Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : February 5, 2018
Accepted : March 22, 2018
Published online : June 30, 2018
doi:10.24659/gsr.5.2_75

*Original article*

# Effect of melatonin intake on postprandial blood glucose in the breakfast

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## Abstract

***Objectives*:** The link between sleep and life-style diseases related to glycolipid metabolism has been gaining considerable concern. This study conducted a crossover trial to examine how nocturnal melatonin intake influenced blood glucose level following the next breakfast.

***Methods*:** Participants in the research were 12 healthy individuals (4 males and 8 females, with a mean age of 22.9 ± 1.7). Subjects participated in two examinations with a one-week interval. In the first test, the standard test meal for breakfast was steamed rice (200 g, 294 kcal). In the second test, 2 mg of melatonin was administered at 21:00 before the test day. On the following morning the standard test meal was ingested. In both tests, blood glucose level was examined at 15, 30, 45, 60, 90, and 120 minutes after the time of intake of the standard meal to measure levels using a self-monitoring blood glucose meter. This study was conducted with the approval of an ethical review committee.

***Results*:** Three cases were eliminated for data analysis: the area under the curve (AUC) in the second examination of the blood glucose response curve had great changes (± 50% or greater). Among the nine participants, eight participants had significantly lower AUC values due to the melatonin ingestion the night prior to the test day (from −6.4 to −31.0%). The other participant showed an increase of 5.7%. AUC was significantly lowered due to the melatonin ingestion ($p < 0.05$).

***Conclusion*:** It was suggested that the melatonin ingestion of the previous night improved the participant`s quality of sleep, which improved postprandial hyperglycemia. We reported on the mechanism of the improvement of postprandial hyperglycemia, adding some literature review.

***KEY WORDS*:** postprandial hyperglycemia, melatonin, quality of sleep

## Introduction

Glycation is a reaction of the bonding of reducing sugar molecules, such as glucose or fructose, lipid, or alcohol-derived aldehyde, to *in vivo* proteins without the controlling action of an enzyme to form carbonylated proteins or advanced glycation end products (AGEs). Aldehyde-load-induced stress to living organisms is referred to as glycative stress [1, 2)]. Glycative stress is a risk factor for physical aging and contributes to the development of skin aging or diabetic complications.

Up to 40% of patients with diabetes, which is strongly linked to glycative stress, have sleep disorders. Meanwhile, sleep apnea syndrome (SAS), which is a major disease accompanying the decline of sleep quality, is frequently associated with complications of obesity or diabetes [3,4)]. That is to say, there is a bi-directional correlation between sleep and carbohydrate metabolism. To reduce glycative stress, prevention and treatments for the disorder of glycolipid metabolism and sleep disorders must be performed simultaneously. Prior research revealed that as for a glycative stress marker, skin autofluorescence (AF) showing an intensity of AGEs-derived fluorescence is affected by duration of sleep. Individuals with a shorter sleep duration showed that, in the graphic chart of the level of skin AF by age, the AF value line showing changes by age was higher in comparison to persons with a longer duration of sleep (***Fig. 1***) [5)]. In short, the persons with a shorter sleep duration had a larger amount of AGEs accumulated in the skin, while

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the persons with a longer sleep duration showed reduced glycative stress.

For this study, we focused on melatonin to influence the quality of sleep and examined melatonin for the anti-glycation effect *in vitro*. Melatonin did not show activity for the formation of AGEs [6]. In the AGEs/RAGE signaling, using a cultured macrophage, melatonin had no effect [7]. However, melatonin showed an effect in promoting the degradation of AGEs [8].

Some treatment methods for reducing glycative stress are categorized as follows: the reduction of postprandial hyperglycemia by food intake, the inhibition of glycation, and the enhancement of AGE degeneration and excretion.

The methods to reduce glycative stress are as follows: to control postprandial blood glucose levels, to restrict glycation reactions, and to promote the degradation and the excretion of AGEs. Specifically, the methods for controlling postprandial blood glucose levels include selecting food with a low glycemic index (GI) as a staple, which mildly increases postprandial blood glucose level, eating dietary fiber such as vegetables first and carbohydrate later, and restricting carbohydrates. This study examines whether melatonin ingestion affects postprandial blood glucose levels.

## *Methods*

### *Subjects*

Participants were recruited from students related to Department and Graduate School of Life and Medical Sciences, Doshisha University. The inclusion criteria was for individuals who were healthy and over 20 years of age and who did not meet the exclusion criteria. The exclusion criteria was for individuals with the following: who are allergic to food or drugs, who are pregnant or lactating, who are receiving pharmacotherapy, who have a disease during a follow-up observation, who have a diagnosis of diabetes, who show significant disorders of cardiopulmonary functions, who ingest medicine for the treatment of hypertension, who have had a gastrointestinal surgery or who are suspected of having an infectious disease. Participants were fully informed of this study and written consent for voluntary participation was obtained.

The participants of this study were 12 healthy individuals (4 males and 8 females, with the mean age of 22.9 ± 1.7).

### *Protocol for blood glucose test*

This study was conducted referring to Unified Protocol of Japanese Association established by the Study for Glycemic Index (GI) [9, 10].

The guidelines as below were to be followed on the night before the test day: refrain from strenuous exercise, do not eat food after 22:00, do not overeat or overdrink, do not intake a great amount of alcohol, and do not stay up late at night.

In cases where participants felt sick on the day before the test day, prior to or during the test, the test was postponed or canceled.

On the day of the test, subjects measured fasting blood glucose levels by themselves, using a self-monitoring blood glucose meter. Measurements were performed twice, and the mean value was employed as a measurement value. When an error of measurement was 10 % or greater, another measurement was performed as the third measurement, two data entries that had the smaller error gap were employed to calculate the mean value. The standard meal or the test meal was ingested within a ten minute period and with approximately thirty chewing cycles per mouthful of food. Measurement of blood glucose level was conducted, from the start of the food ingestion, at 15 min (the second time), 30 min (the third time), 45 min (the fourth time), 60 min (the fifth time), 90 min (the sixth time) and 120 min (the seventh time). Area under curve (AUC) was calculated using the chart of alternation in postprandial blood glucose levels. To measure blood glucose levels, a self-monitoring blood glucose meter (Glucocard G black blood glucose meter GT-1830; Arkray, Kyoto, Japan) was employed.

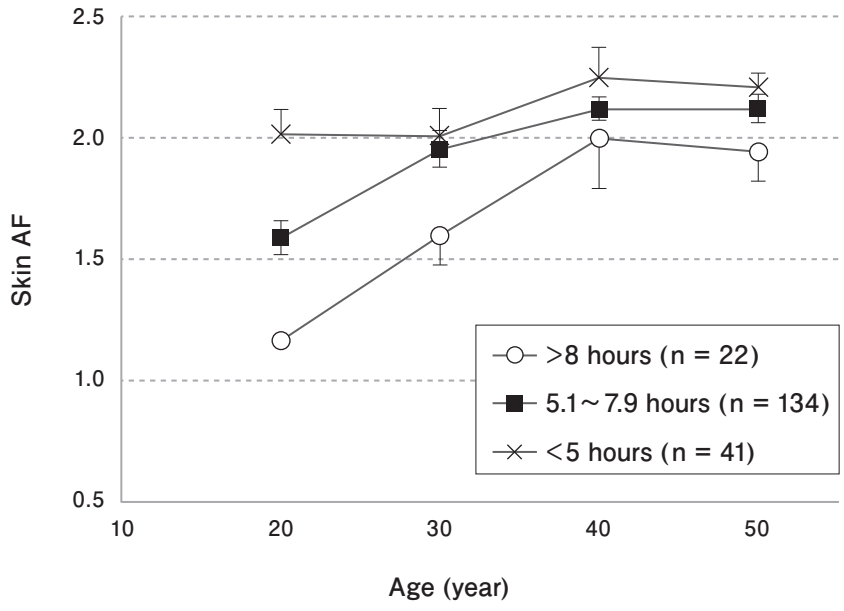


***Fig. 1.*** **Skin AF and sleeping time.**
Data are expressed as mean ± SEM. AF, AGE-derived fluorescence measured by AGE Reader; SEM, standard error mean. Figure is made by using the data in Reference 5).

### *Clinical study design*

This study employed 200 g of steamed rice as the standard meal (Sato No Gohan Koshihikari Made in Niigata; Sato Foods Co., Ltd., Niigata, Japan). On the intake of steamed rice, 2.5 g of *furikake*, a dry Japanese seasoning meant to be sprinkled on top of steamed rice (Noritama; Marumiya Shokuhin Kogyou Co. Ltd., Suginami-ku, Tokyo, Japan) was ingested with the rice. For melatonin, 2 mg of Melatonin Controlled-Release (Douglas Laboratories, Pittsburgh, PA, USA) was used.

Melatonin (–): In the first test, blood glucose level was measured at the intake of the standard meal.

Melatonin (+): The second test, 2 mg of melatonin was ingested at 21:00 on the day prior to the test day and the blood glucose level was measured for the intake of the standard meal on the following morning.

### *Statistical analysis*

The amount of change Δ was determined by subtracting the fasting blood glucose value from the postprandial blood glucose value of passing time after the ingestion of the test food. From the start of the ingestion to 120 minutes was calculated AUC, the maximum concentration of the blood glucose value (Cmax) and the maximum change (ΔCmax). Results were expressed as standard errors of the mean (mean ± standard error: SE). For the data analysis, cases where AUC showed great gaps in change rate between two tests (± 50 % or greater) were eliminated. Statistical analysis of paired t-test was employed for comparison between the two groups (IBM SPSS Statics24; IBM Japan, Ltd., Minato-ku, Tokyo, Japan). Data was analyzed with a two-sided test and a 0.05 level of significance. A hazard rate less than 5 % was considered to be statistically significant.

### *Ethical standards*

The Doshisha University Ethics Review Committee on Research with Human Subjects was held to deliberate the ethics and validity of this study. Under their approval (Application number: #16027) this clinical test was conducted with UMIN Clinical Trials Registry (UMIN# 00002795).

## *Results*

First, the results of blood glucose alternation (Cmax and AUC) in all the cases are shown (***Table 1***). Three participants with change rates of ± 50 % or greater in AUC between the first and the second test were excluded for further analysis. The reasons for the great changes of AUC were not identifiable. The remaining nine participant`s changes in blood glucose levels after the ingestion of the standard meal are shown in ***Table 2*** and ***Fig. 2***.

Blood glucose levels in cases with melatonin ingestion were significantly lower at 15 and 120 minutes. In cases with ingestion of melatonin, Δ blood glucose was significantly lower at 120 min. There was no significant difference in Cmax. However, AUC was lower in the cases with melatonin ($p < 0.05$).

There was no significant difference in the time of sleep between cases with and without the ingestion of melatonin.

***Table 1. AUC alteration in all the cases.***

| ID | Melatonin (–) | Melatonin (+) | %Change |
|---|---|---|---|
| 1 | 6191.3 | 5617.5 | –9.3 |
| 2 | 3198.8 | 2958.8 | –7.5 |
| 3 | 4115.0 | 3851.3 | –6.4 |
| 4 | 4630.0 | 4141.3 | –10.6 |
| 5 | 3488.8 | 5873.8 | **68.4** |
| 6 | 7427.5 | 7848.8 | 5.7 |
| 7 | 6843.8 | 5052.5 | –26.2 |
| 8 | 3865.0 | 2665.0 | –31.0 |
| 9 | 3177.5 | 5207.5 | **63.9** |
| 10 | 8013.8 | 3731.3 | **–53.4** |
| 11 | 4590.0 | 3506.3 | –23.6 |
| 12 | 4215.0 | 3567.5 | –15.4 |

AUC, area under curve with units in mg/dL·min. Three participants (ID 5, 9, 10) are excluded in the further analysis.

***Table 2. Effect of melatonin on postprandial blood glucose.***

| Index | | Melatonin (–) | Melatonin (+) | p value |
|---|---|---|---|---|
| **BG** | **0 min** | 87.4 ± 2.49 | 85.4 ± 3.1 | 0.533 |
| | **15 min** | 105.1 ± 3.79 | 100.1 ± 3.1 | **0.008** |
| | **30 min** | 149.5 ± 4.85 | 144.9 ± 5.5 | 0.388 |
| | **45 min** | 153.3 ± 4.20 | 145.1 ± 4.9 | 0.202 |
| | **60 min** | 147.4 ± 4.23 | 134.7 ± 4.5 | 0.076 |
| | **90 min** | 120.7 ± 6.93 | 118.3 ± 5.4 | 0.705 |
| | **120 min** | 116.2 ± 2.90 | 106.1 ± 4.3 | **0.005** |
| **Cmax** | | 160.8 ± 4.0 | 153.2 ± 3.8 | 0.113 |
| **AUC** | (mg/dL·min) | 5008.5 ± 392.5 | 4356.5 ± 434.1 | **0.016** |
| **Sleeping time** | (hour) | 6.4 ± 0.2 | 6.4 ± 0.4 | 0.999 |

Data are expressed as mean ± SEM, n = 9, statistical analysis conducted by paired-t test. BG, blood glucose concentration in mg/dL. Cmax, maximum concentration; AUC, area under curve.

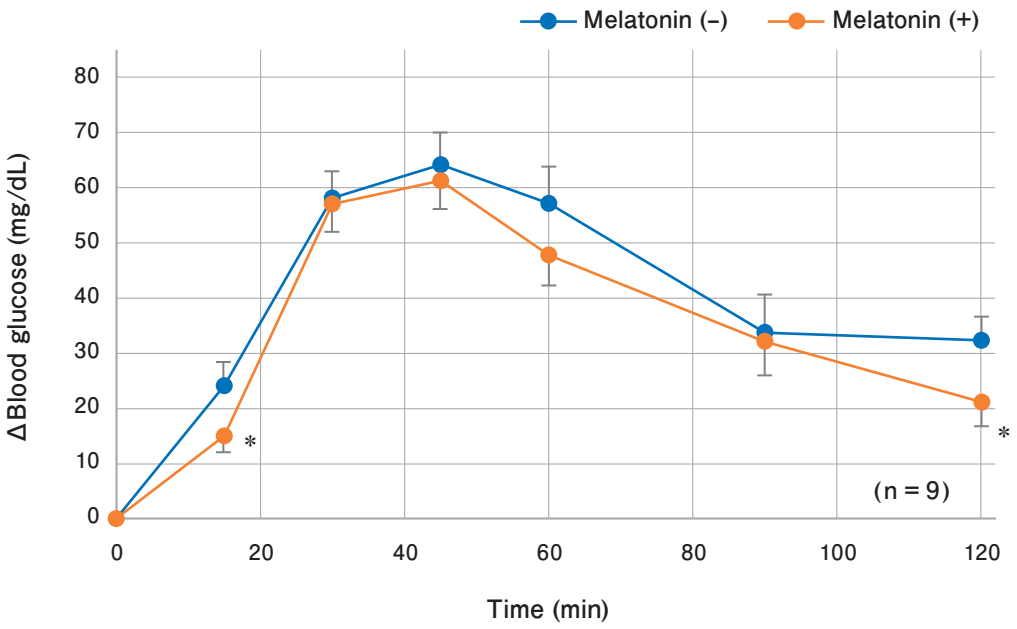


***Fig. 2.*** **Effect of melatonin on Δpostprandial blood glucose.**

Melatonin 2 mg was orally administered the day before the test day. Postprandial blood glucose was measured after intake of steamed rice (200 g). Bar indicates standard error mean. *p < 0.05, **p < 0.01 by paired-t test.

## *Discussion*

This trial with 12 healthy subjects (4 males and 8 females) examined the influences of melatonin ingested the night prior to the test day on postprandial blood glucose levels after breakfast on the following day. Steamed rice (200 g, 294 kcal) was ingested as the standard meal. Two blood glucose tests were performed after the ingestion of the standard meal. Three sets of data with AUC change rates of ± 50 % or greater between the first and the second test were excluded for data analysis. The data results of the remaining nine cases showed that eight in nine cases were lower in AUC (between −6.4 % and −31.0 %) and an elevation in AUC was recognized in one case (5.7 %). AUC was significantly lowered due to the ingestion of melatonin ($p < 0.05$). Previous studies have reported that the ingestion of melatonin improved glycolipid metabolism. However, this study is the first to report that the single ingestion of melatonin improved the postprandial blood glucose level on the following morning. The mechanism for how the postprandial blood glucose level was lowered remains to be examined in further investigations. We reported this case with some literature reviews as below.

Sleep disorders have been an increasingly serious concern in society today. Research has frequently reported relations between shorter sleeping time and weight gain, diabetes, hypertension, and glycolipid metabolism disorders. Furthermore, erratic sleeping habits such as shift work sleep disorder have diversified the risks for disease onset such as breast cancer, diabetes, premature labor, miscarriage, low birth weight, small-for-gestational-age infants, interrupted menstrual cycles, infertility, and ischemic heart disease [11].

### *Melatonin and glycolipid metabolism*

***Figure 3*** shows the mechanism of melatonin to improve glycolipid metabolism and reduce glycative stress.

Firstly, melatonin has an antioxidative effect [12-22]. This effect is based on two functions of melatonin, which are a powerful free-radical scavenger to eliminate ROS and wide-spectrum antioxidants (to promote activities of superoxide dismutase [SOD] and glutathione peroxidase) [23, 24].

Secondly, melatonin promotes the degradation of AGEs [25]. In the disorder of carbohydrate metabolism of diabetes, the acceleration of endoplasmic reticulum (ER) stress in pancreatic beta cells reduces the secretion of insulin [26]. AGEs increase ER stress in pancreatic beta cells and decreases the production and secretion of insulin [27]. Therefore, decreased AGEs due to the degradation induces the reduction of ER stress, and consequently, the ability of insulin secretion is improved.

Thirdly, melatonin reduces glycative stress via hormones. Melatonin reduced the secretion of glucocorticoid, for example, cortisol from the adrenal cortex. Glucocorticoid promotes the acceleration of protein catabolism and the gluconeogenesis, augment insulin resistance, thus inducing hyperglycemia. Glucocorticoid activity, of which cortisol accounts for 95 %, directly modulates lipid metabolism. Cortisol, which is secreted due to acute stress, has an effect on the degradation of lipolysis and promotes the utilization of carbohydrates, lipids and amino acids in mitochondria. However, chronic excessive cortisol levels inhibit PPARγ (Peroxisome Proliferator-Activated Receptor γ) of white adipose tissue to induce the accumulation of lipids [28].

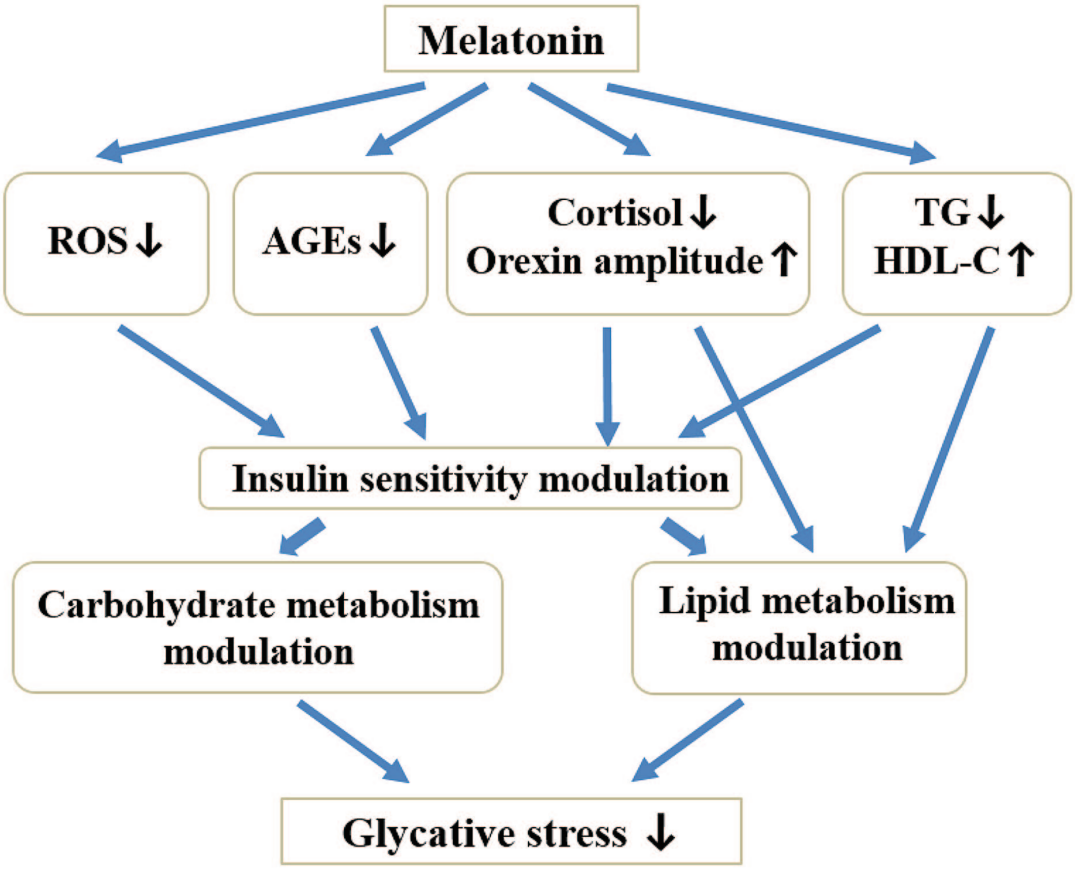


***Fig. 3.*** **Mechanism of melatonin actions on glycative stress.**
ROS, reactive oxygen species; AGEs, advanced glycation end products; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol.

Orexin, one type of cerebral hormone, effects the regulation of arousal. Orexin shows low levels during sleep at night and is secreted around daybreak as well as diurnal time (variation in orexin) [29-31]. Width of orexin oscillation decreases with aging. Orexin and blood glucose changes bidirectionally affect each other and it is essential to maintain proper variations of orexin for the control of blood glucose levels. Melatonin recovers the variations of orexin by reducing the accelerated secretion of orexin during night time.

Fourthly, melatonin has an effect to improve lipid metabolism. Animal model experiments have showed that melatonin administration to hyperlipidemic rats reduced levels of TG and LDL-C and also a healthy rat increased in HDL-C [32-34]. Part of these results involved the effects of insulin, as the administration of melatonin improved insulin resistance. Pinealectomized rats were lacking in the secretion of melatonin and showed the disorder of glycolipid metabolism [35], which revealed that melatonin played an influential role in maintaining the homeostasis for glycolipid metabolism.

As stated, there are four actuating paths for melatonin to reduce glycative stress, melatonin directly affects glycolipid metabolism in most cases, partly via insulin effects. Though the mechanism of effect on β cells of the pancreas is not simple, melatonin reduces fasting insulin in the condition of hyperinsulinemia such as borderline or early stages of type 2 diabetes [36]. In skeletal muscles, the effects of insulin are enhanced, and glucose uptake is activated [37, 38], which results in the decrease of HOMA-IR (homeostasis model assessment of insulin resistance). It is assumed that the insulin resistance is reduced. Furthermore, the secretion of insulin is decreased in the condition of intensive oxidative stress and glycative stress where the AGE formation increases and ER stress in pancreatic beta cells increases. In these conditions, the secretion of insulin from β cells is partly supported by melatonin, which has an anti-oxidative effect and an anti-glycative effect (to promote AGE degradation). The reduction of the melatonin secretion is a risk factor for the onset of type 2 diabetes [39]. In addition, melatonin involves the hypertrophy and activation of brown adipose tissue [40]. It is considered that melatonin is related to controlling not only glycolipids but whole energy metabolism.

### *Relation to circadian rhythm*

Circadian clocks have been widely observed in living organism and affect diverse life phenomenon including the response of the endocrine system under stressful stimuli, as previously reported [41]. Secretions of hormones such as crostini and orexin show the circadian rhythm according to the internal clock. Disorders of the circadian rhythm for biological processes would increasing the risk for the onset

of diseases such as psychiatric disorder, immunopathy or the life-style related diseases of obesity and type 2 diabetes [42].

Animal experiments indicate that food ingested late before bed time is not consumed as nutrition to synthesize muscle glycogen and resulted in the accumulation of fat [43]. Diurnal changes of muscle glycogen are minor in humans [44] and a mechanism between time of the ingestion and the fat accumulation has not been fully clarified. It was proven by Jurgen Aschoff in the 1960s that the circadian cycle had a period of approximately 25 hours. At present the circadian period is considered to be 24 hours and 10 minutes based on experiments where light environments are completely controlled. The deviation from a 24-hour cycle of the rotation period of the Earth is adjusted by resetting the circadian rhythm through entraining agents such as exposure to light and darkness, having meals, exercise, and social activities. Above all, the most important factor is entrainment of the natural light-dark cycle. The function of melatonin is to transmit information concerning the light-dark cycle to the tissues of the body. Ingestion of melatonin at bedtime would be very effective to synchronize the human circadian rhythm with the Earth rotation rhythm especially to persons at middle or advanced ages, who have a reduction in the variations of melatonin secretion.

### *Research limitations*

The number of participants in this research is small, and participants are young adults in their early twenties, who have little variation of melatonin in comparison to the peak-aged (between 12 and 14 years). Three cases in 12 had great AUC changes (over ± 50 %) in the same person's data and the examination method had some inevitable dispersions. However, it was interpreted that this study was able to indicate the importance of the role of melatonin, observing the inhibition of blood glucose elevation on the following morning due to the ingestion of melatonin the night prior to the test day even without a great number of cases.

## *Conclusion*

The crossover trial with 12 young, healthy adults was conducted to examine the influences of the ingestion of melatonin on the blood glucose level the following morning. It was suggested that the ingestion of melatonin the day prior to the test day improved the quality of sleep, and there was a possibility of the reduction of postprandial blood glucose levels due to the melatonin. We reported on the mechanism of the improvement of postprandial hyperglycemia, adding some literature review. It has been reported that melatonin has effects to eliminate ROS, to promote the degradation of AGEs, to regulate the secretions of glucocorticoid and orexin, to improve insulin resistance and to modulate glycolipid metabolism. This study was not inconsistent with the mechanism in previous studies.

## *Conflict of Interest Statement*

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

## *Acknowledgements*

This work was supported by JSPS KAKENHI Grant Number #26350917.

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