JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/13327

The association between insulin resistance, sleep disorders, and inflammation in obese children

Dilek Konuksever[1], Sevinc Puren Yücel Karakaya[2]

[1]*Department of Pediatrics, Ankara City Hospital, Turkish Ministry of Health, Bilkent, Ankara, Turkey*
[2]*Department of Biostatistics, Cukurova University, Adana, Turkey*

Received: 2023-04-24.
Accepted: 2023-05-16

J Clin Med Kaz 2023; 20(3):82-87

Corresponding author:
Dilek Konuksever.
E-mail: dilekkonuksever@hotmail.com;
ORCID: 0000-0003-2334-9590

Abstract

Aim: Both obesity and sleep disorders cause chronic subclinical inflammation. Inflammation is a significant factor in triggering insulin resistance. This study aimed to analyze the association between sleep disorders, inflammation, and insulin resistance in obese/overweight children.

Material and methods: In this cross-sectional study, 150 overweight/obese children were included. Sleep disorder was measured by using the Sleep Disturbance Scale for Children. The homeostasis model of assessment for insulin resistance (HOMA-IR) was calculated according to fasting glucose and insulin results. Logistic regression models and Spearman Rank Correlation Coefficients were used to estimate associations between parameters.

Results: A statistically significant raising was found in insulin resistance and C-reactive protein levels in those with sleep disorders ($p<0.05$). However, no correlation was found between sleep disorders and the HOMA-IR, C-reactive protein, and neutrophil-to-lymphocyte ratio levels. On the other hand, HOMA-IR was weak positively correlated with neutrophil-to-lymphocyte ratio ($r=0.222$, $p=0.006$), and CRP ($r=0.390$, $p<0.001$).

Conclusion: Although we did not detect the association between sleep disorders and insulin resistance and C-reactive protein levels, we revealed that children with sleep disorders had higher insulin resistance and C-reactive protein levels than those without.

Key words: sleep, insulin resistance, children, obesity, neutrophil-lymphocyte ratio, C-reactive protein

Introduction

Obesity is an important clinical problem worldwide that is increasingly prevalent among both children and adults [1]. It is estimated that 17% of children and adolescents aged 2 to 19 suffer from obesity [2]. The increasing rate of obesity has been linked with an increase in sleep disorders [3]. Although some studies have shown that obesity contributes to sleep disorders, other studies have also shown that sleep disorders compose a predisposition to obesity [4, 5]. As a result, both clinical disorders are acknowledged to be bi-directionally connected [6, 7].

Obesity and sleep disorders cause chronic low-grade systemic inflammation and independently increase the risk of insulin resistance [6, 8]. Their frequent coexistence has a synergistic effect, contributing to the pathophysiological effects of each other's metabolism. Inflammation is thought to be the most essential mechanism linking these effects [9, 10].

Obesity is defined as an overaccumulation of adipose tissue in the organism. The primary role of adipose tissue is to depot excess energy in the structure of triacylglycerol. Furthermore, adipose tissue secretes many peptides as an endocrine organ. Adipocytes need the anabolic effects of insulin to depot the exceeding

energy. The increased lipid storage need is supplied by the anabolic ability of hyperinsulinemia. Eventually, adipocytes compass a threshold where no further anabolic pressure can be compensated, which puts stress on the adipocytes. Thus, impaired adipogenesis leads to inflammatory cytokine release, necrosis, increased immune cells, and inflammation. Tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels that increase with inflammation may trigger insulin resistance. In addition, C-reactive protein (CRP) levels, an important proinflammatory indicator, increase with obesity [8, 9]. Obesity-induced low-grade inflammation reduces sleep quality and duration. Because this increased TNF-α and IL-6 levels shift from night to morning, causing daytime sleepiness and less slow-wave sleep. As sleep disorders continue, the inflammatory response progresses, causing further TNF-α, IL-6, and CRP levels to increase. On the other hand, chronic-systemic inflammation also induces hyper-stimulation of the central nervous system. And this causes excessive activation of the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic system. Eventually, these mechanisms maintain the vicious circle between inflammation, insulin resistance, and obesity in the body [6, 10, 11].

TNF-α, IL-6, and CRP have been investigated for the potential to be beneficial biomarkers in the diagnosis of sleep disorders and obesity-induced inflammation. CRP is more accessible and less expensive than TNF-α and IL-6 biomarkers. The neutrophil-to-lymphocyte ratio (NLR) has also been reported as a potential inflammatory marker. NLR, like CRP, is inexpensive and more easily accessible than TNF-α and IL-6 [12]. Therefore, we planned to examine the NLR besides the traditional inflammatory parameter CRP while evaluating the relationship between sleep disorders, obesity, and insulin resistance with inflammation.

The present study aimed to analyze the association of sleep disorders, inflammation levels, and insulin resistance in obese/overweight children. We hypothesized that concomitant sleep disorders in obese/overweight patients are associated with increased inflammation (increased CRP, NLR) and insulin resistance.

Material and methods

This study was performed by the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ankara City Hospital (No: E2-22-2231). All children and/or their parents signed the Consent and Informed Form.

Patients and study design

This prospective and cross-sectional study was performed at the pediatric outpatient of a tertiary care children's hospital. Obese or overweight children aged 6-16 years were included in the study for 5 months after obtaining permission from the ethics committee. This study covered 150 obese or overweight children and adolescents. The limits of overweight and obesity were determined by the World Health Organization (WHO) references. Accordingly, if body mass index (BMI) was more than 2 standard deviations from the median obesity was considered, and if it was more than 1 standard deviation, it was considered overweight [13]. The participant's height and weight measurements were taken by trained pediatric nursing staff, and BMI was calculated by a pediatrician. Children with chronic diseases such as diabetes, rheumatological diseases, liver diseases, or other comorbid sleep disorders (adenoids, insomnia, narcolepsy, and restless legs syndrome), those with acute or chronic infections, and those who use drugs that may affect sleep were excluded.

Sleep disturbance scale

The Children's Sleep Disorder Scale (SDSC) questionnaire was used to detect sleep disorders. [14, 15]. The SDSC is a parents-report measure of children's sleep disorders in the last six months. SDSC included 26 items and six subscales. These are disorders of initiating and maintaining sleep (DIMS), sleep-breathing disorders (SBD), disorders of arousal (DA), sleep-wake transition disorders (SWTD), disorders of excessive somnolence (DOES), and sleep hyperhidrosis (SHY).The scores of the items on this five-point Likert type (1=least severe and 5=most severe) scale supply a total sleep score from 26 to 130. A total score of more than 70 is considered a sleep disorder.

Assessment of insulin resistance, CRP, and NLR levels

Glucose levels were measured automatically by the glucose oxidase method. CRP levels were measured by a latex-enhanced immunoturbidimetric method, and insulin levels were determined via chemoluminescence immunoassays. All three parameters were measured using Atellica Solution Immunoassay & Clinical Chemistry Analyzers (Siemens Healthcare Diagnostics, Erlangen, Germany). Hemograms and accordingly neutrophil/lymphocyte ratio levels were performed using the ADVIA 2120 Hematology System (Siemens Healthcare Diagnostics, Erlangen, Germany). Blood samples were drawn simultaneously, between 08.00-10.00 A.M, .after 10-12 hours of fasting. HOMA-IR was estimated as insulin (μU/ml)x glucose (mg/dl) /405 and HOMA-IR ≥ 2.5 was considered insulin resistance [16].

Statistical analysis

Categorical variables were revealed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and median and minimum-maximum where appropriate. Chi-square test was used to compare categorical variables between the groups.

The distribution normality of continuous variables was approved by the Kolmogorov-Smirnov test. For the comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. To evaluate the correlations between measurements, Spearman Rank Correlation Coefficient was used. Logistic regression analysis was performed to determine significant predictors of insulin resistance variable. In univariate analysis, variables significant at the $p < 0.25$ level were entered in backward logistic regression analysis. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

This study enrolled 150 patients with a mean age of 12.1±2.7 years, including 83 (55.3%) boys and 67 (44.7%) girls. All patients had a median BMI of 27.6 (kg/m2) and a median BMI SD of 2.1; 72 (48.0%) were overweight, and 78 (52.0%) were obese.

The children's mean total SDSC questionnaire score was 44.3±13.2 (min: 27.0, max: 113.0). The number of children with total SDSC scores greater than 70, indicating a sleep disorder is 11 (7.3%). The characteristics of the participants with and without sleep disorders are given in Table 1. There was no statistical variation between sleep disorder groups for age, gender, BMI, glucose, and NLR. However, the sleep disorders group was higher HOMA-IR and CRP ($p<0.001$ and $p=0.004$,

Table 1 Demographic and clinical characteristics according to sleep disorders groups

	Sleep Disorders		p
	No (n=139)	Yes (n=11)	
Age(year)	12.0(7.0-16.0)	13.3(7.6-16.0)	0.997
Gender, n(%)			
Girls	76(54.7)	7(63.6)	0.755
Boys	63(45.3)	4(36.4)	
BMI	27.6(19.2-49.4)	28.7(23.7-38.6)	0.174
Glucose	84.0(68.0-100.0)	87.0(77.0-106.0)	0.261
HOMA-IR	2.9(0.7-15.1)	5.2(4.0-30.0)	<0.001
N/L	1.7(0.7-4.4)	2.3(1.0-4.2)	0.444
CRP	2.0(0.0-19.2)	5.4(0.0-12.1)	0.004

Unless otherwise specified data was expressed as mean±standard deviation, median(min-max).
BMI: Body mass index, NLR: Neutrophil-to lymphocyte ratio, CRP: C-reactive protein, HOMA-IR: Homeostasis model of assessment for insulin resistance, SDSC: Sleep Disturbance Scale for Children

respectively) (Figure 1). Age, BMI, glucose, NLR, and CRP increased significantly with IR (p=0.013, p<0.001, p<0.001, p=0.023, and p=0001, respectively). Although the median SDCD total score did not differ significantly between the insulin resistance groups, all individuals with sleep disorders (n=11) were found to be in the insulin resistance group (p=0.004). There were no significant differences among the insulin resistance group concerning DIMS, SBD, DA, SWTD, DOES, and SHY (p>0.05 for all) (Table 2).

In correlations analysis, HOMA-IR was significantly positively correlated with age (r=0.233, p=0.004), BMI (r=0.359, p<0.001), NLR (r=0.222, p=0.006), and CRP (r=0.390, p<0.001). However, no association was found between SDSC total score and demographic characteristics, inflammation markers, or HOMA-IR (Table 3). The univariate and multiple logistic regression analyses are expressed in Table 4. Multiple logistic regression analysis revealed that independent risk factors for insulin resistance were BMI (OR= 1.13, 95% CI: 1.03-1.25, p=0.009) and CRP (OR= 1.21, 95% CI: 1.03-1.42, p=0.022). Every one unit increase in BMI and CRP resulted in a 13%, and 21% increase in the occurrence of insulin resistance, respectively.

Table 2 Demographic and clinical characteristics according to insulin resistance groups

	Non-IR (HOMA-IR<2.5) (n=59)	IR (HOMA-IR≥ 2.5) (n=91)	
Age(year)	11.3(7.0-16.0)	12.6(7.3-16.0)	0.013
Gender, n(%)			
Girls	35(59.3)	48(52.7)	0.533
Boys	24(40.7)	43(47.3)	
BMI	25.6(21.0-38.9)	28.0(19.2-49.4)	<0.001
Glucose	82.6±5.9	86.1±6.1	<0.001
NLR	1.4(0.7-4.0)	1.8(0.7-4.4)	0.023
CRP	0.8(0.0-12.6)	2.3(0.0-19.2)	0.001
Sleep Disorders			
SDSC total score	42.0(29.0-59.0)	40.0(27.0-113.0)	0.894
Sleep disorders, n (%)			
No	59(100.0)	80(87.9)	0.004
Yes	-	11(12.1)	
DIMS	13.0(8.0-22.0)	13.0(7.0-29.0)	0.879
SBD	4.0(2.0-12.0)	3.0(3.0-15.0)	0.332
DA	4.0(3.0-12.0)	3.0(3.0-15.0)	0.160
SWTD	10.0(6.0-17.0)	9.0(6.0-29.0)	0.657
DOES	7.0(5.0-14.0)	7.0(5.0-25.0)	0.357
SHY	3.0(2.0-10.0)	3.0(2.0-10.0)	0.182

Unless otherwise specified data was expressed as mean±standard deviation or median(min-max). Sleep disorders state as defined by SDSC total score>70 IR: Insulin resistance, HOMA-IR: homeostasis model of assessment for insulin resistance, BMI: Body mass index, CRP: C-reactive protein, NLR: Neutrophil-to lymphocyte ratio, DIMS: Disorders of initiating and maintaining, SBD: Sleep-breathing disorders, DA: Disorders of arousal, SWTD: Sleep-wake transition disorders, DOES: Disorders of excessive somnolence, SHY: Sleep hyperhidrosis.

Table 3 Correlation coefficients

	BMI	N/L	CRP	HOMA-IR	SDSC total score
Age(year)	0.552(<0.001)	0.323(<0.001)	0.072(0.383)	0.233(0.004)	-0.035(0.675)
BMI	-	0.245(0.002)	0.204(0.012)	0.359(<0.001)	-0.034(0.682)
N/L		-	0.251(0.002)	0.222(0.006)	-0.020(0.812)
CRP			-	0.390(<0.001)	0.130(0.112)
HOMA				-	0.071(0.389)
SDSC total score					-

Data was expressed as correlation coefficient and corresponding p-value.
BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, HOMA-IR: homeostasis model of assessment for insulin resistance, SDSC: Sleep Disturbance Scale for Children

Table 4 Univariate and multiple logistic regression analysis for the prediction of IR

	Univariate		Multiple	
	OR (95%CI)	p	OR (95%CI)	p
Age(year)	1.17(1.04-1.33)	0.012		
Gender(2)	1.31(0.67-2.54)	0.429		
BMI	1.15(1.06-1.26)	0.002	1.13(1.03-1.25)	0.009
N/L	1.77(1.08-2.92)	0.025		
CRP	1.25(1.07-1.46)	0.005	1.21(1.03-1.42)	0.022
SDSC total score	1.02(0.99-1.04)	0.238		

OR: Odds ratio, CI: confidence interval. Nagelkerke R^2=0.136
BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, HOMA-IR: homeostasis model of assessment for insulin resistance, SDSC: Sleep Disturbance Scale for Children

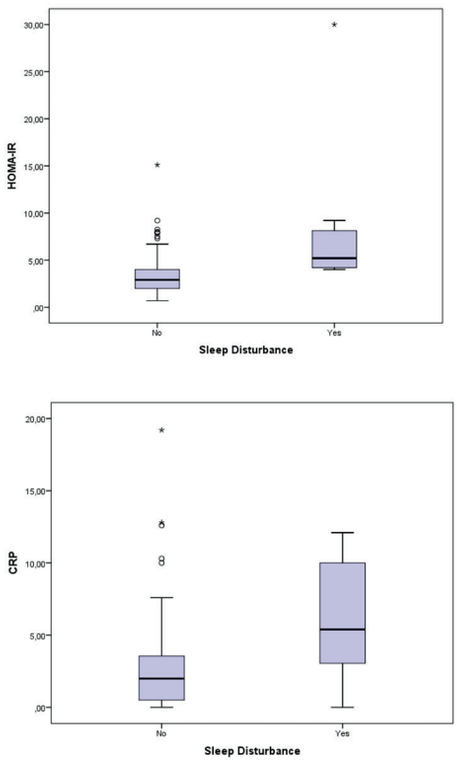

Figure 1 - Distribution of HOMA-IR and CRP according to sleep disturbance groups

Discussion

This study evaluated the association of sleep disorders, inflammatory markers (CRP, NLR), and insulin resistance in obese/overweight children. It is demonstrated that the estimation of insulin resistance via the HOMA-IR formulation in overweight/ obese children is not associated with sleep disorders. However, age, BMI, NLR, and CRP were associated with HOMA-IR. Especially NLR and CRP were detected independently associated with HOMA-IR.

Sleep disorders have been associated with increased inflammatory mechanisms and sustained activation of the HPA axis and sympathetic nervous system. As a result, an increase is observed in cortisol levels, TNF-α, IL-6, CRP, and noradrenaline levels [10, 17]. In this study, we demonstrated that CRP levels are higher in those suffering from sleep disorders. However, they were not associated with each other. NLR, another indicator of systemic inflammation, was higher in those with sleep disorders, but this was not statistically significant. Previous studies have analyzed the relationship between sleep disturbance severity and NLR in patients with obstructive sleep apnea, and conflicting results have been reported [18, 19]. In addition, several studies demonstrated NLR levels are linked to IL-6 [20]. However, while high levels of IL-6 are commonly detected in sleep disorders, there are conflicting results regarding NLR levels. We suppose that this may be due to the difference in leukocyte glucocorticoid sensitivity emerging in patients with metabolic syndrome [21].

Obesity is also associated with systemic inflammation. Increased intestinal bacterial antigens in the circulation due to increased intestinal permeability, excessive adipokine secretion by hypertrophic adipocytes, relative hypoxia of expanding adipose tissue, and mechanical stress caused by excessive accumulation of triglycerides in adipocytes each trigger the inflammatory cascade [9]. Finally, TNF-α, IL-6, and CRP levels increase in obese [1]. A few studies demonstrated that NLR is also associated with obesity [22] and insulin resistance in obese [23]. In this study, CRP and NLR were correlated with BMI and HOMA-IR.

Studies evaluating the link between sleep disorders and insulin resistance have reported conflicting results. Numerous studies [2, 24, 25] support an association between sleep disorders and insulin resistance while others do not [26-28]. This disagreement may be associated with the different exploration methods for sleep disorders, diverse study populations, and the different accepted HOMA-IR cut-off levels. For instance, Siriwat et al. investigated sleep pathologies via polysomnography in 2- 18 aged obese children. They accepted the cut-off level of HOMA-IR ≥ 3 for insulin resistance [2]. Chen et all used the actigraphy watch to obtain sleep data and considered insulin resistance to be 90th percentile and upper of HOMA-IR for age [25]. In another study involving the 7-16 age group, the questionnaire method was preferred for sleep assessment, and HOMA-IR above 3.16 were accepted as insulin resistance [28]. In our study, insulin resistance was detected in all individuals with sleep disorders, but no statistically significant correlation was detected between these two parameters.

Numerous reports have revealed a direct link between inflammation and insulin resistance [1, 9, 29]. Both sleep disorders and obesity independently trigger inflammation. Besides their independent effects, they can contribute indirectly to inflammation through their bidirectional interaction. For this reason, we suspected that the emerging insulin resistance possibility may increase via the increased inflammatory response in the coexistence of these two clinical pathologies. In this study, we found higher HOMA-IR and CRP levels in obese patients with sleep disorders than in obese patients without sleep disorders. However, there was no significant correlation between these parameters and sleep disorders.

This study has several limitations. It was performed as a single-center study, so the generalizability of the study is limited. Secondly, due to the cross-sectional nature of the study, the sample group with sleep disorders was small. A larger sample size with sleep disorders might suggest more reliable

results. Thirdly, sleep disorder was detected using the parent questionnaires in this study and this method is a subjective evaluation. Finally, we did not use different HOMA-IR cut-off values for children and adolescents.

In conclusion, our findings demonstrated that insulin resistance was associated with CRP and NLR, but not with sleep disorders. The hypothesis that comorbid sleep disturbances in obese children are associated with increased levels of inflammation and insulin resistance has not been confirmed. There were no significant correlations between sleep disorders with HOMA-IR, CRP, and NLR. Nonetheless, CRP and HOMA-IR levels were higher in those with sleep disorders. Considering that metabolic risk may continue from childhood to adulthood, early detection of factors that may facilitate this is important to avoid possible negative effects. Therefore we speculate that future studies with large samples may be helpful to determine whether sleep disorders may increase the risk of insulin resistance in obese/overweight children and which markers may be early indicators of this.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. Amin MN, Hussain MS, Sarwar MS, Moghal MMR, Das A, Hossain MZ, Chowdhury JA, Millat MS, Islam MS: How the association between obesity and inflammation may lead to insulin resistance and cancer. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews.* 2019; 13:1213-1224. https://doi.org/10.1016/j.dsx.2019.01.041
2. Siriwat R, Wang L, Shah V, Mehra R, Ibrahim S: Obstructive sleep apnea and insulin resistance in children with obesity. *J Clin Sleep Med.* 2020; 16:1081-1090. https://doi.org/10.5664/jcsm.8414
3. Koren D, Taveras EM: Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome. *Metabolism*. 2018; 84:67-75. https://doi.org/10.1016/j.metabol.2018.04.001
4. Maugeri A, Medina-Inojosa JR, Kunzova S, Agodi A, Barchitta M, Sochor O, Lopez-Jimenez F, Geda YE, Vinciguerra M: Sleep duration and excessive daytime sleepiness are associated with obesity independent of diet and physical activity. *Nutrients*. 2018; 10:1219. https://doi.org/10.3390/nu10091219
5. Chehal PK, Shafer L, Cunningham SA: Examination of Sleep and Obesity in Children and Adolescents in the United States. *American Journal of Health Promotion.* 2022; 36:46-54. https://doi.org/10.1177/08901171211029189
6. Rodrigues GD, Fiorelli EM, Furlan L, Montano N, Tobaldini E: Obesity and sleep disturbances: The "chicken or the egg" question. *European Journal of Internal Medicine.* 2021; 92:11-16. https://doi.org/10.1016/j.ejim.2021.04.017
7. Deng X, He M, He D, Zhu Y, Zhang Z, Niu W: Sleep duration and obesity in children and adolescents: evidence from an updated and dose-response meta-analysis. *Sleep medicine.* 2021; 78:169-181. https://doi.org/10.1016/j.sleep.2020.12.027
8. Al-Mansoori L, Al-Jaber H, Prince MS, Elrayess MA: Role of inflammatory cytokines, growth factors and adipokines in adipogenesis and insulin resistance. *Inflammation*. 2021; 1-14. https://doi.org/10.1007/s10753-021-01559-z
9. Karczewski J, Śledzińska E, Baturo A, Jończyk I, Maleszko A, Samborski P, Begier-Krasińska B, Dobrowolska A: Obesity and inflammation. *European cytokine network.* 2018; 29:83-94. https://doi.org/10.1684/ecn.2018.0415
10. Irwin MR: Sleep and inflammation: partners in sickness and in health. Nature Reviews Immunology. 2019; 19:702-715. https://doi.org/10.1038/s41577-019-0190-z
11. Muscogiuri G, Barrea L, Annunziata G, Di Somma C, Laudisio D, Colao A, Savastano S: Obesity and sleep disturbance: the chicken or the egg? *Critical reviews in food science and nutrition.* 2019; 59:2158-2165. https://doi.org/10.1080/10408398.2018.1506979
12. Lee YH: Association between the neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio and rheumatoid arthritis and their correlations with the disease activity: a meta-analysis. *Journal of Rheumatic Diseases.* 2018; 25:169-178. https://doi.org/10.4078/jrd.2018.25.3.169
13. Apperley LJ, Blackburn J, Erlandson-Parry K, Gait L, Laing P, Senniappan S: Childhood obesity: A review of current and future management options. *Clinical Endocrinology.* 2022; 96:288-301. https://doi.org/10.1111/cen.14625
14. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, Giannotti F: The Sleep Disturbance Scale for Children (SDSC) Construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *Journal of sleep research*. 1996; 5:251-261. https://doi.org/10.1111/j.1365-2869.1996.00251.x
15. Agadayi E, Çelik N, Baser DA: Cocuklar Icin Uyku Bozuklugu Olceginin Turkce Gecerlik ve Guvenirlik Calismasi/Turkish Validity and Reliability of the Sleep Disturbance Scale for Children. *Journal of Turkish Sleep Medicine*. 2020; 7:65-73.
16. Koren D, Gozal D, Philby MF, Bhattacharjee R, Kheirandish-Gozal L: Impact of obstructive sleep apnoea on insulin resistance in nonobese and obese children. *European Respiratory Journal.* 2016; 47:1152-1161. https://doi.org/10.1183/13993003.01430-2015
17. Kheirandish-Gozal L, Gozal D: Obstructive sleep apnea and inflammation: proof of concept based on two illustrative cytokines. International journal of molecular sciences. 2019; 20:459. https://doi.org/10.3390/ijms20030459
18. Oyama J-i, Nagatomo D, Yoshioka G, Yamasaki A, Kodama K, Sato M, Komoda H, Nishikido T, Shiraki A, Node K: The relationship between neutrophil to lymphocyte ratio, endothelial function, and severity in patients with obstructive sleep apnea. *Journal of cardiology*. 2016; 67:295-302. https://doi.org/10.1016/j.jjcc.2015.06.005
19. Zorlu D, Ozyurt S, Bırcan H, Erturk A: Do complete blood count parameters predict diagnosis and disease severity in obstructive sleep apnea syndrome? *European Review for Medical and Pharmacological Sciences*. 2021; 25:4027-4036.
20. Adamstein NH, Cornel JH, Davidson M, Libby P, de Remigis A, Jensen C, Ekström K, Ridker PM: Association of Interleukin 6 Inhibition With Ziltivekimab and the Neutrophil-Lymphocyte Ratio: A Secondary Analysis of the RESCUE Clinical Trial. *JAMA cardiology.* 2022. https://doi.org/10.1001/jamacardio.2022.4277
21. Mauss D, Herr RM, Jarczok MN, Motoc I, Fischer JE, Bosch JA: The association of cortisol levels with leukocyte distribution is disrupted in the metabolic syndrome. *Obesity Research & Clinical Practice*. 2021, 15:78-84. https://doi.org/10.1016/j.orcp.2020.12.003

22. Rodríguez-Rodríguez E, López-Sobaler AM, Ortega RM, Delgado-Losada ML, López-Parra AM, Aparicio A: Association between neutrophil-to-lymphocyte ratio with abdominal obesity and healthy eating index in a representative older Spanish population. *Nutrients*. 2020; 12:855. https://doi.org/10.3390/nu12030855
23. Karakaya S, Altay M, Efe FK, Karadağ İ, Ünsal O, Bulur O, Eser M, Ertuğrul DT: The neutrophil-lymphocyte ratio and its relationship with insulin resistance in obesity. *Turkish Journal of Medical Sciences*. 2019; 49:245-248. https://doi.org/10.3906/sag-1804-68
24. Rawat A, Gangwar AK, Tiwari S, Kant S, Garg RK, Singh PK: Sleep quality and insulin resistance in adolescent subjects with different circadian preference: A cross-sectional study. *Journal of family medicine and primary care.* 2019; 8:2502. https://doi.org/10.4103/jfmpc.jfmpc_400_19
25. Chen P, Baylin A, Lee J, Dunietz GL, Cantoral A, Rojo MMT, Peterson KE, Jansen EC: The association between sleep duration and sleep timing and insulin resistance among adolescents in Mexico City. *Journal of Adolescent Health.* 2021; 69:57-63. https://doi.org/10.1016/j.jadohealth.2020.10.012
26. Thumann BF, Michels N, Felső R, Hunsberger M, Kaprio J, Moreno LA, Siani A, Tornaritis M, Veidebaum T, De Henauw S: Associations between sleep duration and insulin resistance in European children and adolescents considering the mediating role of abdominal obesity. *PloS one.* 2020; 15:e0235049. https://doi.org/10.1371/journal.pone.0235049
27. Shaw ND, McHill AW, Schiavon M, Kangarloo T, Mankowski PW, Cobelli C, Klerman EB, Hall JE: Effect of slow wave sleep disruption on metabolic parameters in adolescents. *Sleep*. 2016; 39:1591-1599. https://doi.org/10.5665/sleep.6028
28. Navarro-Solera M, Carrasco-Luna J, Pin-Arboledas G, González-Carrascosa R, Soriano JM, Codoñer-Franch P: Short sleep duration is related to emerging cardiovascular risk factors in obese children. *Journal of pediatric gastroenterology and nutrition.* 2015; 61:571-576. https://doi.org/10.1097/MPG.0000000000000868
29. Mansyur MA, Bakri S, Patellongi IJ, Rahman IA: The association between metabolic syndrome components, low-grade systemic inflammation and insulin resistance in non-diabetic Indonesian adolescent male. *Clinical nutrition ESPEN.* 2020; 35:69-74. https://doi.org/10.1016/j.clnesp.2019.12.001