Bosphorus Medical Journal
Boğaziçi Tıp Dergisi

Original Article

DOI: 10.14744/bmj.2023.94834

Bosphorus Med J 2023;10(3):146–152

Visceral Adiposity Index and Insulin Resistance in Restless Legs Syndrome

Huzursuz Bacak Sendromunda Viseral Yağ İndeksi ve İnsülin Direnci

Gülhan Sarıçam,[1] Orkun Sarıçam[2]

ABSTRACT

Objectives: It has been reported that restless legs syndrome (RLS) is seen at a higher rate in obese and diabetic patients than in the normal population. In this study, we aimed to investigate obesity, insulin resistance (IR), and visceral adiposity index (VAI) rates and the relationship of these values with the severity of RLS in individuals without a diagnosis other than RLS.

Methods: This prospective study was conducted with 149 patients diagnosed with RLS and 105 healthy volunteers. Patients were evaluated with the RLS Severity Rating Scale and classified according to symptom severity. Demographic characteristics of the patients, iron, inflammation, and blood cholesterol levels were measured, and body mass indexes (BMI), VAI, and IR values were calculated.

Results: A majority (64.8%) of the patients were female and the symptoms were severe in 35.6%. C-reactive protein, BMI, and VAI levels were found to be significantly higher in patients with RLS than in the control group ($p<0.001$). The number of IR and obese patients in the RLS group was significantly higher than the control group. In patients with severe RLS symptoms, the VAI levels and the ratio of those with IR were significantly higher than in those with mild symptoms ($p=0.006$, $p=0.001$).

Conclusion: It was shown that patients with RLS had a higher rate of IR, VAI, and obesity compared to the control group. Although VAI and IR were significantly higher in patients with severe RLS symptoms, we did not find a relationship between obesity and disease severity. VAI and IR parameters could be useful markers for assessing the risk of developing RLS and disease prognosis.

Keywords: Body mass index; insulin resistance; restless legs syndrome; visceral adiposity index.

ÖZET

Amaç: Huzursuz bacak sendromunun (HBS) obezlerde ve diyabetik hastalarda normal popülasyona göre daha yüksek oranda görüldüğü bildirildi. Bu çalışmada, HBS olan bireylerde obezite, insülin direnci ve viseral yağ indeksi (VYİ) oranlarının ve bu değerlerin HBS şiddeti ile ilişkisinin araştırılması amaçlandı.

Yöntem: Bu prospektif çalışma HBS tanısı alan 149 hasta ve 105 sağlıklı gönüllü ile yapıldı. Hastalar HBS Şiddet Değerlendirme Ölçeği ile değerlendirilerek, semptom şiddetine göre sınıflandırıldı. Hastaların demografik özellikleri, demir, inflamasyon ve kan kolesterol seviyeleri ölçüldü, beden kitle indeksi (BKİ), VYİ ve insülin direnci değerleri hesaplandı.

Bulgular: HBS tanılı hastaların %64,8'i kadındı ve %35,6'sında semptomlar şiddetliydi. HBS olan hastalarda C-reaktif protein, BKİ, VYİ düzeyleri kontrol grubundan anlamlı derecede fazla bulundu ($p<0,001$). HBS'li grupta insülin direnci ve obez olanların sayısı kontrol grubundan anlamlı derecede fazlaydı. HBS semptomları şiddetli olan hastalarda VYİ düzeyleri ve insülin direnci olanların oranı semptomları hafif olanlardan anlamlı derecede fazlaydı ($p=0,006$, $p=0,001$).

Sonuç: HBS tanısı olan hastalarda insülin direnci, VYİ ve obezitenin kontrol grubuna göre daha yüksek oranda olduğu tespit edildi. HBS semptomları şiddetli olan hastalarda VYİ ve insülin direnci anlamlı olarak daha yüksek olmasına rağmen obezite ile hastalık şiddeti arasında bir ilişki bulunmadı. VYİ ve insülin direnci parametreleri, HBS geliştirme riskini ve hastalık prognozunu değerlendirmek için yararlı belirteçler olabilir.

Anahtar sözcükler: Beden kitle indeksi; insülin direnci; huzursuz bacak sendromu; viseral yağ indeksi.

[1]Department of Neurology Clinic, Ankara Pursaklar State Hospital, Ankara, Türkiye
[2]Department of Internal Medicine, Ankara Pursaklar State Hospital, Ankara, Türkiye

Cite this article as:
Sarıçam G, Sarıçam O. Visceral Adiposity Index and Insulin Resistance in Restless Legs Syndrome. Bosphorus Med J 2023;10(3):146–152.

Received: 16.06.2023
Revision: 08.08.2023
Accepted: 09.08.2023

Correspondence:
Dr. Gülhan Sarıçam.
Ankara Pursaklar Devlet Hastanesi, Nöroloji Kliniği, Ankara, Türkiye
Phone:
+90 505 629 84 66
e-mail:
gulhansar01@hotmail.com

Restless legs syndrome (RLS) is a common sensory-motor neurological disorder characterized by an uncomfortable urge to move the extremities at rest. It is seen with a prevalence of 5–20% in the adult population, negatively affecting sleep and daytime activities, significantly reducing the quality of life of patients.[1]

Although the etiology in the development of RLS is not known exactly, it is thought that genetic and environmental factors contribute to the phenotype, and causes such as brain dopamine hypofunction and iron metabolism disorders play a role.[2] In recent years, diabetes, obesity, hypertension, and cardiovascular diseases have been frequently associated with RLS, and it has also been suggested that these diseases may play a role in the development and progression of RLS.[3] Previously, obesity has been shown to be associated with decreased dopamine signaling and dopamine receptor two expressions in striatal regions. Hormones such as leptin, glucagon, and insulin that regulate homeostatic nutrition through the hypothalamus are modulators of dopaminergic neurons in mesolimbic networks.[4,5] However, various evidence has shown a decrease in dopamine synthesis and activation in the brain in the development of insulin resistance (IR) and diabetes.[6] Therefore, various factors affecting the dopaminergic state in the brain may actually be common causes in the etiology of all these diseases.

In epidemiological studies, it has been shown that RLS was seen at a higher rate in obese and diabetic patients compared to the normal population.[7] IR is a condition that is associated with a group of diseases, especially diabetes, and obesity, leading to hyperinsulinemia, and impaired glucose tolerance.[8] However, it has recently been reported that the visceral adiposity index (VAI) is a more accurate indicator of diabetes and cardiovascular disease than other simple anthropometric measures such as body mass index (BMI) and waist circumference (WC).[9] To the best of our knowledge, the relationship between VAI and IR, and RLS has not been investigated before. In this study, we aimed to investigate obesity, IR, and VAI rates and the relationship of these values with the severity of RLS in individuals without a diagnosis other than RLS.

Methods

The prospective study was approved by Ankara City Hospital Ethics Committee (E2-22-2470). All procedures were applied in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients who agreed to participate in the study. A total of 149 patients who applied to the neurology outpatient clinic between October 2022 and January 2023 and were diagnosed with RLS were included in the study. Patients with a history of chronic disease (thyroid, diabetes, heart, kidney, liver, lung, and hematological diseases), oncological disease, immunodeficiency, acute or chronic inflammatory disease, pregnancy, drug use, and infection in the past 1 month were excluded from the study. Healthy volunteers who applied to the outpatient clinic for a check-up and had no disease were included in the control group.

The diagnosis of RLS was conducted according to the diagnostic criteria of RLS. The RLS Severity Rating Scale determined by the International RLS Working Group (IRLSSG) has been applied. This scale consists of ten questions and ranges from 0 to 40, with a score of 1–10 mild (Grade 1), 11–20 moderate (Grade 2), 21–30 severe (Grade 3), and 31–40 indicating the presence of (Grade 4) very severe disease.[10,11]

The measurement of biochemistry and hemogram tests of the study population was conducted by enzymatic colorimetric assay after 12-h fasting. Neutrophil/lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. BMI was calculated by dividing weight in kilograms by the square of height in meters. Those with BMI ≥30 kg/m^2 were considered obese. Evaluation of homeostasis model-IR has been calculated through (HOMA-IR)=Fasting glucose (mg/dL) × Fasting insulin (uIU/mL)/405 and patients with HOMA score ≥2.7 were considered positive for IR.[12] Patients with fasting plasma glucose ≥126 mg/dL were not included in the RLS and control groups because they were thought to have diabetes, and those between 110 and 125 mg/dL were considered impaired glucose tolerance.[13]

While using the VAI formula for the patients included in the study, triglyceride (TG), high-density lipoprotein (HDL) mmoL/L, and WC were calculated as cm.

- For males:

VAI= WC/39.68 + (1.88×BMI) × (TG/1.03) × (1.31/HDL)

- For females:

VAI=WC/36.58 + (1.89×BMI) × (TG /0.81) × (1.52/HDL) formulas were used.[14]

Statistical Analysis

The data analysis was conducted by IBM SPSS Statistics 28 program. While evaluating the data, descriptive statistics

(mean±standard deviation) for numerical variables and frequency distributions for categorical variables are given. The Kolmogorov–Smirnov normality test was applied to the numerical variables to decide the statistical method. As a result, it was seen that the variables did not provide the normality assumption, and non-parametric tests were utilized. Chi-square analysis was used to examine the relationships between two independent categorical variables. The Kruskal–Wallis test and the differences between more than two independent groups and the Mann–Whitney U-test were used to control the differences according to the variables between the two independent groups. Statistical significance was taken as 0.05 in the analysis.

Results

One hundred and forty-nine out of the 177 patients studied during the period were included in this analysis (Fig. 1). The mean age of the patients with RLS was 44.64±11.31 years and 64.8% were female. The severity of RLS was mild (Grade 1) in 32.2% of the patients with RLS, moderate (Grade 2) in 32.2%, and severe in 35.6% (Grade 3–4). As a result of the Mann–Whitney U analyses, insulin, HOMA-IR, and WC values of the patients with RLS were found to be statistically significantly higher than the control group (p<0.001) (Table 1).

As a result of Mann–Whitney U analyses, iron, hemoglobin, and HDL levels in patients with RLS were found to be statistically significantly lower than the control group (p<0.001).

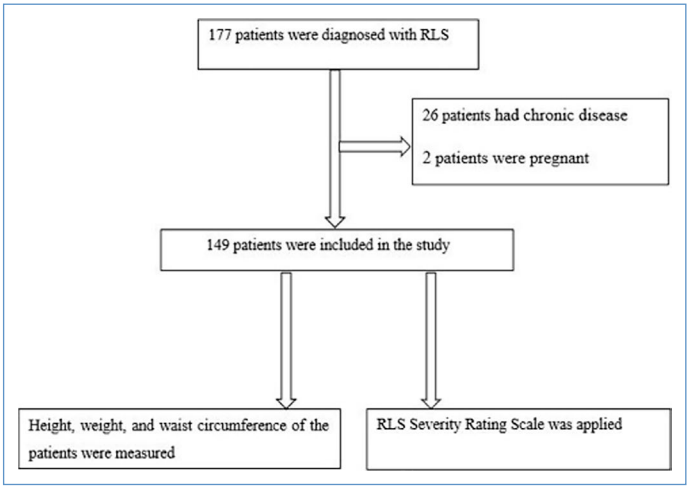

Figure 1. Case selection criteria.

RLS: Restless legs syndrome.

Platelets, TG, C-reactive protein (CRP), BMI, and VAI levels were significantly higher in patients with RLS than in the control group (p<0.05). As a result of the Chi-square analysis, the number of IR and obese patients in the RLS group was significantly higher than the control group (p=0.040, p=0.002) (Table 2).

In Kruskal–Wallis H analyses, VAI values were found to be statistically significantly higher in patients with severe RLS (Grade 3–4) than those with mild (Grade 1) and moderate (Grade 2) (p=0.006) (Fig. 2). The rate of IR in patients with severe RLS was significantly higher than in patients with mild RLS (p=0.001) (Table 3 and Fig. 3).

Table 1. Demographic characteristics of patients by groups

	RLS (n=149)		Controls (n=105)		Chi-square	p
	n	%	n	%		
Gender					0.473	0.492
Female	104	69.8	69	65.7		
Male	45	30.2	36	34.3		
RLS severity					-	-
Grade 1	48	32.2				
Grade 2	48	32.2				
Grade 3–4	53	35.6				
	Mean±SD		Mean±SD		U	p
Age	44.64±11.31		42.30±11.57		6827.0	0.084
Insulin (mu/L)	9.57±7.59		7.20±6.99		5726.5	<0.001*
HOMA-IR	2.19±1.80		1.60±1.64		5807.0	<0.001*
WC	99.59±10.91		92.05±9.44		4673.5	<0.001*

*p<0.05. RLS: Restless legs syndrome; HOMA-IR: Homeostasis model-insulin resistance; WC: Waist circumference; U: Mann–Whitney U.

Table 2. Biochemical test results and differences by groups

	RLS (n=149)		Controls (n=105)		U	p
	Mean±SD		Mean±SD			
Glucose	94.80±8.29		93.60±10.22		6782.5	0.071
Iron (ug/dL)	70.26±35.93		102.15±41.7		4283.0	<0.001*
Ferritin (ng/mL)	49.01±54.12		62.34±67.87		6758.5	0.084
Hb (g/dL)	13.34±1.87		15.92±12.82		4628.5	<0.001*
WBC (×10^3 µL)	6.84±1.52		6.84±1.62		7820.5	0.997
PLT (×10^3 µL)	273.50±63.17		252.76±54.5		6380.5	0.012*
LYM (×10^3 µL)	2.76±3.28		4.15±6.96		7253.0	0.323
NEU (×10^3 µL)	3.68±1.17		4.19±5.20		7687.0	0.814
TG (mg/dl)	178.36±82.12		125.65±62.0		4780.5	<0.001*
HDL (mg/dL)	47.15±11.69		53.20±11.80		5406.0	<0.001*
CRP (mg/L)	0.62±1.39		0.16±0.18		4165.5	<0.001*
BMI	26.30±4.49		23.73±3.90		5256.0	<0.001*
VAI	8.19±5.69		4.87±4.23		4449.0	<0.001*
NLR	1.65±0.80		1.52±0.63		7438.0	0.505
	n	%	n	%	Chi-square	p
IR					4.208	0.040*
Yes	37	24.8	15	14.3		
No	112	75.2	90	85.7		
BMI					9.572	0.002*
Obese	37	24.8	10	9.5		
Non-obese	112	75.2	95	90.5		

*p<0.05. RLS: Restless legs syndrome; U: Mann–Whitney U; SD: Standard deviation; Hb: Hemoglobin; WBC: White blood cell; PLT: Platelets; LYM: Lymphocytes; NEU: Neutrophils; TG: Triglyceride; HDL: High-density lipoprotein; CRP: C-reactive protein; BMI: Body mass index; VAI: Visceral adiposity index; NLR: Neutrophil/lymphocyte ratio; IR: Insulin resistance.

Discussion

RLS is a common neurological movement disorder that affects women more and its prevalence increases after the age of 40. Despite the high prevalence of RLS, the majority of patients have mild-to-moderate clinical feature, with a lower incidence of severe and frequent symptoms. Consistent with the literature, the majority of the patients diagnosed with RLS in our study were women, and according to the RLS Severity Rating Scale applied, the patients' symptoms were mostly mild-to-moderate.[15]

Obesity is considered to be a preventable chronic disease that is quite common in the developing world.[16] In a large-scale prospective study by De Vito et al.,[17] they found that obesity and high cholesterol were significantly associated with an increased risk of developing RLS. In this study, we found that BMI, TG, and VAI rates were significantly higher in patients with RLS than in the control group. The relationship between obesity and RLS etiology is likely to be multi-

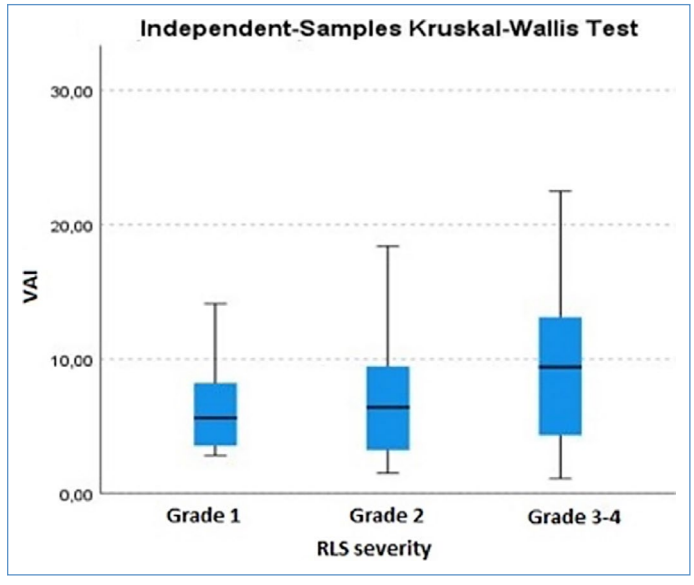

Figure 2. Visceral adiposity index according to restless legs syndrome severity.

RLS: Restless legs syndrome.

Table 3. Relationship between RLS symptom severity and parameters

	Grade 1		Grade 2		Grade 3–4		KW	p	Difference
	Mean±SD		Mean±SD		Mean±SD				
Iron (ug/dL)	74.21±40,93		68.21±37.16		68.53±29.85		0.411	0.814	-
Ferritin (ng/mL)	58.51±70.39		37.45±42.08		50.88±45.27		3.921	0.141	-
NLR	1.69±0.93		1.83±0.84		1.45±0.58		4.671	0.097	-
CRP	0.42±0.61		0.47±0.80		0.94±2.11		4.118	0.128	-
BMI	25.87±3.90		25.53±5.01		27.40±4.35		5.385	0.068	-
VAI	6.77±4.17		7.35±5.44		10.22±6.56		10.127	0.006*	3–4>1,2
	n	%	n	%	n	%	Chi-square	p	
IR							13.652	0.001*	
Yes	5	10.4	10	20.8	22	41.5			
No	43	89.6	38	79.2	31	58.5			
BMI							4.176	0.124	
Obese	8	16.7	11	22.9	18	34.0			
Nonobese	40	83.3	37	77.1	35	66.0			

*p<0.05. RLS: Restless legs syndrome; KW: Kruskal–Wallis; SD: Standard deviation; NLR: Neutrophil/lymphocyte ratio; CRP: C-reactive protein; BMI: Body mass index; VAI: Visceral adiposity index; IR: Insulin resistance.

factorial. In recent years, the association of RLS with cardiovascular diseases has suggested that vascular mechanisms such as oxidative, inflammatory, sympathetic hyperactivity, and cardiac vagal modulations play a role in its etiology.[18] In obesity, dopamine D2 receptors were found to be lower in the striatal region of the central nervous system, and there was an inverse between BMI and dopamine receptors.[19] The alleviation of RLS symptoms by dopamine agonists and the demonstration of striatal dopaminergic changes in these patients strengthen the relationship of the disease with obesity.[20] VAI is a higher predictor for obesity, which has been used frequently recently, and which can distinguish visceral and subcutaneous fat. It is an index that has a value and is closely related to many metabolic diseases.[21] In our study, we found VAI to be significantly higher in patients with severe RLS compared to those with mild and moderate RLS, but we could not find a relationship between RLS symptom severity and obesity. These results showed that VAI can be a useful index to show the risk and severity of developing RLS.

Previously, it has been observed that the risk of developing RLS in diabetic patients is higher than in the general population.[22] RLS developing in diabetic patients has been associated with fiber neuropathy. Diabetic polyneuropathy was found in 96% of patients with Type 2 diabetes mellitus (T2DM) and RLS, suggesting that their pathophysiology may be common.[23] Ning et al.[24] elaborated that RLS had a higher prevalence in DM patients than in patients without diabetes. IR is the most important factor that plays a role in the pathogenesis of T2DM, characterized by dysfunctional insulin secretion by pancreatic beta cells. However, obesity and visceral adiposity are common risk factors for IR, T2DM, and cardiovascular complications.[25] In our study, the rate of patients with RLS who were not diagnosed with diabetes was significantly higher than the control group. However, we found the IR rate to be significantly higher in those with severe RLS symptoms than in those with mild RLS. We

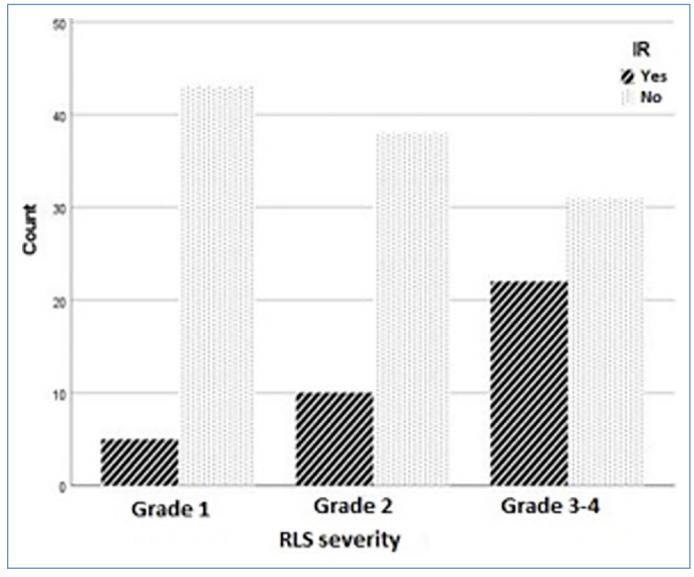

Figure 3. Insulin resistance according to restless legs syndrome severity.

RLS: Restless legs syndrome.

thought that these results showed the relationship between the severity of symptoms and IR in patients with RLS, as well as the development of peripheral IR in these patients without a diagnosis of diabetes.

Iron deficiency affects many cellular functions such as oxidative phosphorylation, immune function, DNA synthesis, and oxygen delivery.[26] The relationship between decreased peripheral iron levels and increased RLS prevalence and severity of symptoms has been shown previously.[27] In our study, blood iron and hemoglobin levels in patients with RLS were found to be significantly lower than in the control group, but no correlation was found between them and symptom severity. Recently, the presence of systemic inflammation in most of the diseases known to be associated with RLS has led to the investigation of the relationship between systemic markers and RLS.[28] Jiménez et al. [29] found higher CRP and NLR rates in patients diagnosed with RLS compared to controls. Similarly, we found CRP and platelet levels to be significantly higher in our RLS patients than in the control group, but we could not find a significant difference in NLR rates.

This study has some limitations. The number of cases with RLS was relatively small, and the diagnosis of RLS and the severity of symptoms were based on self-reports. Therefore, some degree of error in diagnosis and assessment of symptom severity is likely.

Conclusion

The results of this study show that IR, VAI, and obesity are higher in patients with RLS. In addition, low iron and high CRP levels were associated with the presence of RLS. The fact that VAI and IR were significantly higher in patients with severe RLS symptoms indicates that these parameters can be useful markers that can be used to show the risk of developing RLS and disease prognosis.

Disclosures

Ethics Committee Approval: The study was approved by Ankara City Hospital No. 2 Clinical Research Ethics Committee, Date: 28.09.2022, decision number: E2-22-2470.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – G.S., O.S.; Design – O.S., G.S.; Supervision – O.S., G.S.; Fundings – G.S.; Materials – G.S.; Data collection &/or processing – G.S.; Analysis and/or interpretation – G.S., O.S.; Literature search – O.S.; Writing – G.S., O.S.; Critical review – O.S., G.S.

References

1. Garcia-Borreguero D, Odin P, Schwarz C. Restless legs syndrome: An overview of the current understanding and management. Acta Neurol Scand 2004;109:303–17.
2. Vlasie A, Trifu SC, Lupuleac C, Kohn B, Cristea MB. Restless legs syndrome: An overview of pathophysiology, comorbidities and therapeutic approaches. Exp Ther Med 2022;23:185.
3. Innes KE, Selfe TK, Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: A systematic review. Sleep Med Rev 2012;16:309–39.
4. Jais A, Brüning JC. Arcuate nucleus-dependent regulation of metabolism-pathways to obesity and diabetes mellitus. Endocr Rev 2022;43:314–28.
5. Gaziano I, Corneliussen S, Biglari N, Neuhaus R, Shen L, Sotelo-Hitschfeld T, et al. Dopamine-inhibited POMCDrd2+ neurons in the ARC acutely regulate feeding and body temperature. JCI Insight 2022;7:e162753.
6. Caravaggio F, Borlido C, Hahn M, Feng Z, Fervaha G, Gerretsen P, et al. Reduced insulin sensitivity is related to less endogenous dopamine at D2/3 receptors in the ventral striatum of healthy nonobese humans. Int J Neuropsychopharmacol 2015;18:pyv014.
7. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000;160:2137–41.
8. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: Insights into mechanisms and therapeutic strategy. Signal Transduct Target Ther 2022;7:216.
9. Wei J, Liu X, Xue H, Wang Y, Shi Z. Comparisons of visceral adiposity index, body shape index, body mass index and waist circumference and their associations with diabetes mellitus in adults. Nutrients 2019;11:1580.
10. IRLSSG. Diagnostic criteria for RLS. Available at: https//irlssg.wildapricot.org/Diagnostic-Criteria. Accessed Sep 14, 2023.
11. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32.
12. Wiweko B, Indra I, Susanto C, Natadisastra M, Hestiantoro A. The correlation between serum AMH and HOMA-IR among PCOS phenotypes. BMC Res Notes 2018;11:114.
13. Türk Endokrinoloji ve Metabolizma Derneği (TEMD); Diabetes Mellitus Çalışma ve Eğitim Grupları. Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Kılavuzu. 15. Baskı. Ankara: Türkiye Endokrinoloji ve Metabolizma Derneği; 2022; p.15-20.
14. Qin Z, Jiang L, Sun J, Geng J, Chen S, Yang Q, et al. Higher visceral adiposity index is associated with increased likelihood of abdominal aortic calcification. Clinic Sao Paulo. 2022;77:100114.
15. Gossard TR, Trotti LM, Videnovic A, St Louis EK. Restless legs syndrome: Contemporary diagnosis and treatment. Neurotherapeutics 2021;18:140–55.
16. De Lorenzo A, Romano L, Di Renzo L, Di Lorenzo N, Cenname G, Gualtieri P. Obesity: A preventable, treatable, but relapsing disease. Nutrition 2020;71:110615.

17. De Vito K, Li Y, Batool-Anwar S, Ning Y, Han J, Gao X. Prospective study of obesity, hypertension, high cholesterol, and risk of restless legs syndrome. Mov Disord 2014;29:1044–52.
18. Gottlieb DJ, Somers VK, Punjabi NM, Winkelman JW. Restless legs syndrome and cardiovascular disease: A research roadmap. Sleep Med 2017;31:10–17.
19. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. Lancet 2001;357:354–7.
20. Vellieux G, d'Ortho MP. Restless legs syndrome. Rev Med Interne [Article in French] 2020;41:258–64.
21. Pan L, Xu Q, Liu J, Gao Y, Li J, Peng H, et al. Dose-response relationship between Chinese visceral adiposity index and type 2 diabetes mellitus among middle-aged and elderly Chinese. Front Endocrinol Lausanne 2022;13:959860.
22. Greco D. Restless legs syndrome and diabetes mellitus: An accidental association? Recenti Prog Med [Article in Italian] 2011;102:212–6.
23. Greco D, Gambina F, Pisciotta M, Abrignani M, Maggio F. Clinical characteristics and associated comorbidities in diabetic patients with restless legs syndrome. Exp Clin Endocrinol Diabetes 2009;117:496–9.
24. Ning P, Mu X, Yang X, Li T, Xu Y. Prevalence of restless legs syndrome in people with diabetes mellitus: A pooling analysis of observational studies. EClinicalMedicine 2022;46:101357.
25. Ndisang JF, Vannacci A, Rastogi S. Insulin resistance, type 1 and type 2 diabetes, and related complications 2017. J Diabetes Res 2017;2017:1478294.
26. Pamuk GE, Top MŞ, Uyanık MŞ, Köker H, Akker M, Ak R, et al. Is iron-deficiency anemia associated with migraine? Is there a role for anxiety and depression? Wien Klin Wochenschr 2016;128:576–80.
27. Bang YR, Jeon HJ, Park HY, Yoon IY. Symptom persistence after iron normalization in women with restless legs syndrome. Psychiatry Investig 2018;15:390–5.
28. Trotti LM, Rye DB, De Staercke C, Hooper WC, Quyyumi A, Bliwise DL. Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. Brain Behav Immun 2012;26:1239–43.
29. Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG. Inflammatory factors and restless legs syndrome: A systematic review and meta-analysis. Sleep Med Rev 2023;68:101744.