Sleep architecture in children with Diabetes Mellitus Type 1

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Abstract:

Background: Type 1 Diabetes Mellitus is one of the most common chronic health conditions in youth. Sleep is a crucial determinant of psychological, emotional, and physical health. There are evidences suggest that Type 1 Diabetes Mellitus may be associated with sleep disorders. **Objective:** Our aim is to study sleep architecture in children with Diabetes Mellitus Type 1, by using polysomnography and correlating the findings to glycemic state. **Methods:** Forty children were included in this study, divided into two groups: twenty diabetic patients and twenty healthy volunteers. All children were subjected to thorough clinical assessment, and polysomnography. Diabetic children were also subjected to the random blood sugar and HbA1c. **Result:** the diabetic group showed statistically significant difference in the lighter sleep (N1 stage) (P value = 0.001) and respiratory parameters (average oxygen saturation and lowest oxygen saturation) (P values = 0.018) in comparison to the control group. However, no statistically significant difference was found on the deep sleep (N2, N3 & REM), Apnea Hypopnea index or snoring. **Conclusion:** Polysomnography can give valuable information helping to detect the effect of Type 1 Diabetes Mellitus on increasing the lighter sleep (N1 stage) and decreasing oxygen saturation in children with Type 1 Diabetes Mellitus.

Keywords: Sleep architecture; polysomnography; glycemic state.

1. Introduction:

The relationship between sleep and Type 1 Diabetes Mellitus is dynamic and bidirectional. Type 1 Diabetes Mellitus can contribute to sleep changes. On the other hand, sleep problems and disruption can affect insulin sensitivity and glucose regulation. [1].

Sleep Disordered Breathing (SDB) has primarily been studied in adults with Type 2

Diabetes Mellitus (T2DM). There is an association between poor glucose control and the severity of SDB [2]. The complications of diabetes (such as neuropathy) also increase the frequency of apneas and prolong their duration [3].

SDB in poorly controlled children (hemoglobin A1c ≥ 8.0%) with Type 1 Diabetes Mellitus (T1DM) compared to healthy children had more frequent and longer apneas compared with patients with better controlled diabetes and controls [4].

Inadequate amounts of sleep and SDB may be particularly problematic for individuals with Type 1 Diabetes Mellitus [5]. However, the relationship between sleep quantity and quality in children with Type 1 Diabetes Mellitus is largely unstudied.

Sleep architecture may be altered in adults with Type 1 Diabetes Mellites. In some studies, diabetic patients spent more time in lighter stages of sleep (N1 and N2) [6], Rapid Eye Movement (REM) and less time in Slow Wave Sleep (SWS) [7], in contrast, other studies did not show a difference in sleep architecture compared to healthy participants. However, these studies demonstrated that patients with Type 1 Diabetes Mellitus had more frequent and longer awakenings [8].

In this study, we hypothesize that Type 1 Diabetes Mellitus in children can affect sleep architecture.

2. Aim of the work:

Is to study sleep architecture in children with Diabetes Mellitus Type 1.

3. Patients and Methods:

Twenty Diabetic Children and twenty healthy children (case control study), with age and sex matching.

■ **Inclusion criteria:**

- 10-15 year's old children with T1DM

- Male and female patients.

- Diagnosed by fasting blood sugar

- Performing HBA1c within one month before polysomnography (PSG) to detect the glycemic control (Controlled HbA1c < 6.5, uncontrolled HbA1c ≥ 6.5 [9].

- Random blood sugar just before performing PSG to detect the glycemic state (Hyperglycemia: RBS ≥ 180, normoglycemia: RBS < 180 [9].

Exclusion criteria:

- Type 2 DM (T2DM)

- Overweight (weight between 85 - 95% of growth chart) & obese children (weight more than 95% of growth chart) [10].

- Down syndrome children

- Other medical problems (chest disease, cardiovascular disorder and hypertension).

3.2 All patients were subjected to:

■ **Neuropediatric assessment:**

1- History taking regarding the presence of manifestation of Diabetes mellitus: polyuria, polydipsia, nocturnal enuresis, and weight loss.

- Examination of measurements (weight, height and Body Mass Index)
- **laboratory investigations**: HbA1c and random blood sugar.
- **Neurophysiological assessment**: One night of laboratory-based polysomnography (PSG). PSG was performed using Somnoscreen plus PSG+ and DOMINO software. The following electrophysiological data was recorded:

A- Electroencephalography (EEG) electrodes (C3/A2, C4/A1, F3/A2, F4/A1, O1/A2 and O2/A1) were applied according to the international 10-20 system of electrode placement.

B- Electrooculography (EOG) electrodes: the left and right active electrodes were placed on the lateral side of infraorbital and supraorbital surfaces respectively.

C- Sub mental and tibial EMG electrodes.

D- ECG electrodes were applied over the anterior chest.

E- Respiratory monitoring: an airflow cannula and thermistor to measure respiratory airflow, thoracic and abdominal sensor belts to measure respiratory effort.

F- Finger pulse oximetry to detect oxygen saturation.

G- Snoring neck microphone

H- The PSG was scored manually according to the American Academy of Sleep Medicine guidelines. Sleep parameters were obtained for each participant included;

1- Percentage of each stage (%) (N1, N2, N3 & REM)

2- Average and lowest Oxygen saturation (%)

3- Snoring.

4- Apnea event: reduction in the respiratory flow through the thermistor > 90% for more than 10 seconds.

5- Hypopnea event: reduction in the nasal pressure > 30 % for more than 10 seconds associated with reduction in oxygen saturation > 3 % or arousal.

6- Apnea index: the number of apnea events per hour of sleep

Hypopnea index: the number of hypopnea events per hour of sleep [11].

Apnea Hypopnea index (AHI): the number of apneas and hypopneas detected per hour of sleep. It was graded as 'mild' (1–4.9/h), 'moderate' (5–9.9/h), or 'severe' (>10/h) [12].

Statistical methodology

• Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data.

Comparisons between quantitative variables were done using the non-parametric Mann-

Whitney test [13]. For comparing categorical data, Chi square (χ2) test was performed.

Bivariate correlation test to test association between variables. Exact test was used instead when the expected frequency is less than 5 [14]. P-values less than 0.05 were considered as statistically significant.

4. Results:

This study was carried on 20 Egyptian patients with type 1 diabetes mellitus and 20 control subjects, age and sex matching.

4.1 DEMOGRAPHIC RESULTS

A- Age (Yrs): The age of the patients and controls ranged between 10 to 15 years with a mean of 12.13 ($\pm$1.49) years in patients' group and 11.55 ($\pm$1.70) years in control group. There was no statistically significant difference between the age of the patients and that of the control group, as shown in table (1).

B- Body Mass Index (Kg/ m^2): There was no statistically significant difference between BMI of the patients and that of the control group, as shown in table (1).

Table (1): Age & BMI distribution in T1DM patients and control groups

Group		Minimum	Maximum	Mean	$\pm$ SD	P value
Patients	Age	10	14.5	12.13	1.49	0.265
Control		10	14	11.55	1.70	
Patients	BMI	13.70	21.40	17.48	2.32	0.289
Control		14.00	21.70	16.81	1.75	

B- Gender: the study includes 6 males (30%) and 14 females (70%) in the patient and control groups. as shown in table (2)

Table (2): Gender distribution in T1DM patients and control groups

	No	Males	Percent	Females	Percent	P value
Patients	20	6	30	14	70	1
Control	20	6	30	14	70	

4.4 Polysomnography Results:

Sleep stages (%): There was statistically significant difference between stage 1 and there were no statistically significant differences in stage N2, N3 or REM of the patients and that of the control group, as shown in table (3) and figure (1).

Table (3): sleep stages in T1DM patients and control groups

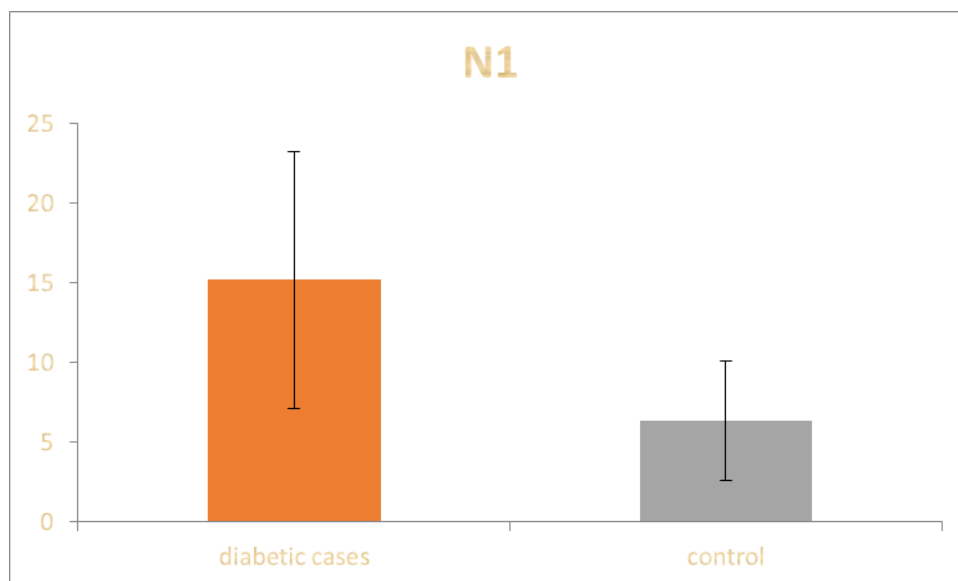|	Group										P value
	diabetic cases					Control					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
N1	15.19	8.08	14.30	4.10	36.20	6.32	3.75	6.20	1.60	17.20	< 0.001
N2	37.67	9.16	35.55	23.60	55.30	42.32	9.00	41.10	20.40	65.80	0.056
N3	37.63	9.85	38.15	19.60	56.60	39.31	10.71	41.00	8.60	67.20	0.512
REM	10.52	4.53	9.75	4.50	19.80	12.50	4.52	11.30	5.90	22.60	0.242

Figure (1): N1 in T1DM patients and control groups

Apnea/Hypopnea index (AHI): There was no statistically significant difference between AHI of the patients and that of the control group, as shown in table (4).

Table (4): AHI in T1DM patients and control group.

	Group										P value
	diabetic cases					control					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
AHI	2.05	5.01	0.00	0.00	20.00	0.50	2.24	0.00	0.00	10.00	0.429

Average and Lowest Oxygen saturation (%): There was statistically significant difference between Oxygen saturation of the patients and that of the control group, as shown in table (5) & figure (2), (3)

Table (5): O2 saturation in T1DM patients and control groups.

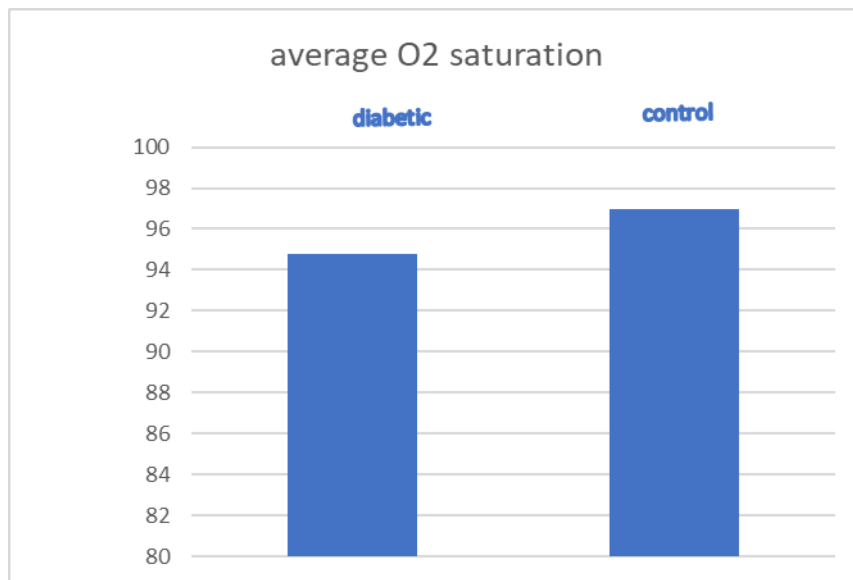|	group										P value
	diabetic cases					control					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
average O2 saturation	94.8	2.07	94.5	88	98	96.25	1.59	97	93	98	0.018
lowest O2 saturation	85.45	5.39	84.00	73.00	95.00	89.55	5.07	90.50	79.00	96.00	0.018

Figure (2): Average O2 saturation in T1DM patients and control groups.
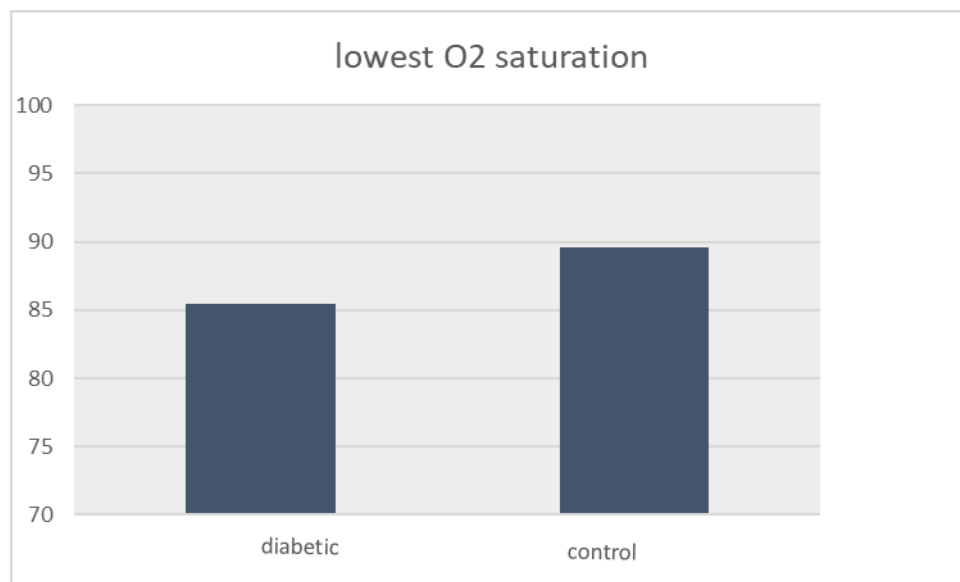

Figure (3): Lowest O2 saturation in T1DM patients and control groups.

Snoring: There was no statistically significant difference between snoring of the patients and that of the control group, as shown in table (6)

Table (6): snoring in T1DM patients and control groups.

		Group				
		diabetic cases		control		P value
		Count	%	Count	%	
snoring	Yes	8	40.0%	4	20.0%	0.168
	No	12	60.0%	16	80.0%	

4.5 Correlation results

1- Correlation between Hemoglobin A1c, Random Blood Sugar & BMI with sleep parameters: There was a significant positive correlation between HbA1c and N1 stage, in addition to a significant negative correlation between HbA1c and REM stage. As shown in table (8) & figure (4), (5). There was also a significant negative correlation between the Body Mass Index and Oxygen saturation. As shown in table (8) & figure (6), (7).

Table (8): Correlation between HbA1c, RBS & BMI with sleep parameters.

Sleep parameters		HbA1c	RBS	BMI
N1	R	.453	.422	.248
	P value	.045	.064	.292
N2	R	-.139	.056	-.215
	P value	.558	.816	.363
N3	R	-.178	-.204	-.082
	P value	.453	.387	.730
REM	R	-.600	-.164	-.199
	P value	.005	.488	.400
AHI	R	-.338	-.045	-.162
	P value	.145	.851	.495
Snoring	R	-.148	.290	-.110
	P value	.534	.214	.644
Average O2. S	R	-.259	-.146	-.501
	P value	.271	.538	.024
Lowest O2. S	R	-.121	-294	-.494
	P value	.611	.209	.027

HbA1c; glycosylated Hemoglobin, RBS; Random Blood Sugar, BMI; Body Mass Index, REM; Rapid Eye Movement, AHI; Apnea Hypopnea Index.
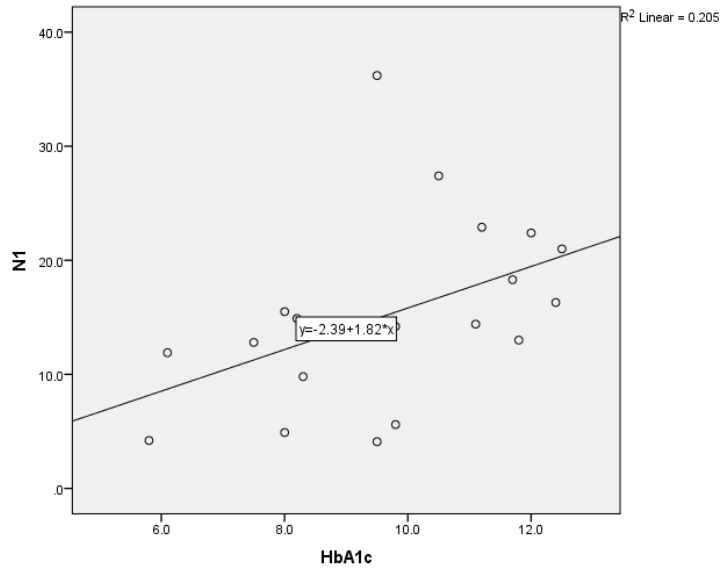
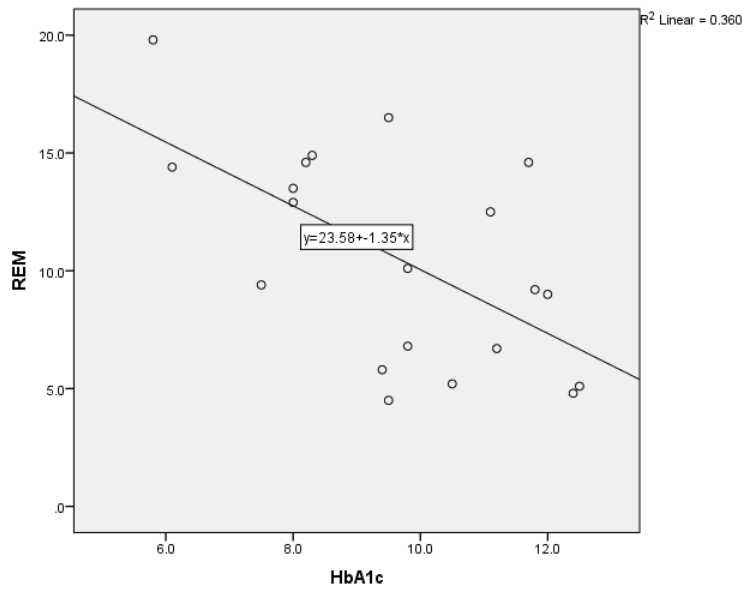**Figure (4): significant positive correlation between HbA1c & N1 stage.**

Figure (5): significant negative correlation between HbA1c & REM stage.
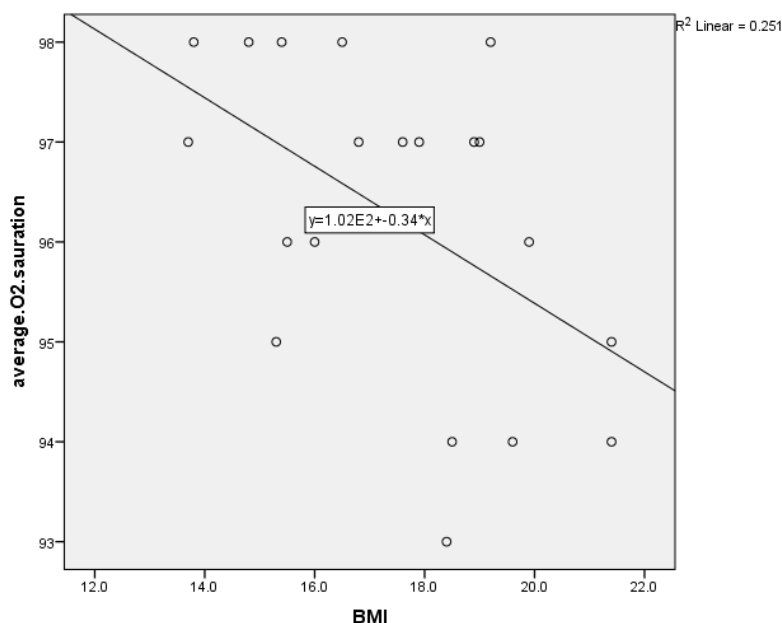
Figure (6): significant negative correlation between BMI & average O2 saturation.
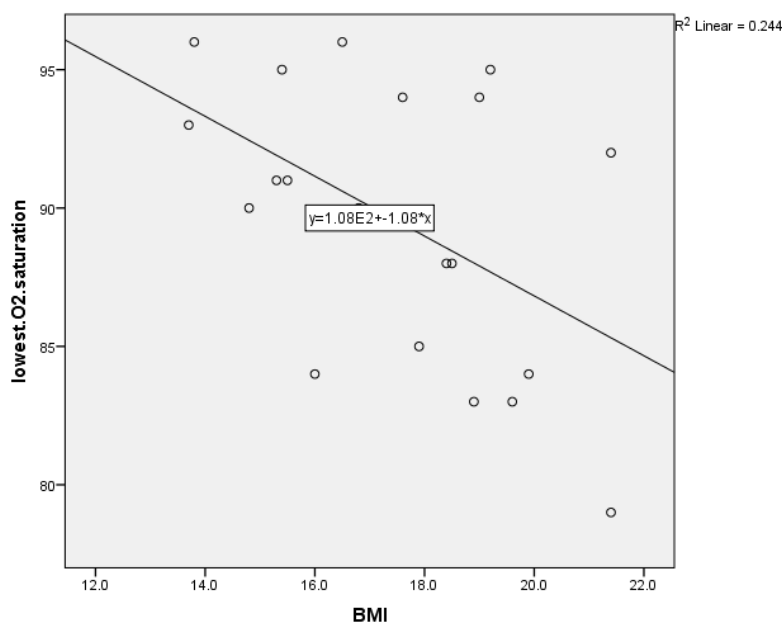

Figure (7): significant negative correlation between BMI & lowest O2 saturation.

5. Discussion:

Type 1 diabetes mellitus is an autoimmune condition that affects about one in every 400 children and adolescents [15]. The clinical research in Diabetes Mellitus was risen to study the sleep-related disorders in this population. It has shown that up to one third of patients with Diabetes Mellitus suffered from concomitant sleep disorders, as compared to control groups [16].

Our study aimed at demonstrating relationship between Type 1 Diabetes mellitus and sleep stages in addition to sleep parameters compared to healthy children. The two study groups were age, sex and BMI matched.

Our finding showed that children with Type1 Diabetes Mellitus had longer light stage (stage N1) as compared to control and correlated to HbA1c (The higher the HbA1c, the more the percentage of the N1 stage. This was compatible with the study of *Perfect and colleagues* [17] which proved that light stage of sleep was high in percentage than deep sleep. *Miller and colleagues* [18] also approved that spending more time in lighter stages had a negative effect on the cognitive functions. The cognition includes a variety of mental processes such as memory, problem solving, language, forward planning and attention which have serious real-life consequences.

Hyperactivity of hypothalamic pituitary axis may be attributed to increasing the light sleep [19]**.** Adreno-Cortico-Trophic Hormone (ACTH) and cortisol are increased in diabetic patients which influence sleep fragmentation and awakening interrupting sleep [20]**.**

Furthermore, average Oxygen saturation and lowest Oxygen saturation in our study were significantly decreased in Type 1 Diabetes Mellitus and inversely correlated with the Body Mass Index (The higher the Body Mass Index, the lower the Oxygen

saturation). Hypoxemia activates hypothalamic–pituitary–adrenaln axis, sympathetic nervous system and increases in the cortisol level. Increased level of cortisol and sympathetic nervous system overactivity could alter glucose metabolism through glycogenolysis, gluconeogenesis, insulin resistance, and β-cell dysfunction [21]**.**

The correlation of Body mass Index with Oxygen saturation signifies its important role in prediction of the severity of blood oxygen saturation during apnea and hypopnea event and could exacerbate sleep disordered breathing in obese patients [22]**.**

The relationship between Type1 Diabetes Mellitus and Apnea Hypopnea Syndrome is age dependent and related to long standing Diabetes mellitus [23]**.** A study was performed on adults (20-79 years) with body mass index less than 40 kg/ m^2 [24] using respiratory polygraphy (measured body position, air flow through nasal cannula, oximetry, pulse rate and respiratory effort via thoracic and abdominal bands) revealed that the prevalence of Obstructive Sleep Apnea in adults with Type1 Diabetes mellitus was high and approached that of type 2 Diabetes mellitus. The differences in ages and measurements (BMI) would explain the discrepancy between our finding and that study.

Another study was performed on 67 patients (mean age 54 ± 10 years) using polysomnography and respiratory polygraphy

for patient that refused to sleep at hospital [23]. They stated that habitual snoring was associated with increase the prevalence of Obstructive Sleep Apnea in patients with Type 1 Diabetes Mellitus. We suggest that the difference was due to discrepant ages, high duration of DM and presence of snoring in the patients of the corresponding study.

6. Conclusion and Recommendations:

Polysomnography can give valuable information, helping to detect the effect of Type 1 Diabetes Mellitus on increasing the lighter sleep (N1 stage) and decreasing oxygen saturation in children with Type 1 Diabetes Mellitus.

Our recommendations for future work are:

- Studying the effect of Type 1 Diabetes Mellitus on sleep parameters with using of continuous glucose monitoring (free style libre) during sleep.

- We also recommend increasing the number of patients to detect the effect of Type 1 Diabetes Mellitus on Total Sleep Time and efficient correlations.

7- References:

1. Macaulay GC, Galland BC, Boucher SE, Wiltshire EJ, Haszard JJ, Campbell AJ, Black SM, Smith C, Elder D, Wheeler BJ (2019). Impact of type 1 diabetes mellitus, glucose levels, and glycemic control on sleep in children and adolescents: a case–control study. Sleep, zsz226.

2. Aronsohn RS, Whitmore H, Van-Cauter E, Tasali E (2010). Impact of untreated obstructive sleep apnea (OSA) on glucose control in type 2 diabetes, Am J Respir Crit Care Med, 181: 507-513.

3. Bottini P, Dottorini ML, Cordoni MC, Casucci G, Tantucci C (2003). Sleep-disordered breathing in non-obese diabetic subjects with autonomic neuropathy, Eur Respir J, 22: 654-660.

4. Villa MP, Multari G, Montesano M, Pagani J, Cervoni M, Midulla F, Cerone E, Ronchetti R (2000). Sleep apnoea in children with diabetes mellitus: effect of glycoemic control. Diabetologia, 43 (6): 696-702.

5. Perfect MM, Elkins GR, Lahroud TL, Posey JR (2010). Stress and quality of sleep among individuals diagnosed with diabetes. Stress Health, 26: 61-74.

6. Jauch-Chara K, Schmid S M, Hallschmid M, Born J, Schultes B (2008). Altered neuroendocrine Sleep architecture in patients with type 1 diabetes. Diabetes care.2008; 31:1183–8.

7. Pallayova M, Domic V, Gesova S, Pergrim I, Tomori Z (2010). Do differences in sleep architecture exist between persons with Type 2 diabetes and nondiabetic controls?. J Diabetes Sci Technol (Online), 4: 344-352

8. Matyka KA, Crawford C, Wiggs L, Dunger DB, Stores G (2000). Alterations in sleep physiology in young children with insulin-

dependent diabetes mellitus: relationship to nocturnal hypoglycemia. J Pediatr, 137 (2): 233-238.

9. American Diabetes Association (2015). Standards of medical care in diabetes-2015.Diabetes care, 38: S41–S48.

10. Güngör NK (2014). Overweight and obesity in children and adolescence. J Clin Res Pediatr Endocrinol, 6 (3): 129-143.

11. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, Vaughn BV. (2017). AASM Scoring Manual Updates for 2017 (Version 2.4). Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine, 13 (5), 665–666.

12. Roland PS, Rosenfeld RM, Brooks LJ , Friedman NR, Jones J, Kim TW, Kuhar S, Mitchell RB, Seidman MD, Sheldon SH, Jones S, Robertson P (2011). Clinical practice guideline: Polysomnography for sleep-disordered breathing prior to tonsillectomy in children. Otolaryngol Head Neck Surg; 145 (1):S1- S5.

13. Chan YH (2003a): Biostatistics102: Quantitative Data – Parametric & Non-parametric Tests. Singapore Med J.;44(8): 391-396.

14. Chan YH (2003b): Biostatistics 103: Qualitative Data –Tests of Independence. Singapore Med J.;44(10): 498-503.

15. Pettitt D.J, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, Liese AD, Linder B, Mayer-Davis EJ, Pihoker C,

Saydah SH, Standiford DA, Hamman RF (2014). Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. Diabetes Care, 37 (2): 402-408

16. Sridhar GR, Madhu K (1994). Prevalence of sleep disturbances in diabetes mellitus, Diabetes Res Clin Pract; 23: 183–186.

17. Perfect MM, Patel PG, Scott RE, Wheeler MD, Patel C, Griffin K, Sorensen ST, Goodwin JL, Quan SF (2012). Sleep, glucose, and daytime functioning in youth with type 1 diabetes. Sleep; 35: 81–8.

18. Miller MA, Wright H, Hough J, Cappuccio F P (2014). Sleep and Cognition, Sleep and its Disorders Affect Society, Chris Idzikowski, IntechOpen.

19. Schultes Bf, Kern W, Bong W, Wellhoener P, kerner W, born J, Fehm H, peters A (2015). Supraphysiological Hyperinsulinemia Acutely Increases Hypothalamic-Pituitary-Adrenal Secretory Activity in Humans. The Journal of Clinical Endocrinology & Metabolism; 84 (9): 3041- 3046.

20. Hirshkowitz M, harafkhaneh A (2005). Handbook of Clinical Neurophysiology, Vol. 6

21. Rusu A, Bala CG, Anca-Elena Craciun AE (2017). HbA1c levels are associated with severity of hypoxemia and not with apnea hypopnea index in patients with type 2 diabetes: Results from a cross-sectional study, Journal of Diabetes; 9 (6): 555- 561.

22. Peppard PE, Ward NR, Morrell MJ (2009). The Impact of Obesity on Oxygen

Desaturation during Sleep-disordered Breathing, American Journal Of Respiratory And Critical Care Medicine; 180 (8): 788–793.

23. Manin G, Pons A, Baltzinger P, Moreau F, Iamandi C, Wilhelm JM, Lenoble p, Kessler L, Kessler R (2015). Research: Complications Obstructive sleep apnoea in people with Type 1 diabetes: prevalence and association with micro- and macrovascular complications, Diabet. Med; 32: 90–96.

24. Vale J, Manuel P, Oliveira E, Oliveira AR, Silva E, Melo V, Sousa M, Alexandre JC, Gil I, Sanchez A, Nascimento E, Torres AS (2015). Obstructive Sleep Apnea and Diabetes Mellitus. Rev Port Pneumol; 21 (2): 55-60.