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Original paper

Effect on sleep quality of bedding with a high user rating in a post-marketing survey: A non-controlled open-label study

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Abstract

***Objectives*:** An increasing number of studies have suggested the association of poor quality sleep and various medical conditions. The objective of this study was to determine whether the use of a particular type of mattress, that received a high user rating in a post-marketing questionnaire survey (i.e. the test mattress), can improve sleep quality, and also affect various physical parameters.

***Methods*:** In this non-controlled open-label study, a total of 11 men and women with sleep-related complaints (5 men and 6 women; mean age 51.0 ± 6.3 years) were asked to use the test mattress for 4 weeks and then were examined for changes in various physical parameters. The test mattress was provided by Nishikawa Sangyo Co., Ltd. (Tokyo, Japan). The subjects underwent examination for subjective and objective symptoms, anthropometry, blood biochemistry, and urine and saliva analysis before and at 4 weeks after the start of study. They were asked to record in a diary any adverse events occurring during the study, and their severity, as well as the details of their lifestyle and dietary/exercise habits. This study was conducted with the approval of an ethics committee.

***Results*:** In the assessment using the Pittsburgh Sleep Quality Index (PSQI-J), significant improvements were observed in the sleep quality, time to fall asleep, difficulty sleeping and difficulty staying awake during the daytime at week 4. The global PSQI score (PSQIG) was significantly improved from 9.5 ± 0.4, indicating severe disorder, to 7.1 ± 0.7, indicating mild disorder. As for oxidative stress, a significant decrease was observed in the creatinine-adjusted concentration of 8-OHdG in urine. Among glycolipid metabolism parameters, while no significant change was observed in the fasting blood glucose level or HbA1c, the HDL cholesterol level showed a 7.5% significant increase from the baseline value (73.7 ± 5.1 mg/dL) at week 4 ($p < 0.01$). Insulin-like growth factor-I (IGF-I), a second messenger for growth hormone, showed a 10.2% significant increase from the baseline value (173.8 ± 17.4 ng/dL) at week 4 ($p < 0.01$).

***Conclusion*:** These results suggest that the 4-week use of the test mattress improved sleep quality, as demonstrated by improvement in subjective symptoms, and it promoted growth hormone/IGF-I secretion, reduced oxidative stress and improved lipid metabolism, as demonstrated by biochemical analysis.

***KEY WORDS*:** sleep quality, oxidative stress, glycative stress, lipid metabolism, insulin-like growth factor (IGF-I)

Introduction

Poor-quality sleep is an age-related change. Many Japanese people, both adults and children, seem to suffer from a chronic lack of sleep. Various complaints due to poor sleep are reported by not only middle-aged to elderly people, but also children in their childhood and adolescence periods, indicating an association of poor sleep with various lifestyle-related diseases and metal well-being [1-7)]. Growing attention has also been paid to the association between poor quality sleep, as manifested as sleep apnea syndrome or other symptoms, and type-2 diabetes, a typical lifestyle-related disease associated with high glycative stress [8-12)]. It is therefore important to maintain high-quality sleep from the perspective of preventive medicine.

In order to maintain high-quality sleep, each individual should use the appropriate mattress suited for their condition. In this study, we asked a total of 11 men and women with sleep-related complaints to change their mattress from one they were regularly using to the one that received a high user rating in a post-marketing questionnaire survey (i.e. the test

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mattress). After they used the test mattress for 4 weeks, we evaluated its effect on physical parameters, including sleep quality, in a non-controlled open-label study. The primary outcome measures included sleep-related parameters, as well as parameters related to oxidative and glycative stress, which are major risk factors for aging.

Methods

Subjects

We recruited 31 healthy men and women aged 40 to 65 years who were not obese or too thin who had sleep-related complaints, such as difficulty falling asleep, waking after sleep onset, waking in the early morning, and difficulty achieving deep sleep. These candidates were interviewed and 12 of them were selected as the subjects for this study according to the inclusion and exclusion criteria. Although the target male/female ratio was 1:1, 1 subject was withdrawn due to a personal reason and the remaining 11 subjects (mean age 51.0 ± 6.3 years), including 5 men (47.2 ± 3.7 years) and 6 women (54.2 ± 6.4 years), were included in the analysis.

Subjects had to to meet the following inclusion criteria:
1) healthy male or female aged ≥40 and <65 years at the time of informed consent for participation in the study;
2) good health status and currently not receiving any treatment for a medical condition;
3) BMI from 18.5 kg/m^2 to <25.0 kg/m^2;
4) have sleep-related complaints, such as difficulty falling asleep, waking after sleep onset, waking in the early morning, and difficulty achieving deep sleep;
5) have a duration from going to bed (turning the light off) to waking up of ≥4 hours;
6) have a habit of going to bed (turning the light off) and getting up at consistent times every day, with a bedtime (light-off time) of before 24:00;
7) have a habit of sleeping on a Japanese *futon* mattress on a daily basis;
8) able to sleep on the test mattress during the study period;
9) able to sleep alone during the sleep assessment period;
10) able to comprehend the full explanation of the purposes and details of the study, have the ability to give consent, and voluntarily decide to participate in the study based on a full understanding by providing a written informed consent; and
11) deemed by the investigator to be appropriate for inclusion in the study.

Subjects were excluded from the study for the following reasons:
1) receiving medication therapy for a chronic disorder;
2) suspected of having sleep apnea syndrome (SAS) or has a current or previous history of treatment for SAS;
3) suspected of having nocturia, prostatic hyperplasia or overactive bladder at present or in the past;
4) a current or previous history of severe liver disorder, kidney/heart disease, lung disease, gastrointestinal disorder (including gastrectomy), organ failure, diabetes, thyroid disease, or other serious diseases;
5) skin conditions, such as atopic dermatitis and cutaneous hypersensitivity;
6) current or previous history of hepatitis or similar disease;
7) severe anemia;
8) a resting systolic blood pressure of ≥160 mmHg or a resting diastolic blood pressure of ≥100 mmHg;
9) were taking, or took within the past 3 months, or were scheduled to take during the study period on a regular basis any of the following products that may affect test results: medicinal drugs, quasi drugs, foods with health claims (foods for specified health use), health food, and supplements;
10) a mean daily alcohol consumption of >60 g/day;
11) donated >200 mL of blood within the past 1 month or >400 mL within the past 3 months;
12) were likely to have any change in sleep environment or lifestyle during the study period (e.g. night shift work, long-term trip, transfer to a new workplace);
13) were currently participating in another human clinical study or had participated in such a study within 3 months before screening;
14) were pregnant, nursing, suspected of being pregnant, or planning a pregnancy; or
15) were considered by the investigator to be inappropriate for inclusion in this study for other reasons.

Study design

This study was conducted as a non-controlled open-label study

The *Seiatu*® *Shiki-Futon* mattress (REGULAR HF2521R; Nishikawa Sangyo Co., Ltd., Tokyo, Japan) was used as the test mattress. The test mattress was of single size (9×97×200 cm) and was provided with a fitted sheet by Nishikawa Sangyo. At the beginning of the study, subjects were asked to replace the mattress they were using with the test mattress.

The core of the test mattress was designed with new computer-controlled technology to achieve an ideal, unique 3D structure that supports the whole human body at about 1,900 points to mitigate the feeling of being compressed while allowing ventilation. In terms of safety, the product was placed on the market in September 2001, and a total of 369,911 mattresses were sold as of September 2015, with no serious adverse event having been reported to date regarding the use of the product.

Subjects underwent an examination for subjective and objective symptoms, anthropometry, blood biochemistry and tests for measuring oxidative, glycative and psychosomatic stresses before and 4 weeks after the start of study. All study participants were asked to record in a diary any adverse events occurring during the study, as well as their severity, and the details of their lifestyle and dietary/exercise habits. This study was conducted between November 2015 and March 2016.

Outcome measures

(1) Subjective symptoms

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI-J) [13]. According to the PSQI scoring table, scores were calculated for each of the following variables: sleep quality, time to fall asleep, sleep length, sleep efficiency, difficulty sleeping, use of sleep medicine, and difficulty staying awake during the daytime. The scores for each variable were summed to obtain the PSQI global (PSQIG) score.

The obstructive sleep apnea (OSA) sleep inventory MA version [14,15] was used to score time to go to bed, time to get up and sleep length in a 4-point scale. Results were summarized for each of the following 5 factors: factor 1 “sleepiness on rising”; factor 2 “initiation and maintenance of sleep”; factor 3 “frequent dreaming”; factor 4 “feeling refreshed; and factor 5

"sleep length".

Subjective symptoms were assessed using the Anti-Aging QOL Common Questionnaire (AAQOL)[16]. Subjective symptoms were divided into physical and mental symptoms and scored in a 5-point scale of 1 to 5.

(2) Anthropometry

Anthropometric parameters included body height and weight, body fat percentage, body mass index (BMI), systolic and diastolic blood pressures and pulse rate. Body composition measurement was performed using a body composition analyzer (DC-320, Tanita Co., Ltd., Tokyo, Japan).

(3) Blood biochemistry

The following blood biochemical parameters were evaluated: total protein, albumin, A/G ratio, total bilirubin, liver/kidney function tests [AST (GOT), ALT (GPT), γ-GTP, CPK, uric acid, urea nitrogen (BUN) and creatinine], glucose metabolism-related [fasting blood (plasma) glucose level, HbA1c [NGSP] (whole blood), pentosidine (plasma)], lipid metabolism-related [total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C) and triglyceride (TG)] and serum electrolytes (sodium, potassium, chloride, calcium and iron). The following circulating hormones were measured: insulin-like growth factor-I (IGF-I), dihydroepiandrosterone-sulfate (DHEA-s), cortisol, 3 fractions of catecholamine (adrenaline, noradrenaline and serotonin in plasma) and serotonin in whole blood. Except for pentosidine, which was measured at the Japan Institute for the Control of Aging, NIKKEN SEIL Co., Ltd. (Shizuoka, Japan), all other parameters were measured at Health Sciences Research Institute Inc. (Yokohama, Japan). Unless specifically indicated as "plasma" or "whole blood", all parameters were measured in serum samples.

(4) Urinalysis

The first urine collected after rising was used as the sample. Subjects were asked to collect the first urine after getting up on their own and record urine volume, time of voiding in the morning and last time of voiding during the night. Oxidative stress-related parameters, including 8-hydroxy-2'-deoxyguanosine (8-OHdG)[17] and 15-isoprostane F2t)[18], were measured and the rate of production of these substances was calculated. The following steroid hormone metabolites were measured: free cortisol and 17-ketosteroid (17-KS) fractions (androsterone, etiocholanolone, DHEA, 11-keto-androsterone, 11-keto-etiocholanolone, 11-OH-androsterone and 11-OH-etiocholanolone). All urinalysis parameters were measured at the Japan Institute for the Control of Aging, NIKKEN SEIL Co., Ltd.

(5) Saliva analysis

A saliva sample was collected immediately after rising using a saliva sampling swab for the measurement of salivary melatonin level (at Health Sciences Research Institute Inc.).

(6) Sleep assessment by Sleepscan

A Sleepscan sleep meter (SL-503; Tanita) was used to assess the quality of sleep. The sleep meter was placed under the test mattress before a subject went to bed and turned on to start measurement. Subjects were instructed to sleep alone on the mattress. Sleeping with a pet was also prohibited. The parameters measured included the dates of starting/finishing measurement, sleep length, sleep score and sleep stage (4 stages from waking/shallow sleep to deep sleep). The sleep quality score was calculated from the results of these measurements. This measurement was performed during a 1-week period before the start of use of the test mattress and another 1-week period starting 3 weeks after the start of use of the test mattress.

- Statistical analysis

For statistical analysis, statistical analysis software SAS 9.4 (SAS Institute Japan, Tokyo, Japan) or SPSS (Statistics19; Japan IBM, Tokyo, Japan) was used to perform paired t-test. Differences were considered significant and marginally significant at significance levels of 5% and 10%, respectively. No criteria were defined for determining outliers. For missing data due to testing problems or major weakness in the reliability of data, no substitution was performed.

- Ethics review

This study was conducted in compliance with the Declaration of Helsinki (revised at the WMA General Assembly, Fortaleza, Brazil, 2013) and the Ethical Guidelines for Medical Research in Humans (notification from the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare). The ethical aspects and appropriateness of the present study were reviewed by the human research ethics committee at General Incorporated Association Oriental Occupational Health Association Tokyo Branch (Tokyo, Japan). The study was started after approval by the committee and conducted according to the approved protocol. The study was registered in advance with UMIN #000020017.

Results

Subjective symptoms

The 4-week use of the test mattress resulted in improvement in subjective symptoms, as detailed below. In the PSQI-J assessment, significant improvement was observed in the scores for sleep quality ($p = 0.008$), time to fall asleep ($p = 0.034$) and difficulty sleeping ($p = 0.046$) (***Table 1***). The PSQIG score was significantly improved from 9.5 ± 0.4, indicating severe disorder, to 7.1 ± 0.7, indicating mild disorder ($p = 0.005$). The score for difficulty staying awake during the daytime was also significantly improved from 1.7 ± 0.1 at baseline to 0.7 ± 0.2 at week 4 ($p = 0.002$).

In the assessment using the OSA sleep inventory, significant improvements in scores were observed for factor 1 "sleepiness on rising" ($p = 0.036$), factor 2 "initiation and maintenance of sleep" ($p = 0.014$) and factor 4 "feeling refreshed" ($p = 0.048$) (***Table 1***).

In the AAQOL assessment, significant improvements in scores were observed for 3 of 33 physical symptoms, including "eye pain" ($p = 0.039$), "muscular pain/stiffness" ($p = 0.046$) and "lethargy" ($p = 0.008$), and 5 of 21 mental symptoms, including "shallow sleep" ($p = 0.014$), "difficulty in falling asleep" ($p = 0.038$), "inability to solve problems" ($p = 0.034$), "inability to sleep due to worries" ($p = 0.026$) and "feeling tense" ($p = 0.025$) (***Table 2***). No significant change was observed in other symptoms.

The assessment using Sleepscan showed no significant difference between the sleep quality during the first 1 week after the start of use of the test mattress and that during the

Table 1. Sleep quality evaluation

		Before	After 4 weeks	p value
PSQI-J	Sleep quality	2.1 ± 0.1	1.5 ± 0.2	**0.008**
	Time to fall asleep	2.3 ± 0.3	1.7 ± 0.3	**0.034**
	Sleeping time	1.6 ± 0.2	1.5 ± 0.3	0.157
	Sleep efficiency	0.4 ± 0.2	0.6 ± 0.2	0.257
	Difficulty sleeping	1.4 ± 0.2	1.0 ± 0.0	**0.046**
	Use of sleep inducers	0.1 ± 0.1	0.1 ± 0.1	1.000
	Daytime difficulty waking	1.7 ± 0.1	0.7 ± 0.2	**0.002**
	PSQIG	9.5 ± 0.4	7.1 ± 0.7	**0.005**
OSA sleep Questionnaire	First factor	9.9 ± 0.5	11.8 ± 0.6	**0.036**
	Second factor	11.2 ± 0.6	14.3 ± 0.6	**0.014**
	Third factor	6.7 ± 0.3	7.0 ± 0.2	0.405
	Forth factor	6.7 ± 0.3	8.2 ± 0.5	**0.048**
	Fifth factor	5.2 ± 0.3	5.8 ± 0.3	0.223
Sleep quality score		49.6 ± 4.2	46.4 ± 4.5	0.110

Results are expressed as mean ± standard error mean, paired t test, n=11. PSQI-J, Pittsburgh Sleep Quality Index (Japan version) questionnaire; PSQIG, PSQI global score; OSA, obstructive sleep apnea syndrome; Sleep quality score is measured by Sleepscan.

Table 2. AntiAging QOL Common questionnaire

	Before	After 4 weeks	p value
Physical symptoms			
Eye pain	2.30 ± 0.30	1.50 ± 0.20	**0.039**
Muscular pain/stiffness	3.60 ± 0.40	2.90 ± 0.40	**0.046**
Lethargy	3.20 ± 0.30	2.50 ± 0.20	**0.008**
Mental symptoms			
Shallow sleep	3.60 ± 0.30	2.80 ± 0.40	**0.014**
Difficulty in falling asleep	3.50 ± 0.30	2.90 ± 0.40	**0.038**
Inability to solve problems	2.30 ± 0.20	1.70 ± 0.20	**0.034**
Inability to sleep because of worries	2.80 ± 0.30	1.80 ± 0.20	**0.026**
A sense of tension	2.60 ± 0.30	2.20 ± 0.30	**0.025**

Data are expressed as mean ± standard error mean, paired t test, n=11.

last 1 week of use of the test mattress (***Table 1***).

Anthropometric parameters

No significant change was observed in body weight, BMI, body fat percentage or blood pressure during the observation period (***Table 3***).

Blood tests, urinalysis and saliva analysis (Table 4)

In the serum electrolyte analysis, significant increases, although mild and within the reference range, were observed in sodium (+1.1%, p = 0.001), potassium (+4.7%, p = 0.039) and chloride (+1.4%, p = 0.006) levels. For liver function parameters, a significant change within the reference range of AST (+28.9%, p = 0.001) was observed. No significant change was observed in any of the kidney function parameters or serum proteins. The results of oxidative/glycative stress, lipid metabolism and endocrine parameters are described separately in the following sections.

Oxidative stress parameters

For oxidative stress-related parameters, 8-OHdG and isoprostane levels in the first urine collected in the early morning were measured. The creatinine-adjusted concentration of 8-OHdG was significantly improved from 9.87 ± 0.84 ng/mg crea at baseline to 7.13 ± 0.45 ng/mg crea at week 4 (-27.8%, p = 0.006). No significant change was observed in the rate of 8-OHdG production. No significant finding was observed for isoprostane.

Glycative stress parameters

Among the glycative stress-related parameters tested, no significant change was observed in the fasting blood glucose or HbA1c levels while the plasma pentosidine level showed a slight but marginally significant increase from 0.04 ± 0.01 μg/mL at baseline to 0.06 ± 0.01 μg/mL at week 4 (p = 0.057).

Lipid metabolism parameters

Among the lipid metabolism parameters tested, the TC level was significantly increased from 209.50 ± 7.90 mg/dL at baseline to 222.40 ± 7.60 mg/dL at week 4 (+ 6.2%, p = 0.011) while no significant change was observed in LDL-C level or atherogenic index. The HDL-C level was also significantly increased from 73.70 ± 5.10 mg/dL at baseline to 79.20 ± 5.20 mg/dL at week 4 (+ 7.5%, p = 0.006).

Endocrine parameters

The endocrine parameters tested included IGF-I and DHEA-s, which are known to be related to hormonal age in the anti-aging medicine field, sleep-related hormone melatonin in saliva, and psychosomatic stress-related factors, including cortisol, adrenaline, noradrenaline, dopamine, serotonin and urinary steroid hormone metabolites.

The serum IGF-I level was significantly increased from 173.84 ± 17.40 ng/mL at baseline to 191.54 ± 15.88 ng/mL at week 4 (+10.2%, p = 0.008). No significant change was observed in serum DHEA-s level or salivary melatonin level.

The plasma noradrenaline level was significantly increased from 508.30 ± 46.90 pg/mL at baseline to 634.70 ± 54.60 pg/mL at week 4 (p = 0.011). The blood serotonin level was significantly decreased from 211.15 ± 32.29 ng/mL at baseline to 197.05 ± 32.95 ng/mL at week 4 (p = 0.024).

Significant increases were observed in the urine levels of the following DHEA metabolites: androsterone from 0.73 ± 0.18 mg/day at baseline to 1.02 ± 0.24 mg/day at week 4 (p = 0.037); and etiocholanolone from 0.80 ± 0.18 mg/day at baseline to 1.03 ± 0.21 mg/day at week 4 (p = 0.023). No significant change was observed in the other metabolites.

Table 3. Anthropometry

		Before	After 4 weeks	p value
Height	cm	164.06 ± 8.23	– –	–
Weight	kg	57.52 ± 8.08	57.69 ± 7.52	0.584
Body fat	%	25.21 ± 5.43	25.44 ± 5.22	0.327
BMI	–	21.27 ± 1.64	21.35 ± 1.57	0.515
Blood pressure (systolic)	mmHg	117.3 ± 3.4	116.2 ± 4.0	0.738
(diastolic)	mmHg	73.4 ± 2.5	72.5 ± 3.0	0.530
Pulse	/min	69.1 ± 2.8	70.2 ± 3.3	0.616

Data are expressed as mean ± standard error mean, paired t test, n=11. BMI, body mass index.

Table 4. Blood, urine, salivary examination

Blood chemistry		Before	After 4 weeks	p value
Total bilirubin	mg/dL	0.62 ± 0.07	0.62 ± 0.07	1.000
AST	U/L	17.3 ± 1.5	22.3 ± 1.6	**0.001**
ALT	U/L	16.5 ± 1.6	17.6 ± 1.7	0.361
γ-GTP	U/L	31.8 ± 9.0	28.6 ± 6.2	0.299
CPK	U/L	122.1 ± 28.0	175.6 ± 43.3	0.075
Uric acid	mg/dL	4.59 ± 0.44	4.76 ± 0.37	0.266
BUN	mg/dL	12.7 ± 0.9	12.9 ± 0.6	0.784
Creatinin	mg/dL	0.73 ± 0.05	0.70 ± 0.04	0.084
Na	mEq/L	140.9 ± 0.4	142.4 ± 0.4	**0.001**
K	mEq/L	4.26 ± 0.10	4.46 ± 0.08	**0.039**
Cl	mEq/L	103.2 ± 0.7	104.6 ± 0.5	**0.006**
Ca	mg/dL	9.47 ± 0.06	9.57 ± 0.04	0.161
Fe	μg/dL	89.4 ± 9.9	96.2 ± 8.1	0.484
Total protein	g/dL	7.19 ± 0.08	7.31 ± 0.06	0.058
Albumin	g/dL	4.42 ± 0.06	4.43 ± 0.03	0.839
A/G ratio		1.61 ± 0.06	1.55 ± 0.04	0.064
Oxydative stress markers in urine				
8-OHdG	ng/mL	10.2 ± 2.5	6.9 ± 1.1	0.124
Creatinine	mg/dL	98.0 ± 18.0	98.6 ± 15.6	0.953
8-OHdG [creatinine-adjusted]	ng/mg crea	9.9 ± 0.8	7.1 ± 0.5	**0.006**
8-OHdG production rate	ng/kg/hr	7.1 ± 1.3	5.3 ± 0.6	0.181
Isoprostane	ng/mL	3.0 ± 0.6	3.4 ± 0.8	0.655
Isoprostane [creatinine-adjusted]	ng/mg crea	3.0 ± 0.3	3.4 ± 0.4	0.405
Isoprostane production rate	ng/kg/hr	2.1 ± 0.3	2.6 ± 0.6	0.471
Glycative stress related markers				
FPG	mg/dL	95.1 ± 2.6	97.8 ± 3.1	0.294
HbA1c [NGSP]	%	5.5 ± 0.1	5.5 ± 0.1	0.779
Pentosidine	μg/mL	0.04 ± 0.01	0.06 ± 0.01	0.057
Total cholesterol	mg/dL	209.5 ± 7.9	222.4 ± 7.6	**0.011**
LDL-C	mg/dL	120.5 ± 7.6	127.5 ± 7.2	0.063
HDL-C	mg/dL	73.7 ± 5.1	79.2 ± 5.2	**0.006**
TG	mg/dL	83.4 ± 12.0	84.6 ± 8.3	0.833
Arteriosclerosis index		1.95 ± 0.22	1.90 0.17	0.567

Hormonal examination		Before	After 4 weeks	p value
Melatonin (saliva)	pg/mL	17.55 ± 4.26	17.76 ± 3.67	0.931
IGF-I	ng/mL	173.8 ± 17.4	191.5 ± 15.9	**0.008**
DHEA-s	μg/dL	163.3 ± 36.3	166.3 ± 34.4	0.751
Cortisol	μg/dL	9.02 ± 0.95	9.91 ± 0.68	0.309
Adrenaline	pg/mL	46.7 ± 6.8	45.7 ± 6.7	0.806
Noradrenaline	pg/mL	508.3 ± 46.9	634.7 ± 54.6	**0.011**
Serotonin	ng/mL	211.15 ± 32.29	197.05 ± 32.95	**0.024**
Steroid hormone metabolites in urine				
Free cortisol	μg/day	30.35 ± 5.73	26.59 ± 5.80	0.232
Androsterone	mg/day	0.73 ± 0.18	1.02 ± 0.24	**0.037**
Etiocholanolone	mg/day	0.80 ± 0.18	1.03 ± 0.21	**0.023**
DHEA	mg/day	0.19 ± 0.09	0.15 ± 0.04	0.630
11-keto-androsterone	mg/day	0.02 ± 0.00	0.02 ± 0.00	1.000
11-keto-etiocholanolone	mg/day	0.19 ± 0.06	0.20 ± 0.06	0.516
11-OH-androsterone	mg/day	0.58 ± 0.18	0.48 ± 0.13	0.098
11-OH- etiocholanolone	mg/day	0.17 ± 0.07	0.18 ± 0.07	0.607

Data are expressed as mean ± standard error mean, paired t test, n=11. BMI, body mass index; IGF-I, insulin-like growth factor-I; DHEA, dehydroepiandrosterone; DHEA-s, DHEA-sulfate; Arteriosclerosis index = (TC－HDL-C)/HDL-C.

Discussion

Sleep is a major component of a person's lifestyle. Poor quality sleep leads to an impairment of quality of life (QOL). A nationwide epidemiological survey of sleep conducted in 1997 showed that the prevalence of insomnia was 17.3% (14.6-20.0%) in men and 21.5% (18.8-24.3%) in women, that of poor quality sleep was 17.8% (15.3-20.3%) in men and 20.2% (17.6-22.7%) in women, and that of regular hypnotic use was 3.5% (2.3-3.7%) in men and 5.4% (4.1-6.8%) in women [19].

The quality of sleep decreases with age. Aging is associated with decreased melatonin secretion from the pineal gland [20], changes in the sleep-wake rhythm and sleep structure, greater difficulty in falling asleep, shallower sleep, reduced length of sleep with a feeling of sound sleep, and an increased incidence of sleep-related problems, such as awakening early and difficulty in achieving deep sleep [21,22]. Maintaining a good quality sleep is important to achieve healthy longevity [23]. Sleep disturbance is also observed in younger people; for example, various sleep disorders have been reported in college students [24-29]. There is an increasing awareness of the importance of preventing depression in the area of workplace mental health. Considering that poor quality sleep is often observed in an early stage of the onset of depression, it is of great significance to detect poor quality sleep early so that the onset of depression can be prevented at an early stage [30,31]. In order to establish a comfortable sleep environment and improve sleep quality, each individual should use an appropriate mattress suited for their condition.

Assessment of sleep quality and mattress quality

Various attempts have also been made in Japan to assess sleep quality and mattress quality. These include the use of questionnaire forms [32-38], polysomnography [39], ActiGraph (Actigraph Corp., Pensacola, FL, USA) [40] or other types of 3D acceleration sensors for body motion monitoring [41-43], assessment of autonomic function by frequency analysis of the acceleration pulse wave a-a interval [44], and measurement of psychosomatic stress markers in saliva [chromogranin A [45]] and oxidative stress markers in blood [diacron reactive oxygen metabolites (dROM [46])] or urine [8-OHdG [47]], in addition to a questionnaire. In this study, although conducted in a non-controlled open-label design, we observed significant improvement in subjective symptoms, as well as a decrease in the creatinine-adjusted concentration of 8-OHdG in urine (-27.8%), a measure of oxidative stress, and an increase in IGF-I level (+10.2%), a measure of hormonal age.

Subjective symptoms and background factors

Known influencing factors for sleep quality include room temperature [48], noise [49], alcohol consumption [50], work load [51] and frequent urination [52]. The present study also included these factors in the analysis, but identified no significant findings.

The use of the test mattress resulted in improvement in subjective symptoms, as detailed below.

In the AAQOL assessment, significant improvement in scores were observed for 3 physical symptoms, including "eye pain", "muscular pain/stiffness" and "lethargy", and 5 mental symptoms, including "shallow sleep", "difficulty in falling asleep", "inability to solve problems", "inability to sleep due to worries" and "feeling tense". In a previous study where an α-Gel Mat was used as the test mattress [47], significant improvement was observed in physical symptoms "tired eyes", "lethargy" and "coughing and sputum", and mental symptoms "no feeling of happiness", "shallow sleep" and "difficulty falling asleep", of which the physical symptom "lethargy" and mental symptoms "shallow sleep" and "difficulty falling asleep" were also improved in the present study. The discrepancy between the two studies in terms of symptoms with significant changes before and after use of the test mattress may be explained by the differences in the age/gender distribution of subjects and subjective symptoms evaluated. Improvement in the scores for physical symptoms "eye pain" and "tired eyes" can both be interpreted as an improvement of eye strain, although "eye pain" is more severe than "tired eye" in terms of the severity of eye symptoms. Recent development in IT devices, such as smartphones, has posed an increasing burden on eye function. The differential impact on improvement of sleep quality between physical symptoms "eye pain" and "tired eyes" may reflect this social situation.

In the PSQI-J [13] assessment, improved scores for sleep quality, time to fall asleep and difficulty sleeping resulted in a significant improvement in the PSQIG score from "severe" to "mild" disorder, which was likely associated with an improvement in the daytime activity and a significant improvement in the score for difficulty staying awake during the daytime.

The OSA sleep inventory is a psychological scale used for the self-evaluation of sleep immediately after rising in middle-aged to elderly people, and is characterized by the requirement of a relatively short length of time to complete and ease of use in clinical practice [14,15]. This inventory consists of 16 questions of 5 factors, including factor 1 "sleepiness on rising", factor 2 "initiation and maintenance of sleep", factor 3 "frequent dreaming", factor 4 "feeling refreshed" and factor 5 "sleep length". In the present study, significant improvement was observed in factors 1, 2 and 4.

Oxidative stress

Poor quality sleep, such as the lack of sleep, sleep deprivation and intermittent sleep, leads to the activation of the oxidative stress production mechanism in various organs, including the brain. This high oxidative stress condition, if transient and mild in severity, can be managed by activating anti-oxidative enzymes, such as superoxide dismutase (SOD) and glutathion peroxidase (GPX) to eliminate oxidative stress. However, chronic impairment of sleep quality or the presence of severe and persistent sleep disorders, such as SAS, leads to damage to brain cells and a subsequent increase in the risk of cognitive impairment, depression and anxiety [53]. Melatonin, an anti-oxidant secreted during sleep, protects the brain from oxidative damage during sleep [20]. Since melatonin secretion decreases with age, the defense function against oxidative stress also declines with age.

In experimental animals, sleep disruption resultes in decreases in SOD activity and the level of reduced glutathione (a substrate for GPX) and an increase in the level of oxidized glutathione in the brain. Continued arousal has also been shown to increase the level of oxidative stress in the brain [53]. These observations suggest that sleep protects the brain by reducing oxidative stress.

8-OHdG is an oxidative damage product of guanine, a component of DNA. Several reports have been available regarding the correlation between sleep quality and urinary 8-OHdG level. In a study involving 146 workers in sales occupations, the creatinine-adjusted urinary concentration of 8-OHdG showed a U-shape correlation with the previous night's sleep length in women, but not in men, with the minimum value recorded in women with a sleep length of 7 to 7.5 hours [54]. In a clinical study conducted with αGel Mat as the test mattress in 20 subjects with a Pittsburgh Sleep Quality Index (PSQI) of ≥7, a significant decrease in the creatinine-adjusted urinary concentration of 8-OHdG was observed [47]. In another study, night sleep deprivation in healthy subjects resulted in no significant change in urinary 8-OHdG concentration [55]. In this sleep deprivation study, while subjective sleepiness was improved to the baseline level after 1 night of normal sleep (7 hours), fatigue, confused feeling and higher cognitive functions could only be improved after at least 2 nights of normal sleep. Thus, controversy remains regarding the relationship between sleep quality and 8-OHdG.

SAS is a major condition associated with poor quality sleep. In particular, obstructive sleep apnea (OSA) has been associated with abnormalities of various cytokines, including inflammatory cytokines such as tumor necrosis factors (TNF-a) and interleukins (IL)-1 and -6, adipocytokines such as leptin, adiponectin and plasminogen activator inhibitor-1 (PAI-1), and vascular endothelial growth factor (VEGF) [56,57]. OSA patients have significantly higher levels of thiobarbituric acid reactive substances and peroxides and a significantly lower level of antioxidant enzyme paraoxonase-1 [58]. OSA has also been associated with an increased activity of the sympathetic nervous system, suggesting the involvement of sympathetic activity in cytokine abnormalities in OSA [57]. It has also been suggested that intermittent hypoxia in OSA mimics ischemic reperfusion of tissues and resulting hypoxic stress and oxidative stress lead to the activation of transcription factors and the subsequent induction of expression of various cytokines.

Through these mechanisms, poor quality sleep leads to increased oxidative stress. In the present study, the use of the test mattress resulted in a significant improvement in the creatinine-adjusted urinary concentration of 8-OHdG from 9.87 ± 0.84 ng/mg crea at baseline to 7.13 ± 0.45 ng/mg crea at week 4, which is comparable to the corresponding change reported in a previous study (from 7.66 ± 1.87 ng/mg crea at baseline to 6.38 ± 1.87 ng/mg crea at week 4), suggesting that an improvement in sleep quality led to a reduction in oxidative stress. However, the precise mechanism for this remains unknown. Although no significant change was observed in salivary melatonin level in this study, increased

melatonin secretion resulting from improved sleep quality is expected to lead to reduced oxidative stress via the anti-oxidative effect of melatonin [20]. It is impossible to determine the daily melatonin secretion only by measuring the salivary melatonin level once in the morning. Future studies should therefore include measurement of the urinary concentration of melatonin metabolites, such as 6-hydroxy-melatonin sulfate [59].

Hormonal age

The secretion of growth hormone (GH) and its second messenger hormone IGF-I start to decline around 30 years of age, and decreased levels of these hormones lead to a poorer prognosis and impaired QOL [60]. Decreased secretion of these hormones is referred to as somatopause, which not only causes reduced cell divisions and protein synthesis, but is also deeply associated with declines in neuropsychiatric function, reproductive function, digestive function and bone metabolism. Somatopause has also been associated with lifestyle-related diseases, such as fatty liver [61]. Lifestyle improvement to prevent the decline of GH/IGF-I secretion is effective for the maintenance of youth and health. High-quality sleep, adequate exercise, appropriate protein/amino acid intake, and eating on hunger and the resulting promoted ghrelin secretion are known to promote GH secretion. In contrast, lack of sleep, lack of exercise, impaired sleep quality due to psychosomatic stress and excessive carbohydrate intake are associated with suppressed GH secretion. SAS is associated with a poorer sleep quality, as well as decreased GH secretion and a subsequent decrease in IGF-I levels during sleep, and therefore it requires active intervention. A significant increase in IGF-I level (+ 10.2%) was observed in the present study. This is likely because improved sleep quality achieved by the use of the test mattress resulted in increased GH secretion and a subsequent increase in the IGF-I level.

Dihydroepiandrosterone (DHEA) is an important hormone for the determination of hormonal age. DHEA is the most abundant steroid hormone in the human body as a precursor of more than 50 kinds of hormones, including reproductive hormones and cortisol [62]. It is secreted from the adrenal cortex and its secretion declines with age. DHEA in circulation exists either as the stable sulfate form (DHEA-s), which accounts for 99% of all DHEA, or as free DHEA, which accounts for 1%. Thus, the routine measurement of DHEA targets DHEA-s. Decline in DHEA-s secretion is referred to as adrenopause, which has been associated with impaired immunological function and decreased resistance to stress, as well as increased risk of metabolic syndrome (MetS), fatty liver, diabetes, hyperlipidemia, hypertension, osteoporosis and other lifestyle-related diseases [63].

Various steroidal hormone metabolites are present in urine; 17-ketosteroid (17-KS) is a group of neutral steroids having a keto group at position C-17 among C-19 compounds, which account for a large proportion of all androgens. 17-KS is further divided into 11-deoxy-17-KS and 11-oxy-17-KS; the former consists of 3 fractions (androsterone, etiocholanolone and DHEA) which are produced in the adrenal gland and testis, while the latter consists of 4 fractions (11-keto-etiocholanolone, 11-OH-androsterone, 11-OH-etiocholanolone and 11-keto-androsterone) which are derived from glucocorticoid (cortisol) [64]. In healthy adult men, about a quarter of all 17-KS compounds originate from the testis and the remaining from the adrenal gland. In contrast, the majority of 17-KS compounds in children and women originate from the adrenal gland and are derived from DHEA and DHEA-s. In the present study, significant increases in the levels of androsterone and etiocholanolone, but not 11-oxy-17-KS fraction steroids, were observed following the use of the test mattress. The fact that only the levels of 11-deoxy-17-KS fraction steroids (*i.e.* DHEA metabolites originating from the adrenal cortex) were increased suggests that the use of the test mattress leads to an increase in the DHEA-s/cortisol ratio in circulation. Although no significant change was observed in the circulating DHEA-s or cortisol level in this study, the results of analysis of urinary steroid hormone metabolites suggest that the use of the test mattress resulted in improved sleep quality and a subsequent improvement in the psychosomatic stress balance.

Psychosomatic stress

In an anti-aging medical checkup, psychosomatic stress is assessed based on the serum DHEA-s/cortisol ratio [62]. The intensity of psychosomatic stress, resistance to stress, and stress balance are generally evaluated based on the cortisol level, DHEA-s level, and DHEA-s/cortisol ratio, respectively. The DHEA-s/cortisol ratio is generally considered optimal if it is 20-25 μg/dl, suboptimal at 15-20 μg/dl, borderline at 10-15 μg/dl and poor at <10 μg/dl [65]. The detection of an abnormally high level of DHEA-s warrants close examination of the adrenal gland.

In this study, we observed no significant change in the serum DHEA-s or cortisol level, rather we noted increases in DHEA metabolites in the analysis of urinary 17-KS fractions (steroid hormone metabolites), as mentioned above, suggesting improved stress hormone balance as a result of the use of the test mattress.

Psychosomatic stress is also closely related to the onset of depression and affects serotonin/adrenaline metabolism.

In the human body, 90% of serotonin is distributed in the intestine, 8% in the blood and 2% in the brain. Intestinal serotonin is involved in gastrointestinal peristalsis and promotes digestion and absorption. In the stomach, serotonergic nerves distributed in the antrum induce contraction of the pyloric sphincter. In blood, the majority of serotonin is present in platelets and it contributes to vasoconstriction and subsequent hemostasis. Massive destruction of platelets due to injury or other causes and the subsequent release of serotonin into blood causes nausea/vomiting. Serotonin is also suggested to be involved in migraine attacks, as evidenced by a decreased serotonin level in platelets and an increased serotonin level in plasma during a migraine attack [66]. Brain serotonin interacts with the sympathetic nervous system to adjust the body's internal clock and maintain arousal (a condition in which a person can vigorously perform activities). Serotonin is also involved in the control of mood and emotion and the suppression of impulsive and dependent behaviors by regulating dopamine and noradrenaline actions. Other functions of serotonin include the suppression of pain sensory nerve activity and the regulation of memory and learning processes in the hippocampus. Although the significance of the plasma serotonin level has not been fully elucidated, several reports have shown increased plasma serotonin levels in association with increased psychosomatic stress induced by visual display terminal (VDT) work [67] and

in severely depressed patients with strong suicidal ideation [68]. High plasma serotonin levels have also been reported in diabetic patients [69]. Serotoin also contributes to the progression of arteriosclerosis by promoting vascular smooth muscle contraction and platelet aggregation [70]. The platelet poor plasma (PPP) serotonin to whole blood (WB) serotonin ratio (PPP/WB) significantly correlates with the Framingham Risk Score (FRS) for the 10-year risk of having a coronary heart disease, and thus can be a new biomarker for predicting the risk of arteriosclerotic cardiovascular diseases [71]. In the present study, there was a significant decrease in the plasma serotonin level from 211.15 ± 32.29 ng/mL at baseline to 197.05 ± 32.95 ng/mL at week 4, suggesting reduced psychosomatic stress. It is also likely that a reduced plasma serotonin level has a favorable effect on serotonin-related headaches. In contrast, one study showed that foot massaging results in a decreased plasma noradrenaline level and decreased blood pressure and pulse rate, whereas the plasma serotonin level increases [72]. Since different results may be obtained by assessing the short-term change in the plasma serotonin level or by measuring the serotonin level before its change is observed, further analyses are needed to establish the optimal method for assessing plasma serotonin levels.

Change in the noradrenaline level is associated with a depressive state. Serotonin-noradrenaline reuptake inhibitors (SNRIs) exert an anti-depressive effect by increasing the availability of serotonin and noradrenaline in postsynaptic cells in the brain. Recent evidence suggests reuptake of dopamine by noradrenaline autoreceptors, suggesting the possibility of enhanced dopamine signaling by SNRIs. Tricyclic antidepressants are known to increase not only plasma serotonin but also noradrenaline levels [73]. Exercise therapy for depression treatment is suggested to improve psychiatric symptoms by stimulating the noradrenergic nervous system and suppressing depression by maintaining activity [74]. As a measure for improving the psychosomatic function of young women in the late luteal phase, comfortable self-paced exercise has been shown to significantly increase the plasma noradrenaline level and increase the psychological scores for vitality and pleasure [75].

The plasma noradrenaline level is used for the diagnosis of orthostatic hypotension. The diagnosis of orthostatic hypotension is based on a ≥20 mmHg decrease in the systolic blood pressure or a ≥10 mmHg decrease in the diastolic blood pressure in a standing test or a head-up tilt test, and is further supported by the absence of an increased plasma noradrenaline level in patients with orthostatic hypotension [76]. The plasma noradrenaline level is also used as a measure of short-term change in stress levels, for such purposes as stress reduction during indwelling needle puncture for securing a venous line [77]. Essential hypertension patients are known to have higher resting plasma noradrenaline levels compared to individuals with optimal blood pressure [78].

Little is known about the significance of measuring a resting plasma noradrenaline level. The present results showed a significant increase in this parameter from 508.30 ± 46.90 pg/mL at baseline to 634.70 ± 54.60 pg/mL at week 4. The mean systolic and diastolic blood pressure measurements were 117.30 ± 3.40 and 73.40 ± 2.50 mmHg, respectively, which included the data from the hypotensive subjects with low plasma noradrenaline levels. Autonomic nervous system disorder due to excessive psychosomatic stress is one of the known causes of hypotension [79-81]. Thus, improved psychosomatic stress balance resulting from improved sleep quality is expected to lead to improvement of hypotension. The increased noradrenaline levels in these hypotensive subjects may be reflected in the present results.

Glycative stress

A logistic multiple regression analysis showed a correlation between decreased sleep quality and an increased risk of MetS [82]. This analysis also showed an increased prevalence of hypertriglyceridemia and a high insulin resistance index (HOMA-IR) in subjects with a sleep length of ≤5 hours or ≥9 hours and also an increased prevalence of hypertriglyceridemia, hypo-HDL-cholesterolemia and high fasting insulin and high HOMA-IR in the poor sleep group [82]. In a study to compare the prevalence of arteriosclerotic risk factors between 207 OSA patients (OSA group) and control subjects who underwent a comprehensive medical checkup (control group), a significantly higher prevalence of visceral fat obesity, hypertriglyceridemia and hypo-HDL-cholesterolemia, as well as higher fasting glucose levels (findings suggestive of insulin resistance) were observed in the OSA group [83]. In a study to examine the association between the apnea hypopnea index (AHI) and various physical parameters in 121 men who underwent a comprehensive medical checkup, significant correlations were observed between the AHI and BMI, blood pressure, HDL-C, HOMA-IR and blood insulin concentration [84]. A study on the association between OSA and insulin resistance/MetS showed a high prevalence of insulin resistance in OSA (58.1%) and a significant correlation between insulin resistance and BMI, liver enzyme, triglyceride and HDL-C levels [85]. An association between SAS and HDL-C has also been suggested in other studies, although some studies have demonstrated an association between poor quality sleep and decreased HDL-C [86,87], while yet others showed no significant change in HDL-C [88,89].

Abnormal changes in lipid metabolism parameters observed in this study included increased TC (+ 6.2%), increased LDL-C (+ 5.8%) and increased HDL-C (+ 7.5%) levels. The mean baseline LDL-C level was 120.50 ± 7.60 mg/dL, which included the data from subjects with hypo-LDL-cholesterolemia. The observed increase in LDL-C level may reflect an improved physical condition and appetite in the subjects with low baseline LDL-C levels and a subsequent increase in LDL-C levels. The week-4 LDL-C level was 127.50 ± 7.20 mg/dL. LDL-C levels less than 130 mg/dL should not raise any concern. In contrast, the HDL-C level significantly increased from 73.70 ± 5.10 mg/dL at baseline to 79.20 ± 5.20 mg/dL at week 4. Although the only factor known to increase the HDL-C level was exercise/physical activity, the results of the present study suggest the potential of improved sleep quality as an additional factor contributing to an increased HDL-C. The mechanism by which improved sleep quality leads to increased HDL-C remains to be elucidated. The observed increase in TC was likely to be the result of increases in both LDL-C and HDL-C levels.

We measured the level of pentosidine, an advanced glycation end product (AGE), as a measure of glycative stress [90]. The pentosidine level changed from 0.04 ± 0.01 μg/mL at baseline to 0.06 ± 0.01 μg/mL at week 4, with a significant increase observed only in its percent change. This change in pentosidine level was considered negligible, as the pre- and post-intervention change was within the range of physiological variation; the absolute values were relatively small, and the statistical analysis of the measured values and their change showed no significant difference.

Thus, these changes were considered negligible.

Safety

No adverse event was observed in association with the use of the test mattress. Although significant changes in some electrolytes (sodium, potassium and chloride) were observed in blood biochemistry, these changes were mild and within the range of physiological variation and considered likely due to thickening of blood caused by the blood collection procedure. Thus, these changes were considered negligible.

Conclusion

We conducted a non-controlled open-label study of the 4-week use of the test mattress in 11 men and women with a sleep disorder who had a PSQIG score of ≥7 according to the PSQI-J. We observed a significant improvement in subjective symptoms, as well as a significant decrease in the creatinine-adjusted concentration of 8-OHdG in urine (a measure of oxidative stress), a significant increase in IGF-I level (a measure of hormonal age), and a significant increase in HDL-C level (a lipid metabolism parameter). In the analysis of urinary 17-KS steroid hormone metabolites, no significant change was observed in cortisol metabolites while significant increases were observed in DHEA metabolites. Other findings included a significant increase in the plasma noradrenaline level and a significant decrease in the plasma serotonin level, changes that improve a depressive state. These findings suggest that the use of the test mattress improves sleep quality and has favorable effects on various physical parameters, including parameters related to oxidative stress, psychosomatic stress and lipid metabolism.

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Conflict of Interest Statement

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