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Chapter XIX

Sleep Disturbances and Glucose Variability

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Summary

Aim of this study is to evaluate the relationship of sleep fragmentation with the level and the variability of the fasting blood glucose values (FBG). We used the Armband an instrument that records the number and the duration of the awakenings during sleep (AW), for six consecutive days in 60 obese type 2 diabetic subjects on diet alone or oral hypoglycemic agents and with a history of sleep disturbance (37 M, 23 F); age 61.6 ± 5 ; BMI = 28 ± 1.3 kg/m². All of them recorded their blood glucose level in duplicate upon awakening with the same brand of glucometer using an interference free electrochemical method throughout the observation period. The values were downloaded, and the Standard Deviation (SD) was calculated as an index of variability. All the data were log transformed. The correlation coefficients were for the FBG .76 ($p = .000$) and the SD .81 ($p = .000$) and the ANOVA $< .001$ for both. With the partial correlation, after removing the effect of BMI, Age and HbA1c the correlation of AW with the FBG was $p = .001$ and with the SD $p = .049$.

Introduction

Glucose variability is suspected to be among the main causes of diabetic complications [1,2]. One follow-up study of a diabetic population reported that the coefficient of variation of the fasting blood glucose was highly correlated to the 5-year mortality.¹⁴ In diabetes the fasting blood glucose (FBG) level reflects mostly the hepatic glucose production and the peripheral glucose handling and is the most stable value throughout the day. This is at least in part because the daily external interferences, like food, stress, physical activity, are missing. Also the effect of the common oral euglycemic agents is very limited because the

pharmacocynetics of most of these drugs, with the single exception of the long acting insulin preparations, tend to be shorter than 12 hours. It is however common experience that irrespective of the patho-physiology people with type 2 diabetes frequently have consistent swings of their FBG.[3]

It has been recently recognized that sleep disruption can cause an increase in glycated hemoglobin (HbA1c) Sleep disturbance is a condition that by definition occurs during the night and may represent a serious stressful condition likely to be reflected on the FBG[4]. The high level of stress caused by irregular sleep has been clearly defined by numerous studies. Less clear than this is the role of disturbed respiration on sleep fragmentation. Diabetic have many conditions predisposing to heavy snoring and Obstructive Sleep Apnea (OSAS) which represents a serious stressor and a potent interference with sleep We thus hypothesized that sleep disturbance might be at least one of the interferences causing a high FBG variability. To this aim we evaluated the data routinely collected from our diabetic population

Materials and Methods

Among 142 diabetic or obese overweight subjects studied for sleep disturbances and inadequate blood glucose control we selected the data of 60 who had no pulmonary or other complications, and were on diet, metformin or gliptins or a combination of them. None of these drugs causes serious hypoglycemia since they do not act on the insulin secretion mechanism.

Table 1. characteristics of the subjects (N=60)

Age	Sex	BMI	Diet	Metformin	Gliptins	Gliptins +Metformin	Statins	Anti aggregant treatment
61.6±5	29 M, 31 F	29.8± 1.2 Kg/m ²	17	23	12	8	9	6

We excluded those on insulin or sulphonylurea drugs and drugs interfering with sleep breathing like benzodiazepines[5,6], nonsteroid antiinflammatory agents[7] or beta blockers[8]. Some of these subjects were on statins, some on antihypertensive agents, a few on antiaggregating agents (table 1)

To evaluate their sleep disturbance we used the Armband, an extensively validated tool that can measure the characteristics of the sleep and the number of awakenings for as long as seven consecutive nights [9,10,11,12,13]. This tool is applied to the forearm and kept in place for seven days, with the exception of the time of the morning shower. Among the different parameters estimated the instrument gives an accurate report of the time spent sleeping (TS), the number (nAW) and the duration of the awakenings (dAW), and the number of daytime sleeping episodes (dtS). To evaluate the impact of the sleep pattern on blood glucose variability we also asked our diabetic patients to record their fasting blood glucose levels upon awakening throughout the period of observation with the home blood glucose monitor using an interference free electrochemical method. We also asked them to duplicate the results at least one morning during this period. The Blood glucose meters were routinely

calibrated as per the internal procedure of our department. All the values were downloaded and the Standard Deviation (SD) of the FBG was calculated as an index of glucose variability[14]. The data were log transformed to improve the distribution.

Results

The number of episodes of daytime sleepiness were remarkably few, with a nonsignificant trend to increase with age and inversely to the time spent sleeping. All the available physical parameters and those relevant to sleep, TS, nAW, dAW, dtS were entered in the multiple correlation. After removing the effect of the BMI, Age and HbA1c only the number of awakenings remained significantly related to the SD of the fasting blood glucose ($\text{corr}=.76$, $p=.001$). We had the same result when the average FBG of each day of observation was substituted for the SD. The ANOVA among the different SD and FBG groups was $p<.001$. the data were analyzed with the SPSS package ver 19. (Figure 1 and 2)

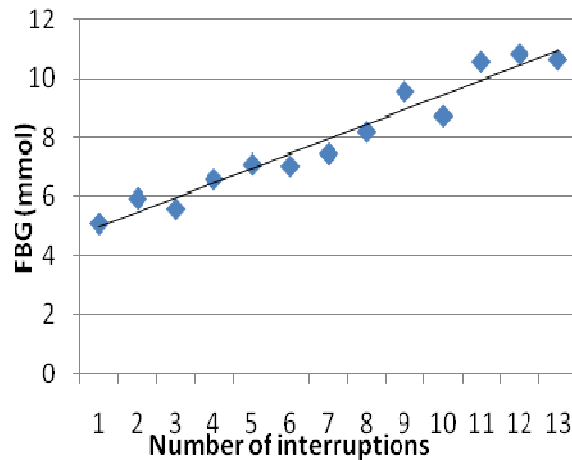


Figure 1. Interruptions vs FBG.

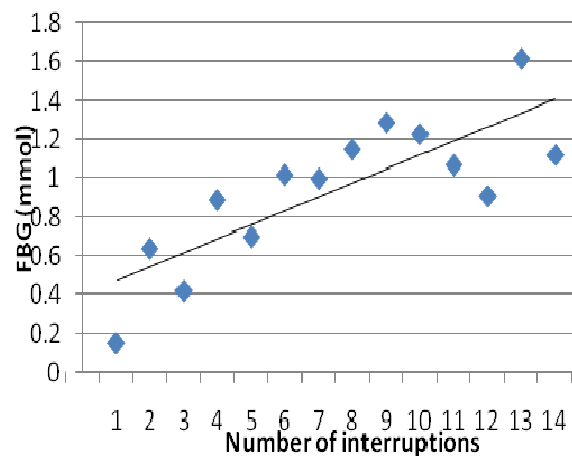


Figure 2. Interruptions vs SD.

Discussion

The role of sleep disturbance on glucose metabolism is being increasingly recognized [15,16]. Spiegel et Al in 1999 [17] assessed carbohydrate metabolism, thyrotropic function, activity of the hypothalamo-pituitary-adrenal axis, and sympathovagal balance in 11 young men after time in bed had been restricted to 4 hours per night for 6 nights. These authors compared the sleep-debt condition with measurements taken at the end of a sleep-recovery period when participants were allowed 12 h in bed per night for 6 nights. They could demonstrate that Glucose tolerance was lower in the sleep-debt condition than in the fully rested condition ($p < 0.02$), as were thyrotropin concentrations ($p < 0.01$). Evening cortisol concentrations ($p = 0.0001$) and activity of the sympathetic nervous system were increased in the sleep-debt condition ($p < 0.02$). This was one of the first studies to demonstrate a role of sleep debit on glucose metabolism. Furthermore these Authors observed that during sleep deprivation there was 30% reduction of the first peak of insulin response that can be reverted to normal after restoration of the normal sleeping pattern. This observation is extremely interesting because the absence of the first peak of insulin secretion is a characteristic of the early diabetes mellitus [18]. In a recent paper Tasali et Al demonstrated that all-night selective suppression of slow wave sleep (SWS), without any change in total sleep time, resulted in marked decreases in insulin sensitivity, without adequate compensatory increase in insulin release, leading to reduced glucose tolerance and increased diabetes risk [19]. More recently a study of the Sleep Research Center of Pennsylvania evaluated 1741 subjects of both sexes, using both results from the sleep laboratory and questionnaires, and reported that insomnia with short sleep duration was associated with increased odds for diabetes [20]. Although this study has merits the presence of sleep disorders was based on a standard questionnaire completed by the subjects, and this technique has an inherent uncertainty. Moreover if the questionnaires were self filled or completed with the help of the medical staff is not stated, although this aspect may have a significant bearing on the results. Another recently published study with 6-ys follow-up of 1455 non diabetic subjects linked short sleep duration to the development of Impaired Fasting Glucose. [21] This association was apparently mediated by an increase in insulin resistance. Another study of 40 diabetic subjects also demonstrated that, after adjusting for the covariates, 10% higher sleep fragmentation was associated with a 9% higher FGB level, 30% higher fasting insulin level and 43% higher insulin resistance index (HOMA) [22]. However interesting this study included subject treated with insulin and, or, sulphonylurea drugs, which by themselves may cause hypoglycaemia and glucose variability, thus confusing the statistical evaluation.

Collectively taken these studies point to a critical role of sleep in the control of blood glucose levels. On the other hand they fail to identify a single culprit. It is reasonable to hypothesize that all the aspects of the sleep participate to the regulation of the blood glucose. However it is also undeniable that with our current technique we have really hard times in exploring this dimension [23].

We selected 60 subjects treated with metformin or diet alone, thus the possibility of drug induced nocturnal hypoglycaemia was substantially nil. The high correlation level with the number of awakenings is not surprising. Any form of nocturnal awakening is a stressful condition and thus can induce an increase in blood glucose. Since the sleep recording time spanned for seven nights the results are sound. We did not include the HbA1c in our outcome

evaluation since this analyte is a long term (3 months) index, and any relationship with the sleeping behaviour of only 7 nights out of 90 may be deceptive. The use of the SMBG may be a moot point, since all the available glucose meters have an inherent error that may reach $\pm 15\%$. However with the most recent methods the error is minimized, and the SMBG is the most affordable way to evaluate the FBG. Furthermore the consistent number of subjects studied for a long period gives substantial statistical support to the results. We chose to use the Standard deviation of the FBG as a proxy for the glucose variability even if this parameter may be influenced by the average because the SD is the most widely used and reproducible measure available. We also did not include the blood glucose values taken during the waking hours because the variability may be attributable to many other interfering variables, physical activity, meals, driving and any other stressful conditions. This was a further reason to use the SD instead of the MAGE, that was originally derived from values around the clock. However the possibility that disturbed sleep by interfering with the appetite may also influence the size / quality of the meals and the post-prandial blood glucose value is rather probable. Many studies point to a role of sleep on the hormones regulating appetite [24,25]. In brief our observation of a strict correlation between the number of awakenings and the fasting glucose variability has a sound statistical and logical basis. Since the increased variability of the FBG was identified as a risk factor for increased morbidity and mortality [26] our data rise the possibility that sleep disturbance may be a “masked killer” behind glucose variability.

Although our observation may add to the growing data linking sleep and glucose metabolism many more aspects remain to be clarified. We do not know the role of disturbed respiration / OSAS that are closely linked to sleep, the role of the different phases of sleep, the role of clock time when sleeping starts, the role of the many drugs that diabetic patients take. However from our data the time spent sleeping does not seem to have a major role.

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