

Original article

Sleep quality, physical activity, and glycative stress in the elderly: The Yurin Study.

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Abstract

Objective: In research targeting the Japanese elderly, the relationship between glycative stress, a risk factor of diabetes, and the quality of sleep has not been clarified. This research measured the amount of physical activity in daily living targeting the elderly on a continuous basis and verified the relationship between the quality of sleep and the amount of physical activity and glycative stress.

Methods: This research was conducted with 23 subjects (78.7 ± 6.1 years) who were practicing a walking motion on a daily basis in the Yurin area of Kyoto. Evaluations with the Pittsburgh Sleep Quality Index (PSQI-J) and Anti-Aging QOL Common Questionnaire (AAQOL) were conducted and the measurements of skin autofluorescence (SAF) were carried out using serum cortisol and insulin-like growth factor-I (IGF-I), a melatonin metabolite (6-sulfatoxymelatonin; SaMT) in the urine pooled during the night and an AGE Reader TM. In order to exclude the amount of activity from daily living, the amount of activity with an intensity greater than 3 METs was measured.

Results: The average amount of activity of the subjects per month for approximately two months was 59.1 ± 53.5 Ex, and they were classified into three groups of H (high), M (medium) and L (low) in accordance with the amounts of activity for analysis. As a result of the analysis, the higher the amount of activity in the group, the lower the level of serum cortisol, and the higher the level of IGF-I, the higher the formation of SaMT in urine tends to be. No significant finding was observed in PSQI-J. In AAQOL, the score of "Difficulty in falling asleep" of the H group was significantly higher than that of M group ($p = 0.019$). The amount of activity and the number of steps at night (18:00 - 23:00) of the H group were significantly higher than those of the L group ($p < 0.05$). A weak correlation was found between the glycative stress index SAF and the score of PSQI-J "Difficulty sleeping" ($r = 0.375$, $p = 0.077$).

Conclusion: The amount of physical activity of the elderly possibly affects the quality of sleep, and exercise at night, in particular, can interfere with sleep. It was suggested that sleep quality is closely related to the lifestyle habits increasing glycative stress.

KEY WORDS: physical activity, sleep quality, melatonin, 6-sulfatoxymelatonin, the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J)

Introduction

The existence of nursing care is closely involved with the extension of healthy life expectancy. The primary cause of people requiring long term nursing care aged 65 or older is cerebrovascular disease (17.2%) and the total cases of cerebrovascular disease and cardiac disease account for 21.9% of all elderly ¹⁾. These two disorders are closely

associated with lifestyle-related diseases, and it is known that insufficient sleep and difficulty sleeping increase the risk of the onset of lifestyle-related diseases such as obesity, high-blood pressure, impaired glucose tolerance, cardiovascular disease and metabolic syndrome ²⁾. According to a survey of 5,747 workers (average age: 43.8 years), it is reported that the ratio of sleeping disorders among those who have lifestyle-

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related diseases is higher than in those who do not³⁾.

So far, it has been reported that there is a bidirectional relationship between sleep quality and diabetes⁴⁾ and that aggravation in the control of blood glucose of diabetes impairs deep sleep and easily reduces sleep quality⁵⁾. It is known that the progress of diabetes is related to glycative stress. Glycative stress is a concept comprehensively capturing the stress in a living body caused by aldehyde load derived from reducing sugar and fats and the resulting reactions. In glycative stress, aldehyde derived from dietary reducing sugar, fats and alcohol non-enzymatically and irreversibly react with the proteins in the living body, resulting in the production of advanced glycation end products (AGEs). It is known that AGEs are risk factors of atherosclerosis and osteoporosis and they are involved in the worsening of degenerative diseases such as Alzheimer's type dementia and the progress of diabetes^{6,7)}. Therefore, glycative stress, which has recently gained more attention as a risk factor for aging, is considered to be another factor affecting sleep. In this research, the intensity of fluorescence derived from AGEs in the skin was measured in a non-invasive manner as an index of glycative stress and the result was expressed as skin autofluorescence (SAF).

In this research, the amount of physical activity in the daily lives of the non-diabetic elderly was measured, and the relationship among the amount of physical activity, glycative stress and the quality of sleep was verified.

Method

Subjects

The investigation for this research was conducted from March to May, 2017. The subjects were 23 elderly persons (10 males and 13 females, age: 78.7 ± 6.1 years) without the contraindication of exercise, living in the Yurin area, Shimokyo-ku, Kyoto, Japan. *Figure 1* shows subject selection. This laboratory has been conducting intervention research in this area through a health enhancement program as preceding research since December 2008⁸⁾. This research targeted the participants in this program.

Measurement of Amount of Activity

An activity meter, 3-axis acceleration sensor-type (HJA350IT: Omron Colin Co., Kyoto, Japan), was lent to each subject. They were asked to continue to wear the meter on their lower back for the entire day, excluding the times when they slept, took a bath or were immersed in water for other reasons. This activity meter was developed as a device to discern various daily activities, such as normal walking, moderate walking, jogging, housecleaning, and washing, and to estimate the amount of each activity. The amount of activity was recorded on a computer once a month using exclusive software (BI-link Professional Edition 2.0, Omron Healthcare). In order to exclude the days when subjects did

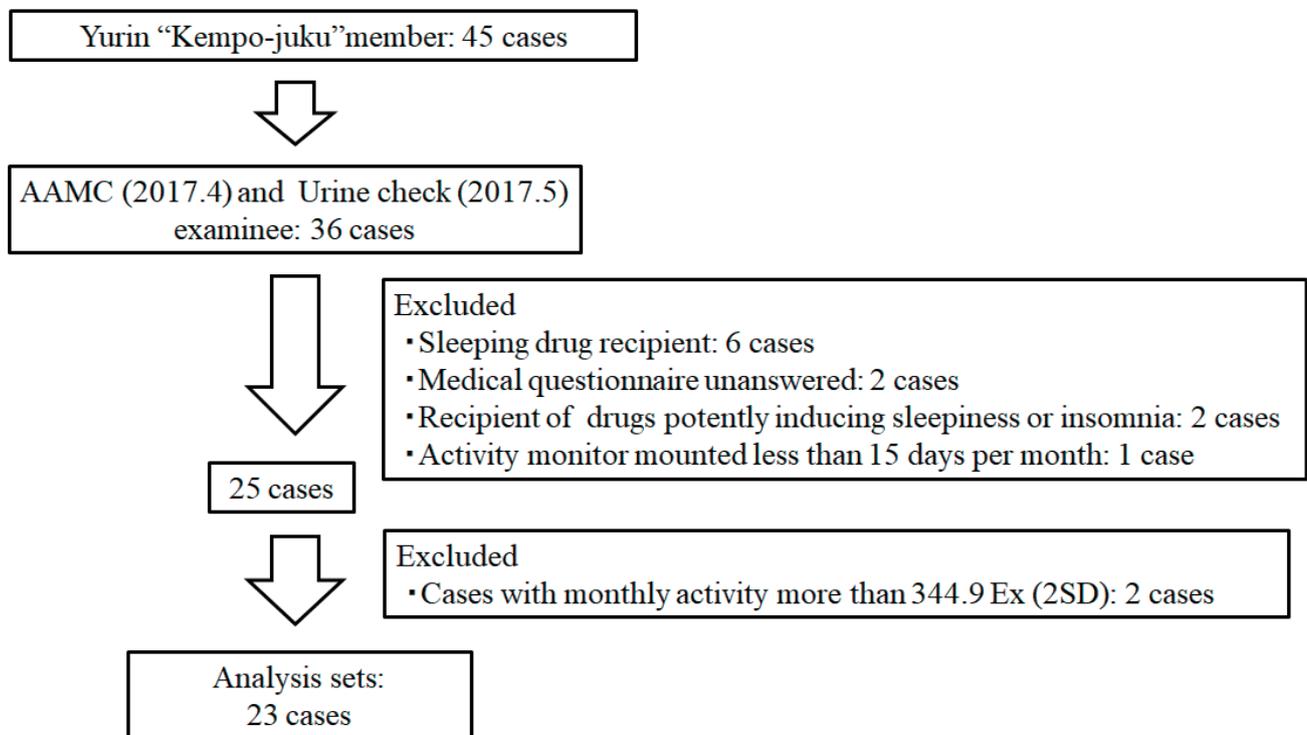


Fig. 1. The number of analysis sets.

Average monthly activity of 25 cases = 92.8 ± 126.0 Ex (mean \pm SD). AAMC, Anti-Aging Medical Checkup; SD, standard error.

not wear the activity meter, only the data of the days when the wearing time was 100 minutes or more were used for analysis.

The amount of physical activity was presented with METs and Ex (Exercise). MET is a unit of measurement for intense exercise and physical activity; resting state is deemed as one, and the amount of activity is shown as how many times energy of the resting state was consumed. For example, walking is defined as the activity of 3 METs. Ex is the value of the intensity of activity expressed by METs multiplied by hours, which is internationally used as a unit to measure the amount of exercise and activity. In order to exclude the amount of activity gained via daily activities, only activity amounts with an intensity of 3 METS or more were used.

Classification by Amount of Physical Activity

The subjects of this research were classified by the average amount of physical activity per month. It was obtained by calculating the average amount of activity per day for the period from March 15 to March 23, 2017 and multiplying it by 30. The subjects were classified into three groups based on the average amounts of activity per month, H (high), M (medium) and L (low) in descending order, and a group comparison of each item concerning the amount of physical activity and the quality of sleep was conducted.

Evaluation by Pittsburgh Sleep Quality Questionnaire

Pittsburgh Sleep Quality (the Japanese version of the Pittsburgh Sleep Quality Index: PSQI-J) is a self-administered questionnaire consisting of 18 items for the purpose of evaluating the subjective quality of sleep for the past month⁹⁾. The responses were scored from 0 to 3 and added up, and the total scores were evaluated. It was judged that the higher the total score, the more sleep was impaired. The seven factors quality of sleep, sleeping hours, time to fall asleep, sleep efficiency, difficulty sleeping, use of sleep agent, and daytime difficult waking and total scores were also targeted for analysis. Sleep efficiency was obtained from the following equation:

$$\text{Sleep efficiency (\%)} = \frac{\text{Actual sleep time (hr)}}{\text{Time in bed (hr)}} \times 100$$

Assessment by Anti-Aging QOL Common Questionnaire

The score of each item was assessed by breaking it into five stages from 1 to 5, using the Anti-Aging QOL Common Questionnaire (AAQOL)¹⁰⁾.

Measurement of Hormone Secretion

In this research, blood cortisol, insulin-like growth factor-I (IGF-I) and urinary melatonin metabolite (6-sulfatoxymelatonin; SaMT)¹¹⁻¹³⁾ were measured as the hormones related to the quality of sleep.

Ten subjects out of 23 urinated at night more than once, and as a result, the hours of pooled urine became short.

However, in this research, the time from last urination to the time of urine collection was deemed as the hours of urine collection, and the result was shown by SaMT formation speed, as shown in the following equation:

$$\text{SaMT formation rate (pg/hr)} = \frac{\text{measured value (pg/mL)} \times \text{amount of urine (mL)}}{\text{hours of pooled urine (hr)}}$$

Because the information of hours of pooled urine of a subject out of 23 could not be obtained, the analyses were conducted for 22 subjects excluding the one. The measurements were implemented by LKSI Medience Corporation, Tokyo.

Assessment of Glycative Stress

AGE ReaderTM (DiagnOptics, Groningen, Netherlands) was used for the assessment of glycative stress, and at the time of ultra-violet irradiation, SAF, the integral data for autofluorescence value derived from AGEs, was measured^{14,15)}. The measurement was conducted on the region 10 cm from the elbow of the back side of the right upper arm in a posture holding the arm horizontal to the ground and bent at right angle.

Statistical Analysis

SPSS Statistics 24 (IBM Japan, Tokyo, Japan) was used for the analysis of each measurement value. A one-way analysis of variance was used for the comparison among the three groups; in the case of equal variances, Tukey HSD method was used, and in the case when equal variances cannot be assumed, Games-Howell method was used. For the analyses of SAF and sleep difficulty, in the case of normal distribution, the Person correlation analysis was conducted, and in the case where normal distribution could not be assumed, the Spearman correlation analysis was conducted. For the purpose of calculation of odds ratio for sleep difficulty, a binomial logistic regression analysis was conducted. A risk ratio of 5% or less in a two-sided test was regarded as a significant difference.

Ethical Approval

This research was conducted in compliance with the Helsinki Declaration (Revised at the 2013 WMA General Assembly, Fortaleza) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Notice by the Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health and Welfare). Before the research started, it was explained to the subjects that they are free to determine whether they participate in this research or not, and that even if they stopped participating in this research, they will not suffer any disadvantage, and their consent was obtained. This research obtained ethical approval from the Ethics Committee of Doshisha University for research involving human subjects (Application No. #14089).

Result

Body Measurement Values and Lifestyle Habits

The average amounts of activity per month of the 23 subjects was 59.1 ± 53.5 Ex; that of the H group (9 subjects) was 107.9 ± 18.1 Ex, that of the M group (7 subjects) was 42.9 ± 4.8 Ex, and that of the L group (7 subjects) 12.5 ± 2.4 Ex (**Table 1**). There were no significant differences in age, body height, body weight and body mass index (BMI) among the groups. There was also no significant difference in any items of the amounts of alcohol intake and water intake, sleeping hours or sleep efficiency in the analysis among the groups.

Subjective Symptom

There were no significant differences in the scores of “Sleep quality,” “Time to fall asleep,” “Difficulty sleeping,” or “Daytime difficulty waking,” or in any total scores among the groups (**Table 2**).

The average values of the responses to the three items: “Shallow sleep,” “Difficulty falling asleep,” and “Inability to sleep due to worries” relating to sleep among AAQOL, and the results of comparisons among the groups are shown in **Table 2**. The score of response to “Difficulty falling asleep” was significantly higher in the H group than the M group ($p = 0.019$, **Fig. 2**). There were many subjects who had problems falling asleep in the H group. There was no significant difference in any other item of AAQOL among the groups.

Table 1. Comparison of physical information and lifestyles.

	Mean \pm SEM				p value		
	Total n = 23	H n = 9	M n = 7	L n = 7	H vs M	M vs L	H vs L
Age (years)	78.7 ± 1.3	75.7 ± 1.6	78.4 ± 2.7	82.7 ± 1.9	0.600	0.345	0.054
Height (cm)	155.0 ± 1.5	153.0 ± 1.8	155.0 ± 2.9	157.7 ± 3.3	0.843	0.768	0.413
Weight (kg)	55.1 ± 2.0	51.0 ± 3.0	56.3 ± 2.1	59.3 ± 4.8	0.517	0.830	0.217
BMI	22.8 ± 0.6	21.7 ± 1.0	23.5 ± 1.0	23.7 ± 1.3	0.468	0.996	0.417
Activity (Ex)	59.1 ± 11.2	107.9 ± 18.1	42.9 ± 4.7	12.5 ± 2.4	0.017	0.001	0.002
Alcohol intake (Gou/week)	2.7 ± 0.9	1.8 ± 1.5	2.0 ± 1.3	4.5 ± 1.9	0.997	0.563	0.481
Water intake (L/day)	1.4 ± 0.1	1.5 ± 0.4	1.4 ± 0.1	1.5 ± 0.1	0.961	0.954	0.999
Sleep duration (hr/day)	6.9 ± 0.2	7.0 ± 0.3	7.0 ± 0.5	6.6 ± 0.4	0.992	0.784	0.827
Sleep efficacy (%)	89.5 ± 1.7	89.3 ± 3.3	88.3 ± 3.8	91.0 ± 1.5	0.973	0.821	0.910

H: High activity group, M: Medium activity group, L: Low activity group. Statistical analysis by Tukey HSD or Games-Howell method. BMI, body mass index; Gou, one Gou = 180 mL of Japanese Sake equivalent; SEM, standard error mean.

Table 2. Comparison of scores in PSQI- J and AAQOL.

	Mean \pm SEM			p value		
	H n = 9	M n = 7	L n = 7	H vs M	M vs L	H vs L
PSQI- J						
Total score	5.3 ± 1.2	4.9 ± 0.7	4.4 ± 0.5	0.928	0.948	0.767
“Sleep quality”	1.2 ± 0.3	1.1 ± 0.1	1.1 ± 0.1	0.969	1.000	0.969
“Time to fall asleep”	2.6 ± 0.6	1.1 ± 0.8	1.0 ± 0.4	0.245	0.986	0.186
“Difficulty sleeping”	4.9 ± 0.9	4.6 ± 1.2	4.4 ± 1.1	0.974	0.995	0.946
“Daytime difficulty waking”	0.6 ± 0.2	1.0 ± 0.4	1.1 ± 0.3	0.576	0.949	0.389
AAQOL						
“Shallow sleep”	2.4 ± 0.3	2.3 ± 0.4	2.6 ± 0.5	0.954	0.875	0.971
“Difficulty falling asleep”	2.3 ± 0.3	1.1 ± 0.1	1.7 ± 0.3	0.019	0.228	0.363
“Inability to sleep due to worries”	2.2 ± 0.4	1.6 ± 0.3	1.9 ± 0.3	0.418	0.856	0.753

H: High activity group, M: Medium activity group, L: Low activity group. Statistical analysis by Tukey HSD or Games-Howell method. PSQI- J, the Japanese version of the Pittsburgh Sleep Quality Index; AAQOL, Anti-Aging QOL Common Questionnaire; BMI, body mass index; Gou, one Gou = 180 mL of Japanese Sake equivalent; SEM, standard error mean.

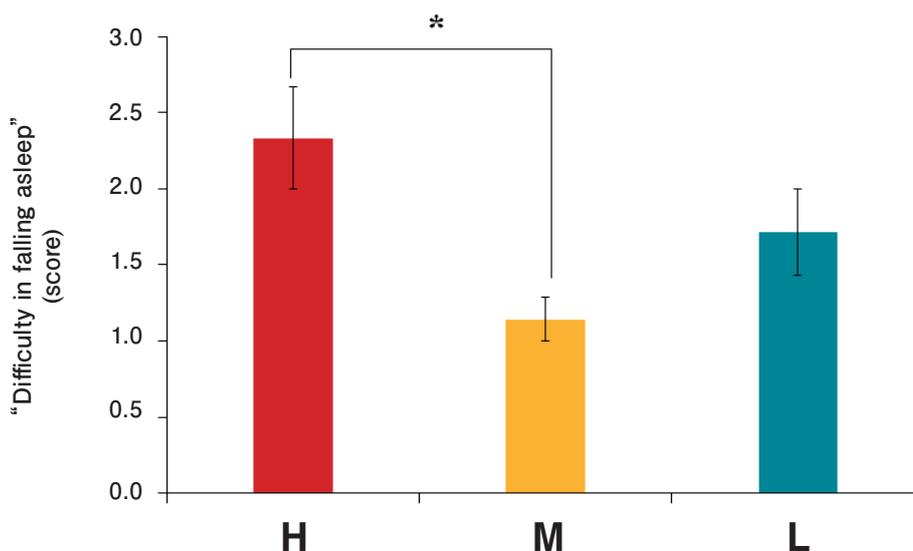


Fig. 2. AAQOL scores of “Difficulty falling asleep.”

Results are expressed as mean \pm SEM, * $p < 0.05$, Tukey HSD. **H:** High activity group ($n = 9$), **M:** Medium activity group ($n = 7$), **L:** Low activity group ($n = 7$). AAQOL, Anti-Aging QOL Common Questionnaire; SEM, standard error mean.

Hormone Secretion

The concentrations of serum cortisol and serum IGF-I, and the formation of urine SaMT of each group are shown in [Table 3](#). No significant difference in any item was observed among groups.

Steps and Physical Activity in Each Time Period

The steps and physical activity in each time period were examined. The average values of steps and physical activity per hour from 00:00 to 23:00 per day for a month from April 24 to May 23, 2017 were obtained, and furthermore, the steps and physical activity in the morning (06:00-11:00), afternoon (12:00-17:00) and night (18:00-23:00) were calculated.

There was no significant difference in the steps during the morning period among the groups. The numbers of steps of the H group in the afternoon and night time periods were significantly larger than those of the L group ([Fig. 3-a](#)).

Differences in physical activity among groups were observed from the morning. The physical activity of the H group tended to be higher than that of the M group, and was significantly higher than that of the L group ([Fig. 3-b](#)). The physical activity in the morning time period was higher than the other groups in the H group, M group and L group, respectively, and the physical activity was significantly different among groups. The activity in the night time period tended to be higher in the H group than the M group, and was significantly higher than the L group.

SAF of Glycative Stress

SAF in H group was 2.59 ± 0.40 , M group was 2.43 ± 0.59 , L group was 2.43 ± 0.59 , and there were no significant differences among the groups ([Table 4](#)).

Next, single correlation analyses of SAF with each item were conducted. No significant correlation between SAF and body height, body weight, BMI, age, and physical activity amount was observed. As a result of a quadratic regression curve analysis of BMI and SAF, when BMI was 23.1, SAF showed to be a minimum value of 2.4 ($p < 0.01$). As a result of the analysis of PSQI-J and SAF, a weak correlation tendency was observed between the score for “Difficulty sleeping” and SAF ($r = 0.375$, $p = 0.077$, [Fig. 4](#)). No significant correlations were observed between SAF and other items of PSQI-J. No significant correlations were observed between each item of AAQOL and SAF.

In order to discuss the factors leading to “Difficulty sleeping,” a binomial logistic regression analysis using the score of “Difficulty sleeping” as the objective score was conducted. Based on the result of the single correlation analysis, BMI, average activity per month and night-time activity, which correlation coefficients were 0.1 or more or less than -0.1 , were selected as explanatory variables from the biometric information and physical activity index, and SAF, IGF-1 and neutral fat, which correlation coefficients were 0.2 or more, were selected from the glycative stress index. These six explanatory variables were then added with gender, bringing the total to seven explanatory variables. In order to convert gender to variables, male was replaced with 1 and female with 2.

Because the PSQI-J score of “Difficulty sleeping” was 4.7 ± 2.7 points, the three cut-off values of four points, five points, and six points were set up, and the analysis was conducted. When the cut-off value for SAF was four points, the odds ratio was 55.7 ($p = 0.066$), when it was five points, the odds ratio was 64.5 ($p = 0.094$), and when it was six points, the odds ratio was 5.7 ($p = 0.261$). This showed the possibility that SAF is independently involved in the score for “Difficulty sleeping.”

Table 3. Comparison of hormone secretion.

Hormone	Mean ± SEM			p value		
	H n = 9	M n = 7	L n = 7	H vs M	M vs L	H vs L
Serum cortisol (µg/dL)	8.2 ± 1.1	9.8 ± 1.1	12.0 ± 2.0	0.711	0.564	0.167
Serum IGF-I (ng/mL)	98.4 ± 11.0	90.3 ± 0.6	84.7 ± 12.6	0.873	0.945	0.684
Urine SaMT (pg/hr)	1081.7 ± 258.5	841.0 ± 294.5	724.2 ± 205.2	0.679	0.996	0.737

H: High activity group, **M:** Medium activity group, **L:** Low activity group. Statistical analysis by Tukey HSD. IGF-I, insulin-like growth factor-I; SaMT, 6-sulfatoxymelatonin, one of melatonin metabolites; SEM, standard error mean.

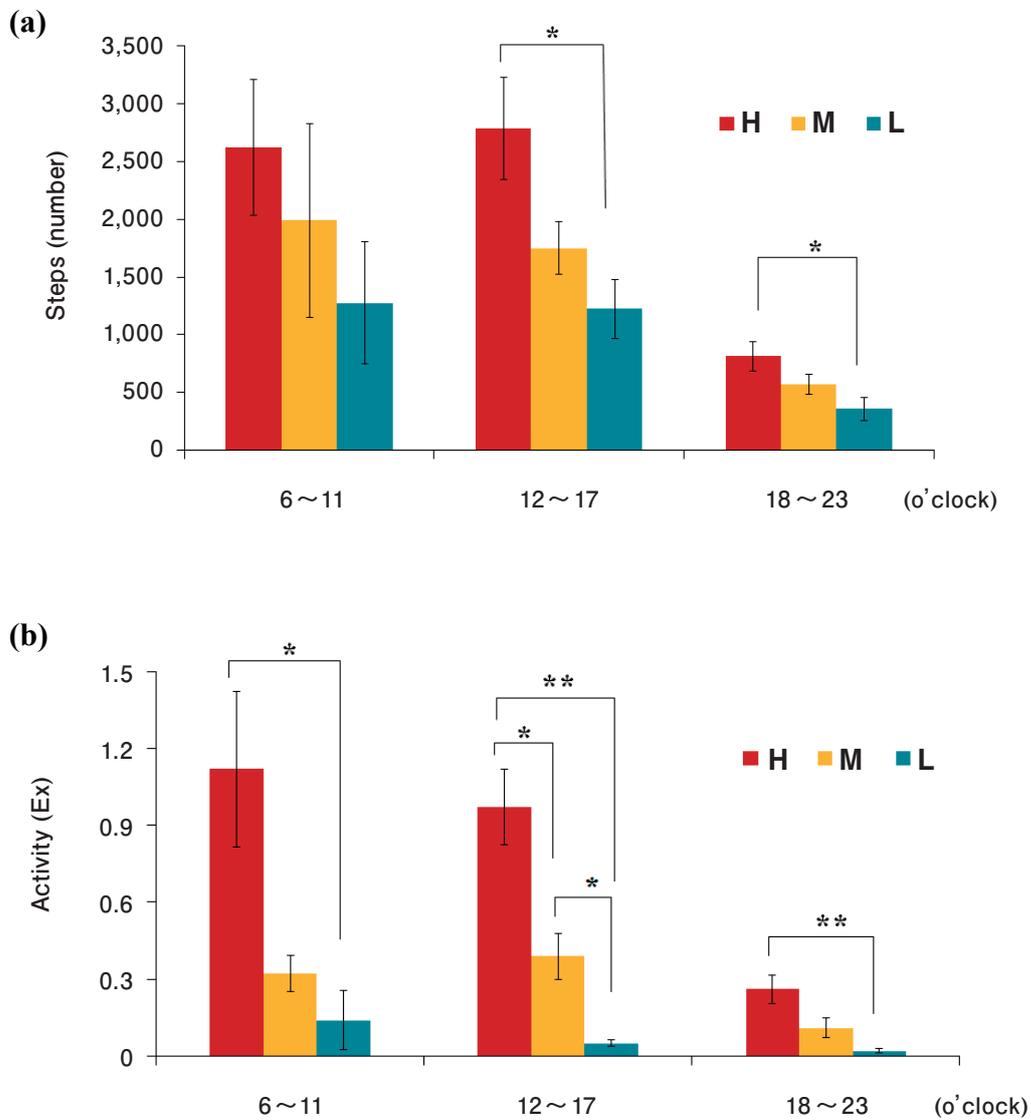


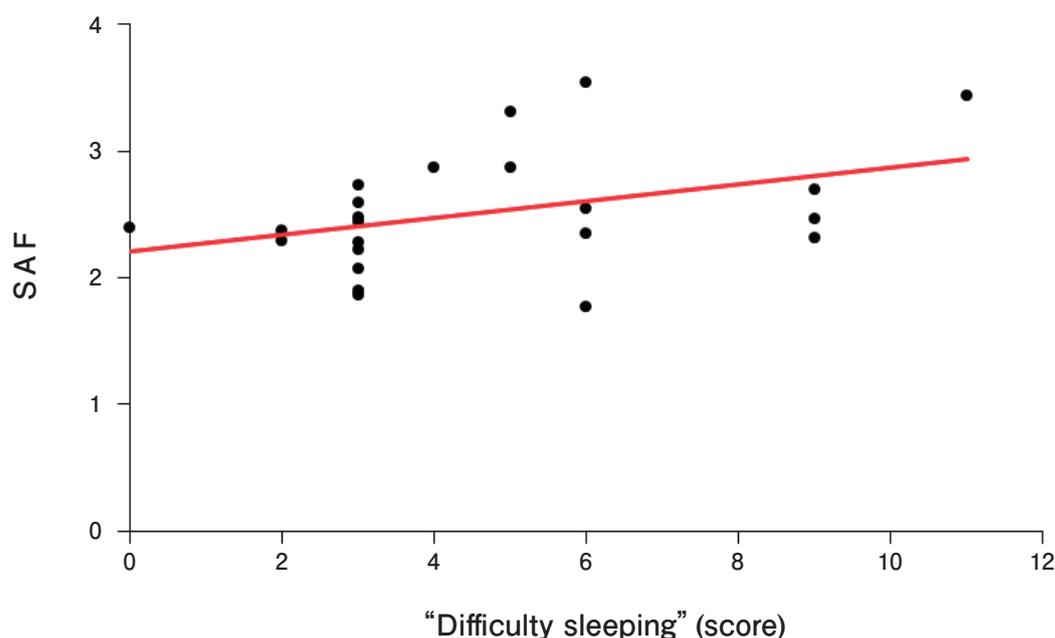
Fig. 3. Steps and physical activity in each time zone.

a: steps, **b:** physical activity. Results are expressed as mean ± SEM, * p < 0.05, ** p < 0.01, Tukey HSD. H: High activity group (n = 9), M: Medium activity group (n = 7), L: Low activity group (n = 7).

Table 4. Comparison of SAF.

	Mean ± SEM				p value		
	Total n = 23	H n = 9	M n = 7	L n = 7	H vs M	M vs L	H vs L
SAF	2.52 ± 0.46	2.59 ± 0.40	2.43 ± 0.59	2.43 ± 0.59	0.807	0.944	0.957
(95%CI)	(2.3-2.7)	(2.3-2.9)	(1.9-3.0)	(2.1-2.9)			

H: High activity group, M: Medium activity group, L: Low activity group. Statistical analysis by Tukey HSD. SAF, SAF, skin autofluorescence measured by AGE Reader TM; SEM, standard error mean; 95%CI, 95% confidence interval.

**Fig. 4. Correlation between SAF and “Difficulty sleeping” score in PSQI- J.**

$r = 0.375$, $p = 0.077$, $n = 23$, Spearman's simple correlation analysis. SAF, skin autofluorescence measured by AGE Reader TM; PSQI- J, the Japanese version of the Pittsburgh Sleep Quality Index.

Discussion

About Physical Activity

The Ministry of Health, Labour, and Welfare recommends the physical activity of 10 Ex/week (about 40 Ex/month) disregarding the intensity as a guideline for those 65 years old or older¹⁶⁾. This guideline is set up mainly for the purpose of preventing a lack of physical activity from the elderly. However, it is desirable for the elderly to engage in exercise including more than 3 METs, if possible, aiming at maintaining and improving physical activity¹⁶⁾. Because the subjects of this research were accustomed to doing exercise due to participating in previous research, there were many who had been exercising at an intensity of more than 3 METs, which exceeded this guideline. The average activity of the M group (42.9 ± 12.4 Ex) was equivalent to this guideline. All subjects of this research are considered to be at the level of national guideline or above.

Amount of Activity and Quality of Sleep

• Subjective Symptom and Assessment of Physical Activity

In this research, the AAQOL score for “Difficulty falling asleep” was significantly higher in the H group, which also had higher physical activity, than the M group. It was observed that the total PSQI-J score was higher in the group in which physical activity was higher, and the quality of sleep tended to decline. Even though no significant difference was observed in the time of falling asleep, it was higher in the H group, which had higher physical activity, than the other groups. From these findings, it is possible that there were many who had the problem of falling asleep in the H group. It was suggested that excessive physical activity has a negative effect on falling asleep.

• Assessment by Measured Values of Hormones

Serum cortisol was lower, IGF-I was higher and SaMT

in urine was higher in the group in which physical activity per month was higher; however, no significant differences were observed among the groups. Regarding the effect of physical activity of the elderly on the quality of sleep, what can be estimated from the result of the measurements of hormones will be described.

The secretion of cortisol, called stress hormone, generally increases when individuals feel stress¹⁷⁾; and when stress is strong, sleep becomes shallow. If the concentration of cortisol is low, they will not feel much stress; therefore, they are less likely to experience insomnia. As for the reason why the subjects of the H group have “Difficulty falling asleep,” it is unlikely that excess physical activity led to stress.

IGF-I is the second messenger of growth hormone (GH), and when the GH secreted from the pituitary reaches the liver, the production of IGF-I is stimulated¹⁸⁾. When IGF-I is high, the secretion of GH is active during non-REM sleep, and rest by non-REM sleep is considered to be enough. Even though the score of “Difficulty in falling asleep” was high in the H group, it is presumed that the quality of sleep after falling asleep was sufficient.

It has been known that melatonin induces sleep in human beings¹⁹⁾, and much clinical research has been conducted on the topic. SaMT in urine reflects the secretion of melatonin^{12, 13)}. When the volume of melatonin secretion is large, it is considered to lead to the state appropriate for rest and for good sleep quality. If the bedroom is bright, the secretion of melatonin is inhibited. Although the score of “Difficulty falling asleep” in the H group was high, the secretion of melatonin was not inhibited. The bedroom was sufficiently dark, and it was presumed that the quality of sleep after falling asleep was not bad.

• Assessments by Steps and Physical Activity by Each Time Zone

In the research concerning physical activity and sleep, it is said that intensive physical activity before going to bed enhances the level of arousal, when in turn inhibits sleep²⁰⁾. In this research, according to the assessment of subjective symptoms of the H group, which had the highest physical activity by each time zone, it tended to have more of a problem in the time before falling asleep and difficulty falling asleep than the other groups. Steps and physical activity were significantly higher at night in the H group compared with the L group; the steps in the H group were about 2.3 times greater, and activity with an intensity of 3 METs or more was about 13 times those of the L group. Such intensive activity at night stimulates sympathetic nerve before going to bed and it is one of the causes inhibiting sleep with high possibility²¹⁾. Generally, although exercise therapy is recommended, in order to increase activity, it is necessary to take the time period when practicing exercise into consideration.

Glycative Stress and Quality of Sleep

• Assessment by Subjective Symptom and Physical Activity

From the correlations analysis regarding the items of PSQO-J and AAQOL used in this research, weak positive correlation tendencies were found between the scores of items regarding sleep difficulty and SAF. In the preceding research targeting 244 male and female subjects, aged from

20 to 59 years conducted by the author et al., a negative correlation tendency was recognized between sleeping hours and SAF²²⁾, and if the decrease in sleeping hours is taken as a reduction in the quality of sleep, it does not contradict the result of this research.

One of the reasons the correlation was not high is considered to be the difference in ages of the subjects. Although the correlation between the reduction of the quality of sleep and age is high, the correlation between SAF and age is not so high. Generally, in the case of the elderly, SAF differs substantially between individuals compared with that of the middle- and old-aged due to the accumulation of the effects of exercise and lifestyle habits for extended periods¹⁵⁾.

The elderly who participated in this research significantly improved their SAF due to continuous walking exercise for three years; the same as was shown in the previous research²³⁾.

In other words, they were the group which included many of those whose glycative stress and SAF were lower than the average values in the same generation. The comparison of SAF among three groups showed that even though there were no significant differences among the groups, the SAF of the H group was highest in spite of having high activity and their total PSQI-J score being the highest. It does not contradict the preceding research²²⁾ that the reduction of the quality of sleep had a correlation tendency with the increase of SAF.

• Assessment by Measurement Values of Hormone

The higher the physical activity the groups had for a month, the lower the serum cortisol, the higher IGF-I, and the larger the formation amount of SaMT in urine became; however, no significant differences were observed among the groups. Then, it was described that the relationship between glycative stress and the quality of sleep of the elderly can be estimated by the measurement value of hormones.

There are several stages for the glycative stress reduction method. The first stage is to inhibit glucose spikes (postprandial hyperglycemia), the second stage is to inhibit the formation of AGEs, the third stage is to promote the dissolution of AGEs and the fourth stage is to control AGEs/RAGE signal. Because an oxidation reaction is involved in a part of the process of the formation of AGEs of the second stage, the formation of AGEs can be alleviated to some extent due to the functional ingredients having an antioxidant effect.

Melatonin, a hormone deeply involved in the quality of sleep, has the effects of alleviating glucose spikes²⁴⁾ in the first stage, alleviating the formation of AGEs, mediated by anti-oxidation²⁵⁾, in the second stage, and promoting the dissolution of AGEs²⁶⁾. Therefore, if the quality of sleep is improved and the secretion of melatonin becomes active, it works toward controlling glycative stress.

Cortisol, a stress hormone, has the effect of enhancing gluconeogenesis in the liver, gluconeogenesis caused by protein catabolism in skeletal muscles, and postprandial hyperglycemia by the enhanced insulin resistance, all of which exacerbate glycative stress. Contrarily, if the cortisol level is lower, it leads to the alleviation of glycative stress.

The glucose metabolism and quality of sleep affect the secretion of GH/IGF-I system. High quality of sleep activates the secretion of GH, but hyperglycemia inhibits the secretion of GH.

It is unclear whether the condition where glycative stress is strong and there are lots of AGEs has the same effect as the

above on the secretion of these hormones. It is known that in pancreatic beta cells, ER stress increases, and the secretion of insulin decreases, due to the load of AGEs²⁷⁾. In the cells secreting other hormones, it is possible that the secretion of hormones is inhibited by AGEs through the same mechanism.

It can be considered that glycative stress and the quality of sleep bi-directionally interfere with each other; however, detailed mechanism combining glycative stress and the quality of sleep is not clear.

• SAF Odds Ratio and Cut-off Value for Sleep Difficulty

In a binomial logistic regression analysis with objective variables of RSQI-J sleep difficulty score (4.65 points on average), SAF was extracted as an independent explanatory variable ($p = 0.066$). Those whose SAF was 2.5 or more (2.5 on average) were defined as subjects with a high value, and those whose SAF was less than 2.5 were defined as subjects with a low value. When the cut-off value for sleep difficulty was set at a relatively mild degree of 4 points, both sensitivity and specificity were highest in the assessment of the relationship between SAF and sleep difficulty. The result of the analysis was that if SAF increases 1.0 times, the probability of having difficulty sleeping increases up to 15.4 times. It was suggested that SAF, an index of glycative stress, has possibly exerted its influence since the time when difficulty sleeping was still mild.

Limitation of Research

There are limits in the credulity in the survey items relating to sleep by medical questionnaire used in this research, because it was impossible to take the depth of sleep

and interrupted sleep into consideration due to the assessment of sleep being based upon self-assessment. It was possible that the evaluation criteria were changed by respondents. In order to conduct an accurate survey regarding sleep, the assessment of the quality of sleep using polysomnography during sleep and a more objective sleep index are required.

Conclusion

There is a possibility that the amount of physical activity has an effect on the quality of sleep for the elderly, and an excess physical activity at night, in particular, interferes with sleep. It was suggested that glycative stress is possibly a life factor which reduces the quality of sleep. The clarification of the mechanism connecting glycative stress and the quality of sleep will be a task in the future.

Conflict of Interest Statement

The authors state that the performance of this study entailed no issues representing a conflict of interest.

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