicting, and others reported that there was no association between lower BMI and OH [13, 14]. The reason for the inconsistency may be because the population of these studies might be inhomogeneous. Most of these studies included patients with diabetes mellitus and/or hypertension, and those taking drugs that might influence BP. Patients with PD were even combined in these studies [13, 14]. Atli et al.

examined OH in healthy elderly subjects excluding those with antihypertensive treatment, diabetes mellitus, history of myocardial infarction, cardiac failure, or medications that may cause OH, and found that there was no difference in BMI between subjects with and without OH [3]. In the present study, we excluded patients with such diseases and/or use of drugs that possibly affect BP, except for antiparkinsonian medication, from the analysis. Thus, the association with lower BMI and OH may be a specific feature of elderly PD. On the contrary, in our results, patients in the middle-aged groups showed a poor correlation between BMI and orthostatic SBP decrease. Inconsistent associations were also noted in the middle-aged general populations. Rose et al. could not find any difference in BMI between middle-aged subjects with and without OH [15], whereas Fedorowski et al. showed that OH may be determined by female sex, antihypertensive treatment, and low BMI in a multivariate analysis [16]. In our results, the number of patients who showed OH was small in the middle-aged female subgroup; thus, further observations with more PD patients with OH, especially including middle-aged female subjects, are necessary to clarify this issue.

Although the detailed mechanism underlying the association between lower BMI and OH is not clear, one possible explanation is that the effect is related to increased autonomic activity in the patients with higher BMI associated with retention of salt and water (e.g., a higher plasma volume) [17]; this is likely caused by activation of the renin-angiotensin-aldosterone system, which suggests decreased autonomic activity in subjects with lower BMI and decreased retention of salt and water. In addition, water-bolus treatment is a useful orthostatic aid [18]. Drinking, in rapid succession, two 250-mL glasses of water has been shown to increase standing SBP by >20 mm Hg for about 2 h, and the mechanism involves the activation of sympathetic adrenergic neurons as well as an increase in the plasma concentrations of

norepinephrine [19, 20]. Thus, sympathetic nervous system responses may play an important role in orthostatic BP control. Recently, an association between BMI and dysautonomia has been reported in early untreated PD patients. Mochizuki et al. reported that higher BMI is associated with decreased autonomic dysfunction when assessed by cardiac ^{123}I-metaiodobenzylguanidine imaging [21]. On the other hand, Umehara et al. reported that lower BMI is associated with reduced autonomic function, including a decrease in blood pressure on head-up tilt-table testing and a higher cardiac washout ratio by ^{123}I-metaiodobenzylguanidine imaging [22]. The results of these two studies are conflicting, but our results and those of Umehara et al.'s study indicate that lower BMI is associated with sympathetic dysfunction leading to orthostatic hypotension in PD patients.

We recently reported that in PD patients, lower leptin levels are associated with grater decrease in SBP change during the head-up tilt test and that low levels of leptin appears to be associated with OH in PD [11]. Leptin, a protein secreted by adipose tissue, has an integral role in endocrine regulation of metabolism and contributes to controlling food intake, energy expenditure, and body weight. Furthermore, leptin acts on the autonomic nervous system and is involved in the control of sympathetic excitation and BP. Many studies have shown that leptin levels are correlated with BMI [23-25] and body fat percentage [26]. This suggests that the leptin levels of patients with lower BMI, especially lower body fat percentage, are low, and thus, sympathetic excitation mediated by leptin is inhibited in these subjects. In our previous study, we also found a correlation between BMI and leptin levels; however, the association between orthostatic SBP change and BMI was found only in female PD patients, and no correlation was found in male PD patients [11]. This may be because the number of patients was smaller than in the present study, and the patients were not divided into middle-aged and

elderly groups.

Overall, based on our supposition that leptin or water and salt retention are involved in these processes, we believe that weight, rather than height, drove the association between BMI and OH. We also confirmed that there was a significant association between weight and orthostatic SBP change in both elderly men ($r = 0.403$, $p = 0.020$) and women ($r = 0.320$, $p = 0.04$) but no association between height and orthostatic SBP change (men: $r = -0.107$, $p = 0.344$; women: $r = -0.203$, $p = 0.202$; data not shown in the results). Thus, longitudinal studies on changes in body weight/body fat, leptin levels, body fluid volume, and SBP changes during the head-up tilt test in individual subjects may elucidate this issue.

Previous reports have shown that disease duration, the use of dopaminergic drugs, and higher supine SBP are associated with OH in PD [1, 2]. In our study, baseline SBP was higher in PD patients with OH than in those without in both men and women, which is consistent with the results of previous studies. However, we found an association between orthostatic DBP decline and BMI in elderly men but not in elderly women. This may be because the variations in DBP changes were smaller compared to those of SBP, leading to the small effect size. In addition, disease duration tended to be longer, and levodopa equivalent dose tended to be higher in PD patients with OH than in those without in men but not in women. Sympathetic neural and vascular resistance responses during orthostatic stress are reported to be attenuated in women [27], particularly when they are hypovolemic [28, 29]; thus, our findings of gender differences may reflect gender differences in autonomic function.

This study had some limitations. First, this was a retrospective study with no control subjects; thus, there are some limitations intrinsic to the study design. Additionally, the results may have had a referral bias, especially relating to subjects who were referred for the tilt study.

Comparing the regression line as shown in Fig. 1 between PD patients and healthy control subjects may clarify whether the association between lower BMI and orthostatic SBP decrease is a specific finding in PD patients. Additionally, body fat amounts or body fluid volumes were not examined, and these metrics may be more meaningful than BMI alone.

In the pathophysiology of PD, cardiac sympathetic denervation combined with an impaired peripheral vasoconstrictor response due to baroreflex abnormalities is thought to account for OH [9, 30]. However, we believe that lower BMI, which may be associated with lower leptin levels or decreased retention of water and salt, may be associated with OH in PD, especially in elderly subjects. Management of body weight may be one of the solutions for OH in elderly PD patients.

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Figure legends

Figure 1. Relationship between orthostatic SBP changes and BMI in male and female PD patients. Orthostatic SBP changes significantly correlated with BMI in elderly male PD (A) and elderly female PD (B) patients. No correlation was noted in the middle-aged subjects in any analysis. Open circle and solid lines indicate the data for elderly PD patients, and black triangle and dashed lines indicate the data for middle-aged PD patients. SBP, systolic blood pressure; BMI, body mass index; PD, Parkinson’s disease.

Table 1 Comparison of the demographics and the results of the head-up tilt test between PD patients with and without OH.

	Male			Female		
	OH (n = 13)	No OH (n = 51)	*p*	OH (n = 12)	No OH (n = 63)	*p*
Age (y)	64 ± 9	64 ± 10	0.923	66 ± 7	63 ± 8	0.356
Disease duration (y)	7.4 ± 5.1	4.5 ± 4.4	0.077	5.0 ± 4.3	4.8 ± 4.3	0.883
HY	2.5 ± 1.3	2.3 ± 1.0	0.560	2.1 ± 0.8	2.3 ± 1.2	0.525
LED (mg)	403 ± 331	221 ± 294	0.056	282 ± 318	322 ± 352	0.727
Body mass index	20.3 ± 3.1	22.3 ± 2.5	0.020	18.5 ± 2.5	20.5 ± 3.1	0.035
Baseline						
SBP (mm Hg)	129 ± 19	115 ± 1	0.003	130 ± 23	114 ± 20	0.025
DBP (mm Hg)	73 ± 15	71 ± 18	0.775	69 ± 7	69 ± 15	0.882
HR (bpm)	67 ± 10	64 ± 10	0.450	70 ± 12	68 ± 10	0.633
Head-up tilt test						
⊿SBP (mm Hg)	-29 ± 7	2 ± 10	< 0.001	-26 ± 13	4 ± 12	< 0.001
⊿DBP (mm Hg)	-11 ± 9	6 ± 8	< 0.001	-9 ± 5	7 ± 10	< 0.001
⊿HR (bpm)	10 ± 10	12 ± 8	0.378	15 ± 11	10 ± 7	0.071

PD, Parkinson's disease; OH, orthostatic hypotension; HY, The Hoehn and Yahr scale; LED, levodopa equivalent dose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 2 Comparison of the demographics and the results of the head-up tilt test between PD patients with and without OH in the middle-aged and elderly groups.

	Male					
	Middle-aged			Elderly		
	OH (n = 6)	No OH (n = 25)	*p*	OH (n = 7)	No OH (n = 26)	*p*
Age (y)	57 ± 6	56 ± 6	0.715	71 ± 4	72 ± 5	0.527
Disease duration (y)	8.1 ± 5.9	4.2 ± 5.2	0.131	6.9 ± 4.7	4.7 ± 3.6	0.196
HY	2.8 ± 1.2	2.1 ± 0.9	0.118	2.1 ± 1.4	2.4 ± 0.9	0.541
LED (mg)	505 ± 396	184 ± 295	0.033	316 ± 263	256 ± 294	0.626
Body mass index	21.5 ± 3.5	22.5 ± 2.4	0.402	19.4 ± 2.6	22.1 ± 2.7	0.020
Baseline						
SBP (mm Hg)	128 ± 23	114 ± 16	0.093	130 ± 16	115 ± 12	0.010
DBP (mm Hg)	75 ± 19	74 ± 12	0.899	71 ± 12	68 ± 22	0.775
HR (bpm)	68 ± 7	68 ± 10	0.993	65 ± 13	61 ± 8	0.249
Head-up tilt test						
⊿SBP (mm Hg)	-27 ± 6	-0 ± 8	<0.001	-30 ± 8	4 ± 12	<0.001
⊿DBP (mm Hg)	-11 ± 9	5 ± 8	<0.001	-10 ± 10	6 ± 8	<0.001
⊿HR (bpm)	9 ± 14	13 ± 9	0.351	11 ± 6	7 ± 11	0.876
	Female					
	Middle-aged			Elderly		
	OH (n = 3)	No OH (n = 31)	*p*	OH (n = 9)	No OH (n = 32)	*p*
Age (y)	55 ± 4	57 ± 6	0.700	70 ± 4	70 ± 3	0.513
Disease duration (y)	4.8 ± 3.0	5.2 ± 4.7	0.884	5.0 ± 4.8	4.4 ± 3.8	0.659
HY	1.7 ± 0.6	2.5 ± 1.2	0.244	2.2 ± 0.8	2.2 ± 1.3	0.922
LED (mg)	233 ± 404	388 ± 398	0.523	298 ± 312	254 ± 289	0.676
Body mass index	20.4 ± 3.9	20.5 ± 3.4	0.952	17.9 ± 1.7	20.2 ± 3.0	0.031
Baseline						
SBP (mm Hg)	114 ± 18	110 ± 20	0.805	135 ± 23	119 ± 19	0.042
DBP (mm Hg)	63 ± 2	65 ± 18	0.872	71 ± 8	73 ± 1	0.467
HR (bpm)	69 ± 16	70 ± 12	0.952	70 ± 11	67 ± 8	0.375
Head-up tilt test						
⊿SBP (mm Hg)	-22 ± 1	1 ± 12	0.002	-28 ± 15	6 ± 12	<0.001
⊿DBP (mm Hg)	-13 ± 5	5 ± 10	0.005	-8 ± 5	9 ± 10	<0.001
⊿HR (bpm)	11 ± 9	10 ± 5	0.820	16 ± 11	10 ± 9	0.119

PD, Parkinson's disease; OH, orthostatic hypotension; HY, The Hoehn and Yahr scale; LED, levodopa equivalent dose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

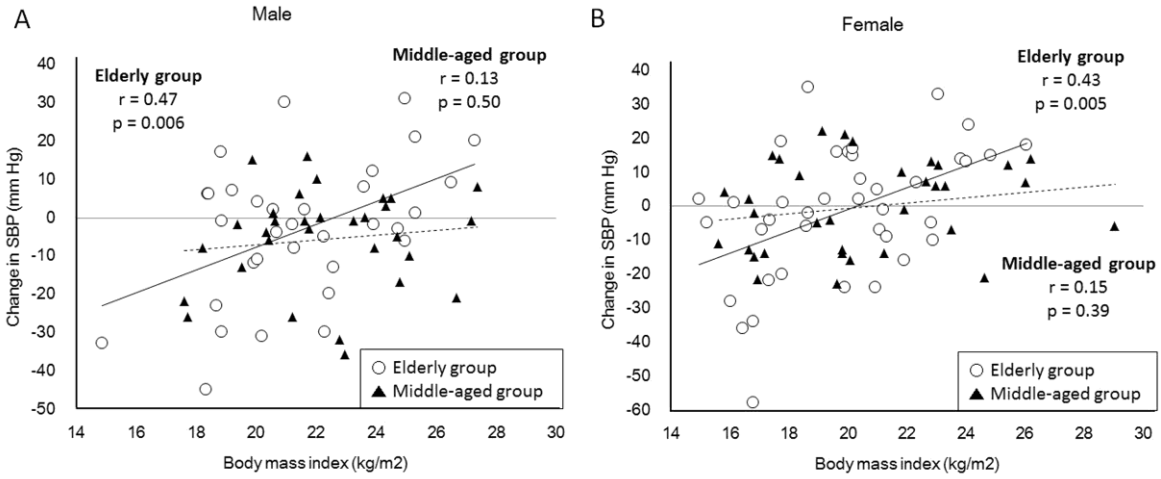
A
Male
Elderly group
r = 0.47
p = 0.006
Middle-aged group
r = 0.13
p = 0.50
Change in SBP (mm Hg)
Body mass index (kg/m2)
Elderly group
Middle-aged group
B
Female
Elderly group
r = 0.43
p = 0.005
Middle-aged group
r = 0.15
p = 0.39
Change in SBP (mm Hg)
Body mass index (kg/m2)
Elderly group
Middle-aged group

Fig.1