Evaluation of Orexin A and Orexin B Levels after Bariatric Surgery in Patients with Obesity

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Abstract

Aim: This study aimed to evaluate the changes in serum Orexin A and B levels following laparoscopic sleeve gastrectomy (LSG) in patients with obesity.

Methods: Preoperative, postoperative 3rd-, and 6th-month venous blood samples were collected from 30 obese patients diagnosed with obesity and undergoing LSG to measure Orexin A and B levels. The obtained values and body mass indexes (BMI) calculated at the same time intervals were compared.

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital (Approval Date: August 5, 2021; Approval No: 11/10) and was conducted in accordance with the Declaration of Helsinki.

Results: A significant reduction in BMI was observed at postoperative 3 and 6 months ($p < 0.001$). Orexin B levels significantly declined at 6 months compared to preoperative and 3-month values ($p = 0.002$), while changes in Orexin A were not statistically significant. No correlation was found between orexin levels and BMI.

Conclusions: Previous experimental studies have shown that orexin peptides are activated in the fasting state and play an active role in obesity by increasing food intake. In this study, we found that Orexin B levels were significantly reduced in patients who experienced weight loss. We believe that monitoring orexin levels can be beneficial in the treatment of obesity, and inhibiting its activity at the hypothalamic level can contribute to treatment by reducing food intake. Conducting new studies with a larger number of patients and longer follow-up periods will lead to radical and effective changes in the treatment of obesity.

Keywords: *Bariatric surgery, body mass index, laparoscopic sleeve gastrectomy, Orexin A, Orexin B*

1. Introduction

Obesity is a prevalent and significant health condition worldwide, with high comorbidity rates that pose challenges for the future of humanity. It is characterized by the excessive accumulation of fat in the body, resulting from an imbalance between energy intake and expenditure.[1] The body mass index (BMI), a measure commonly used by the World Health Organization, helps define and classify obesity. BMI is calculated by dividing body weight in kilograms by the square of height in meters (kg/m^2). Based on BMI values, the World Health Organization classifies individuals as underweight, normal weight, overweight, obese, morbidly obese, or super obese (Table 1).[2]

While obesity is a significant health issue on its own, it also contributes to the development of numerous comorbid diseases. Examples of these diseases include diabetes mellitus, hypertension, coronary artery disease, hypercholesterolemia, and degenerative joint disorders.[3]

Table 1

Definitions of underweight, normal weight, overweight, and obese based on body mass index values.

Weight Category	Body Mass Index (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese	>30
1st Degree	30–34.9
2nd Degree	35–39.9
3rd Degree (morbid)	>40

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Given its impact on public health and the economic burden it poses on countries, obesity has been extensively studied.[4] Among various medical treatments and interventions, bariatric surgery has proven to be the most effective and sustainable approach. Laparoscopic sleeve gastrectomy (LSG) is the most commonly performed surgical procedure, associated with fewer comorbidities compared to other methods.[5]

Orexin, a neuropeptide found both peripherally and in the hypothalamus, plays a crucial role in various vital functions such as weight regulation, sleep-wake cycles, and metabolic rate control.[6] The term "orexin" originates from the Greek word "orexis," meaning appetite. It acts through G protein receptors, with two forms known as orexin A and B. Additionally, there are prepro-orexin forms that activate orexin-1 (OXR1) and orexin-2 (OXR2) receptors.[7] Animal experiments have shown that orexins stimulate food consumption, and orexin mRNA levels are regulated in response to fasting, leading to increased food intake proportional to the rise in prepro-orexin mRNA levels during fasting.[8] Prepro-orexin mRNA synthesis occurs not only in the brain but also in organs such as the stomach, colon, kidney, pancreas, and adrenal gland.[9] While orexin A reduces the feeling of satiety, it also influences food intake.[10]

The objective of this study is to investigate the relationship between weight loss rate before and after bariatric surgery, changes in serum levels of orexin A and B proteins, the impact of gastric surgery on orexin hormone, and its correlation with early and late weight loss. In addition to surgical methods, orexins and their antagonists can be utilized in the monitoring and treatment of obesity, leading to the development of more effective treatment protocols in combating this public health issue.

2. Materials and Methods

Thirty patients diagnosed with morbid obesity who underwent laparoscopic sleeve gastrectomy at our hospital's General Surgery Clinic were included in this study. The study was approved by the Health Sciences University Antalya Training and Research Hospital Clinical Research Ethics Committee (protocol number 11/10, approval date: 05/08/2021), and was conducted in accordance with the principles of the Declaration of Helsinki. Preoperative, postoperative 3rd-, and 6th-month blood samples were collected from the patients for the analysis of serum orexin A and B levels. Additionally, the patients' body weight was measured to calculate their BMI, and all data were analyzed and compared. The correlation between weight loss and changes in orexin peptide levels was examined.

The study included a total of 30 patients, consisting of 5 males and 25 females, aged between 18 and 65 years. Laparoscopic sleeve gastrectomy was performed on all patients, who were followed up postoperatively. Patients who did not provide informed consent, those scheduled for revision or alternative bariatric surgical procedures, those who experienced surgical complications, those with a history of previous abdominal surgery, and those with malignancies were excluded from the study. In the preoperative evaluation, all patients underwent upper gastrointestinal endoscopy and abdominal ultrasonography. Consultations were also conducted with the psychiatry, endocrinology, and anesthesiology departments to identify any endocrinological diseases contributing to obesity or comorbid conditions that could hinder surgery.

Surgical Method

For patients deemed suitable for bariatric surgery, a subcutaneous administration of 40 mg enoxaparin was given 8 hours prior to the operation. Antiembolic stockings were applied on the day of surgery to prevent venous thromboembolism. After the patient was transferred to the operating table, an intravenous dose of 2 g cefazolin was administered for antibiotic prophylaxis, in accordance with the decision of the infectious diseases committee at our hospital. Once the patient was intubated, they were positioned in the Fowler position, lying supine with the legs apart, and the operating table was slightly tilted to the right.

During laparoscopic sleeve gastrectomy (LSG), four or five ports were used depending on the degree of obesity. Initially, a 10-mm trocar was inserted through the supraumbilical region after CO_2 insufflation, using either an open technique or a Veress needle, with intra-abdominal pressure maintained at up to 12 mmHg. Subsequently, one or two 5-mm trocars, one 12-mm trocar, and one 10-mm trocar were inserted under direct vision. Trocar placement sites included the subxiphoid region (left upper quadrant), lateral to the falciform ligament on the right side, and approximately 4–5 cm inferior to the left costal margin.

When retraction of the left hepatic lobe was required, a 5-mm trocar was placed in the subxiphoid region, and a Nathanson liver retractor was introduced through an additional 5-mm trocar. A 30° laparoscope was used through the supraumbilical port. Routine intra-abdominal exploration was performed. The gastroepiploic arcade was then divided using a vessel-sealing device (LigaSure™, USA), and the greater omentum was opened. Omental dissection was carried out close to the stomach up to the angle of His, with ligation of the short gastric vessels superiorly and dissection initiated 2–4 cm proximal to the pylorus inferiorly.

The stomach was elevated toward the anterior abdominal wall to allow visualization of the posterior aspect. Adhesions involving the greater omentum and the posterior surface of the stomach and fundus were carefully released, preserving the left gastric artery and its branches, splenic vessels, and the pancreas. Dissection was considered complete when the gastrohepatic ligament was divided and the left crus was fully visualized.

Subsequently, a 36-French bougie was advanced into the stomach by the anesthesiologist under the surgeon's guidance and passed beyond the pylorus. Correct alignment of the bougie along the lesser curvature was confirmed before initiating sleeve gastrectomy. Gastric transection was started 4 cm proximal to the pylorus using a 4.1-mm green cartridge surgical stapler (Echelon Flex™ Powered Plus 60-mm stapler with Echelon™ 60-mm reloads). The following two firings were performed using a 3.8-mm yellow cartridge, and the remaining gastric transection was completed with a 3.5-mm blue cartridge.

After specimen extraction through the 10-mm trocar, 50–100 mL of methylene blue dye was administered by the anesthesiologist, according to the surgeon's preference, to assess the staple line for leakage. The procedure was completed with placement of a Jackson–Pratt drain along the staple line.

Measurement of Biochemical

Blood samples were collected in the morning after a 12-hour fasting period. Samples were drawn into tubes containing a separator gel and centrifuged at 3000 rpm for 10 minutes to separate the serum. The serum samples were then stored at −80°C until biochemical analysis.

For the analysis of serum orexin A and B levels, 50 µL of standard solutions and serum samples, prepared at concentrations ranging from 2000 to 31.25 pg/mL, were added to the ELISA wells. Immediately thereafter, 50 µL of biotinylated detection antibody was added to each well, and the plate was incubated at 37°C for 45 minutes. During this incubation, orexin A in the standard and serum samples bound to the capture antibodies, forming a sandwich ELISA complex with the biotinylated detection antibody.

After incubation, the ELISA plate was washed three times with

wash buffer. Subsequently, 100 µL of peroxidase-conjugated avidin solution was added to each well and incubated at 37°C for 45 minutes, allowing binding to the biotinylated antibody complex. The plate was then washed five times with wash buffer, after which 100 µL of substrate reagent (TMB) was added and incubated at 37°C for 15 minutes. During this step, the enzyme–substrate reaction converted the colorless chromogen into a blue-colored product. Finally, 100 µL of stop solution was added to each well, resulting in a color change from blue to yellow. Optical absorbance was measured at 450 nm using an ELISA reader.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 23.0. The normality of data distribution was assessed using the Shapiro–Wilk test. For variables with a normal distribution, repeated-measures analysis of variance (ANOVA) was used to evaluate temporal changes, and multiple comparisons were performed using the Bonferroni correction. The Friedman test was applied to variables that did not follow a normal distribution, with post hoc comparisons conducted using the Dunn test.

The Pearson correlation coefficient was used to analyze relationships between variables with normal distributions at each time point, while Spearman's rho correlation coefficient was used for variables that did not meet normality assumptions. Results were expressed as mean ± standard deviation or median (minimum–maximum). The p value of <0.05 was considered statistically significant.

Table 2

Comparison of Orexin A , Orexin B, body weight and BMI values

	preoperative		3 months		6 months		Test ist.	p
	Mean ± SD	Median (min - max)	Mean ± SD	Median (min - max)	Mean ± SD	Median (min - max)		
Orexin A	34.61 ± 36.02	31.63 (3.7 – 210.21)	23.93 ± 10.48	25.85 (5.23 – 54.54)	31.39 ± 12.19	29.68 (7.96 – 65.15)	1.8	0.407*
Orexin B	36.73 ± 10.47	33.44 (28.38 – 74.25)b	32.01 ± 9.21	30.2 (17.87 – 68.93)b	29.4 ± 10.96	28.83 (13.91 – 59.92)a	12.067	0.002*
Weight	114 ± 15.58c	114 (80 - 143)	89.37 ± 13.07b	89.5 (70 - 115)	78.63 ± 12.51a	77 (60 - 103)	389.03 4	<0.001* *
BMI	43.14 ± 5.17c	42.44 (33.73 – 52.42)	33.91 ± 5.08b	33.29 (26.26 – 46.07)	29.84 ± 4.85a	29.9 (22.96 – 40.86)	508.54 5	<0.001* *

*Friedman Test; **Repeat Analysis of Variance; a-c: There is no difference between groups with the same letter

Table 3

Examining the comparison between Orexin A, Orexin B, weight and BMI values at each time

		orexin A		orexin B	
		r	p	r	p
Preoperative	weight	0.137	0.470*	0.015	0.939*
	BMI	0.178	0.348*	0.01	0.957*
3. Month	weight	-0.152	0.423**	-0.081	0.672*
	BMI	-0.108	0.571**	-0.049	0.797*
6. Month	weight	-0.015	0.938**	0.134	0.480*
	BMI	-0.079	0.679**	0.045	0.812*

*Spearman's rho Correlation Coefficient; **Pearson Correlation Coefficient

Table 4

Examining the relationship between Orexin A, Orexin B and Weight change values at each time.

		Orexin A		Orexin B	
		r	p	r	p
Preoperative -3rd month change	weight	-0.137	0.469*	0.185	0.329**
	BMI	-0.138	0.466*	0.181	0.338**
Preoperative –6th month change	weight	-0.2	0.289*	0.149	0.432*
	BMI	-0.197	0.296*	0.149	0.432**
3rd– 6th month change	weight	0.101	0.596*	-0.033	0.864*
	BMI	0.101	0.596*	-0.033	0.864*

*Spearman's rho Correlation Coefficient; **Pearson Correlation Coefficient

3. Results

The statistical data obtained before and after surgery were analyzed. Age, sex, height, and BMI values, as well as preoperative and postoperative (3rd and 6th month) serum orexin A and orexin B levels, were compared, and correlations were evaluated. The mean age of the 30 patients included in the study was 37.45 ± 21.10 years, and the mean height was 169.30 ± 8.13 cm. Of the patients, 83.33% were female and 16.66% were male. Comorbidities were present in 50% of the patients; hypertension accounted for 40% and diabetes mellitus for 60% of these comorbid conditions.

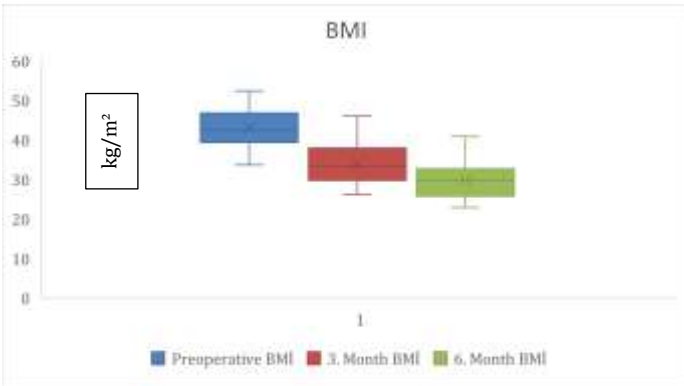

Figure 1. Preoperative, postoperative month 3, and postoperative month 6 BMI values.

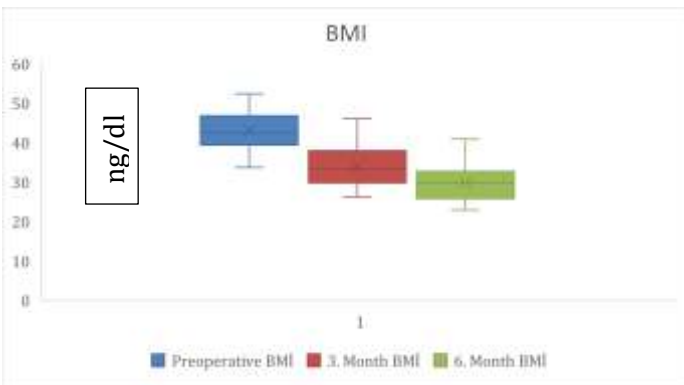

Figure 2. Preoperative, postoperative month 3, and postoperative month 6 orexin A values.

Figure 3. Preoperative, postoperative month 3, and postoperative month 6 orexin B values.

Preoperative and postoperative biochemical parameters of patients undergoing bariatric surgery are presented in Table 2.

Mean BMI values (kg/m^2) were 43.14 ± 5.17 preoperatively, 33.91 ± 5.08 at postoperative month 3, and 29.84 ± 4.85 at postoperative month 6 ($p < 0.001$). Comparison of preoperative and postoperative (3rd and 6th month) BMI measurements demonstrated a statistically significant decrease (Figure 1). Similarly, a significant reduction was observed in body weight when preoperative and postoperative values were compared ($p < 0.001$).

Mean orexin A levels (ng/mL) were 34.61 ± 36.02 preoperatively, 23.93 ± 10.48 at postoperative month 3, and 31.39 ± 12.19 at postoperative month 6, with no statistically significant difference between time points ($p = 0.407$) (Figure 2). Although a decrease in orexin A levels was observed after bariatric surgery, this change was not statistically significant.

Mean orexin B levels (ng/mL) were 36.73 ± 10.47 preoperatively, 32.01 ± 9.21 at postoperative month 3, and 29.40 ± 10.96 at postoperative month 6 ($p = 0.002$) (Figure 3). Orexin B levels showed a significant postoperative decrease, with values at the 6th month being significantly lower than both preoperative and 3rd month measurements.

No statistically significant correlation was found between preoperative orexin A levels and body weight or BMI ($p > 0.05$). Similarly, no significant correlation was observed between preoperative orexin B levels and body weight or BMI ($p > 0.05$). In addition, no statistically significant correlations were identified between body weight, BMI, and orexin A or B levels at postoperative months 3 and 6 ($p > 0.05$) (Table 3).

Analysis of changes in body weight, BMI, and orexin A and B levels between the preoperative period and postoperative month 3, between the preoperative period and postoperative month 6, and between postoperative months 3 and 6 revealed no statistically significant associations ($p > 0.05$) (Table 4).

4. Discussion

Obesity is a chronic disease in which endocrine, genetic, cultural, and environmental factors play a role in its etiology, and its mortality and morbidity are increasing worldwide[1]. Despite various surgical treatment methods and pharmacological treatments, obesity continues to be the health problem that researchers are most interested in. First of all, many obesity-related health problems such as DM, HT, and various cardiovascular diseases have made metabolic syndrome and obesity a mandatory diseases to be treated.

Hypocretin 1 and hypocretin 2 (Hcrt1 and Hcrt2), also known as orexin-A and orexin-B (OX-A and OX-B), are 33- and 28-amino acid neuropeptides, respectively. They show 46% similarity, and their expression by neurons in the dorsal/lateral and perifornical regions of the hypothalamus was demonstrated in 1998[11,12].

The widespread distribution and connections of the orexin system suggest that orexins are involved in many physiological functions such as appetite, sleep-wake cycle, arousal, stress, reward, and autonomic functions. In particular, the activation of orexins supports alertness, nutrition, and energy metabolism and stimulates sympathetic nerve activity, such as the sympathetic vasomotor system and blood pressure, which regulates neuroendocrine and autonomic functions[13,14]. Orexin neurons receive abundant input from the limbic system and have reciprocal connections with the hypothalamic nucleus that regulates feeding. It is also thought that orexin neurons have an important role as a link between energy metabolism and wakefulness states. Orexin

neurons also have a connection with the dopaminergic system in the ventral tegmental nucleus. These findings suggest that the orexin system interacts with systems that regulate emotion, reward, and energy metabolism to maintain sleep-wake states. Therefore, this system is a candidate to be a potentially important therapeutic target for the treatment of sleep disorders, obesity, emotional stress, and addiction[15].

Over the past ten years, it has been revealed that the hypothalamus is central to many signaling and molecular pathways involved in the control of appetite and food intake. Neuronal hypothalamic circuits work to integrate orexigenic and anorexigenic neuropeptides with peripheral neuroendocrine signals to regulate food intake and energy homeostasis. The hyperphagic effects of Orexin-A have been found in many species. Central administration of Orexin-A stimulates food intake, production, and release of Orexin-A and B in mice. Orexin-1 receptor antagonist, SB334867, reduces feeding while upregulated by 48 h fasting[16],[17].

An inverse relationship was found between circulating leptin and orexin. Orexin-related circuits that regulate energy homeostasis are regulated by hormones such as leptin, ghrelin, and glucocorticoids[17],[18].

Human adipose tissue contains both orexin1 and orexin2 receptors. Orexins increase the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) and enhance the browning of adipose tissue. It also shows that orexin treatment increases lipolysis and may be a potential treatment for metabolic dysfunctions such as obesity and hyperglycemia[19].

Orexin has been observed to increase not only food intake but also energy expenditure and reduce thermogenesis and body weight[20].

In an animal study, it was reported that spontaneous physical activity and non-exercise thermogenesis is protective against obesity and the orexin system plays a role in the focal point of this physiological interaction[21].

Orexin neurons influence homeostatic and physiological behaviors such as food intake, attention, sleep/wake cycle, locomotion, addiction, and learning. Over-expression of orexin results in obesity resistance in mice[22]. It has been reported that drugs used in obesity treatment can be effective by targeting orexin receptors, interacting with them, and increasing energy expenditure while at the same time reducing the value of foods with high energy value and preventing their intake[23].

Bariatric surgery can not only reduce the stomach anatomically but also indirectly affect the hypothalamic peptides and adipocytokines, thus contributing to the treatment of obesity. Gupta et al. showed that orexin levels increased in the early period after bariatric surgery. Studies are reporting the opposite[24],[25]. In our study, we found that orexin-A and Orexin B were low in the postoperative 3rd and 6th months after laparoscopic sleeve gastrectomy. However, this decrease was statistically significant only at the 6th-month orexin B level.

In various studies, it has been reported that neurological diseases such as Parkinson's and generalized tonic-clonic seizures, especially depression, are observed in orexin deficiency[26]. Orexin receptor antagonism is considered a very promising therapeutic avenue for the treatment of many psychiatric disorders, especially insomnia[27]. Preclinical studies show that orexin antagonists can play an important role in the treatment of cocaine, opioid, alcohol, and other addictions[28].

Orexin is known to regulate the reproductive system and the release of some hormones such as insulin, leptin, and catecholamines[29]. As a neuroendocrine, ACTH and corticosteroids increase, while prolactin, growth hormone, and TSH decrease effects. They decrease REM sleep and increase locomotor activity[30].

It was determined that feeding was stimulated after orexin infusion in different parts of the brains of rats, especially after the infusion of orexin A in the perifornical hypothalamus and ventral tegmental area. In studies, it has been evaluated that there is a correlation between the amount of mRNA measured in experimental animals that have been stimulated by orexin mRNA due to starvation or long-term fasting and the amount of food taken[31]. It has been observed that the brains of mice with orexin infusion into the lateral hypothalamus were stimulated to activate neurons that control eating and subsequently increase food intake[32].

In many studies, it has been discovered that the orexin molecule given to experimental animals stimulates food intake while it has a stimulating effect on the energy metabolism and movement status of experimental animals[33]. While the effect of orexin on energy metabolism suppresses an-orexinergic arcuate neurons, it also activates orexinergic arcuate neurons, revealing its mechanism of action and suppressing the feeling of satiety[34]. Whether orexins exert their effects on appetite directly or through different neuropeptides to cause hyperphagia is not fully known. Some researchers think that orexins increase food intake by increasing appetite, but they do not cause obesity because they increase the amount of energy used with their effects on metabolism. When orexin B and orexin A were compared in terms of food intake, experiments showed that orexin A showed more effective results in food intake[35]. One study revealed that orexin A given to rats caused an increase in food intake within 2 hours and that orexin-A had a more predominant inducer effect than B on food intake and energy metabolism[34].

In our study, orexin A and B levels decreased in our patients after bariatric surgery, and the patients lost a significant amount of weight. Anatomically, the shrinkage of the stomach made us think that the decrease in orexins indirectly caused weight loss by suppressing appetite and food intake.

5. Conclusion

In this study, we evaluated the longitudinal changes in Orexin A and B levels following laparoscopic sleeve gastrectomy and their relationship with weight loss. Our findings suggest that while Orexin A remained relatively unchanged, a significant reduction in Orexin B occurred at six months postoperatively, which may contribute to appetite suppression and weight regulation. These results highlight the potential therapeutic value of targeting orexin pathways in obesity treatment. Future large-scale studies with extended follow-up are needed to validate these findings and explore clinical applications of orexin antagonists as adjuncts to bariatric surgery.

In our study, we think that the decrease in orexin levels after bariatric surgery contributes to the treatment of obesity by helping the weight loss provided by surgery, reducing appetite, and providing a feeling of satiety. The binding of orexin antagonists to orexin receptors and the resulting reduction of the orexin effect may help to provide effective weight loss. The use of orexin antagonists in patients as medical treatment can provide an effective obesity treatment together with bariatric surgery. Comprehensive new studies with longer duration and more patients may help us to understand more clearly the relationship between orexin, obesity, and bariatric surgery. We think that orexins may be an important prognostic factor in the long-term follow-up of obesity, and in the future, orexin antagonists may be used as an adjunct medical treatment to bariatric surgery in the treatment of obesity.

Statement of ethics
Approved by the Clinical Research Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital (Approval No: 11/10, Date: 05.08.2021).

genAI
No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of interest statement
The authors declare that they have no conflict of interest.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions
BYD and UD conceived and designed the project. HYE and MNK performed the literature collection. UD performed the meta-analysis. BYD wrote the manuscript and GYD revised the manuscript. All authors read and approved the final manuscript.

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