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Original article

Functional age and medication in the independent living elderly: Yurin study.

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Abstract

***Aim*:** This study measured physical functional age and the amount of activity in the daily lives of the elderly and examined the influences on functional age by medication to cure and prevent diseases.

***Methods*:** The subjects of this study were 39 (15 males and 24 females, age: 77.6 ± 5.3), who were participants of a health promotion project and underwent an anti-aging medical check-up where their current states of medicine intake was precisely confirmed. In the Yurin Study, 43 participants took the medical check-up. However, 4 participants were excluded as their medication information was unclear. The relationship between functional age and medication was analyzed in this study. Functional age and Δ functional age (Δ functional age = functional age – chronological age) were calculated using Life Style Compass (Nippon Shooter Ltd.). The participant's glycative stress index was examined using AGE Reader to measure the intensity of skin auto-fluorescence (AF) of skin accumulation of advanced glycation end products (AGEs).

***Results*:** Subjects for this analysis were members of a group engaging in a large volume of physical activity and their functional age remained younger than their chronological age. There were no significant difference in functional age between subjects with medication and subjects without medication. Medical effects were recognized in most cases. Subjects with medication showed, in only one item, significantly high ΔVascular age (subjects with medication: –10.1 ± 8.6 year, subjects without medication: –19.8 ± 4.1 year, $p = 0.019$). For drug effects of examination items, no significant differences were noted in bone age between subjects with osteoporosis administration and subjects without medication. However, subjects with anti-hyperlipidemic agent had significantly higher ΔVascular age than subjects without medication. No differences were noted in blood test parameters of glycolipid metabolism disorder but a significantly higher value was shown in glucagon. There was no significant difference in skin AF value between subjects with medication and subjects without medication.

***Conclusion*:** The subjects were a population with a large volume of physical activity and their functional ages were maintained in a good condition. Hyper LDL cholesterolemia is a risk factor of arteriosclerosis and the vascular age of subjects with medication did not reach the level of subjects without medication, even though the former had had medication.

***KEY WORDS*:** elderly, medication, functional age, statins, glucagon

Introduction

Japan is on the forefront of nations with a rapidly aging population. According to an estimation from the National Institute of Population and Social Security Research, the population of Japan has fluctuated around 127 million since 2000, when a national census was conducted. However, the population of Japan is expected to decrease to 124.1 million in 2020 and 116.6 in 2030. The population projection for 2050 and 2060 would estimate that the population of Japan will fall below 100 million by 2050 and the population in 2060 will not even reach 90 million. Along with the problems that accompany a decrease in the total population, the rise in aging ratio would induce the decrease in population of productive age, an increase in cost of social security and an increase in load and cost of senior care [1]. Thus, the extension of healthy life expectancy is a compelling issue to be solved.

Problems with elderly medication have been reported. In the present medical state, the average rate of injury and disease and the rate of medical assistance have increased in response to the increasing age of the elderly. In accordance with this trend, the volume of prescriptions for

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medications has increased [2]. It has been reported that averagely 5.8 types of medicines were prescribed to the elderly who had two of the following four diseases: hypertonia, diabetic mellitus, dyslipidemia and cognitive impairment [3]. Prescription of multiple medications could cause serious problems, which could not only increase medical care expenditure, but also cause severe adverse effects.

Our research center has been operating a health promotion project named "Yurin Study", which was established in 2008. The participants were the independently-living elderly in the Yurin area of Kyoto city. The core of the health promotion activities is a pedometer-based walking program [4-6]. Even though the participants were independently-living persons, quite a few of the participants contracted diseases related to glycative stress and had undergone internal medicine treatment. This study surveyed the medication situations of the independent elderly living in Yurin area to examine the influences on physical functions in the presence or absence of medication.

Methods

Subjects

Subjects of this study were people of advanced age, who had participated in "Yurin Kenpo-Juku" since December of 2008: 43 subjects, 18 males and 25 females, 77.7 ± 6.4 years (mean ± standard deviation). "Yurin Kenpo-Juku" provided health promotion exercise to people of middle and advanced age living in the Yurin area, Shimogyo-ku, Kyoto. The program employed the use of a physical activity meter, a device which measures the volume of performed physical activity while walking (3-dimensional acceleration sensor for activity volume, Omron Colin, Kyoto, Japan). The average number of walking steps was 6,802 steps/day among the participants (from March 16th to April 20th in 2016).

Anti-aging medical check-up

The anti-aging medical check-up measured the functions of muscle, bone, vascular, neural and hormone systems, which were calculated to estimate the participant's functional age [7-8]. Measurement of muscle strength employed a muscle volume estimation device applying bioelectrical impedance (Physion-MD: Nippon Shooter Ltd., Tokyo, Japan). Muscle age was estimated with a weight bearing index (WBI) and basal metabolic rate index (kcal/day). The stiffness value of calcaneus (fibular tarsal) bone and young adult means comparison (%YAM) were measured by ultrasonography (A-1000: GE Yokokawa Medical System, Hino, Tokyo, Japan). Vascular age was estimated by calculation of arteriosclerosis level, which was measured with a digital photoplethysmography acceleration pulse wave meter (SDP-100: Fukuda Denshi Co., Ltd, Tokyo, Japan). Neural function was estimated based on higher brain function, which was measured by Wisconsin Card Sorting Test (WCST). Subjects underwent a biochemical blood examination, and then insulin-like growth factors-I (IGF-I)and serum concentration of dehydroepiandrosterone-sulfate (DHEA-s) were measured. The functional age for each category was estimated by Life Style Compass (Nippon Shooter).

Glycative stress index, as has been reported, was examined by using an AGE Reader (DiagnOptics, Groningen, Netherlands) to measure intensity of auto-fluorescence (AF) of the fluorescence derived from advanced glycation end products (AGEs) [9-11]. As for the blood index, the following was measured: total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), hemoglobin A1c (HbA1c) [National Glycohemoglobin Standardization Program (NGSP)], immuno-reactive insulin (IRI), cortisol, glucagon and plasma pentosidine (by HPLC ion-paired method). Biochemical examination of the blood was performed by LSI Medience (Tokyo, Japan)

Comparison with the presence or absence of medication

Based on the questionnaire results, grouping was performed based on the presence or absence and types of medicine. The three medications with the greatest representation in the questionnaire were selected; anti-hypertensive, anti-hyperlipidemic agent and anti-osteoporosis were then listed in ascending order. Subsequently, differences in the functional age of participants were analyzed with the presence or absence of each medication.

Statistical analysis

Statistical analysis employed SPSS Statistics 21 (IBM Japan, Tokyo, Japan). Comparisons between chronological age and functional age were compared by paired t-test, and a correlation analysis of serum glucagon value was examined by Pearson analysis. Other analyses were conducted by t-test. In all analyses, two sided test used 0.05 as the cut-off for risk ratio with statically significant difference.

Ethical Standard

Before starting the survey, participants were fully informed regarding not only the period, place, methods and contents of the examination, but also about the potential beneficial and harmful effects due to participation in this research. Written consent was obtained from each participant. This study was approved by the ethics committee of Doshisha University (Application number: #0832, #14089).

Results

Subject information

Among 43 potential subjects, 34 participants were taking medicine on a daily basis at the time of the medical check-up, 5 participants had no medication and 4 participants had an unclear medication status. Thus, the subjects of this study were 34 participants who provided data to be analyzed for this research: 15 males and 24 females, age: 77.6 ± 5.3 years. No subjects were smokers.

Fig. 1 shows the types of medicine administrated to the subjects. In ascending order, anti-hypertensives: 21 cases, anti-hyperlipidemic agents: 11 cases, anti-osteoporosis: 10 cases, gastric secretion inhibitors: 9 cases, non-steroidal anti-inflammatory drugs (NSAIDs), anti-diabetics and sleeping pills: 5, respectively, were administrated. As for anti-hyperlipidemic agents, 7 cases were hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statin-related medicine). Nine subjects (23%) among 39 subjects in this study were

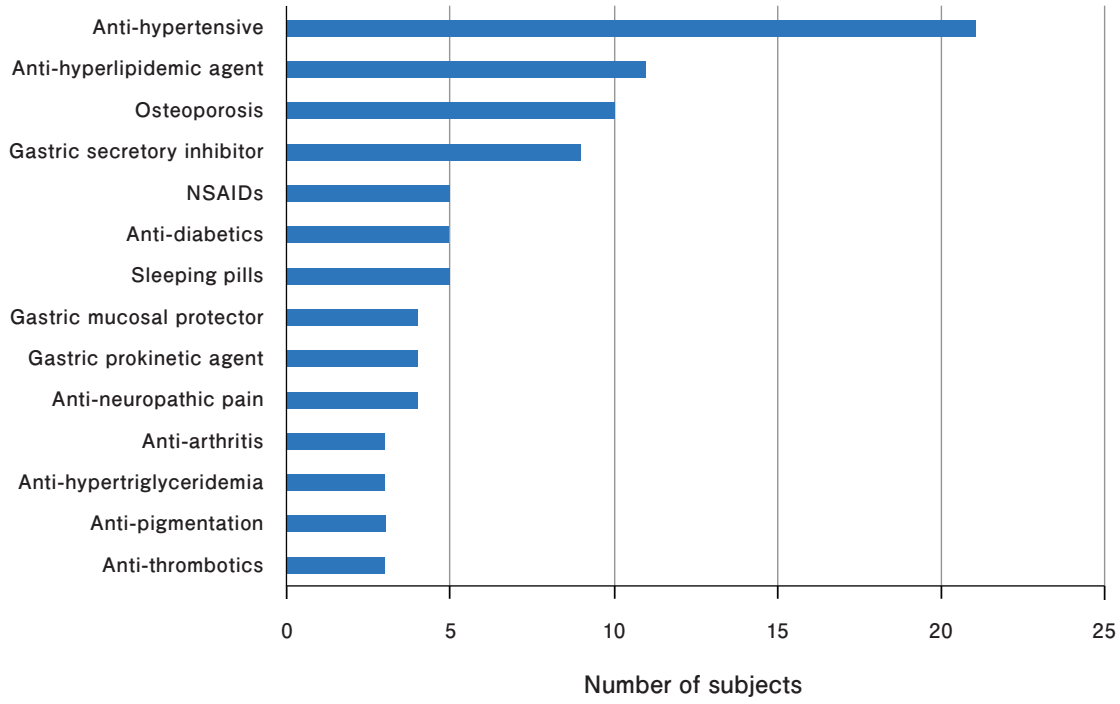

Fig. 1. **The type of medicine and number of medications.**
Admitted multiple responses. Total subject number is 34. NSADS, non-steroidal anti-inflammatory drugs.

prescribed more than 5 types of medicine, which has been reported to be an increased risk factor for a sudden rise in side effects.

Table 1 shows the results of the anti-aging medical check-up. Δfunctional age was defined as follows: functional age − chronological age. In comparisons between genders, males and females, Neural age and ΔNeural age of males were significantly higher than those of females: Neural age, males: 77.2 ± 12.8 years, females: 67.5 ± 13.2 years, p = 0.035. There was significant correlation in between bone functional age and chronological age by correlation analysis of functional age (y) and chronological age (x).

$y = 0.525x + 18.18$, $R^2 = 0.722$, n = 39.

However, no correlation was recognized in other functional ages.

Comparisons in functional age with the presence or absence of medication

Comparing chronological and functional ages with medication states, this study examined the deviation of physical age of the subjects (***Table 2***).

There was no significant difference in functional ages between medication of 34 subjects (12 males and 22 females, 77.2 ± 5.3 years) and non-medication of 5 subjects (3 males and 2 females, 80.0 ± 5.8 years). Participants in the medication and non-medication groups maintained functional ages lower than their chronological ages. ΔVascular age was significantly higher in medication than in non-medication; ΔVascular age, Medication arm −10.1 ± 8.6 years, Non-medication arm −19.8 ± 4.1 years, p = 0.019. No significant difference was noted between males and females by gender specific analysis.

*Analysis with the presence or absence of anti-hypertensive medication (**Table 3**)*

No significant difference was recognized between the anti-hypertensive medication group (21 subjects, 9 males and 12 females, 77.5 ± 5.8 years) and non-medication group (18 subjects, 6 males and 12 females, 77.7 ± 5.0 years). ΔFunctional age analysis did not show significant difference. Gender specific analysis did not show significant difference.

*Analysis with the presence or absence of anti-osteoporosis medication (**Table 4**)*

The subject group with anti-osteoporosis medication contained 10 females (78.5 ± 3.3 years). Neural age and ΔNeural age were significantly higher in the anti-osteoporosis medication group than the non-medication group (29 subjects, 15 males and 14 females, 77.3 ± 5.9 years); Neural age, medication arm 70.0 ± 9.8 years, non-medication arm 64.9 ± 8.4 years, p = 0.034. Comparing the medicated group of 10 females and the non-medicated group of 14 females, no significant difference was seen between Neural age and ΔNeural age. Females were younger in Neural age than males, which resulted in a significant difference in Neural age and ΔNeural age by an analysis comparing males and females.

Analysis with the presence or absence of anti-hyperlipidemia medication

There was no significant difference in functional age between the group with anti-hyperlipidemia medication (11 subjects, one male and 10 females, 75.2 ± 5.4) and the group

Table 1. Data profile of functional age and AF.

	Male (n = 15)			Female (n = 24)			Total (n = 39)			
	mean ± SD	95% CI Lower	Upper	mean ± SD	95% CI Lower	Upper	p value	mean ± SD	95% CI Lower	Upper
Age	78.1 ± 4.7	75.5	80.7	77.3 ± 5.6	74.9	79.6	0.624	77.6 ± 5.3	75.9	79.3
Muscle age	58.9 ± 2.4	57.6	60.2	59.0 ± 3.7	57.4	60.6	0.887	59.0 ± 3.3	57.9	60.0
Bone age	70.7 ± 14.7	62.5	78.8	70.1 ± 9.2	66.3	74.0	0.898	70.3 ± 11.6	66.6	74.1
Hormone age	70.1 ± 11.1	64.0	76.3	74.8 ± 8.2	71.4	78.3	0.150	73.0 ± 9.7	69.9	76.2
Neural age	77.2 ± 12.8	70.1	84.2	67.5 ± 13.2	62.0	73.1	**0.035**	71.2 ± 13.9	66.7	75.7
Vascular age	64.1 ± 7.3	60.1	68.2	67.5 ± 9.4	63.6	71.5	0.251	66.2 ± 8.8	63.4	69.1
AF	2.57 ± 0.40	2.35	2.79	2.57 ± 0.36	2.42	2.72	0.995	2.57 ± 0.38	2.45	2.69
ΔMuscle age	-19.3 ± 2.4	-20.6	-18.0	-18.2 ± 3.4	-19.6	-16.8	0.915	-18.6 ± 3.1	-19.6	-17.6
ΔBone age	-7.5 ± 13.2	-14.8	-0.2	-7.1 ± 8.0	-10.5	-3.7	0.063	-7.2 ± 10.3	-10.6	-3.9
ΔHormone age	-8.0 ± 8.6	-12.8	-3.2	-2.4 ± 8.6	-6.0	1.2	**0.050**	-4.6 ± 9.0	-7.5	-1.6
ΔNeural age	-1.0 ± 13.6	-8.5	6.6	-9.7 ± 12.2	-14.9	-4.6	0.140	-6.4 ± 13.5	-10.7	-2.0
ΔVascular age	-14.0 ± 9.2	-19.1	-8.9	-9.7 ± 7.9	-13.0	-6.4	0.995	-11.4 ± 8.7	-14.2	-8.5

ΔFunctional age = Functional age – Chronological age. AF, auto fluorescence in skin; SD, standard deviation; CI, confidence interval.

Table 2. Difference in functional age and AF between medication and non-medication: all drugs.

	Medication's (n = 34)			Non-medication's (n = 5)			
	mean ± SD	95% CI Lower	Upper	mean ± SD	95% CI Lower	Upper	p value
Age	77.2 ± 5.3	75.4	79.1	80.0 ± 5.8	72.8	87.2	0.289
Muscle age	58.9 ± 3.4	57.7	60.1	59.6 ± 2.9	56.0	63.2	0.653
Bone age	70.6 ± 12.4	66.3	75.0	68.3 ± 7.2	59.4	77.2	0.684
Hormone age	73.3 ± 10.1	69.8	76.8	71.3 ± 8.8	60.4	82.2	0.682
Neural age	71.9 ± 14.1	67.0	76.8	66.9 ± 14.2	49.2	84.5	0.463
Vascular age	67.1 ± 9.2	63.9	70.3	60.2 ± 1.8	58.0	62.4	0.107
AF	2.55 ± 0.37	2.42	2.68	2.73 ± 0.45	2.17	3.30	0.313
ΔMuscle age	-18.4 ± 3.1	-19.4	-17.3	-20.4 ± 3.0	-24.1	-16.7	0.173
ΔBone age	-6.6 ± 10.4	-10.2	-3.0	-11.7 ± 10.7	-25.0	1.6	0.314
ΔHormone age	-4.0 ± 9.0	-7.1	-0.8	-8.7 ± 10.0	-21.1	3.8	0.286
ΔNeural age	-5.4 ± 13.6	-10.1	-0.6	-13.1 ± 13.2	-29.5	3.2	0.238
ΔVascular age	-10.1 ± 8.6	-13.1	-7.1	-19.8 ± 4.1	-24.9	-14.7	**0.019**

ΔFunctional age = Functional age – Chronological age. Statistical analysis by Student's t test. AF, auto fluorescence in skin; SD, standard deviation; CI, confidence interval.

Table 3. Difference in functional age and AF between medication and non-medication: anti-hypertensive.

	Medication's (n = 21)			Non-medication's (n = 18)			
	mean ± SD	95% CI Lower	Upper	mean ± SD	95% CI Lower	Upper	p value
Age	77.5 ± 5.8	74.8	80.1	77.7 ± 5.0	75.2	80.2	0.889
Muscle age	58.6 ± 3.0	57.2	59.9	59.4 ± 3.7	57.6	61.3	0.438
Bone age	68.2 ± 12.5	62.6	73.9	72.8 ± 10.8	67.4	78.2	0.235
Hormone age	71.0 ± 9.8	66.5	75.5	75.4 ± 9.6	70.6	80.2	0.169
Neural age	72.9 ± 12.4	67.3	78.5	69.3 ± 15.9	61.4	77.2	0.434
Vascular age	65.0 ± 9.9	60.5	69.5	67.7 ± 7.7	63.9	71.5	0.359
AF	2.60 ± 0.45	2.39	2.80	2.54 ± 0.30	2.39	2.69	0.636
ΔMuscle age	-18.9 ± 2.9	-20.2	-17.6	-18.3 ± 3.4	-20.0	-16.6	0.557
ΔBone age	-9.2 ± 10.1	-13.8	-4.6	-4.9 ± 10.6	-10.2	0.3	0.204
ΔHormone age	-6.5 ± 7.8	-10.0	-2.9	-2.3 ± 10.3	-7.5	2.8	0.163
ΔNeural age	-4.6 ± 14.1	-11.0	1.8	-8.4 ± 13.2	-15.0	-1.9	0.389
ΔVascular age	-12.5 ± 9.2	-16.7	-8.3	-10.1 ± 8.3	-14.2	-5.9	0.399

ΔFunctional age = Functional age – Chronological age. Statistical analysis by Student's t test. AF, auto fluorescence in skin; SD, standard deviation; CI, confidence interval.

Table 4. Difference in functional age and AF between medication's and non-medication's: anti-osteoporosis.

	Medication's (n = 10)			Non-medication's (n = 29)			
	mean ± SD	95% CI Lower	Upper	mean ± SD	95% CI Lower	Upper	p value
Age	78.5 ± 3.3	76.2	80.8	77.3 ± 5.9	75.0	79.5	0.542
Muscle age	60.0 ± 3.1	57.8	62.2	58.6 ± 3.4	57.3	59.9	0.273
Bone age	73.3 ± 6.8	68.4	78.1	69.3 ± 13.0	64.4	74.3	0.373
Hormone age	73.4 ± 9.0	66.9	79.8	72.9 ± 10.3	69.0	76.8	0.902
Neural age	64.1 ± 10.4	56.7	71.5	73.7 ± 14.4	68.2	79.2	**0.034**
Vascular age	70.0 ± 9.8	63.0	77.0	64.9 ± 8.4	61.7	68.1	0.123
AF	2.61 ± 0.34	2.37	2.85	2.56 ± 0.40	2.40	2.71	0.721
ΔMuscle age	-18.5 ± 3.6	-21.1	-15.9	-18.7 ± 3.0	-19.8	-17.5	0.911
ΔBone age	-5.3 ± 7.5	-10.6	0.1	-7.9 ± 11.3	-12.2	-3.6	0.406
ΔHormone age	-5.1 ± 7.7	-10.7	0.4	-4.4 ± 9.7	-8.1	-0.7	0.822
ΔNeural age	-14.4 ± 10.5	-21.9	-6.9	-3.6 ± 13.6	-8.8	1.6	**0.002**
ΔVascular age	-8.5 ± 10.3	-15.9	-1.1	-12.3 ± 8.2	-15.5	-9.2	0.238

ΔFunctional age = Functional age – Chronological age. Statistical analysis by Student's t test. AF, auto fluorescence in skin; SD, standard deviation; CI, confidence interval.

without medication (28 subjects, 14 males and 14 females, 78.5 ± 5.1 years) (***Table 5, Fig. 2***). The ΔVascular age of the medicated group was significantly higher than the group without medication; ΔVascular age, medication arm −6.3 ± 8.7 years, non-medication arm −13.4 ± 8.1, p = 0.022. Comparing the medicated group of 10 females and the non-medicated group of 14 females, no significant difference was noted in functional age and Δfunctional age.

For more detailed data, comparisons of biochemical blood analysis were conducted to examine the influences on ΔVascular age by anti-hyperlipidemia medication (***Table 6***). Glucagon values of the medicated group of 11 subjects were significantly higher than the non-medicated group of 28 subjects; Glucagon medication arm 136.2 ± 27.3 pg/mL, non-medication arm 115.0 ± 21.0 pg/mL, p = 0.013. In the analyses of anti-hypertensive medication and anti-osteoporosis medication, no significant difference was recognized in any test categories of blood biochemical examination with the presence or absence of medication.

A significant correlation between glucagon and IGF-I was shown by the results of correlation analysis between glucagon and blood biochemical examination indexes (r = 0.733, p = 0.010).

Discussion

History of Yurin Study

Yurin Study has conducted exercise programs and surveys since 2008. The participants, including persons who joined midway, were provided with an exercise program of walking with a pedometer and instruction sheets [4]. Participants had been guided and motivated in continuing their exercise programs. This study not only provided exercise programs but also conducted a cohort study [5]. for two and a half years, on the physical influences of the walking program. Yurin Study has shown the importance of physical activities, especially for people of middle and advanced age. Preceding studies conducted by our research center [6]. indicated that the elderly of this program maintained their daily life close to the level of adult physical activity recommended by the Ministry of Health, Labour and Welfare guidelines. It was also shown that the independently-living elderly were significantly younger in Neural age than the elderly needing support or the elderly requiring long-term care. It is important to lead a mentally and physically active life, remaining healthy in neural function, in order to be an elderly person requiring no nursing care.

Medication of the elderly

The "Guidance statement on appropriate medical services for the elderly", which was published by "the Japan Geriatrics Society" showed medical adverse events for the elderly are mainly caused by two factors, multiple medications and heightened chemical sensitivity due to aging [12]. At present, most clinical guidelines are written for young or middle-aged patients, and therefore, it is difficult for medical professionals to provide appropriate medicine for the elderly.

The subjects of this study had 3.6 medications on average. It has been reported that actively taking greater than 5 medications increases the risk for adverse side effects [12]. One in 5 subjects took more than 5 medications. However, subjects of this study were younger in functional age than chronological age, and furthermore, abnormal level values were not detected during the blood examination. It was assumed that their lifestyle habits resulted in their excellent conditions. The subjects of this study had been actively involved in our exercise program and had lived a

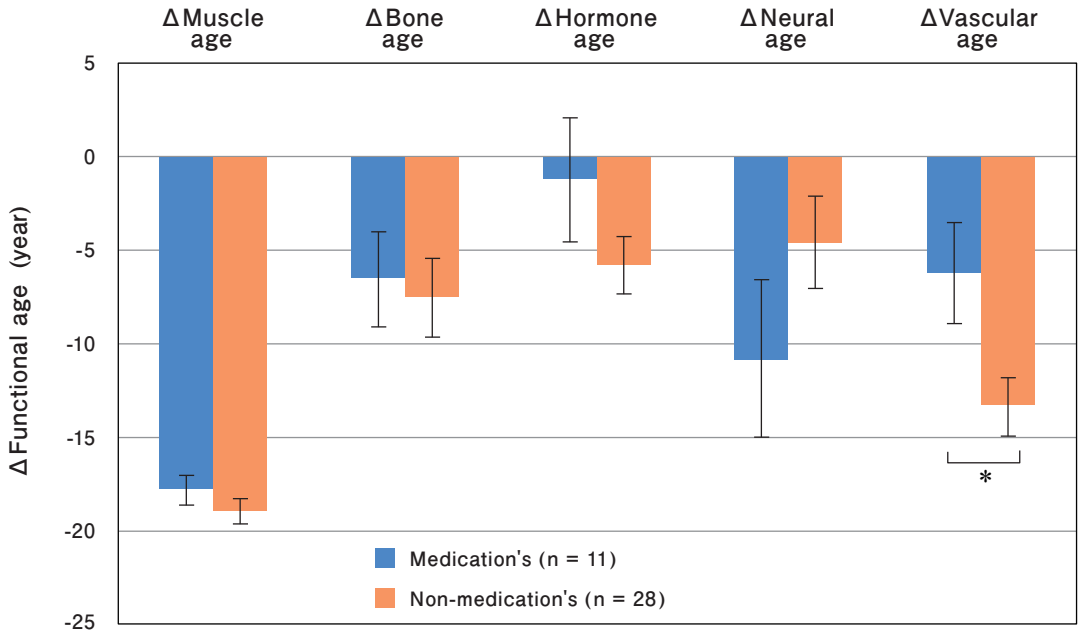

Fig. 2. **Difference in Δfunctional age between medication and non-medication: anti-hyperlipidemia.**
Data are expressed as mean ± SEM. *p < 0.05 by Student's t test. ΔFunctional age = Functional age − Chronological age; SEM, standard error mean.

Table 5. Difference in functional age and AF between medication and non-medication: anti-hyperlipidemia.

	Medication's (n = 11)			Non-medication's (n = 28)			
	mean ± SD	95% CI Lower	Upper	mean ± SD	95% CI Lower	Upper	p value
Age	75.2 ± 5.4	71.5	78.8	78.5 ± 5.1	76.5	80.5	0.079
Muscle age	57.4 ± 2.9	55.5	59.3	59.6 ± 3.3	58.3	60.9	0.063
Bone age	68.7 ± 10.2	61.8	75.6	71.0 ± 12.5	66.2	75.8	0.588
Hormone age	73.9 ± 9.9	67.3	80.6	72.7 ± 10.0	68.8	76.5	0.727
Neural age	64.3 ± 11.8	56.4	72.2	73.9 ± 14.1	68.5	79.4	0.053
Vascular age	68.9 ± 11.7	61.0	76.8	65.2 ± 7.6	62.2	68.1	0.245
AF	2.57 ± 0.39	2.30	2.83	2.57 ± 0.39	2.42	2.72	0.960
ΔMuscle age	-17.8 ± 2.6	-19.6	-16.0	-19.0 ± 3.2	-20.2	-17.7	0.297
ΔBone age	-6.5 ± 8.5	-12.2	-0.8	-7.5 ± 11.3	-11.9	-3.2	0.783
ΔHormone age	-1.3 ± 11.1	-8.7	6.2	-5.9 ± 8.1	-9.0	-2.7	0.161
ΔNeural age	-10.8 ± 13.9	-20.2	-1.5	-4.6 ± 13.3	-9.8	0.6	0.202
ΔVascular age	-6.3 ± 8.7	-12.1	-0.4	-13.4 ± 8.1	-16.5	-10.2	**0.022**

ΔFunctional age = Functional age – Chronological age. Statistical analysis by Student's t test. AF, auto fluorescence in skin; SD, standard deviation; CI, confidence interval.

Table 6. Difference in glycative stress-related index between medication and non-medication: anti-hyperlipidemia.

	Medication's (n = 11)			Non-medication's (n = 28)			
	mean ± SD	95% CI Lower	Upper	mean ± SD	95% CI Lower	Upper	p value
TC (mg/dL)	231.3 ± 25.9	213.9	248.7	213.6 ± 36.5	199.4	227.7	0.151
TG (mg/dL)	140.5 ± 99.2	73.9	207.2	97.3 ± 35.0	83.7	110.8	0.185
HDL-C (mg/dL)	70.6 ± 20.1	57.1	84.2	64.1 ± 19.8	56.4	71.8	0.360
LDL-C (mg/dL)	127.2 ± 21.1	113.0	141.4	124.2 ± 28.6	113.1	135.3	0.758
DHEA-s (μg/dL)	65.1 ± 40.3	38.0	92.1	87.4 ± 62.8	63.0	111.7	0.284
Cortisol (μg/dL)	10.3 ± 3.4	8.0	12.5	10.9 ± 3.2	9.6	12.1	0.617
IRI (μU/mL)	5.01 ± 1.49	4.01	6.01	4.74 ± 2.03	3.95	5.52	0.688
FPG (mg/dL)	96.1 ± 12.6	87.6	104.6	95.8 ± 22.8	87.0	104.7	0.971
HbA1c [NGSP] (%)	5.95 ± 0.48	5.62	6.27	6.17 ± 0.80	5.86	6.48	0.394
IGF-I (ng/mL)	85.5 ± 23.8	69.4	101.5	88.4 ± 32.1	76.0	100.9	0.783
Glucagon (pg/mL)	136.2 ± 27.3	117.8	154.5	115.0 ± 21.0	106.9	123.2	**0.013**
Pentosidine (μg/mL)	40.6 ± 14.5	30.8	50.4	46.0 ± 12.3	41.3	50.8	0.245

Statistical analysis by Student's t test. TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol: LDL-C, low-density lipoprotein-cholesterol; DHEA-s, dehydroepiandrosterone-sulfate; IRI, immune reactive insulin; FPG, fasting plasma glucose; IGF-I, insulin-like growth factor-I; NGSP, National Glycohemoglobin Standardization Program; SD, standard deviation; CI, confidence interval.

life with the awareness of the importance of maintaining good health. The physical activity level of the subject had been far superior to that of the average elderly.

No significant difference was recognized in any functional age between medicated and non medicated study participants. It was interpreted that the therapeutic effects of medication had been mostly exerted. Examining medical properties, no significant difference was seen in Bone age between subjects with anti-osteoporosis medication and subjects without medication. The therapeutic effects of medication were exerted in osteoporosis. High blood pressure is a major risk factor for atherosclerosis. No difference was recognized in the Vascular age between subjects using an anti-hypertensive agent and subjects not using one. The anti-hypertensive agent was moderately effective in achieving the desired aim.

Anti-hyperlipidemic agent and Vascular age/Diabetes

In a comparison between 11 subjects using LDL-C cholesterol-lowering medications and subjects who were not using medications, there was no difference in carbohydrate metabolic parameters (FPG, HbA1c, TC, LDL-C, HDL-C and TG) and glycative stress index (auto-fluorescence [AF] of skin AGE accumulation). This means that the medication effects sufficiently controlled the level of subjects using an anti-hyperlipidemic agent to a level comparable to those who were non-medicated. However, the data analysis indicated that the medicated group had a significantly higher ΔVascular age than the non-medicated group, which could be interpreted as follows: Hyper LDL-C cholesterolemia is a major risk for atherosclerosis, and subjects with hyper LDL cholesterolemia would have progressed atherosclerosis in comparison to subjects without atherosclerosis. However, the subjects of this study had improved due to the anti-hyperlipidemic agent medication, the conditions to equivalent level of serum lipid parameters of non-medication so that their vascular ages improved to a similar vascular age of the non-medicated group. It would be a reasonable interpretation that there still remained significant differences in Vascular age between the medicated group and the non-medicated group.

For anti-hyperlipidemic medications for Hyper LDL-C cholesterolemia, 4 subjects used atorvastatin (Lipitor, Pfizer, USA), 2 subjects used lovastatin (Crestor, AstraZeneca, the UK), one subject used pravastatin sodium (Mevalotin, Daiichi Sankyo, Chuo-ku, Tokyo, Japan) and 4 subjects were taking unknown medications.

These 3 types of medication were HMG-CoA reductase inhibitor. This inhibitor has the effect of reducing blood cholesterol levels by the inhibition of the enzyme which intermediates cholesterol synthesis in the liver. Recent research findings have reported that taking statins is associated with an increased risk of type 2 diabetes [13-16]. Preceding studies have clarified that statin not only increases the risk for incidence of type 2 diabetes, but also has adverse effects on both sensitivity and the secretion quantity of insulin. Insulin regulates lipolysis in peripheral tissues, and the reduction of insulin can induce the increase of triglyceride and cholesterol [17].

Both type-2 diabetes and hyperlipidemic are lifestyle-related diseases. The progression of lifestyle-related diseases cannot be avoided when not improving lifestyle habits and only depending on medication. It should be kept in mind for people with hyper LDL cholesterolemia to maintain the volume of physical activity to be performed even if LDL-C value was improved by statin medication.

Medication for hyper LDL cholesterolemia and glucagon

In comparison of carbohydrate and lipid metabolic parameters between 11 subjects with anti-hyperlipidemic agent medication and subjects with no anti-hyperlipidemic agent medication, the medicated group has a significantly higher value of glucagon. This kind of report has never been reported before.

Glucagon, which is secreted from α cells of pancreatic Langerhans islets, is a blood glucose increasing hormone [18-19] and has the function of maintaining blood glucose in the correct concentration, with insulin lowering blood glucose levels. Serious risk of diabetes has been reported that abnormally high glucagon secretion paralleled by decreasing insulin secretion causes diabetes [19].

A previous study reported that insulin and glucagon regulate gluconeogenesis and statin medication can affect this reaction [20]. Statins inhibit the activities of HMG-CoA reductase and inhibits the production of cholesterol in the liver. Consequently, HMG-CoA reductase is accumulated and insulin secretion is increased. Excessive secretion of insulin induces hypoglycemia. The correction of appropriate blood glucose status, as is reported, induces increased glucagon secretion. The mechanism related to the accumulation of HMG-CoA reductase and the increase of insulin secretion has yet to be clarified.

The influences of statin medication on carbohydrate metabolism has been analyzed by meta-analysis and it was concluded that the influence is limited [21]. The tentative theory of mechanism of influences on carbohydrate metabolism by statin is as follows: 1) inhibition of GLUT4 (glucose transporter type 4) expression, 2) insulin secretion from β cells of the pancreas [22-23]. Statins differ considerably in terms of their influences on carbohydrate metabolism. It has been confirmed that the onset of diabetes can be delayed or prevented when the combination of pitavastatin and improved lifestyle habits were performed.

Influences on carbohydrate metabolism depend on the types of statins. It has been confirmed that the incidence of diabetes in patients with impaired glucose tolerance can be delayed or prevented with the combination of pitavastatin administration and improved lifestyle habits (J-PREDICT) [24]. J-PREDICT achieved excellent outcomes and the intervention to improve physical activity and lifestyle habits played a leading role for this achievement. Actually, the popularization of incretin-related drugs as a new medication for diabetes has been accelerating research of diabetes and glucagon and the supersecretion of glucagon is evaluated as an important factor and seen in a fresh light [18-19].

Glucagon and diabetes

The theory of the causes of type-2 diabetes has been changing from *insulin-centric* idea to *bi-hormonal idea*; from "the sensitivity and decreased secretion of insulin" to "insulin deficiency and glucagon excess" [25-26].

Incretin medication became widely used around 2009 and is the most remarkable medication for diabetes at present. Incretin hormones include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which

stimulates the pancreas to promote increased insulin secretion. Incretin has two types of medications: an oral "DPP-4 (dipeptidyl peptidase-4) inhibitor" which breaks down incretin, prolongs reaction time of incretin and promotes the secretion of insulin, and the injection agent "GLP-1 receptor agonist", which has a mechanism to change the structure of GLP-1 and promote insulin secretion, which has a slightly greater effect than DPP-4 inhibitor. Each incretin medication functions only on the condition of hyperglycemia and has the advantage of not inducing hypoglycemic symptoms [27-30]. GLP-1 and incretin-related drugs are greatly different from insulin-related drugs in terms of inhibitory effects against glucagon secretion [31-32] for diabetes patients [33].

Among the 5 subjects in this study using medication for diabetes, 2 subjects used a DPP-4 inhibitor. Results of the data analysis showed no significant difference in functional age, blood glucose level, insulin value and glucagon value regardless of medication types. This study did not have a sufficient number of subjects, and was within the range to examine only individual differences. Therefore, it has not clarified whether or not incretin-related drugs had inhibitory effects on glucagon. There still remain problems to be solved to perform an accurate measurement and obtain reproducibility. Future examination is required for the establishment of a measurement system.

Conclusion

This study examined correlations between functional age and medication with 39 subjects (medication: 34 subjects, non-medication: 5 subjects). The subjects were participants of a health promotion program conducted by our research center, excluding participants who had no information for data analysis. The population of this study lived a life with a sufficient volume of physical activity so that they maintained a younger functional age than chronological age. Aging was recognized in Vascular age among functional age items. Vascular age of the medicated group was lower than that of the non-medicated group and this tendency was especially shown in subjects with anti-hyperlipidemic agent medication. It is expected that patients with LDL hypercholesterolemia have a risk for atherosclerosis and have a higher vascular age. It was interpreted that anti-hyperlipidemic agent medication improved the vascular age of subjects to some extent, which did not reach the same level as the non-medicated group. Subjects taking anti-hyperlipidemic medication tended to show a higher value of serum glucagon. We will continue to provide the health promotion program and encourage participants to maintain their volume of physical activities. This program and research would play a forceful role in preventing or delaying the onset of diabetes.

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Conflict of interest

The authors claim no conflict of interest in this study.

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