e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(4); 91-96

Original Research Article

To Investigate the Correlation between Metformin Treatment and the Amount and Quality of Sleep in Individuals Diagnosed with Type 2 Diabetes

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Received: 25-01-2024 / Revised: 23-02-2024 / Accepted: 26-03-2024

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Conflict of interest: Nil

Abstract:

Background: Individuals with diabetes often exhibit suboptimal sleep patterns, characterized by challenges in both initiating and maintaining sleep. Certain individuals with diabetes have excessive sleep, whilst others encounter difficulties in obtaining sufficient sleep. As to the National Sleep Foundation, a majority of 63% of American adults fail to get the sleep required for maintaining excellent health, ensuring safety, and achieving optimal performance.

Aim: To investigate the correlation between metformin treatment and the amount and quality of sleep in individuals diagnosed with Type 2 diabetes.

Material and Methods: This research includes a cohort of 100 participants diagnosed with Type 2 diabetes. The patients were separated into two groups of equal size. Group A was administered metformin, whereas Group B did not receive metformin. This research included patients from all age groups. There are 50 patients in group A and 50 patients in group B.

We included consecutive, verified outpatients diagnosed with Type 2 diabetes who were referred for sleep apnea screening due to symptoms such as excessive daytime drowsiness, nocturnal snoring, disrupted sleep, nighttime urination, or other related symptoms.

Results: The research comprised a total of 100 patients. Out of them, a total of 50 individuals were undergoing treatment with metformin. There were no significant differences in demographic features between those who used metformin and those who did not, except for BMI, the number of anti-diabetic drugs, and the percentage of patients on sulphonylurea treatment. The two groups exhibited notable differences in terms of total sleep duration and sleep efficiency. Metformin users had a total sleep time of 6 hours and 43 minutes, whereas non-users had a total sleep time of 6 hours and 7 minutes (P = 0.003). Additionally, the sleep efficiency of metformin users was 70.37±4.26%, but non-users had a sleep efficiency of 78.23±4.47% (P = 0.004). The prevalence of apnoea or hypopnea, mostly obstructive, did not substantially vary between the groups of patients treated with metformin and those who were not (data not shown). However, the metformin-treated patients had a higher BMI (P = 0.03).

Conclusion: Ultimately, we provide fresh evidence that metformin has a distinct impact on both the amount and quality of sleep. Randomized clinical studies are necessary to validate this advantageous correlation and ascertain if metformin's capacity to reduce blood glucose levels could also be linked to its impact on sleep (in addition to its established mechanisms of action), given that sleep problems are connected to high glycaemia.

Keywords: Metformin, Quality of sleep, Type 2 diabetes.

Introduction

Type 2 diabetes mellitus (T2DM) poses a substantial impact on public health. Based on the present trajectory, it is projected that by 2050, about one out of every three Americans would have Type 2 Diabetes Mellitus (T2DM)[1]. Insomnia is becoming recognized as a potential component that may be changed or modified in order to reduce the chance of developing Type 2 Diabetes Mellitus (T2DM). Experimental sleep deprivation in short-term laboratory trials resulted in elevated blood

sugar levels, known as hyperglycemia, which were then reversed upon restoration of regular sleep [2].The investigations on induced-insomnia have been restricted to small sample sizes and short durations. They have not investigated whether persistent sleep disruption raises the likelihood of acquiring T2DM in persons who are otherwise healthy. In relation to this inquiry, several epidemiologic researches have shown that the amount and standard of sleep might serve as notable indicators of the likelihood of acquiring T2DM. However, it is important to note that not all investigations have yielded the same results. The precise causal mechanisms have not yet been determined, but it is hypothesized that sleep deprivation increases the risk of developing diabetes through various pathways. These pathways include impaired pancreatic β-cell function, changes in adipokine profiles, heightened activation of the sympathetic nervous system, increased inflammation, elevated cortisol levels, increased food consumption, weight gain, obesity, and reduced physical activity [3,4].

A vast number of individuals rely on anti-diabetic medications. Metformin is a commonly used oral medication for diabetes. Metformin has been shown to have a bioavailability of around 50% when taken in fasting conditions [5]. Following consumption, metformin undergoes gradual absorption and attains its maximum concentration in the bloodstream about 1-3 hours. The elimination half-life of metformin is around 1.5-6 hours [5]. Tubular secretion is the primary route by which metformin is eliminated [5]. Metformin use leads to a reduction in the synthesis of glucose by the liver and a decrease in the absorption of glucose in the intestines [5]. Furthermore, metformin may enhance insulin sensitivity by promoting the absorption and use of glucose in peripheral tissues [5].

Like other medications, metformin has recorded side effects. These factors may lead to low adherence in diabetes patients, resulting in inconsistent medicine consumption [5]. In addition to the well-recognized adverse effects of hypoglycemia and diarrhea, metformin has also been shown to cause additional undesirable consequences. The impact of metformin on sleep is intriguing. In this article, the writers provide a comprehensive analysis and presentation of the information about metformin and its impact on sleep disturbances.

Insomnia caused by metformin is often reported in elderly and overweight diabetic patients who have just been diagnosed with diabetes mellitus and taken metformin. Insomnia may manifest after a few days of starting metformin treatment. This is an intriguing adverse effect that is not mentioned in other antidiabetic medications. In an online research published on www.eheathme.com, it was shown that around 1.4% of those who had adverse effects while using metformin reported symptoms of insomnia [6]. There is debate on whether metformin is the causal factor responsible for sleeplessness. Diabetic individuals often have a higher susceptibility to insomnia [7]. The length of sleep is correlated with blood glucose levels, and the increase in blood glucose levels after initiating metformin may be a potential mechanism by which metformin causes insomnia [8]. Furthermore, the coexistence of diabetes mellitus and depression is a prevalent illness that may also lead to insomnia [9]. The dysfunction of the endocannabinoid system, which is a target for drugs, in diabetes mellitus may contribute to the development of metformin-induced sleeplessness [6].

As previously mentioned, metformin may cause sleep disruption, which might potentially impact regular dream patterns. Patients who use metformin have reported experiencing nightmares [10]. Nevertheless, they occur less often than insomnia [11]. The cerebral blood glucose is associated with dreaming, and the alteration in its level after the administration of metformin may be the underlying cause of nightmares [12,13].

Multiple studies have been conducted on the correlation between diabetes and sleep apnea. On the other hand, metformin has been scientifically shown to have a preventative effect on sleep apnea [14,15]. Metformin is beneficial for managing diabetic cases that include metabolic syndrome, a risk factor for sleep apnea. Therefore, metformin may help prevent sleep apnea. Animal model studies have shown that Metformin is an effective therapy for sleep apnea, both in curing and preventing it. This suggests that insulin resistance might affect the desire to breathe independently of weight.

Material and Methods

This research was undertaken at the Department of General Medicine as a prospective observational study. This research includes a cohort of 100 participants diagnosed with Type 2 diabetes. The patients were separated into two groups of equal size. Group A was administered metformin, whereas Group B did not receive metformin. This research included patients from all age groups. There are 50 patients in group A and 50 patients in group B.

We included consecutive, verified outpatients diagnosed with Type 2 diabetes who were referred for sleep apnea screening due to symptoms such as excessive daytime drowsiness, nocturnal snoring, disrupted sleep, nighttime urination, or other related symptoms. We eliminated individuals who had unstable or uncontrolled cardiovascular disorders, a history of upper airway surgery, uncontrolled thyroid diseases, and the aftereffects of stroke. When doing a systematic comparison between individuals who take metformin and those who do not, we carefully examined if they were also using medica-

tions that have a sedative effect. These medications include hypnotics, opioids, neuroleptics, as well as antidepressive, anti-dopaminergic, and antihistaminic medicines. Patients underwent standard polysomnography from 19.00 to 08.00 h using the Brainnet System (Medatec, Brussels, Belgium). This system included an electroencephalogram, an electrooculogram, an electromyogram, continuous nasal airflow measurement, measurement of thoracic and abdominal movements (using strain gauges), and oxygen saturation measurement with a pulse oximeter (Medatec).

The diagnosis of sleep apnea syndrome was made using the criteria outlined in the International Classification of Sleep Disorders. This was based on an apnea/hypopnea index of > 15 episodes per hour. Sleep efficiency is calculated by dividing the total sleep time by the entire sleep duration. A multivariate analysis was conducted to determine if there was a separate association between the use of metformin and the occurrence of sleep disorders. This analysis took into account various factors that are commonly linked to disrupted sleep, such as age, gender, BMI, neck circumference, cumulative cardiovascular risk factors, and insulin use.

Statistical Analyses

Data may be presented in two ways: either as the mean and standard deviation (for quantitative data) or as a percentage (for qualitative data). Quantitative factors were compared between those who took metformin and those who did not using either a student t-test or a Wilcoxon test, depending on the data distribution. For the comparison of qualitative variables between metformin users and non-users, a v2- or Fisher test was employed, as applicable. The relationship between sleeping measures (total sleep and sleep efficiency) and clinical factors was analyzed using either a Pearson or Spearman correlation for quantitative data, or a student t-test for qualitative variables. An analysis of covariance and backward selection were used to investigate the independent connection between metformin usage and each of the sleep characteristics. This approach controlled for clinical covariates with a univariate P-value of less than 0.2. To compare metformin users with non-users, the P-values were corrected using the Bonferroni-Holm technique to prevent any increase in type I error. Test findings with P-values < 0.05 were judged significant, whereas those with P-values > 0.05 were declared non-significant. The statistical analyses were conducted using SPSS Version 25.0.

Results

The research comprised a total of 100 patients. Out of them, a total of 50 individuals were undergoing treatment with metformin. There were no significant differences in demographic features between those who used metformin and those who did not, except for BMI, the number of anti-diabetic drugs, and the percentage of patients on sulphonylurea treatment (Table 1). The two groups exhibited notable differences in terms of total sleep duration and sleep efficiency. Metformin users had a total sleep time of 6 hours and 43 minutes, whereas non-users had a total sleep time of 6 hours and 7 minutes (P = 0.003). Additionally, the sleep efficiency of metformin users was 70.37±4.26%, but non-users had a sleep efficiency of 78.23±4.47% (P = 0.004). Table 2.

The prevalence of apnoea or hypopnoea, mostly obstructive, did not substantially vary between the groups of patients treated with metformin and those who were not (data not shown). However, the metformin-treated patients had a higher BMI (P = 0.03).

Table 1: Basic Parameter of the Participants

	Metformin-treated patients =50		**Patients not treated with metformin n = 50**		**P-value**
Gender	**Number /Mean**	**Percentage**	**Number /Mean**	**Percentage**	**0.18**
Male	33	66	30	60	
Female	17	34	20	40	
Age					0.27
Below 30	4	8	3	6	
30-40	7	14	8	16	
40-50	22	44	25	50	
50-60	9	18	10	20	
Above 60	8	16	4	8	
Age, years	58.54±5.65		59.98±5.99		
BMI, kg/m^2	37.37±3.47		35.11±4.24		0.03
Neck circumference, cm	45		43		0.11
Arterial hypertension,%	39	78	38	76	0.26
Tobacco,%	31	62	29	58	0.22
Hypercholesterolaemia,%	28	56	27	54	0.26

Metabolic syndrome,%	41	82	38	76	0.19
Number of risk factors	4		4		0.12
Number of anti-diabetic medications	1.99±0.11		1.33±0.15		< 0.0001
Sulphonylurea therapy, %	14	28	27	54	< 0.0001
Insulin therapy, %	9	18	7	14	0.32
Sedative/hypnotic drugs, %	7	14	5	10	0.47

Table 2: Sleep Parameter

	Metformin-treated patients =50	Patients not treated with metformin n = 50	P value
Total sleep period, h	8 h 8 min	7 h 58 min	0.15
Total sleep time, h	6 h 43 min	6 h 7 min	0.003
Sleep efficiency,%	78.23±4.47	70.37±4.26	0.004
Apnoea/hypopnoea index	16.76±2.47	20.22±3.48	0.22

Table 3: Univariate and Mutivariate Analysis of the participants

	Univariate analysis P-value		Mutivariate analysis P-value	
	Total sleep time	Sleep efficiency	Total sleep time	Sleep efficiency
Gender	0.001	0.001	0.001	0.001
Age, years	0.003	0.001	-	0.001
BMI, kg/m^2	0.67	0.77	-	-
Neck circumference, cm	0.03	0.02	-	-
Arterial hypertension,%		--	-	-
Tobacco,%	0.00	0.00	-	-
Hypercholesterolaemia,%	-	-	-	-
Metabolic syndrome,%	-	-	--	-
Number of risk factors	0.65	0.56	-	-
Number of anti-diabetic medications	-	-	-	-
Sulphonylurea therapy, %	0.001	0.002	0.001	0.003
Insulin therapy, %	0.19	0.45	-	-

Univariate and multivariate analyses

Table 1 displays the outcomes of both the univariate and multivariate studies. After controlling for confounders, there was still a significant difference between the group treated with metformin and the group not treated with metformin in terms of total sleep duration and sleep efficiency (P = 0.0001 and 0.0003, respectively).

Discussion

Investigations conducted using both cross-sectional and longitudinal methods have consistently shown a significant occurrence of glucose intolerance, insulin resistance, and diabetes in individuals with sleep problems. Conversely, same investigations have also demonstrated that sleep disorders are independently linked to disruptions in glucose metabolism [15-17].

Various mechanistic explanations have been proposed, such as intermittent hypoxia, sleep fragmentation, sleep deprivation causing sympathetic activation, disruptions in the hypothalamus-pituitary axis, production of reactive oxygen species, and increased activity of inflammatory pathways. These factors ultimately result in insulin resistance and impaired glucose tolerance [18-20]. Considering metformin's established impact on insulin resistance, it is likely that this medication has beneficial benefits on sleep. The theory is supported by data obtained from animal trials [21]. Nevertheless, these preclinical findings lacked corresponding clinical evidence. In this study, we provide the first evidence of a positive and separate correlation between metformin treatment and sleep-related attributes in a very large group of individuals.

The current research group exhibited significant obesity, with metformin-treated patients having a body mass index (BMI) approaching 40 kg/m2. Additionally, the population had a high cardiovascular risk, with an average of more than four risk factors per patient. The majority of the individuals had the metabolic syndrome. However, while the individuals in our research had extreme obesity, the average number of apnoea/hypopnoea events indicated a modest sleep apnoea condition. It is important to remember that there was no significant difference in sleep apnea syndrome between the group treated with metformin and the group not treated with metformin.

The two research groups exhibited notable disparities in two crucial sleep variables: one pertaining to the duration of sleep (total sleep time) and the other concerning the effectiveness of sleep (sleep efficiency) ($P < 0.003$ and 0.004, respectively). The multivariate analysis yielded the most remarkable discovery in the current research.

As anticipated, we discovered distinct connections between sleep characteristics and some demographic factors (albeit unexpectedly, not BMI). It is worth mentioning that, even after taking into account other factors, such as age, gender, and metformin medication, the link between the variables remained significant.

This is noteworthy since the patients who were treated with metformin had a higher BMI compared to those who were not treated with metformin ($P = 0.03$). The study had several limitations. Firstly, certain data points, including the metformin dose, duration of metformin therapy, and HbA1c value, were not accessible. Secondly, there were a relatively small number of patients who had not previously taken metformin. Lastly, there were significant differences between the metformin and metformin-naive groups in terms of the number of other anti-diabetic medications being taken concurrently.

Conclusion

Ultimately, we provide fresh evidence that metformin has a distinct impact on both the amount and quality of sleep. Randomized clinical studies are necessary to validate this advantageous correlation and ascertain if metformin's capacity to reduce blood glucose levels could also be linked to its impact on sleep (in addition to its established mechanisms of action), given that sleep problems are connected to high glycaemia.

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