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Effect of D-β-hydroxybutyrate on sleep quality in healthy participants: a randomized, double-blind, placebo-controlled study

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Abstract

We investigated the effects of D-β-hydroxybutyric acid (D-BHB) on sleep quality in healthy Japanese adults. In this randomized, placebo-controlled, double-blind, parallel-group study, each group comprised 30 healthy Japanese adults. Participants received 1.5 g of D-BHB (low D-BHB group), 2.9 g of D-BHB (high D-BHB group), or a placebo beverage (placebo group) for 14 days. Before and after the intervention, the Oguri–Shirakawa–Azumi sleep inventory, middle-aged and aged version (OSA-MA), and sleep state test were conducted. After 14 days, compared to the placebo group, the OSA-MA scores for "Sleepiness on rising" and "Frequent dreaming" were significantly higher in both the low and high D-BHB groups. Additionally, the score for "Initiation and maintenance of sleep" was significantly higher in the low D-BHB group, and the score for "Refreshing on rising" was significantly higher in the high D-BHB group. We found that D-BHB can improve sleep quality in healthy Japanese adults.

Keywords: ketone bodies, D-β-hydroxybutyric acid, sleep quality, OSA-MA, randomized controlled trial

Graphical abstract

D-β-hydroxybutyric acid can improve sleep quality.

Sleep is a basic life process that greatly affects human health. A World Health Organization study found that one in every two individuals with insomnia develops a condition other than sleep disturbance within a year, necessitating medical attention (Ustün *et al.* 1995). Recently, numerous studies on sleep have revealed that a decline in sleep quality is closely related to the progression of lifestyle-related diseases, including diabetes (Hayashino *et al.* 2007; Cappuccio *et al.* 2010), hypertension (Liu *et al.* 2016), and depression (Yokoyama *et al.* 2010; Baglioni *et al.* 2011). Therefore, considering strategies to improve sleep quality is one of the most important issues in maintaining health and preventing a decline in quality of life.

Nutritional ketosis is induced by a ketogenic diet (KD), which comprises a high fat, low carbohydrate, and adequate protein intake. A KD causes a metabolic switch from glycolysis to ketosis through the production of ketone bodies, namely, D-β-hydroxybutyric acid (D-BHB), acetoacetate, and acetone from fat in the liver, where D-BHB accounts for more than 70% of the total ketones produced (Balasse and Féry 1989). Some clinical studies discussed the relationship between nutritional ketosis and sleep quality in some patients.. One study demonstrated that a KD for 3 months improved sleep quality in 70 patients with migraine, regardless of migraine improvements and anthropometric modifications (Merlino *et al.* 2023). Additionally, a nonrandomized controlled study involving 378 patients with type 2 diabetes and obesity showed that after 1 year, sleep quality improved, and the percentage of those identified as "poor sleepers" at baseline (68.3%) was reduced to 56.5% (Siegmann *et al.* 2019). However, the impact of nutritional ketosis, achieved through a 3-week isocaloric KD, on cognitive function was assessed in 11 healthy participants in a randomized, crossover, controlled study. These participants also followed a high-carbohydrate, low-fat isocaloric diet. No differences were observed in sleep quality, morning alertness, or mood between the dietary interventions (Iacovides *et al.* 2019). However, little is known regarding the detailed association between KD and sleep quality.

However, to keep producing ketones in the liver for the state of nutritional ketosis requires strict dietary restrictions. Thus, KD has a significant dietary bias compared with a normal diet, which might hinder an accurate evaluation of the relationship between ketone bodies and sleep. Instead of nutritional ketosis, exogenous ketone supplements, including 1,3-butanediol, medium-chain triglycerides, ketone salts, and ketone esters, are preferred for successfully inducing ketosis (Yurista *et al.* 2021). To the best

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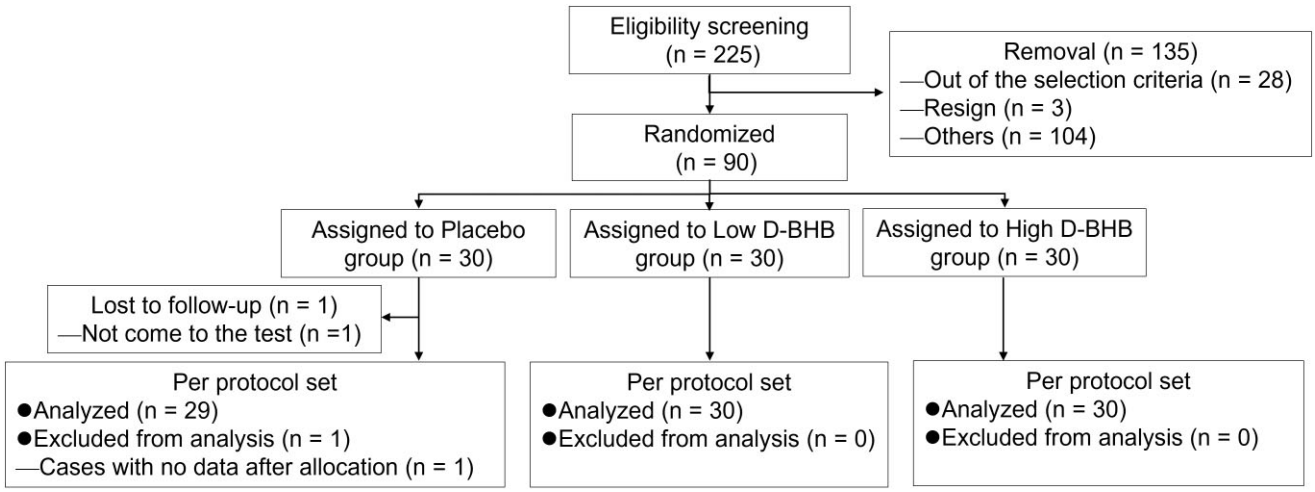

Figure 1. Flowchart of participant selection and randomization to groups. Abbreviation: D-BHB: D-β-hydroxybutyric acid.

of our knowledge, the association between exogenous D-BHB intake combined with a normal diet and sleep quality has not been investigatied.

We hypothesized that the daily intake of D-BHB could improve sleep quality. Therefore, in this study, we conducted a randomized, double-blind, placebo-controlled trial in healthy Japanese adults to determine the effect of D-BHB on sleep quality.

Materials and methods

Study design

This study employed a randomized, placebo-controlled, double-blind, parallel-group design and was conducted at the Maebashi North Hospital, Maebashi-shi, Gumma, Japan, between September 21 and November 25, 2023. The participants were randomly assigned to receive either D-BHB or a placebo for 14 days. The duration of this study was determined with reference to several studies regarding the relationship between ketone bodies and sleep (Iacovides *et al.* 2019; Siegmann *et al.* 2019; Merlino *et al.* 2023). The primary endpoint was sleep quality, which was assessed using the Oguri–Shirakawa–Azumi sleep inventory, middle-aged and aged version (OSA-MA), described later. The secondary endpoint was waking up and fatigue, which was assessed using a visual analog scale (VAS). We followed the Consolidated Standards of Reporting Trials reporting guidelines (Schulz *et al.* 2010).

Ethics statements

This study complied with the principles in the Declaration of Helsinki (2013) and the Ethical Guidelines for Medical Research Involving Human Subjects. The protocol was approved by the Ethical Committee of Kobuna Orthopedics Clinic (Maebashi-shi, Gumma, Japan) (approval number: MK-2309-03; approval date: September 21, 2023), and the study was registered with the University Hospital Medical Information Network Clinical Trials Registry (registration number: UMIN000053656). All participants provided written informed consent before study participation.

Participants

This study included healthy Japanese adults aged 20–49 years with temporary fatigue in daily life and a Pittsburgh Sleep Quality Index (Buysse *et al.* 1989) score ≥6. Pittsburgh Sleep Quality Index score ≥6 indicated poor sleep quality (Doi *et al.* 2000). The exclusion criteria comprised the following: the presence or a history of serious liver, kidney, gastrointestinal, heart, respiratory, endocrine, thyroid, adrenal gland, or other metabolic diseases; a self-reported high risk of idiopathic chronic fatigue or chronic fatigue syndrome; a suspected high risk of depression based on scores of the Center for Epidemiologic Studies Depression Scale or other questionnaires; a history of treatment for sleep disorders or a current medical history; a diagnosis of, or suspected, sleep apnea syndrome; use of medication or supplements (including functional food products) related to sleep and fatigue recovery; digestive disease or a history of digestive surgery; an allergy to the research food; pregnancy, lactation, or planned pregnancy; an infant <1 year of age in the household; sleeping with multiple individuals on one bed; living with someone requiring long-term care; excessive alcohol intake more than 20 g/day of pure alcohol equivalent or a habit of drinking more than 4 days/week; could not stop drinking from 2 days before each measurement; experience of drug dependence, alcohol dependence, or current illness; smoking >20 cigarettes/day or could not stop smoking from the time they woke up on the measurement day until the end of the measurement; shift workers, late-night workers, or workers with irregular working days and holidays; regular engagement in strenuous exercise or work; donation of blood or blood components >200 mL within 1 month prior to the consent date or 400 mL within 3 months prior to the consent date; planned participation in other clinical studies during the study period or participation in another clinical study within the last 1 month; and judged inappropriate for study participation by the principal investigator for other reasons. Of the 225 potential participants, 90 were included (Figure 1). These 90 participants were administered the OSA-MA at screening.

Randomization and blinding

After reaching the target sample size, the allocation manager assigned all participants using a stratified block randomization method, with sex, age, and the OSA-MA (sum of the 5 factors) as allocation factors at the time of screening. Participants were randomly assigned to the low D-BHB, high D-BHB, or placebo group using an allocation table. The allocation table was provided only to the person in charge of shipping the test foods to the participants according to the allocation table. Randomization and allocation data were concealed from the researchers, clinicians at the medical institutions, staff members of the study institution,

Table 1. Participant characteristics at baseline

Variable	Placebo group ($n = 30$)	Low D-BHB group ($n = 30$)	High D-BHB group ($n = 30$)	*P* value
n (men/women)	7/23	8/22	7/23	-
Age (years)	42.2 ± 4.3	43.1 ± 4.7	42.9 ± 5.1	.737
Body weight (kg)	55.5 ± 8.2	58.3 ± 7.4	57.1 ± 6.3	.361
Height (cm)	160.6 ± 8.1	162.5 ± 7.2	162.0 ± 7.7	.626
BMI (kg/m^2)	21.5 ± 2.4	22.0 ± 2.0	21.8 ± 1.4	.601

Data are presented as means ± standard deviations.
P value: ANOVA.
Abbreviations: BMI: body mass index; D-BHB: D-β-hydroxybutyric acid.

members of the ethics committee, clinical laboratories, and participants until the final analyses were completed. The allocation table was sealed and stored until it was opened by an independent controller.

Test beverages

The components of the low D-BHB, high D-BHB, and placebo beverages were as follows. D-BHB (OKETOA®) was provided by Osaka Gas Chemical (Osaka, Japan). The D-BHB content was based on previous studies (Katsuya *et al.* 2023). The low D-BHB beverage contained 1.5 g D-BHB, 0.22 g acidulant, 90 mg sweetener (sucralose, acesulfame potassium, and stevia), and 0.20 g flavorings per 100 mL. The high D-BHB beverage contained 2.9 g D-BHB, 0.40 g acidulant, 90 mg sweetener (sucralose, acesulfame potassium, and stevia), and 0.20 g flavorings per 100 mL. The placebo beverage contained 0.11 g acidulant (DL-sodium malate and DL-malic acid), 90 mg sweetener (sucralose, acesulfame potassium, and stevia), and 0.20 g flavorings per 100 mL. These beverages were produced by API Co., Ltd. (Gifu, Japan).

Participants evaluation

Procedure

The participants visited the clinic on 3 occasions as follows: at the start of the 5-day baseline assessment period, intervention date (0 day), and after 14 days. At each visit, the participants underwent clinical interviews, physical examinations (such as blood pressure, pulse rate, and body weight), and clinical examinations. Blood tests and urinalysis were conducted during the baseline assessment period.

During the treatment period, the participants drank the test beverage 1 h before bedtime. Participants were instructed not to change their daily habits, such as their sleep duration, binge drinking, dieting, smoking, and exercise routine. Participants were prohibited from consuming quasi-drugs, supplements, health foods, and medications that may affect their fatigue and sleep. Alcohol consumption was prohibited from 2 days prior to all examinations until the end of the test day. All consumption except for water was prohibited from a day prior to all examinations until the end of the test day. During the study period, excessive alcohol consumption was not permitted (maximum daily amount: 20 g of pure alcohol equivalent or less per day, up to 3 days per week).

Oguri–Shirakawa–Azumi sleep inventory, middle-aged and aged version

Participants sleep quality was assessed using the OSA-MA. This sleep questionnaire has been standardized to assess the sleep quality of middle-aged and elderly Japanese people (Yamamoto *et al.* 1999; Yokoi-Shimizu, Yanagimoto and Hayamizu 2022). The OSA-MA is a self-reported questionnaire and comprises 16 items measured according to a 4-point rating scale and consolidated into the following 5 factors: sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing on rising, and sleep duration. Participants completed the OSA-MA at home once daily, immediately after waking, for 3 consecutive days before the evaluation test. The standardized scores have an average of 50 points for all 5 factors in a population of 670 individuals aged 26–75 years (both male and female) (Yamamoto *et al.* 1999). Additionally, the polarity of the scores indicates that a better perception of sleep quality corresponds to higher scores.

The visual analog scale

The VAS was represented as a 100 mm-long straight line with the left end representing "the best feeling" and the right end representing "the worst feeling." Participants marked the scale according to the severity of items, and the position was measured as the distance (mm) from the left edge. The evaluated items were: "falling asleep upon waking," "mental fatigue upon waking," "physical fatigue upon waking," "fatigue relief upon waking," "quick thinking upon waking," "concentration upon waking," "perceived stress upon waking," "lightness of body upon waking," "sleep quality upon waking," and "fatigue." The difference in each score between day 0 and day 14 was compared between each intervention and the placebo group.

Safety evaluation

At baseline and during 14 days, blood samples were collected, and the following blood parameters were measured: white blood cell count, red blood cell count, hemoglobin level, hematocrit, platelet count, and total protein, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, plasma glucose, and glycated hemoglobin levels. Urine samples were obtained at baseline and during 14 days, and the protein, glucose, and occult blood levels were measured. All laboratory tests were conducted by the LSI Medience Corporation (Tokyo, Japan). The systolic and diastolic blood pressure, pulse rate, height, body weight, and body mass index (BMI) of the participants were measured at baseline, day 0, and day 14 (Yokoi-Shimizu, Yanagimoto and Hayamizu 2022).

Sample size

The sample size was calculated with reference to the Merlino study (Merlino *et al.* 2023), which evaluated the effect of a KD on sleep quality using the Pittsburgh Sleep Quality Index. We used $d = 1.1$ based on Cohen's study (Cohen 1992). Using $\alpha = 0.05$, $1 - \beta = 0.80$, and accounting for 10% dropout rate, we calculated the required sample size to be 90 individuals (30 per group).

Table 2. Standardized OSA-MA scores for the high D-BHB, low D-BHB, and placebo groups

Group		Sample size	Sleepiness on rising		Initiation and maintenance of sleep		Frequent dreaming		Refreshing on rising		Sleep length	
			Standardized score	*P* value	Standardized score	*P* value	Standardized score	*P* value	Standardized score	*P* value	Standardized score	*P* value
Baseline	Placebo	30	41.9 ± 6.8	.949	39.6 ± 8.5	.954	50.1 ± 9.7	.943	41.0 ± 6.1	.990	44.2 ± 7.2	.973
	Low D-BHB	30	42.3 ± 6.4		39.0 ± 11.3		50.5 ± 9.6		40.9 ± 6.8		44.6 ± 9.1	
	High D-BHB	30	42.4 ± 6.7		38.9 ± 9.6		49.6 ± 10.5		40.8 ± 5.7		42.7 ± 9.5	
0 day	Placebo	29	40.2 ± 5.0	*P* value*	40.7 ± 4.8	*P* value*	47.5 ± 8.0	*P* value*	42.7 ± 6.3	*P* value*	44.4 ± 6.4	*P* value*
	Low D-BHB	30	42.6 ± 6.2	.201	42.3 ± 8.3	.600	53.3 ± 7.3	.009	43.1 ± 4.9	.952	47.2 ± 6.7	.225
	High D-BHB	30	40.4 ± 6.1	.987	40.8 ± 8.1	.997	51.5 ± 7.3	.087	42.7 ± 5.9	1.000	42.2 ± 7.9	.387
14 days	Placebo	29	44.5 ± 5.5	*P* value*	45.0 ± 5.2	*P* value*	48.9 ± 8.2	*P* value*	47.1 ± 5.2	*P* value*	49.3 ± 6.2	*P* value*
	Low D-BHB	30	48.5 ± 6.0	.017	49.1 ± 7.4	.037	54.4 ± 5.5	.005	48.3 ± 5.0	.602	51.4 ± 8.4	.475
	High D-BHB	30	47.9 ± 5.8	.044	48.2 ± 6.8	.122	53.7 ± 6.4	.014	51.0 ± 5.3	.010	50.2 ± 7.7	.862

Data are presented as means ± standard deviations.
P value: ANOVA.
P value*: Dunnett's test (vs. placebo group).
Abbreviations: D-BHB: D-β-hydroxybutyric acid; OSA-MA: Oguri–Shirakawa–Azumi sleep inventory, middle-aged and aged version.

Table 3. Stratified analysis by layer value

Layer Value	Group	ΔSleepiness on rising			ΔInitiation and maintenance of sleep			ΔFrequent dreaming			ΔRefreshing on rising			ΔSleep length		
		Sample size	Score	*P* value	Sample size	Score	*P* value	Sample size	Score	*P* value	Sample size	Score	*P* value	Sample size	Score	*P* value
50	Placebo	27	4.1 ± 6.3	-	28	4.3 ± 7.4	-	14	5.1 ± 10.1	-	26	4.9 ± 8.8	-	21	7.2 ± 10.9	-
	Low D-BHB	28	7.5 ± 8.4	.009	23	8.4 ± 8.1	.003	7	8.0 ± 9.3	.409	28	5.6 ± 9.4	.839	20	6.8 ± 8.5	.951
	High D-BHB	29	7.0 ± 7.5	.027	26	7.9 ± 8.3	.008	12	4.9 ± 8.3	.996	26	8.3 ± 7.9	.031	25	8.2 ± 10.3	.807
44.8	Placebo	21	4.6 ± 6.7	-	23	4.4 ± 7.4	-	9	5.0 ± 9.5	-	16	7.8 ± 7.0	-	11	7.9 ± 11.0	-
	Low D-BHB	20	9.7 ± 7.7	< .001	18	9.1 ± 8.0	.002	4	7.6 ± 9.5	.654	19	7.7 ± 10.1	.992	11	6.2 ± 6.9	.654
	High D-BHB	24	7.7 ± 7.6	.032	23	8.7 ± 8.3	.003	4	6.0 ± 6.9	.938	21	9.3 ± 7.9	.546	16	10.5 ± 9.2	.363

Data are presented as means ± standard deviations.
P value: Dunnett's test (vs. placebo group).
Δ: The difference in standardized scores between day 0 and day 14.
Abbreviation: D-BHB: D-β-hydroxybutyric acid.

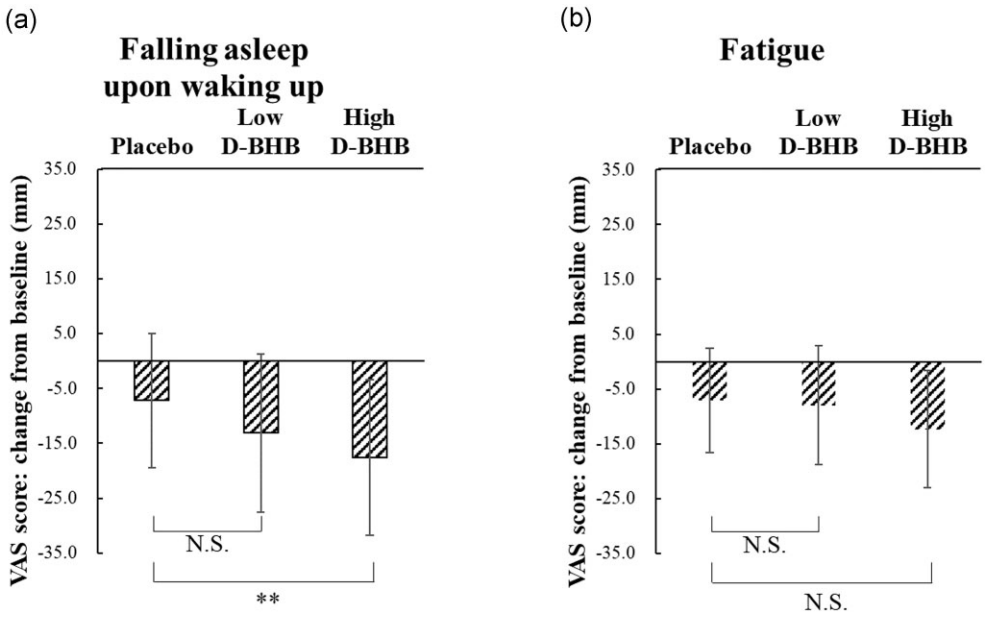

Figure 2. The VAS score for changes from day 0 regarding waking up and fatigue: (a) score of falling asleep upon waking, (b) score of fatigue. The changes in each score were compared between each intervention and the placebo group using Dunnett's test. $^{**}P < .01$, N.S. $P > .05$ (placebo; $n = 29$, low-BHB; $n = 30$, high-BHB; $n = 30$). Abbreviation: VAS: visual analog scale.

Statistical analysis

All outcome variables were assessed for normality of variance. While visual inspections of histograms and normality tests indicated that most variables exhibited normality, some degree of nonnormality was present. However, the extent was not deemed severe enough to require transformation, the use of nonparametric procedures, or descriptive statistics other than means and standard deviations. This decision was particularly justified by the sample size and the robustness of the chosen procedures to deviations from normality (Norman 2010). Data are presented as means and standard deviations and were compared between each intervention and placebo group using Dunnett's test. The participants' background characteristics were compared between the groups using analysis of variance or the Kruskal–Wallis test. All statistical tests conducted were two-sided, and significance was set at a P value $< .05$. IBM SPSS Statistics software version 28.0 or 29.0 (IBM Corp., Armonk, NY, USA) and SciPy 1.12.0 (Fundamental Algorithms for Scientific Computing in Python) were used for the analyses. Subgroups were created using standardized scores of 50.0 and 44.8 for each factor to ensure similar numbers in the bottom 50% and 30% of each factor, respectively. The difference in standardized scores between day 0 and day 14 was compared between each intervention and the placebo group using Dunnett's test.

Results

Participants

Of the 225 potential participants, 90 met the participation criteria and were randomly assigned to one of the three groups (Figure 1). Of these, one participant did not attend the last examination; hence, 89 completed the study. The participants' background information is presented in Table 1. Beverage consumption adherence rate was 100%.

Participant evaluation

The average of each standardized score is presented in Table 2. In both the low and high D-BHB groups, the postintervention scores of "Sleepiness on rising" and "Frequent dreaming" were significantly higher than those in the placebo group. The postintervention scores for "Initiation and maintenance of sleep" in the low D-BHB group was significantly higher than those in the placebo group. Additionally, the score for "Refreshing on rising" was significantly higher in the high D-BHB group (Table 2).

To examine the impact on individuals with more sleep disturbances, we further analyzed the group with a 0-day standardized score of ≤50. Degrees of change following the intervention in the individual items among the two groups were compared (Table 3). Each stratified difference in standardized scores between 0 day and 14 days of "Sleepiness on rising" and "Initiation and maintenance of sleep" in the low and high D-BHB groups was significantly higher than that in the placebo group. However, no significant difference in "Frequent dreaming" was found between each D-BHB group and the placebo group, contrary to overall analyses.

Each VAS score for changes from baseline regarding waking up and fatigue was compared among the 3 groups. The improvement in "falling asleep upon waking" in the high D-BHB group was significantly greater than that in the placebo group. However, the VAS scores for other aspects of waking up and fatigue were not significantly different among the groups (Figure 2 and Figure S1).

No adverse events were identified during the study period (Tables S1–S3). During the study period, significant variations were observed in systolic blood pressure (mmHg), body weight (kg), BMI (kg/m^2), total protein (g/dL), albumin (g/dL), γ-glutamyl transpeptidase (U/L), urea nitrogen (mg/dL), HDL-cholesterol (mg/dL), glucose (mg/dL), and HbA1c (NGSP). However, all changes and differences remained within the reference range, and the principal investigator determined that there were no safety concerns.

Discussion

In this study, 90 participants with temporary fatigue and poor sleep quality were randomly assigned to three groups as part of a randomized controlled trial. The results of the OSA-MA score showed that in both the low and high D-BHB groups, the postintervention scores for "Sleepiness on rising" and "Frequent dreaming" were significantly higher than those in the placebo group. The VAS score in the high D-BHB group also demonstrated a significantly larger improvement in "falling asleep upon waking" compared to the placebo group. Nevertheless, the VAS scores related to other factors of waking up and fatigue showed no significant differences between the groups.

Some studies have shown that KD improves sleep quality in humans (Siegmann *et al*. 2019; Merlino *et al*. 2023). The state of nutritional ketosis by KD requires strict dietary restrictions. The evaluation of sleep quality improvement by KD may have been incorrect due to significant dietary bias. Additionally, sleep quality has the following 4 attributes in general: sleep efficiency, sleep latency, sleep duration, and waking after sleep onset. Antecedents include physiological (eg age, circadian rhythm, BMI, non-rapid eye movement [REM], and REM), psychological (eg stress, anxiety, and depression), and environmental (eg room temperature and television/device use) factors, as well as family/social commitments (Nelson, Davis and Corbett 2022). Thus, participants in this study were instructed not to alter their lifestyle or diet during the intervention period to omit the impact of environmental factors and dietary bias on the results. Therefore, this study may suggest that D-BHB has a sleep-improving effect, as it involves less dietary bias than KD and does not involve changes to environmental factors. Some studies have shown that a state of nutritional ketosis improves sleep quality in certain patients, such as those with migraine and type 2 diabetes (Siegmann *et al*. 2019; Merlino *et al*. 2023). Meanwhile, the results of a study in healthy individuals demonstrated that KD for 3 weeks did not affect subjective sleep quality (Iacovides *et al*. 2019). Thus, nutritional ketosis may be more effective for those who are moving slightly away from good health. Hence, we further analyzed the group with a 0-day standardized score of ≤50. In the categories of "Sleepiness on rising" and "Initiation and maintenance of sleep," lower 0-day values correspond to a significantly larger difference in standardized scores between day 0 and day 14 compared to the placebo group. D-BHB may effectively enhance these aspects of sleep in individuals with poor sleep quality.

D-BHB may have multiple mechanisms to improve sleep quality. The clinical effects of KD on sleep patterns are being studied. The research revealed that the KD significantly enhanced REM sleep in 8 healthy men compared to a control diet (Phillips *et al*. 1975). In a similar study, 6 women who adhered to the KD for 1 week also exhibited a notable increase in REM sleep (Kwan, Thomas and Mir 1986). This suggests that D-BHB, resulting from nutritional ketosis induced by the KD, may play a role in increasing REM sleep. In general, an increase in REM sleep correlates with more frequent dreaming (Peever and Fuller 2016). The results of dreaming in this study may be related to REM sleep. Furthermore, some animal or cell studies have demonstrated that KD and ketone bodies have been known to elicit neuroinhibitory effects through adenosine A1 receptors (Masino *et al*. 2011), vesicular glutamate transporters (VGLUTs) (Juge *et al*. 2010), and adenosine triphosphate-sensitive potassium channels (Ma, Berg and Yellen 2007). In the case of VGLUTs, ketone bodies such as BHB and acetoacetate bind to VGLUTs and inhibit their activity, leading to neural inhibition by reducing glutamate release (Juge *et al*. 2010). Given that glutamate is a typical neurotransmitter in the arousal system, the suppression of glutamate release by ketone bodies is thought to contribute to sleepiness and enhanced sleep depth. The improvement in the VAS score for "falling asleep upon waking" observed in the high D-BHB group in this study may be attributed to the inhibition of glutamate release. On the other hand, there were factors for which no changes were observed in other VAS scores and OSA-MA. These may be improved by adjusting the timing of intake. In this study, it was decided to consume D-BHB 1 hour before bedtime since the peak concentration in the blood after D-BHB intake is reached within 1 hour; however, the optimal timing may vary (Cuenoud B *et al*. 2020).

Our findings suggest that D-BHB improves sleep quality, resulting in an increased standardized OSA-MA score. To the best of our knowledge, this is the first study to elucidate the effect of exogenous D-BHB administration on sleep quality in humans.

Limitation

The relevance of our findings is limited by the relatively small sample size and by the assessment of sleep quality based on a self-reported scale.

Conclusion

We found that D-BHB can improve sleep quality in healthy Japanese adults aged 20–49 years who experience temporary fatigue and poor sleep quality in their daily lives. This study may serve as a reference for future research on the efficacy of D-BHB in improving sleep quality.

Supplementary material

Supplementary material is available at *Bioscience, Biotechnology, and Biochemistry* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contribution

Conceptualization: J.T., S.K., J.K., and Y.K.; investigation: S.K.; writing—original draft: S.K.; formal analysis: Y.K.; writing—review & editing: J.K., Y.K., and J.T.; supervision: J.T.

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Disclosure statement

S.K., Y.K., Y.K., and J.K. are employees of Osaka Gas Co., Ltd. (Osaka, Japan). J.K. is an employee of Osaka Gas Chemicals Co., Ltd. (Osaka, Japan).

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