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ORIGINAL STUDY

Evaluation of Serum Melatonin Levels in Type 2 Diabetic Patients in Relation to Sleep Quality

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Abstract

Overview: The negative impact of diabetes mellitus on the quality of life is not limited to the clinical aspects, it also extends to the psychological and economic sides of their lives. Deteriorated sleep quality is one of the major factors that affect diabetics' health-related quality of life. This research is an attempt to track the pathophysiology of sleep disturbance in type 2 diabetic patients by evaluating serum melatonin levels as a key hormone that induces sleep.

Methods: Eighty-eight relatively glycemic-controlled type 2 diabetic patients were recruited in a cross-sectional study to evaluate their quality of sleep. The study then tends to examine the nighttime serum melatonin levels in both good and poor sleepers groups.

Results: Poor sleepers were dominant, with 47 patients out of 88. A significant difference was recorded in serum melatonin levels between good and poor sleep quality. Melatonin concentrations were 17.32 ± 2.26 pg/mL in good sleepers; on the other hand, poor sleepers recorded mean serum melatonin of 11.15 ± 2.81 (p-value 0.001). Waist circumferences were noted to be significantly different, with a mean of 97.8 ± 11.37 cm and $105.614.34$ cm for the good and poor sleepers, respectively (p-value = 0.007).

Conclusion: Poor sleep quality is more prevalent in the type 2 diabetic sample population, with a significantly lower nighttime serum melatonin level in the patients with poor sleep quality.

Keywords: Pittsburgh sleep quality index (PSQI), Serum melatonin, Poor sleepers, Good sleepers, Waist circumference

Sleep disturbances, especially in diabetics, are poorly correlated with health-related quality of life (HRQoL) [1]. Diabetes both affects and is impacted by sleep quality. On the one hand, diabetes impairs sleep quality due to nocturia and peripheral diabetic neuropathy. On the other hand, poor sleep quality leads to the production of stress hormones. Furthermore, sleep deprivation causes disruptions in appetite-controlling hormones such as leptin and ghrelin [2].

Melatonin is a neuromodulatory hormone that is derived from serotonin and secreted by the pineal gland. Specifically, pinealocytes under the control of suprachiasmatic Nuclei in the hypothalamus. Accordingly, damage to the SCN is associated with loss of circadian rhythm [3]. Melatonin is also

produced, to a lesser extent, in several other organs, including but not limited to the ocular tissues, heart, kidneys, adrenal glands, and immune cells [4]. Originally, the pineal gland was photosensitive; however, this trait was lost. The alternative pathway is the retinal ganglionic cells, the only cells that directly connect to the brain through the retinohypothalamic tract [5].

Intrinsic photosensitive retinal ganglionic cells have the ability to transport light signals to the SNC. These signals are moved through the retinohypothalamic tract. The pathway then extends to the paraventricular nucleus. Preganglionic sympathetic neurons carry the information to the intermediolateral column. On the other side, postganglionic sympathetic neurons synapse with

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the pineal gland, stimulating melatonin production [6]. Melatonin production suppression during the daytime belongs to the activation of SNC to release γ -Aminobutyric Acid (GABA), which inhibits sending information to the pineal gland at the paraventricular nucleus level [7].

Two melatonin receptors were distinguished: MT1 and MT2. These receptors are distributed through different parts of the brain, for example, the hypothalamus, cerebral cortex, midbrain, and cerebellum [8]. They were also detected in certain peripheral tissues, including the retina, liver, and cardiovascular systems [9]. These receptors belong to the G-protein-coupled receptor (GPCR) group. When melatonin binds to its receptor in SNC, it inhibits adenylyl cyclase, leading to inhibition of cAMP. That in turn inhibits protein kinase A (PKA), blocks the phosphorylation of cAMP response element-binding protein, and inhibits pituitary adenylyl cyclase activating peptide (PACAP), ending the melatonin transcription pathway by inhibiting neuronal firing and promoting sleep [10].

The third melatonin receptor is coded MT3, which is a nuclear receptor in contrast to the other membrane receptors, MT1 and MT2 [11]. The MT3 receptor belongs to the retinoic acid-related orphan receptor (ROR). This nuclear receptor may explain the immunomodulatory activity affecting both pro- and anti-inflammatory mediators [12,13]. Melatonin has been found to enhance the circadian clock through the activation of the PI3K/AKT signaling pathway, which increases Bmal1 protein levels [14].

Assessment of sleep quality can be conducted using certain objective or subjective techniques. Objective techniques like polysomnography and actigraphy are considered as golden standards because of their high sensitivity, however, their high cost represents a serious challenge in the practical field. In addition, their specificity is also limited because of the first-night effect associated with their complicated procedure [15].

Subjective sleep assessment is an easy and rapid method based on recording patients' diaries or using questionnaires. Bias is a major weakness of this technique. The Pittsburg Sleep Quality Index was released by Daniel J. Buysse in 1989. It is classified as one of the most powerful subjective techniques, with a sensitivity rate of 89.6% and a specificity rate of 86.5% [16]. It is been widely used for academic purposes for the last three decades. Its comprehensive scope through its 19 questions that cover seven sleep quality functions enabled the PSQI to be a well-trusted sleep quality assessment tool with a reliability of 87% [17].

The study aims to evaluate sleep quality in type II diabetic patients with a relatively good glycemic control profile and neither micro- nor macrovascular complications. The study tries to determine the role of serum melatonin in the deterioration of sleep quality and its level of correlation with the PSQI score.

2. Materials and methods

This research is a cross-sectional study that involves selecting eighty-eight diabetic patients with specific inclusion criteria to avoid as many cofounders as possible. These conditions include the absence of micro- and/or macrovascular complications, as long as these complications and the associated medications negatively affect the quality of sleep. The selected patients should be glycemic controlled according to the American Physicians Association guidelines (APA) in order to neutralize the impact of nocturia. The study extended for four months (December 2022–March 2023).

2.1. Evaluation of sleep quality

The PSQI technique was used to evaluate sleep quality. It's made up of 19 questions deliberately distributed to assess seven sleep functions: sleep duration, sleep disturbance, sleep latency, sleep efficiency, daytime dysfunction, subjective sleep quality, and use of hypnotic medications. Based on PSQI scores, the patients were then distributed into two groups: good or poor sleepers. Patients with a PSQI score less than five were classified as having good sleep quality, according to Buysse et al. [16].

2.2. Assessment of serum melatonin

Serum Melatonin was measured using an Enzyme-Linked Immunoassay (ELISA). A sandwich enzyme immunoassay technique was adopted in this research, where the evaluation of serum melatonin principle which is based on the antibody sandwich technology. The principle involves the addition of a serum melatonin sample to pre-coated melatonin monoclonal antibodies in the wells and leaving them for 60 min at 37 °C to complete the reaction. Anti-melatonin antibodies labeled with biotin will then be added to unite with streptavidin-HRP, forming immune complexes. Unbound enzymes are then removed by washing five times. Finally, the chromogen solutions A and B are added, and the solution should be incubated at 37 °C for 19 min. The solution becomes blue in color and turns yellow under the influence of the acid. Serum

melatonin concentration is positively correlated with the color of the solution. ELISA kit was commercially provided from Biont, catalog number: YLA0321HU.

2.3. Statistical analysis

XLSTAT 2023 was used to organize, summarize, and analyze the study data. The mean and standard deviation were used to express the central tendency and dispersion of the collected values. A t-test with two samples assuming unequal variances was used to compare serum melatonin levels in good or poor sleepers groups.

3. Results

The study sample was made up of 51 males and 37 females. **Table 1** summarizes the mean and standard deviation of the general characteristics of the whole study patient, poor, and good sleeper groups. The average age of the selected patients was 50.83 ± 8.58 years, with a significant difference based on the sample gender (49.24 ± 8.43 years for males and 53.03 ± 8.3 for females; p -value = 0.041). The anthropometric indicators showed an average weight of the total sample of 86.39 ± 14.69 kg (an insignificant sex-wise difference of 85.04 ± 14.3 kg for males and 88.24 ± 15.01 kg for females, p -value = 0.32). The mean height of the whole study population was 1.67 ± 0.076 m, exhibiting a significantly shorter average in females (1.72 ± 0.06 , 1.61 ± 0.04 m for females and males, respectively, p -value <0.001). A significant difference based on gender was also noted in waist circumference and body mass index, with a p -value lower than 0.001 in both. While waist circumference total sample mean value was 101.94 ± 13.6 cm, male patients' was 97.43 ± 9.48 , and female patients' 108.16 ± 15.79 cm; the BMI mean value of the study sample was 30.96 ± 5.94 kg/m², for males 28.59 ± 4.63 kg/m², and for females 34.23 ± 5.99 kg/m².

The duration of diabetes in the total study population was 7.22 ± 4.93 years (6.8 ± 4.75 , 7.78 ± 5.1 years for males and females, respectively, p -value = 0.37). Glycated hemoglobin A1c (HbA1c) illustrated an insignificant difference between males and females with a p -value of 0.69. The average HbA1c for men was $6.96 \pm 0.87\%$, for women $6.88 \pm 0.92\%$, and for the total population it was $6.93 \pm 0.089\%$. Serum melatonin level also demonstrated an insignificant sex-wise difference with a p -value of 0.25 and a mean study sample value of 14.03 ± 4.01 pg/ml, 14.43 ± 4.4 pg/ml for men, and 13.47 ± 3.32 pg/ml for women.

The majority of the sample suffered from poor sleep quality, with a rate of 53.41% ($n = 47$). Good sleepers represent 46.59% ($n = 41$). Melatonin levels were significantly lower in patients with poor sleep quality compared to those who are good sleepers. Melatonin levels were 11.15 ± 2.81 pg/ml and 17.32 ± 2.26 pg/ml in the poor and good sleep quality groups, respectively (p -value <0.001). **Fig. 1** compares serum melatonin levels in the different study groups.

Waist circumference also indicated a significant difference when its value was compared based on sleep quality. Poor sleepers indicated a significantly greater waist circumference value compared to good sleepers, with a mean value of 105.6 ± 14.34 cm and 97.8 ± 11.37 cm, respectively (p -value = 0.007). The rest of the parameters mentioned in the general character table were found to be insignificantly affected by sleep quality. **Table 2** describes the comparison of study variables based on sleep quality.

4. Discussion

Deteriorated health-related quality of life (HrQoL) represents a serious challenge in terms of clinical aspects as well as psychological and economic dimensions, which negatively affect productivity per capita [18]. Diabetes in general and, particularly,

Table 1. Summarizes the mean and standard deviation of the general characteristics of the different study groups at the time of the data collection.

Parameter	Whole Study Patients	Male	Female	p-value male vs. female
Anthropometric indicators				
Weight (kg)	86.39 ± 14.69	85.04 ± 14.3	88.24 ± 15.01	0.32
Height (m)	1.67 ± 0.076	1.72 ± 0.06	1.61 ± 0.04	<0.001***
Waist Circumference (cm)	101.94 ± 13.6	97.34 ± 9.48	108.16 ± 15.79	<0.001***
Body Mass index (kg/m ²)	30.96 ± 5.94	28.59 ± 4.63	34.23 ± 5.99	<0.001***
Duration of the disease (years)	7.22 ± 4.93	6.8 ± 4.75	7.78 ± 5.1	0.37
Age (years)	50.83 ± 8.58	49.24 ± 8.43	53.03 ± 8.3	0.041*
HbA1c %	6.93 ± 0.089	6.96 ± 0.87	6.88 ± 0.92	0.69
Serum melatonin (pg/ml)	14.03 ± 4.01	14.43 ± 4.4	13.47 ± 3.32	0.25

*: p -value <0.05, **: p -value <0.01, ***: p -value <0.001.

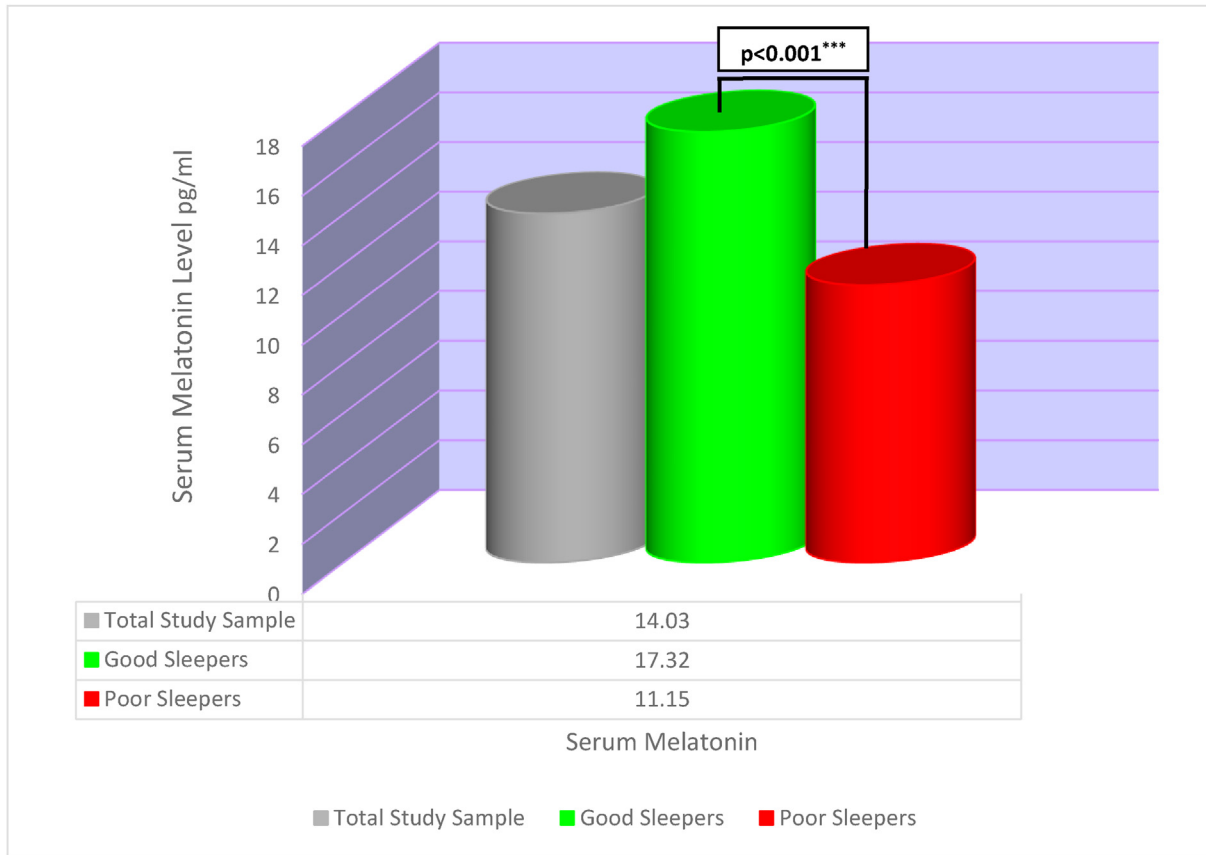


Fig. 1. Mean serum melatonin of total study sample, good sleepers and poor sleepers groups.

associated sleep disorders are major contributors to reduced HRQoL. Understanding sleep pathophysiology paves the way for better understanding and improving sleep quality, which in turn improves HrQoL too [19].

The current study showed the dominance of poor sleep quality with a rate of 53.41% in spite of the relatively controlled glycemic levels of the recruited type 2 diabetic patients. A significantly lower serum melatonin level was noticed in the poor sleepers. That aligns with Tutuncu et al., who indicated a blunting of the circadian level of serum serotonin secretion in type 2 diabetic patients. The authors

recorded a fall in serum melatonin measured at 4:00–6:00 p.m. down to 15.6 ± 3.2 pg/mL compared to 99.2 ± 29 pg/mL in an apparently healthy control group [20]. The results also concur with Kalere et al., who assured serum melatonin reduction in type 2 diabetic patients compared to the control group [21]. However, the HbA1c in the current study was better controlled, with an average of 6.93%.

While Tutuncu et al. justified the results with significant autonomic neuropathy, which is a leading cause of obstructive sleep apnea (OSP), Kalere et al. correlated low serum melatonin levels and consequently poor sleep quality to obesity, where

Table 2. Summarizes the mean and standard deviation of the general characteristics between good and poor sleepers.

	Parameter	Good Sleep Quality	Poor Sleep Quality	p-value
Anthropometric indicators	Weight (kg)	84.59 ± 13.17	87.96 ± 15.73	0.282
	Height (m)	1.67 ± 0.08	1.67 ± 0.07	0.961
	Waist Circumference (cm)	97.8 ± 11.37	105.6 ± 14.34	0.007*
	Body Mass index (kg/m^2)	30.29 ± 5.7	31.55 ± 6.07	0.326
Duration of the disease (years)		7.85 ± 4.98	6.66 ± 4.81	0.263
Age (years)		51.98 ± 9.31	49.83 ± 7.94	0.251
HbA1c %		6.91 ± 1.02	6.94 ± 0.76	0.89
Serum melatonin (pg/ml)		17.32 ± 2.26	11.15 ± 2.81	<0.001*

* = p-value <0.05.

poor sleepers had a significantly higher mean body mass index (BMI). In spite of the insignificance of the BMI recorded in the current study, the significant difference in the waist circumference calls for further investigations using other obesity indices like the visceral adiposity index and the lipid accumulation product. This is because, unlike BMI, these indices rely on waist circumference as a determinant in obesity quantification.

5. Conclusion

Relatively well-controlled type 2 diabetic patients complain of poor sleep quality with a significantly lower nighttime serum melatonin level. The study is a benchmark for further potential studies that may look at the reasons for such melatonin reduction, including evaluation of nerve conductivity and obesity indices.

Ethical approval

The study design was reviewed and accredited by the Institutional Review Board (IRB), College of Medicine, Al-Nahrain University, Iraq on January 10, 2023: No. 87/3/2.

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