Original Article

Melatonin Levels in Saudi Female with Type 2 Diabetes Mellitus

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Abstract

Melatonin functioning in diabetes mellitus has been investigated, researchers have recorded a decline in plasma melatonin concentrations in diabetes. The current study aimed to assess melatonin levels and investigate their correlation with glucose levels in type 2 diabetic mellitus patients of female gender. Methods: Case-control research was conducted between January 2017 to January 2019 with 100 diabetic participants and 100 healthy participants from Taibah University following a 24-hour fast, glucose and glycated hemoglobin (HbA1c)melatonin, insulin levels, lipid profile were investigated. GraphPad Prism 7 was used for data processing. Daytime melatonin levels decreased considerably in the diabetic group compared to the non-diabetic group (P =.003) and were lower in the diabetic retinopathy group than in the non-retinopathy groups (P = .02). There was a significantly evident and lowering melatonin levels are negatively correlated with blood sugar levels (r = −0.531, P = .001). Also, there were significant negative correlations between the decreasing melatonin levels with the rise in insulin levels and insulin resistance (IR) (r = 0.421, P =.02, r = 0.634, P =.002, respectively). Diabetes patients had lower melatonin levels, which had a negative correlation with higher IR. Changes in melatonin levels may hasten the development of new issues in diabetes patients, particularly retinopathy.

Keywords: Circadian Rhythm; Diabetic Retinopathy; Melatonin; Type 2 Diabetes; Glucose Metabolism; Glycemia.

1. INTRODUCTION

Melatonin is a hormone that has a role in maintaining the human day-night cycle by controlling other hormones. Retinal photoreceptors, ciliary epithelial cells, and pinacocytes all produce the indoleamine hormone melatonin. [1]. Melatonin is mostly released into the bloodstream at night in vertebrates by the pineal gland. The melatonin concentration in our blood differs during the day and is altered by daylight and darkness (nighttime). Melatonin functioning Functionality in diabetes mellitus (DM) has been studied in animals, and a human investigation shown that people with diabetes have lower plasma melatonin concentrations. [1-2 Current diabetes consequences, primarily retinopathy and autonomic neuropathy, can be affected by melatonin secretion and its alternating levels in the blood [3-4]. A study Peschke and Mühlbauer [3] Analyzing melatonin's effects on the pathways by which glucose is transferred to mouse skeletal muscle cells revealed that it promoted glucose transfer to these cells via the IRS-1/PI-3 kinase pathway, confirming its significance in glucose homeostasis and likely in diabetes. Furthermore, Aging and exposure to light at night can both lead to a reduction in endogenous melatonin concentrations, which can contribute to the development of diabetes. Additionally, some recent studies have revealed that the Eliminating the type 1 melatonin receptor (MT1) severely impairs mice's capacity to metabolize glucose, presumably as a result of increased insulin resistance (IR). This suggests that MT1 receptors are involved in the aetiology of type 2 diabetes. [4-5]. recently, researchers have discovered that a significant percentage of People are intrinsically more vulnerable to the impact of this hormone on blood glucose regulation. [6-7-8], which can cause elevated blood glucose concentrations and eventually a higher chance of contracting type 2 diabetes. In the Nurses' Health Study, researchers compared 370 women with diabetes to 370 control individuals who were the same age and race. [9]. Researchers found that participants in the trial who had low levels of nocturnal melatonin excretion had a roughly twice higher chance of acquiring type 2 diabetes than those who had high levels of nocturnal melatonin secretion. [10-11]. The research revealed other, well-known risk factors for diabetes, including body mass index, a family history of the disease, and lifestyle factors like diet, exercise, smoking, and amount of sleep. They did, however, note

that melatonin secretion remained a major risk factor. [12-13]. However, to our knowledge, there is still a debate in the literature on altered melatonin concentrations in diabetic patients. Therefore, the goal of the current study was to investigate the relationship between melatonin levels and glycemic status in Saudi females with type 2 diabetes.

2. MATERIALS AND METHODS

In this case-control study, 100 diabetic participants and 100 age-matched non-diabetic females (control) provided blood samples according to the manufacturer's recommendations, blood samples were taken in the morning from 10:00 to 12:00 in order to evaluate fasting serum glucose (FSG), glycated haemoglobin (HbA1c), and lipid profile using the automated ARCHITECT c4000. In the meantime, 2 ml of the leftover blood sample was centrifuged at 1000 g for 5 minutes, and the serum was maintained at a temperature of 200 °C to study the hormones melatonin and insulin. The concentrations of melatonin and insulin hormones were measured by ELISA immunoassay kits using an immunoassay analyzer (CUSABIO Technology LLC, Houston, USA) as per the manufacturer's directions.

The homeostasis model assessment of insulin resistance (HOMA-IR) index (fasting insulin U/mL fasting glucose mg/dl / 405) was used to determine the amount of IR. The range considered healthy is between the values 0.5–1.4. Values less than 1.0 imply that the patient is insulin-sensitive, which is best. Early IR is indicated by a value above 1.9, and significant IR, as previously defined, is indicated by a number above 2.9. (14). additionally, the previously mentioned formula, IS = 1/ IR, was used to determine insulin sensitivity (IS). [14].

2.1Ethical statement

The Faculty of Applied Medical Sciences at Taibah University's Medical Ethical Committee approved this study (MLT 201621). Each participant formally acknowledged their consent in writing.

2.2Statistical analysis

GraphPad Prism 7 was utilized for data processing (GraphPad Software, CA, USA). The mean [SD] was used to express quantitative data. The continuous baseline characteristics of the two groups were compared using the student's t-test (healthy control and type 2 DM). In order to analyses correlations between important variables, Pearson correlation coefficients were calculated. Statistics showed statistical significance at P .05.

3. RESULTS and ANALYSIS

3.1Clinical and laboratory traits of each group of study patients

Table 1 presents the clinical and laboratory characteristics of the patients. There were no significant differences in age across the groups, in the research, 50% of the diabetic women were postmenopausal, 5% received hormone therapy, and 40% had retinopathy (mild vision problems). Compared to non-diabetics, people with diabetes had significant increases in FSG, HbAc1%, and fasting insulin levels (P = .02, P = .001, P = .002, respectively) and significant decreases in melatonin levels (P = .003) (Table 1). While IS was significantly lower in the diabetic group (P =.01), the IR level was noticeably greater in the diabetic group compared to the non-diabetic group (P =.001, student's t-test).

TABLE 1. Clinical and laboratory characteristics of study participants (100 diabetic & 100 non-diabetics)

Parameter	**Diabetic Females N= 100**	**Non-diabetic Females N= 100**	***P*-value**
Age	49.5[12.83]	39.9[10.49]	>.05
Postmenopausal	50 (50%)	Non	-

Hormonal therapy	5 (5%)	Non	-
Retinopathy (mild vision problems)	40 (40%)	Non	-
FSG (mmol/L)	7.95[2.95]	4.1[1.89]	**.02***
HbA1c (%)	7.85[2.97]	4.4[1.73]	**.001****
Fasting insulin Uμ/mL	17.70[2.13]	6.7[1.53]	**.002****
IR (Insulin Resistance)	5.9[0.76]	1.19[0.67]	**.001****
IS (Insulin Sensitivity)	0.169[0.12]	0.84[0.13]	**.01***
Melatonin (pg/mL)	0.7 [0.4]	3.4[1.8]	**.003****
LDL-cholesterol (mmol/L)	3.59[0.95]	1.30[1.5]	**.03***
HDL-cholesterol (mmol/L)	1.9[0.27]	1.77[0.81]	>.05
Total cholesterol (mmol/L)	5.59[0.99]	2.60[1.23]	**.04***
Triglycerides (mmol/L)	2.79[0.92]	1.56[0.82]	>.05

Data presented as mean [SD] for FSG (fasting serum glucose), HbA1C (glycated hemoglobin), lipid profile: LDL (low density lipoprotein-cholesterol), HDL (high density lipoprotein-cholesterol), CHOL (total cholesterol) and TG (triglyceride), IR (Insulin Resistance) and IS (Insulin Sensitivity) for control group and type II diabetic patients. **P*<.05, ***P*<.001.

3.2 Melatonin levels in each group

In comparison to the non-diabetic group, the diabetes group's daytime melatonin concentrations were significantly lower (P =.003). Between diabetic patients with retinopathy (n = 40) and diabetic patients without retinopathy (n = 60), there is a significant difference in the daytime melatonin level, with a P value of.02 (Figure 1).

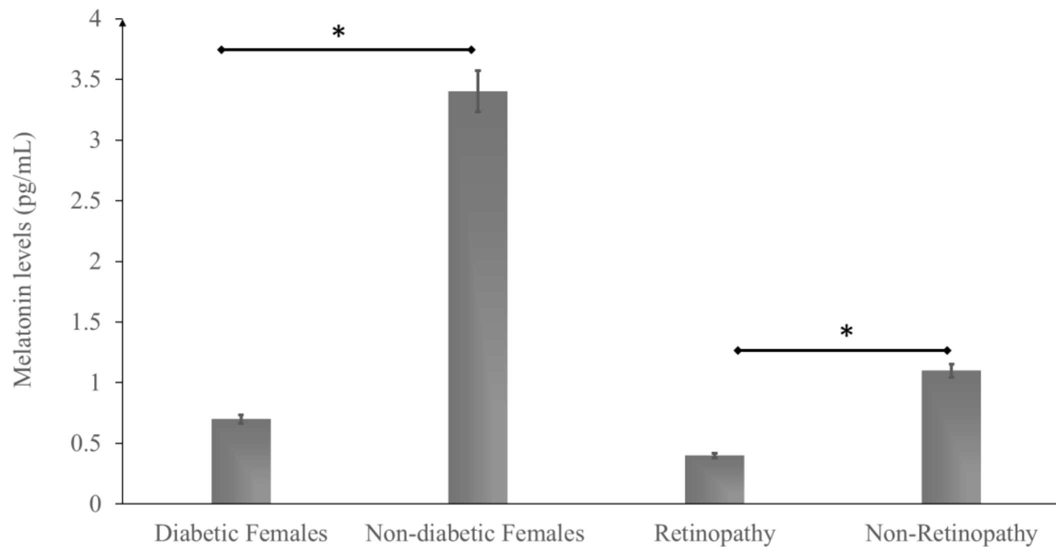

FIGURE 1 Daytime amounts of melatonin in each group. The difference in daytime melatonin levels between the non-diabetic (n = 100) and diabetic (n = 100, P=.003, Student's t-test) groups was significant, and the difference between the diabetic retinopathy group (n = 40) and the non-retinopathy diabetic groups (n = 60, P=.02) groups was also significant.

3-3-The correlations between the level of melatonin and the glycemic status

Correlations between melatonin, glucose, HbAc1, insulin, IR, and IS were investigated (Table 2 & Figure 2). The results indicated strong negative correlations between decreasing melatonin levels and glucose, insulin, and IR ($r = -0.531$, $P = .001$, $r = -0.421$, $P = .02$, and $r = -0.634$, $P = .002$ respectively). Whereas a positive correlation was indicated between melatonin level and IS ($r = 0.491$, $P = .02$).

TABLE 2. Correlation between Melatonin and different variables in type 2 diabetic patients

Parameter	**Melatonin**	
	r	*p*
FBG	-0.531	.001**
HbA1c	0.225	>.05
Fasting insulin	-0.421	.02*
IR (Insulin resistance)	-0.634	.002**
IS (Insulin sensitivity)	0.491	.02*
The Pearson correlation test was employed to examine the data. Each variable's connection with the melatonin level during the day was represented by an r. P<.05*, P<.001**.		

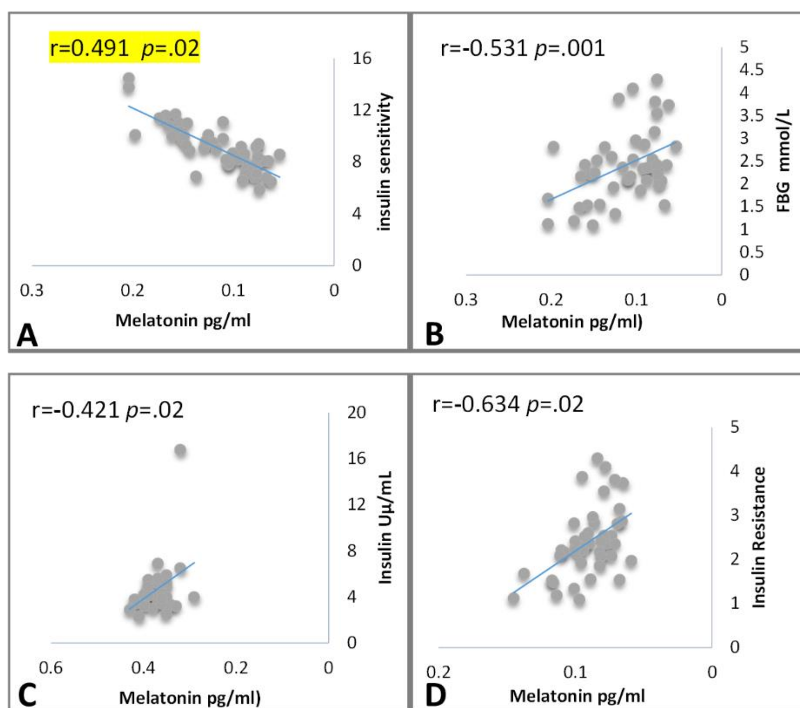

FIGURE 2. In type 2 diabetics, scatter graphs reveal the relationship between melatonin and other factors (A) a positive significant correlation with insulin sensitivity (r=0.491 p=.02) whereas, (B, C and D) there are negative significant correlations between Melatonin and FBG, insulin levels and insulin resistance (r=-0.531, p=.001, r=-0.421, p=.02, r=-0.634, p=.02 respectively).

4. DISCUSSION AND CONCLUSION

To the best of our knowledge, this is the first research examining melatonin levels. Their correlation with glucose levels in diabetic female patients in Al-Madinah Al-Munawarh. The current study showed that diabetic females had a low level of serum melatonin compared to non-diabetic females. In line with earlier research, Hikichi et al. discovered that patients with diabetes had lower melatonin levels than healthy people in their cross-sectional investigation. [15]. Furthermore, this result was confirmed previously in some studies that found that melatonin concentration was lower in six diabetes patients compared to five controls [16-17]. The daytime melatonin level did not significantly differ between the diabetic and non-diabetic groups, according to other investigations. [15]. In the present study, diabetic female patients had a considerable rise in IR and a fall in IS. According to McMullan et al., higher serum melatonin levels were linked to higher IS and lower IR. [16]. Regarding diabetic complications, the current study discovered that patients' melatonin levels were considerably lower with diabetic retinopathy. This result is consistent with the McMullan et al. study, which discovered that patients with proliferative retinopathy who had diabetes had melatonin levels that were lower. [17]. Also, Hikichi et al. revealed that as compared to healthy controls, 14 individuals with diabetic retinopathy had significantly lower levels of nocturnal melatonin. (10.9 pg/ml versus 37.5 pg/ml, $P < .01$) [15]. the retina is important in controlling melatonin secretion. Due to the location of the melatonin receptor 1B on the retina, the reduced nocturnal melatonin concentrations may be due to the occurrence of retinal lesions [17-18-19]. Studies proved that people with type 2 diabetes had a decreased circadian rhythm of melatonin secretion, and that there was a complex relationship between a number of autonomic nervous system components and melatonin production at night. They failed to find a difference between the melatonin levels of diabetic patients with and without retinopathy, though. [22-23]. They thought that the presence in their study of a small number of patients with proliferative diabetic retinopathy but no progressive retinopathy may have obscured the impact of diabetic retinopathy on melatonin functioning. The autonomic nervous system and then the pineal gland get information from the retina about ambient light and dark cycles. Therefore, it makes sense that autonomic neuropathy would produce aberrant melatonin excretion. [18-20-21-22].

Some restrictions applied to the current investigation. The study used a somewhat limited sample size. Also, the blood samples from the participants were taken during the daytime instead of at night because of the difficulty of reaching the patients at that time. Because melatonin is secreted in a pulsatile manner, we may not be able to determine its complete rhythm over the course of a 24-hour period. Also, there is no information according to the participants sleeping pattern which need to investigate. Diabetic patients had a lower serum melatonin level compared to healthy individuals, especially if they had diabetic retinopathy. Diabetic patients also appeared to have increased IR and decreased IS.

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