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Article

Enhancing Night and Day Circadian Contrast through Sleep Nursing Education in Prediabetes and Type 2 Diabetes Mellitus: A Randomized Controlled Trial

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Abstract: Background: Evidence supports a causal relationship between circadian disturbance and impaired glucose homeostasis. Method: To determine the effect of a nursing educational intervention on improving healthy sleep, a parallel, open-label clinical trial in subjects with Impaired Fasting Glucose (IFG) or Type 2 Diabetes Mellitus (T2DM) and 18 and older was performed. Study variables were sex, age, fasting glucose, glycated hemoglobin A1c (HbA1c), Pittsburgh Sleep Quality Index (PSQI), sleep duration and efficiency, BMI, antidiabetic treatment and diet and physical exercise. An individual informative educational intervention was carried out following a bidirectional feedback method. It was intended to develop skills to improve sleep through 9 simple tips. An analysis of covariance was performed on all the mean centered outcome variables controlling for the respective baseline scores. Results: After the intervention, in the experimental group, PSQI dropped, the duration and quality of sleep increased. Further, a decrease in fasting glucose and in HbA1c levels was observed. Conclusion: The proposed intervention has proven to be effective to improve sleep quality, time, and efficiency and in only 3 months, to achieve a decrease in fasting glucose and HbA1c levels. These findings support the importance of sleep and circadian rhythms education focused on improving in T2DM or IFG.

Keywords: glucose metabolism disorders; circadian clocks; sleep; blood glucose; glycated hemoglobin H1Ac

1. Introduction

Diabetes mellitus is a chronic condition of high public health concern. It causes important morbidity, mortality and significant loss of quality of life [1]. It is estimated that 536.6 million adults aged from 20 to 79 worldwide (9.8% of all adults in this age range) have diabetes. Based on the 2021 estimates, 783.7 million adults aged 20 to 79 years are expected to have diabetes in 2045. In Europe, the estimated prevalence in 2021 was about61,425 million people, and by 2045 this number is projected to increase to 1,7%, affecting 69 million people [2].

Type 2 Diabetes Mellitus (T2DM) is the most common type of diabetes, accounting for around 90% of all diabetes worldwide [3,4]. T2DM is an incurable metabolic disturbance that can be controllable in as much as its physiopathological factors are neutralized [5]. However, its management remains a challenge [6]. T2DM onset is preceded by alterations in blood glucose levels known as prediabetes, which refers to the hyperglycemic conditions of Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) [7].

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Hyperglycemia is caused by the inability of the body's cells to fully respond to the insulin, named insulin resistance, which causes an overproduction of insulin as a compensatory mechanism, resulting in a failure of the pancreatic beta cells and a dysfunction in insulin production [8].

T2DM is associated with several risk factors, some of them are not modifiable, but others, such as overweight and obesity, sendentary lifestyle, smoking or dietary patterns can be modified [9,10]. Among them, sleep arises as a significant and easily modifiable risk factor [11,12].

A low quality of sleep is associated with an increase of cortisol, growth hormone and ghrelin levels, and to a decrease in leptin levels [13]. High levels of cortisol and growth hormone have been found to interact with insulin receptors as insulin antagonists [14], while low leptin levels and high ghrelin levels are associated with an increased risk of obesity, either by reducing satiety or stimulating appetite [15]. All these factors result in an increase in insulin resistance and therefore a higher risk of developing T2DM.

Quality of sleep comprises a wide range of dimensions, including efficiency, time, sleep quality and alertness or sleepiness. These can be measured objectively through polysomnography or subjectively through self-reports, such as PSQI [16,17,18]. In line with this, there are no specific instruments to evaluate sleep quality in T2DM and the PSQI is considered an effective tool to assess it [19].

The quality of sleep is a more reliable variable than another that has traditionally been tried to relate to healthy sleep: its duration. In this sense, several studies concluded that both short and long duration of sleep could play a causal role in T2DM [20,21,22] while good sleep quality might be a protective agent [23].

Beyond the restorative function of sleep and its benefits in glucose metabolism, the focus on the duration of sleep invite us to ask ourselves if when to sleep is as important as the quality of sleep itself since it is already known that circadian rhythm disturbance is an emerging environmental risk factor for T2DM [24]. Circadian disturbances are defined as a mismatch between the endogenous circadian system and behavioral circadian cycles (eg, sleep-wake and fast-eat). In today's 24-hour society, circadian disturbance is becoming increasingly common, driven primarily by increased exposure to artificial lighting, rotating and nightshift work and social jet lag [24, 25].

Several lines of evidence support a causal relationship between circadian disturbance and impaired glucose homeostasis. First, people in work conditions characterized by circadian disturbances, such as shift workers and night workers, have a higher prevalence of diabetes, glucose intolerance, and metabolic syndrome. Furthermore, clinical studies conducted in controlled experimental settings show that acute exposure to circadian disturbance results in dysregulation of glucose metabolism characterized by impaired insulin secretion and action [26, 27].

Several studies have been performed in order to test the efficacy of interventions to improve the quality of sleep in comorbid individuals [29], but the theoretical potential effect of a complementary therapy for T2DM and prediabetes based on sleep hygiene in order to improve sleep quality has not been broadly studied [30,31]. Furthermore, all experimental studies in the context of sleep and T2DM have focused on restricting sleep, but no studies have focused on improving its quality. This improvement could lead to better endocrine regulation and result in better management of the disease. The aim of the current study was to analyze the effect of a sleep hygiene intervention in the management of IFG and T2DM.

2. Materials and Methods

Design and study population: Experimental study based on a parallel clinical trial using blocked randomization with equal allocation ratio. The intervention was conducted by Primary Care Nursing of the Primary Health Center of Balaguer in Spain. Due to the nature of the intervention, the trial was open-labelled. The study population was composed of adult subjects diagnosed with IFG or T2DM who attended regular nursing visits.

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Adult subjects (18 or older), with HbA1c higher than or equal to 5.7% at the time of diagnosis (based on diagnostic criteria from the RedGDPS guideline) [32] and PSQI greater than 5 points (poor sleep quality) [17] were included. Subjects diagnosed with obstructive sleep apnea syndrome, narcolepsy, fibromyalgia, dementias, schizophrenia, psychosis, major depression and shift workers, as well as those who refused to participate, were excluded from the study. Participants who required a change of treatment during the study period were not analyzed, since they might have had significant effects on the outcome variables.

Participants were recruited through a consecutive non-probability sampling. Participation was offered to all of those who attended the nursing follow-up consultation until the predefined sample size was obtained.

Intervention: An individual education was carried out following a bidirectional feedback method. It was intended to develop skills to make conscious and autonomous decisions. The explanation consisted of: 1) Information and reading of the educational sheet with subsequent discussion: The 9 tips for a healthy sleep, according to the latest guidelines developed by American Academy of Sleep Medicine [33] the National Health Service [34], and the Health Department of Catalonia [35] These 9 tips emphasized that maintaining a regular and sufficient sleep schedule and establishing a series of routines and habits in the hours prior to starting sleep would prevent early awakenings. They were read, point by point, to the participant. The nurse and the participant discussed those that generated doubt. 2) Confrontation: even if the participant did not ask any questions, the nurse asked if he had understood the advice. 3) Involving information: Questions such as: "Did you already know any of these tips?" were asked the participant. One telephone call per month was made as an educational reinforcement to the intervention.

In the first visit, nursing professionals recruit the patients for the study if they were eligible. At the same visit a PSQI test was hetero administered. Subjects with PSQI result greater than 5 points (poor sleep quality) were randomly assigned either to the control or intervention group. Then, health professionals checked for the most recent laboratory records of fasting glucose and HbA1c levels of the participants. Those values were accepted if recorded within 6 months prior to the visit, and otherwise new blood tests were performed. Anthropometric measures, as well as information regarding diet, physical exercise and current antidiabetic pharmacological treatment were obtained. On another visit, the individual intervention was carried out only on participants assigned to the intervention group and follow up visits were scheduled three months after the first visit for both intervention and control group. One month after the intervention, the nurse carried out telephone contact for educational reinforcement on sleep hygiene recommendations.

On the follow up visit (3 months after the beginning of the intervention), another PSQI test was hetero-administered to the participants and new blood tests were performed for the assessment of basal glycaemia and HbA1c. Updates about sleep hygiene, diet, physical exercise and current antidiabetic pharmacological treatment were asked. The values obtained from the blood tests corresponding to the next follow-up visit, approximately 6 months after the beginning of the intervention, were recorded. A total of three on-site visits in both groups, and one telephone visit were made in the intervention group.

Variables: The main outcome variable was 3 months and 6 months post intervention levels of HbA1c (%). Secondary outcomes were 3 months and 6 months-post intervention fasting glucose (mg/dL), as well as 3 months-post intervention PSQI, declared sleep hours (hours) and sleeping efficiency (number of hours the patient declared having slept divided by the number of hours the patient declared having stayed in bed multiplied by 100 and expressed in percentage).

The independent variables were: pre intervention values of HbA1c (%), basal glycaemia (mg/dL), PSQI score, declared sleep hours (hours) and sleeping efficiency (%), as well as age (years), sex (man, woman), diagnosis (International Classification of Diseases, 10th version: E11 Diabetes Mellitus type 2; R73 Elevated blood glucose level), antidiabetic pharmacological treatment (yes, no), body mass index (kg/m2), change in antidiabetic

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pharmacological treatment in final visit (yes, no); change in diet in final visit (yes, no), change in physical exercise in final visit (yes, no) and change in sleep hygiene in final visit (yes, no).

Sample size: A sample size of 84 individuals was calculated for a significance level of 0.05 and a power of 0.8. Minimal acceptable decrease in HbA1c was established in 0.5, and a standard deviation of 0.8 was anticipated. Due to the characteristics of the subjects and the duration of the trial, a low number of losses were expected. Thus, a final sample size of 86 participants was established.

Statistical analysis: Descriptive statistics were used to summarize the variables in both groups (intervention and control), data normality was evaluated using Shapiro-Wilks test, and the results were described using medians and IQR or means and SD depending on whether the distribution was non-normal or normal, respectively. Count data were described as absolute and relative frequencies. Differences between groups were assessed with a Mann-Whitney test or a Student's T-test for numeric variables depending on the data distribution, and with a Chi-squared test for count data. Changes in the outcome variables during the study period were evaluated with either a paired Mann-Whitney test or with a paired Student's T-Test.

The efficacy of the intervention was assessed with an analysis of covariance on all the outcome variables controlling for the respective baseline scores. For this purpose, and since linear regression models did not fit the assumptions, quantile regressions for each variable were generated, considering the post intervention scores as the response, the group as the predictor variable and the respective baseline score as a covariate. The regression coefficients, the corresponding 95% CI and the statistical significance were estimated. Models first included interactions between basal scores and the intervention, but since no significant effect was observed, they were further removed for better interpretability of the results.

The analysis was carried out in version 3.4.4 of R (R Core Team 2018. R Core Team. R: language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2018. URL https://www.R-project.org/).

3. Results

Recruitment and follow-up took place between November 2017 and November 2018. A total of 133 subjects were assessed for eligibility, and 69 of them were included in the analysis (31 from control group and 38 from intervention group). The flow diagram of the process is specified in Figure 1 and the demographic and clinical descriptions of individuals in both groups are presented in Table 1.

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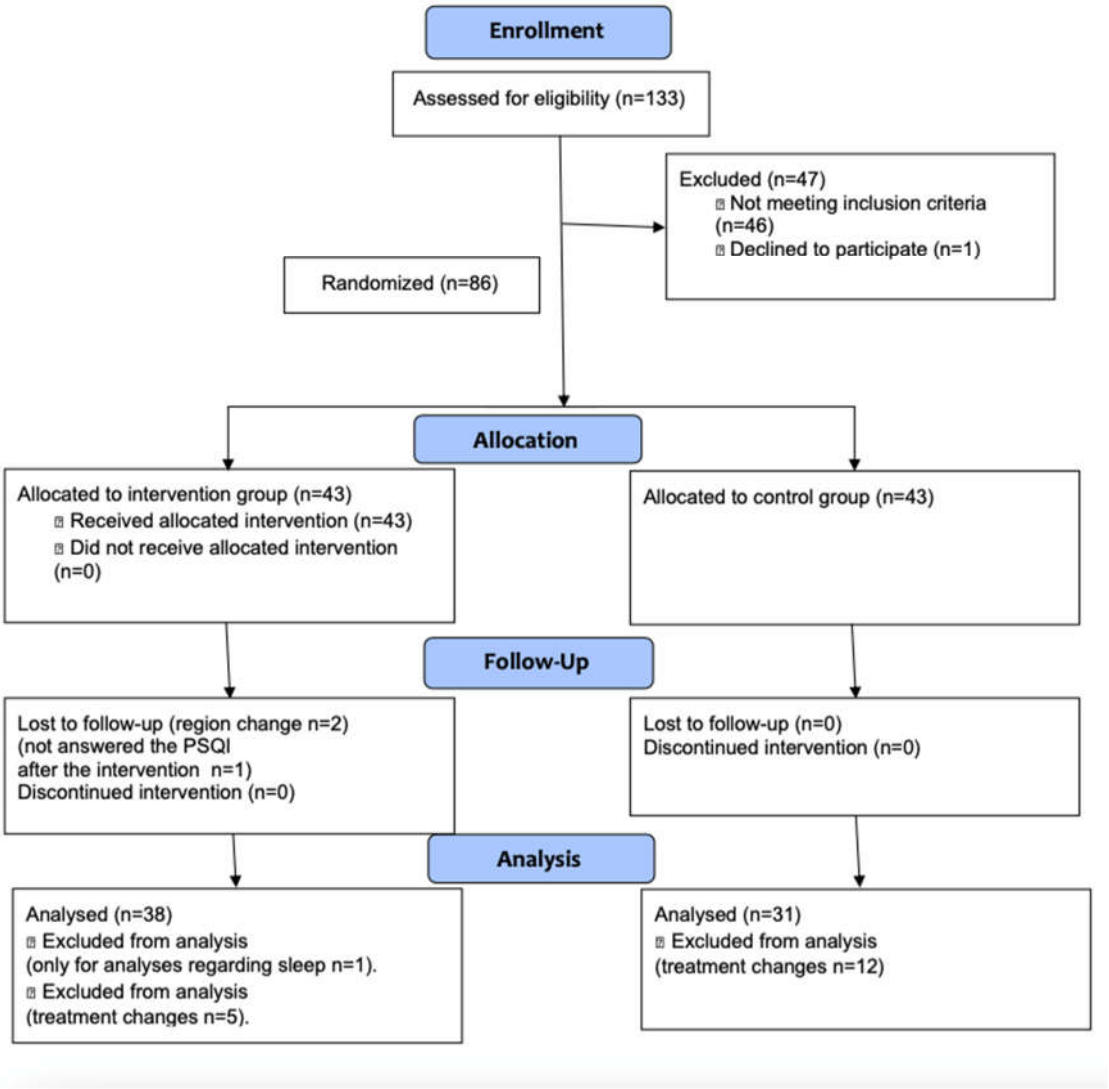

Figure 1. Demographic and clinical characteristics of the intervention.

Treatment changes associated with impairment in T2D were observed in both intervention and control group, but the number of treatment changes in control group was significantly (p<0,005) higher (28% in control group versus a 7% in intervention group). As these changes could lead to a bias in fasting glucose and HbA1c results. For this reason, these subjects were not analyzed.

Table 1. Demographic and clinical characteristics of the intervention and control group.

Variable	Control group (N=31)	Intervention group (N=38)	Total (N=69)
Age (years)	64.5 (12.9)	66.5 (11.3)	65.6 (12.0)
Body Mass Index (Kg/m²)	31.0 (5.6)	29.9 (4.1)	30.4 (4.8)
Time from blood test to intervention (days)	46.0 [19.5; 108]	101 [15.0;138]	62.0 [18.0;133]
Sex (Woman)	15 (48.4%)	22 (57.9%)	37 (53.6%)
Diagnosis (T2DM)	29 (93.5%)	33 (86.8%)	62 (89.9%)
Antidiabetic pharmacological treatment (Yes)	25 (80.6%)	31 (81.6%)	56 (81.2)
Benzodiazepine intake (Yes)	5 (16.1%)	10 (26,3%)	15 (21.7%)

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Preintervention sleep time > 6 hours (Yes)	9 (29.0%)	11 (28.9%)	20 (29.0%)
Diet change (Yes)	2 (6.45%)	4 (10,5%)	6 (8.70%)
Physical activity change (Yes)	3 (9.68%)	1 (2.63%)	4 (5.80%)

Clinical and demographic variables, habit changes and baseline outcome variables were studied to assess group comparability (Tables 1 and 2). Small imbalances were observed between groups regarding all the variables except for benzodiazepine intake.

Table 2. Comparison of quantitative variables in the control group respect to the intervention group before and after the intervention.

Response variables	Pre values			Post values			Change	
	Control group	Intervention group	P value	Control group	Intervention group	P value	Control group	Intervention group
Sleep								
PSQI	8.00 [6.00;11.0]	8.00 [6.00;10.8]	0,98	8.00 [6.00;11.0]	5.00 [3.00;9.00]	**0,008**	−0.61 (3.11)	−2.97 (2.93)**
Hours of sleep	6.00 [5.00;6.75]	6.00 [5.00;6.50]	0,76	6.00 [5.00;6.50]	7.00 [6.00;8.00]	**0,002**	0.00 [−0.50;1.00]	1.00 [0.00;2.00]*
Sleep efficiency	75.0 [58.0;86.3]	77.3 [66.7;84.0]	0,809	66.7 [57.1;84.5]	85.7 [71.4;93.3]	**0,007**	−1.65 (12.0)	6.74 (12.9)**
DM2 management								
Fasting glucose (3 months)	122 [106;134]	126 [112;154]	0,249	127 [112;138]	121 [102;137]	0,473	3.00 [−10.50;13.0]	−12.50 [−27.00;1.00]*
Fasting glucose (6 months)	122 [106;134]	126 [112;154]	0,249	122 [114;140]	120 [106;151]	0,766	4.43 (22.1)	−4.08 (25.8)
HbA1c (3 months)	6.40 [5.85;7.10]	6.45 [5.90;7.15]	0,443	6.40 [6.00;7.10]	6.25 [5.82;7.15]	0,476	0.20 [−0.20;0.55]	−0.20 [−0.50;−0.02]*
HbA1c (6 months)	6.40 [5.85;7.10]	6.45 [5.90;7.15]	0,443	6.75 [6.00;7.43]	6.30 [5.95;7.02]	0,315	0.42 (0.58)**	−0.06 (0.64)

*Statistically significant (paired Mann−Whitney test, p<0.05); **Statistically significant (paired Student's T test, p<0.05)

Effect of the intervention on sleep parameters: 84.2% of participants from the intervention group reported a change in sleep hygiene habits, while 14.0% of participants in the control group also declared to have changed their sleep habits. 3 months after the intervention, the control group did not report any change in PSQI (−0.61 ± 3.11), hours of sleep (0.00 [−0.50; 1.00] hours) or sleep efficiency (−1.65 ± 12.0%), while intervention group reported a statistically significant improvement in all three parameters: PSQI (−2.97 ± 2.93), hours of sleep (1.00 [0.00; 2.00] hours) and sleep efficiency (6.74 ± 12.9%) (Table 2). A significantly higher number of subjects in the intervention group reported more than 6 hours of sleep and an improvement of 3 or more points in PSQI (Table 3). Further, when comparing both groups, intervention group obtained lower post intervention PSQI scores

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(−3.00; 95%CI: −4.86, −1.14), longer perceived sleep time (0.80; 95%CI: 0.16, 1.44) and a higher sleep efficiency (10.77; 95%CI: 4.95, 16.59) (Figure 2).

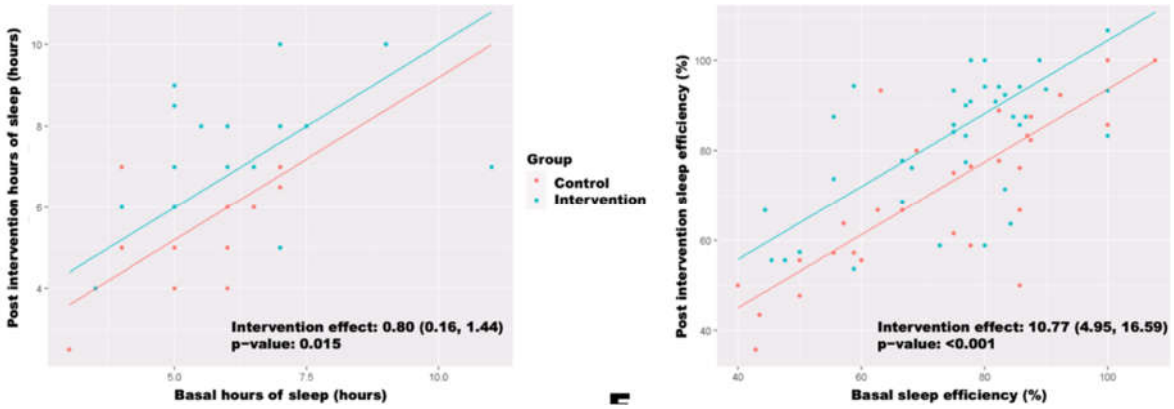

Figure 2. Quantile regression models for the response variables "Post intervention hours of sleep" and "Post intervention sleep efficiency" as a function of the group and the respective basal scores. Each point represents the participant observed score, and the lines represent the fitted models. The intervention effects are shown, with their corresponding 95% confidence interval and p- value.

Effect of the intervention on T2DM management: When assessing the effect on T2DM management, in the control group variation was observed neither in fasting glucose (3.00 [−10.50; 13.0] mg/dL) nor HbA1c (0.20 [−0.20; 0.55] %) levels 3 months after the intervention. However, the intervention group experienced a decrease in both fasting glucose (−12.50 [−27.00; 1.00] mg/dL) and HbA1c (−0.20 [−0.50; −0.02] %) levels (Table 2). When studying 6 months-post intervention values, no changes were observed in the control group regarding fasting glucose (4.43 ±22.1 mg/dL), and higher HbA1c values were observed (0.42 ±0.58 %).

In the intervention group, no changes were detected in fasting glucose (−4.08 ±25.8 mg/dL) or HbA1c (−0.06 ±0.64 %) (Table 2). Furthermore, 6 months after the intervention, a higher proportion of subjects with an improvement of more than 0.5% in HbA1c levels was observed (Table 3).

When comparing both groups, intervention group achieved a significant reduction of 3 months-post intervention fasting glucose (−11.70; CI 95%: −22.63, −0.77) and HbA1c (−0.33; 95%CI: −0.59, −0.08) levels respect to control group, as well as a reduction in 6 months-post intervention HbA1c levels (−0.53; 95%CI: −0.86, −0.20) (Figure 3).

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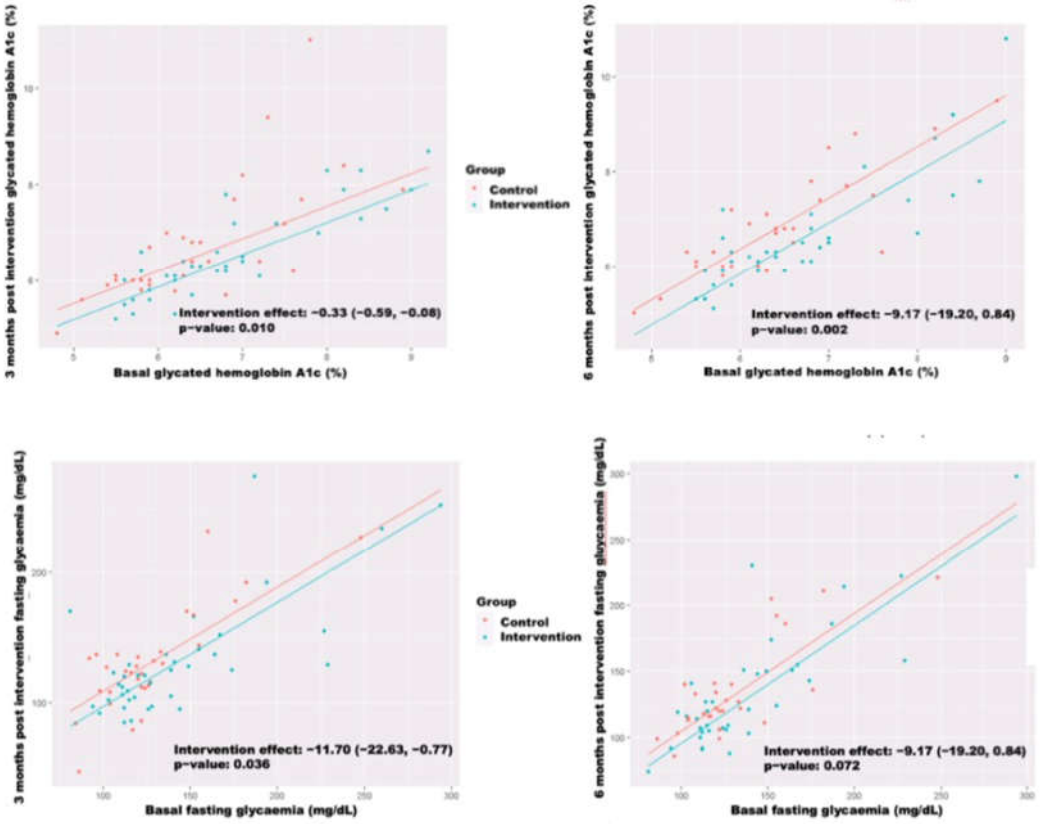

Figure 3. Quantile regression models for the response variables "Post intervention HbA1c" and "Post intervention fasting glycemia" evaluated 3 and 6 months as a function of the group and the respective basal scores. Each point represents the participant observed score, and the lines represent the fitted models. The intervention effects are shown, with their corresponding 95% confidence interval and p- value.

Relationship between change in PSQI and T2DM management: Finally, the effect of the changes in PSQI during the intervention period was tested. No relationship between PSQI changes and fasting glucose changes was found. However, we found a statistically significant association between the change in 3 months HbA1c levels change and the change in PSQI (0.06; 95%CI: 0.02, 0.11) (Figure 4).

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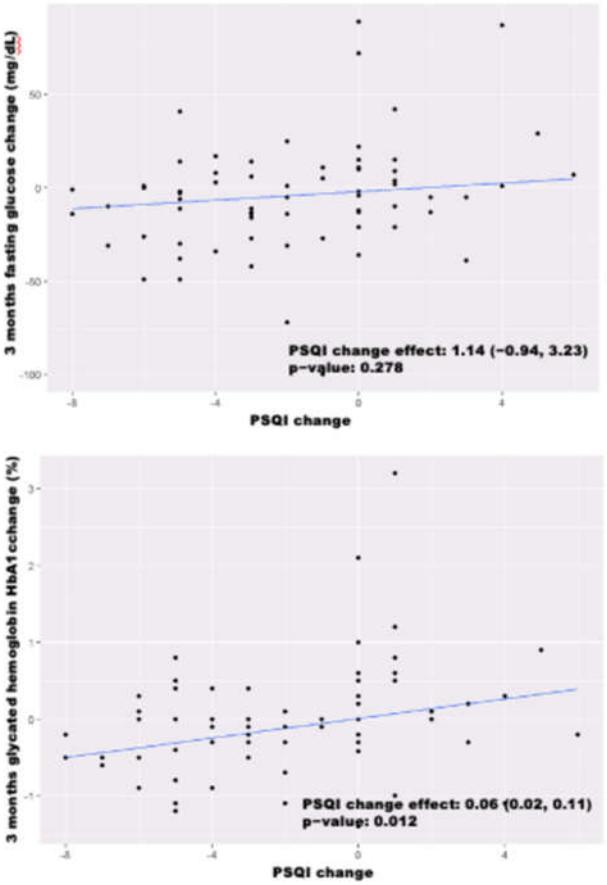

Figure 4. Quantile regression models for the response variables "3 months glucose change" and "3 months HbA1c change" as a function of the PSQI changes. Each point represents the participant observed score, and the lines represent the fitted models. The PSQI change effects are shown, with their corresponding 95% confidence interval and p- value.

4. Discussion

Several studies have determined a causal relationship between the deterioration in the quality and duration of sleep and T2DM onset [36] as well as a worse metabolic management in conditions of sleep restriction [37]. This effect has been attributed to its negative impact on glucose homeostasis [38]. However, to our knowledge, there are no studies regarding interventions focused on improving sleep quality of T2DM subjects in order to partially reverse this effect.

In this context, the study aimed to first check the effectiveness of the sleep hygiene intervention in the improvement of sleep quality, and afterwards evaluate whether this improvement could result in a decrease of the glucose and HbA1c.

The results show a significant improvement in all the measured parameters regarding sleep (sleep quality, time and efficiency) demonstrating the usefulness of the proposed intervention for the aforementioned objective. Moreover, the PSQI score improvement in the intervention group was 3 points higher compared to the control group. An improvement of ≥3 points in PSQI has been previously defined as an identifier of positive response to treatment [39], supporting the clinical relevance of the results. The median sleep time in the intervention group increased by one hour, accomplishing that the number of participants who reported sleeping more than 6 hours after the intervention was doubled, and implying that more than 50% of the participants in the intervention group reached this condition. Six hours is the minimum recommended time of sleep in adults, [40, 41, 42] and shorter sleep times have been related to a higher risk of developing T2DM [43].

Beyond the mere behavioral effect that hygiene measures have on improving the quality and duration of sleep, the effect produced by the intervention could also have

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contributed to enhancing the phenomenon of circadian contrast: being exposed to light during the day and to the dark at night, and fasting at night and eating during the day. The regularity of the sleep pattern and the regularity of the sleep / wake pattern and the magnitude of the difference between daytime and night activity measured with technology based on temperature register has shown an effect on decreasing HbA1c [44].

Regarding T2DM management, a significant improvement was also observed in both fasting glucose and HbA1c levels. The results in HbA1c changes in the intervention group (reductions of 0.34% compared to control group at 3 months, and of 0.53% at 6 months) are comparable to those obtained through nutritional interventions [45] and second line treatments [46]. The main endpoint in order to establish clinical relevance is a reduction of at least 0.5% [47], and a 0.3% endpoint has also been used for evaluating both behavioral interventions and second line treatment effectiveness [48], indicating that the intervention is relevant to obtaining both short-term and mid-term results. The effectiveness of the intervention is reinforced by the fact that we have found significant correlations between the pre-post intervention changes in PSQI with pre-post intervention changes in HbA1c. Interestingly, the generated model intercepts with the 0,0 point, indicating that positive changes in PSQI are related to positive changes in HbA1c, and vice versa.

It is noteworthy that there was a slight (but not statistically significant) improvement in sleep quality in the control group. This could be because of the information offered to the participants as part of informed consent that dealt with the importance of sleep in people with T2DM or IFG. Nevertheless, participants in the intervention group, which disposed of specific guidelines, increased sleep quality to a greater extent.

Nursing professionals in the field of Primary Care have a decisive role in monitoring and management of chronic diseases such as T2D. For this reason and in order to ensure its applicability, the intervention was integrated in the routine visitations of the participants. The present study demonstrates that a simple sleep health educational intervention in the context of the routine visitations of subjects with T2D or IFG has a positive effect on monitoring their metabolic parameters in a short period of time, and could be feasible and useful as a complementary therapy in primary care settings. Our study has some limitations. First, the intervention period was short, and adherence to educational interventions is known to decrease over time [47,49,50]. However, we have demonstrated that following the guidelines has short-term rewarding effects in treatment outcomes and diet and physical exercise changes that could increase adherence and positive reinforcement can be regularly given to the subjects by the nursing professionals thanks to the routine visitations. Second, the fact that we obtained positive results in only 3 months reveals that it is not adequate to accept laboratory results within 6 months prior to the intervention, but we had to assume it was due to laboratory limitations. However, we found similar distributions between groups regarding time from blood test to the initial visit, and we found significant correlations between PSQI changes and HbA1c changes, supporting the reliability of the results. Finally, taking into account that the intervention was open-labelled, the use of subjective variables related to sleep quality instead of objective tests such as polysomnography could lead to biased self-reports in the intervention group. However, the PSQI is considered a valid tool and incorporates all dimensions of sleep and is widely used for assessing sleep quality in T2D subjects [51, 52].

5. Conclusion:

An educational intervention in sleep hygiene and circadian contrast by nursing professionals in the primary care consultation proved to be effective in increasing the sleep quality measured by the PSQI. This intervention lowered HbA1c levels in IFG and T2DM. Sleep nursing education improves T2DM metabolic management.

Conflicts of interest: Jesús Pujol Salud has been advisor for Exeltis Healthcare S.L. (2017-2019) and Idorsia (2021-2022).

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