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Research Article

The Effect of Melatonin on Body Weight and the Potential use of Melatonin as an Anti-Obesity Agent

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ABSTRACT

Background: obesity is a major global health problem with more than 200 million obese men and almost 300 million obese women. Melatonin is a well-known molecule for its involvement in circadian rhythm regulation and has multiple pathological actions including control of appetite, sleep wake cycle and metabolic syndrome.
Aim: to estimate the effect of melatonin supplements on obese patients on a calorie restricted diet in comparison to patients on lifestyle measures only in the form of weight loss, waist circumference and sleep quality.
Subjects and Method: one hundred patients with body mass index > 24 were collected, fifty patients were started on melatonin 5 mg with calorie restricted diet and they were compared to fifty patients who were kept on lifestyle measures. After twelve weeks, patients were re-assessed for weight, waist circumference and sleep duration and quality and the development of any side effects. Data analyzed using paired t test.
Results: patients' group who were treated with melatonin has shown significant reduction in body weight (91.58. Vs 92.88, p value <0.0004) and waist circumference (99.36 +- 10.73 vs 101 +-10.51, p value< 0.0064). Patients treated with melatonin show improved insomnia severity index (5.47+-0.8 vs 9.08 +-3.58, p value <0.0001). 60% of patients noticed decreased appetite,35% reported daytime sleepiness and fatigue, 25% had dizziness and 20% had mild nausea.
Conclusion: Melatonin significantly reduces the body weight, waist circumference and appetite more than placebo, it has been shown to be safe supplement and helpful in patients with sleep disturbance and obesity.

Introduction

Obesity is a condition of increased mass of adipose tissue. Although often inaccurately viewed as increased body weight because lean but very muscular individuals may be overweight by numerical standards without having increased adiposity. Because the choice of a medically meaningful distinction between lean and obese is somewhat capricious, obesity is therefore defined by assessing its association with morbidity or mortality. the most widely used

method to assess obesity is the body mass index (BMI), which is equal to weight/height2 (in kg/m2) (1).

Obesity is a cofactor in association between sleep abnormalities and metabolic syndrome and diabetes. it has been also shown that obesity plays a role in association between sleep disturbances and depression (2).

Sleep has been shown as a potential mechanism of regulating energy intake and expenditure. decreased sleep duration increases an individual's chances of having obesity and increases appetite, while simultaneously decreasing thermoregulation and physical activity.an inverse relationship between sleep duration and BMI was found and individuals who slept less than seven hours a night had a mean BMI that was 1.4 units higher than individuals who slept seven to nine hours (3).

Melatonin is produced primarily by the pineal gland in a circadian rhythm and is regulated by the environmental light/dark cycle via the suprachiasmatic nucleus. Pineal gland cells function as 'neuroendocrine transducers' to secrete melatonin during the night so melatonin is often called the 'hormone of darkness'. Melatonin is involved in sleep regulation, as well as in a number of other cyclical bodily activities (4).

The alimentary tract of vertebrates is another source of melatonin production especially during the daytime and melatonin may act as an endocrine, paracrine, or autocrine hormone influencing the regeneration and function of epithelium. Unlike the photo periodically regulated production of melatonin in the pineal gland, the release of gastrointestinal melatonin seems to be related to food intake (5).

According to a recent systematic review and meta-analysis that included 23 studies, 11 showed beneficial results from melatonin supplementation on weight loss, BMI, or waist circumference, compared with placebo. It was reported that once the standard treatment induces weight gain, melatonin can slightly reduce this effect, and vice versa and melatonin is more effective for children and adolescents (6).

Melatonin has been shown to have significant effect on white adipose tissue and brown adipose tissue. white adipose tissue act as energy storage and brown adipose tissue act as energy consumer. Melatonin stimulates white adipose tissue browning and beige adipocyte formation, improving mitochondrial function, and relieving oxidative stress. It was reported that long- term melatonin treatment turned White adipose tissue into a brown-fat-like function which contributed to thermogenesis and weight control (7).

Melatonin was considered as a novel agent for prevention of obesity and fat accumulation in peripheral organs . The organs of special interest include liver, pancreas, skeletal muscle, adipose tissue and the gut microbiota (8).

The safety of melatonin in humans has been widely studies. In adults, short-term use of melatonin is safe for adults, except for pregnant and breastfeeding women who lack clinical data. There are no studies showing that supplemental melatonin can cause serious side effects, and it has only mild side effects such as dizziness, headache, nausea, morning drowsiness (9).

In studies conducted among pediatric age group, taking melatonin in the short and medium-term produced only mild side effects. During the treatment period (104 weeks), doses of extended-release melatonin (2, 5, or 10 mg per night) were safe and effective. The most common treatment-related adverse events were fatigue (6.3%), lethargy (6.3%), and mood swings (4.2%). No harmful effects on child growth and puberty were observed (10).

The aim of this study was to evaluate the effect of daily melatonin supplementation over the period of twelve weeks on obese patients on calorie restricted diet in terms of sleep quality, appetite control, physical activity alteration, weight reduction and side effects in comparison to obese patients on lifestyle modification only.

Subjects and Methods

This study is a case control prospective study .Fifty patients with body mass index over 24 and age group ranging between 15-55 years were collected, history was taken for appetite and nutrients quality and assessment for comorbidities, physical activity and quality of sleep, with physical examination for height, weight, waist circumference, blood pressure, leg enema and organomegaly. Laboratory investigations to assess thyroid function, hepatic and renal functions were requested. Those patients were started on melatonin tablets 5 mg daily at night with 1500 kcal diet and were compared to obese patients with similar age group, risk factors who were kept on dietary restriction only.

Patients with hypertension, diabetes, ischemic heart disease, chronic renal disease or liver disease and alcoholic patients were excluded. Patients with obstructive sleep apnea and heart failure were excluded as well.

Anthropometric measures (weight and waist circumference) were performed twice; at baseline and after twelve weeks. Assessment for appetite control, quality of sleep and side effects of drug were also implemented.

All results were expressed as the means ± standard of error S.E.M. statistical analysis included student's T-test for the comparison of melatonin group and the control group and a paired T-test for the comparison of the same group before and after supplementation. The hypothesis of normal distribution was assessed by Shapiro-wilk test. Pearson's correlation coefficient was used to quantify the relationship between the parameters measured. The level of significance was set at P value < 0.05.An informed consent was obtained from all patients.

Results

Age group

The age group of the patients involved in the study ranged from 15-55. 15 patients were between 15-24 years, 7 patients were between 25-34 years, 25 patients were between 35-44 years and 3 patients were between 45-55 years while the control group patients' age group distribution was: 15 patients between 15-24, 10 patients between 25-34, 15 patients between 35-44 and 10 patients between 45-55 years as illustrated in Figure 3.

BMI

Body mass index of the study group ranged from 24-40 at the beginning of the study .8 patients were in the range of 25-29, 20

patients were in the range of 30-34 while 22 patients were in the range of 35-40. The BMI of the control group on the other side distributed as follow: 15 in the range of 25-29, 15 in the range of 30-34 and 20 in the range of 35-40.

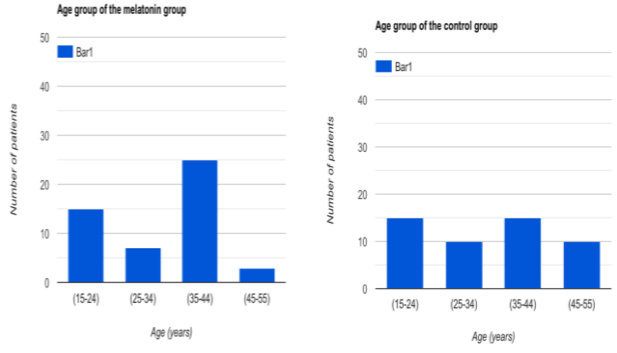

Figure 1: Age distribution of the melatonin group and the control group

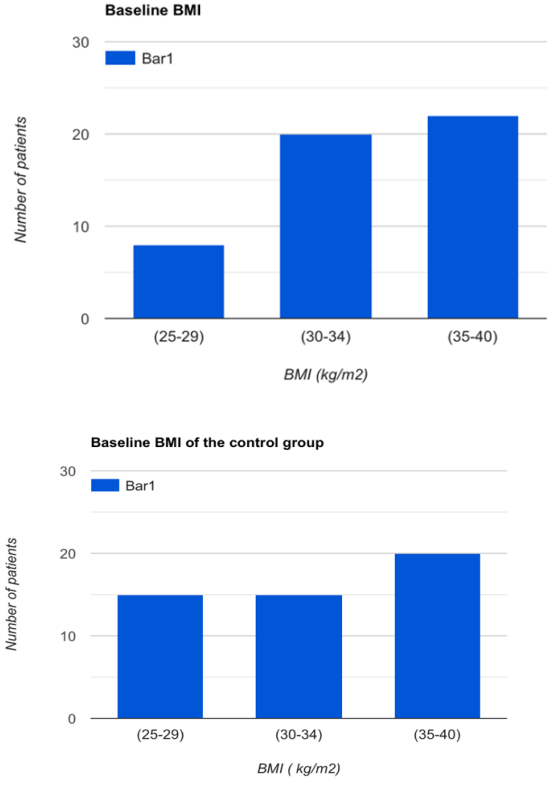

Figure 2: BMI of the study group and the control group

Waist circumference

Waist measurements of the patients at the start of the study ranged from 80-120 cm. 5 patients were in the range of 80-89 cm, 9 patients were in the range of 90-99 cm, 24 patients were in the range of 100- 109 cm while 12 patients were in the range of 109-120 cm while the waist circumference of the control group range was: 5 in the range of 80-89 cm, 20 in the range of 90-99 cm, 15 in the range of 100-109 cm, 10 in the range of 110-120 cm.

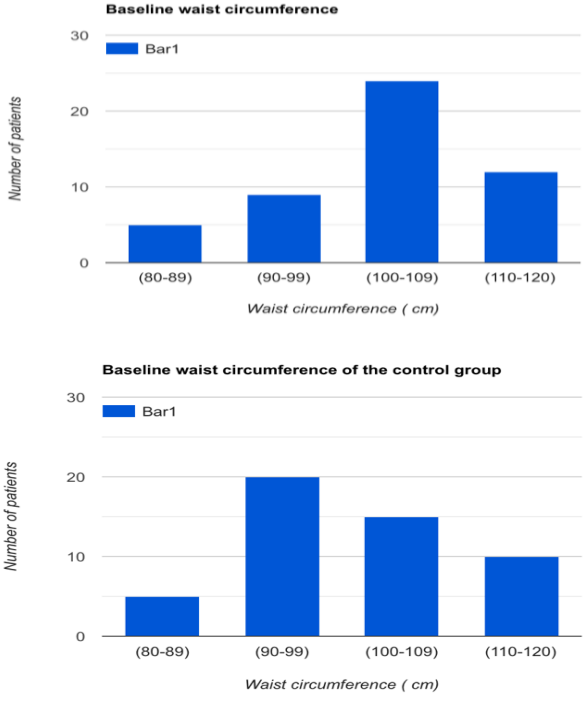

Figure 3: Waist circumference of the melatonin group and the control group

Table 1: General characteristics of the melatonin group and the control group

Characteristics of the study population

Characteristic	Melatonin group	Control group
Mean age (years)	33.64+-9.86 (Confidence interval1.395)	33.693+-10.56 (C.I 1.5)
Mean BMI (kg/m2)	33.4+-3.6 (Confidence interval 0.5)	33.32+- 3.941 (C.I 0.557)
Mean waist circumference (cm)	104.32+-8.846 (Confidence interval 1.251)	105.8+-9.568 (C.I 1.353)
Insomnia severity index score	14+-4.857 (Confidence interval 0.687)	9.8+-3.544 (C.I 0.5)

Correlation between sleep quality and weight

Our study shows significant correlation between insomnia and obesity. patients with higher insomnia severity index (ISI) had higher BMI at the beginning of the study. Using students T-test, t value was 10.40831 and p value was <0.00001. the result is significant at p <0.05.

Study outcomes after 12 weeks

Arthrometric data was re-evaluated and recorded 12 weeks follow up period, T test was used to compare significance of results of patients taking melatonin compared to patients who were kept on dietary measure's alone and also to compare results of patients

taking melatonin before and after intervention. Side effects were also recorded. Patients taking melatonin show significant weight loss, decrease in waist circumference and significant improvement in sleep quality (p value <0.001) as compared to control group as illustrated in table 2 and 3.

Table 2: Comparison of weight, waist circumference and sleep quality between melatonin and control groups

Outcome	group	Mean	p value	T value	confidence interval
Weight (kg)	Melatonin Control	91.58+-10.73 92.88+-10.51	0.0004	3.8284	-1.98 to -0.62
Waist circumference (cm)	Melatonin Control	99.36+-8.01 101+-8.54	0.0064	2.8503	-3.27 to -0.57
Insomnia severity Index	Melatonin Control	5.47+-0.8 9.80+-3.58	0.0001	7.8652	-5.10 to -3.02

Table 3: comparison of weight, waist circumference and sleep quality among melatonin group before and after taking melatonin.*

Outcome	group	Mean	p value	T value	confidence interval
Weight (kg)	Before melatonin	97.44+-11.05	0.0001	13.2241	4.46 to 6.06
	After melatonin	92.18+-11.33			
Waist circumference (cm)	Before Melatonin	103+-44	0.0001	7.2905	3.03 to 5.33
	After melatonin	99.26+-7.84			
Insomnia severity Index	Before melatonin	5.76+-0.77	0.0001	11.2553	-9.71 to -6.77
	After melatonin	14+-4.91			

Side effects

Side effects of melatonin were also reported. 60% of patients noticed decrease in appetite and food seeking behavior and food intake .35% reported daytime sleepiness, 25% reported dizziness and 20% had nausea. These side effects were noticed to be dose related and they subsided when the dose was reduced.

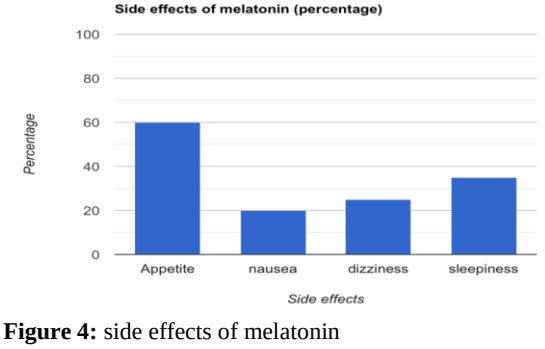

Figure 4: side effects of melatonin

Discussion

The main finding of our study is significant reduction in body weight and BMI in both melatonin and control group; however, more reduction was observed in melatonin group. this was consistent with a study conducted in Iran by Salman Mohamammadi (11). The association between melatonin and obesity has been widely studied in animal models (12,13) but few human studies have been conducted in this topic. In a study done by Kozirog et al., using melatonin (5 mg daily) for one month reduced body weight and BMI in patients with metabolic syndrome (14). The study included 33 healthy volunteers (who were not treated with melatonin) and 30 patients with metabolic syndrome, who did not respond to 3-month lifestyle modifications. Patients with metabolic syndrome were treated with melatonin (5 mg/day, 2 hr before bedtime) for 2 months. Melatonin administered for 2 months significantly improved lipid profile (decrease in LDL-C), and lowered blood pressure beside weight loss benefits (14).

Data are from the VITamins And Lifestyle (VITAL) cohort study of western Washington, multiple supplements marketed for weight control or loss were examined and melatonin was significantly associated with lower levels of weight gain (15). Rastmanesh et al proposed that melatonin may have the potential to prevent and even treat obesity and melatonin effects on eating behavior and body weight were promising (16).

Brown adipose tissue, an organ exclusively found in mammals, acts to keep the balance between energy intake and energy expenditure by means of disposing the extra energy as heat. Interestingly, it has been recently demonstrated that, as opposed to what was presumed before, substantial amounts of metabolically active brown adipose tissue are present in human adults (17,18). Based on this finding, it has been hypothesized that melatonin-induced hypertrophy and functional activation of brown adipose tissue may also apply to humans, thus providing a potential target for the treatment of obesity (19).

In a study conducted by Ferrari e, the circadian rhythm of plasma melatonin reached statistical significance in anorectic patients but not in obese patients. The mean 24 hours melatonin level was significantly higher in anorectic than in obese patients and in control patients. However, both groups of patients shared some abnormalities of melatonin circadian pattern, such as increased ratio between day and night melatonin levels, abnormal secretory peaks during the light hours and great interindividual variability for timing, amplitude, and duration of melatonin nocturnal peak (20).

Leptin is a primary satiety hormone that binds to its receptors in the hypothalamus and regulates appetite-regulating neurons pro-opiomelanocortin (POMC) in the hypothalamus. Based on the fat content of the adipose tissue, leptin is secreted, and excess accumulation of fat in adipose tissue stimulates the abnormal secretion of leptin. The secreted leptin circulating in the bloodstream crosses the blood-brain barrier (BBB) and reach the CSF. Leptin resistance is due to excess leptin, a saturation of its transporters, and deficiency in either the receptor level or signaling in the hypothalamus. Leptin resistance leads to obesity due to excess food intake and less energy expenditure. The sleep disturbance causes obesity with increased lipid accumulation in adipose tissue. Melatonin is the regulator of the sleep-wake cycle secreted by the pineal gland during the night. Research indicates that melatonin plays a vital role in hormonal regulation and energy metabolism, including leptin signaling and secretion. Studying the role of

melatonin in leptin regulation will help us combat the pathologies of obesity caused by leptin resistance (21).

Insomnia severity index was higher among patients with higher BMI and there was significant reduction in BMI and Insomnia severity index after melatonin supplementation as compared to control group. Previous studies have indicated that persons with obesity are significantly more likely to report insomnia or difficulty with sleep (22). Persons with obesity were significantly more likely to develop chronic insomnia. Complaints of chronic emotional stress or sleep disturbance have been reported to be predictors for short sleep duration, rather than voluntary sleep curtailment as previously thought (23). Vgontzas et al further showed that in persons with obesity and without sleep disturbances or emotional stress, sleep duration was similar to non-obese control subjects. This may indicate the importance of detection and treatment of sleep disturbances as a potential therapeutic intervention for obesity (24).

A study by mantel s revealed that disturbed leptin production is associated with eating disorders, leading to alteration in food intake and energy expenditure. Proper regulation of protein homeostasis is critical for metabolic diseases such as obesity. Thus, the purpose of the present work was to study the unfolded protein response, which is implicated in the alleviation of endoplasmic reticulum stress-dependent dysregulation of nutritional status. The effect of leptin deficiency on liver, brain and skeletal muscle tissues in obese mice was studied and the actions of a daily melatonin administration, as a possible treatment and findings showed that the leptin-deficient mice presented tissue-specific alterations of the three adaptive unfolded protein responses. ATF6α arm is strongly activated in all of them, indicating a deregulated lipid metabolism by the lack of leptin. Likewise, melatonin also alleviates unfolded protein response in a tissue-specific manner, acting mainly in the restoration of this disturbed ATF6α pathway. These findings support the use of melatonin as a potential therapeutic treatment against leptin-associated disorders (25).

Our study revealed significant reduction in waist circumference among melatonin-treated patients. This result was consistent with a study conducted by Hadi Bazyar which stated that melatonin consumption for eight weeks significantly reduced waist circumference Which is considered as a useful indicator to predict the risk of coronary vascular disease (CVD) compared with the other anthropometric indices (26).

A study done by Grethe Støa Birketvedt ,patients with insomnia and short sleep , compared with control subjects, had more eating episodes in the 24 hours (mean [SD], 9.3 [0.6] vs 4.2 [0.2]; P<.001) and consumed significantly more of their daily food intake at night than did control group (56% vs 15%; P<.001) and they had attenuation of the nocturnal rise in plasma melatonin and leptin levels (P<.001 for both) and higher circadian levels of plasma cortisol (P = .001),therefore; obese patients who are night eaters are likely to have high cortisol levels and low melatonin levels(27).

Melatonin supplement are likely to be safe, only with mild adverse effects, such as dizziness, headache, nausea, and sleepiness and these side effects were related to the dose and time of administration. It is widely used as a remedy for sleep disorders and is the fourth most popular natural supplement taken by adults, and the second by children in the United States. Indeed, a significant rise in its use from 0.1% in 2007 to 0.7% in 2012 was reported (28).

In this study, 60% of patients noticed decrease in appetite and food seeking behavior and food intake .35% reported daytime sleepiness, 25% reported dizziness and 20% had nausea. A study by Kapica E found that melatonin was well tolerated, only 4 women out of 56 (7.1%) reported general fatigue in the morning in the first two weeks of the starting the drug but without the need of discontinuation of the therapy or dose reduction (29).

A report of 387 people included in 7 trials revealed that only two patients had serious adverse events in children and adolescents, such as migraine and mild generalized epilepsy and confirmed that melatonin is an effective and safe drug for short-term treatment of sleep problems in children and adolescent age groups (30)During the 104 week treatment period, the optimal dose of extended release melatonin (2, 5, or 10 mg per night) was safe and effective for the long-term treatment of children (31).

Limitations of this study were small sample size, short duration of the study and limited facilities regarding sophisticated laboratory investigations.

Conclusion

Melatonin has weight loss benefits and beneficial effects on reducing waist circumference, improving quality and duration of sleep and controlling appetite and excessive food intake with minimal adverse effects and good safety profile.

Recommendations

Future studies are recommended to investigate the potential role of melatonin as anti-obesity especially in adolescent age group and in patients who take drugs that are known to cause weight gain where the safety of other drugs is considered an obstacle.

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Conflict of Interest

Authors declare no conflict of interest

Data availability

Data are available upon reasonable request

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