Available online at www.medicinescience.org

ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2019;8(1):102-5

The relationship between obesity and restless legs syndrome

Fatma Ebru Algul[1], Ayse Cikim Sertkaya[2], Sibel Altinayar[3]

[1]Malatya Educational and Research Hospital, Clinic of Neurology, Malatya, Turkey
[2]Sisli Memorial Hospital, Endocrinology and Metabolism Disorders, Istanbul, Turkey
[3]Inonu University Faculty of Medicine Department of Neurology, Malatya, Turkey

Received 02 August 2018; Accepted 07 September 2018
Available online 16.12.2018 with doi:10.5455/medscience.2018.07.8940

Abstract

Restless legs syndrome (RLS) has been shown to be more common in obese than in non-obese people in many studies. The aim of this study was to investigate passible relationship between obesity and seconder RLS prevalence and severity in the Turkish population. Method: A total of 70 volunteers were included in the study. Of these 44 were obese (BMI≥30 kg/m2) and 26 were non obese(BMI <30 kg/m2. The International RLS Study Group (International Restless Legs Study Group, IRLSS) diagnosis criteria were used for the RLS diagnosis and International RLS criteria to determine the severity. 17 subjects had RLS and of these 13 were in the obese group and 4 in the non-obese group. No significant difference was found between obese and non-obese groups in terms of RLS prevalence (p:0.165) and RLS severity (p:0.918). Our study on a small sample from the Turkish population showed no significant relationship between obesity and RLS presence and severity. The reason may be the small numbers of obese and control group subjects in our study.

Keywords: Restless legs syndrome, obesity, pathology

Introduction

Restless legs syndrome (RLS) is a common movement and sleep disorder characterized by the unpreventable urge to move, along with a marked and disturbing abnormal sensation, especially in the lower extremities [1]. It affects the sleep, daily activity and quality of life in 5-20% of the adults [2]. The diagnostic criteria were updated in 2002 by the International Restless Leg Syndrome Study Group and reviewed in 2012 [3]. RLS is classified as primary and secondary. The primary form has a genetic basis. It is estimated to be inherited in 50-80% of the cases [4]. The secondary form is associated with iron deficiency, magnesium deficiency, vitamin B12 deficiency, folate deficiency, uremia, end stage renal disease, pregnancy, polyneuropathy, rheumatoid arthritis, hypo-hyperthyroidism, myelitis, smoking, diabetes, tricyclic antidepressant use, selective serotonin reuptake inhibitors, lithium and dopamine antagonist use [5,6].

***Coresponding Author:** Fatma Ebru Algul, Malatya Educational and Research Hospital, Clinic of Neurology, Malatya, Turkey E-mail: guzinbilgin@hotmail.com

Dopaminergic hypofunction in the central nervous system (CNS) is thought to play a critical role in the pathophysiology of the disease [7]. Some environmental factors may play a role in the development of RLS by affecting dopamine levels and dopamine metabolism in the CNS. A decrease in the accessibility of dopamine D2 receptors in the brain and an increased risk of RLS formation occurs in obese people [8]. The body mass index (BMI) of the patients with restless leg syndrome has been found to be significantly higher than those without RLS [9]. A direct relationship is present between obesity and obstructive sleep apnea syndrome and insomnia [10]. RLS is also a sleep disorder and has been shown to be related to obesity in many studies [9].

We aimed to investigate the relationship between BMI, fat mass, fat-free body mass (FFM), body water percentage (TBW) and duration of obesity and the seconder RLS presence and severity in this study.

Material and Methods

The necessary explanations were provided to the volunteers included in the study and their consent was obtained. Subjects with anemia, slipped disc, rheumatoid arthritis, kidney failure, liver

failure, thyroid disease, hypercholesterolemia, diabetes, and those using antipsychotics, antidepressant drugs or alcohol, in addition to pregnant women were excluded from the study. Of the 70 volunteers, 44 with BMI>30 were included in the obese group and 26 with BMI<30 were included in the non-obese group. Face-to-face interviews were conducted with all subjects. The International Restless Leg Study Group (IRLSS) diagnostic criteria were used for the RLS diagnosis and the International RLS Study Group (Table 2) criteria for the severity. A score of 1-10 was considered mild, 11-20 moderate, 21-30 severe and 31- 40 very severe. Height, weight, waist circumference and hip circumference were measured and BMI calculated using the kilograms (kg)/height (m2) formula in all subjects. Those with abnormal hemoglobin, hematocrit, fasting blood sugar, HbA1c, iron, iron binding capacity, insulin, total cholesterol, LDL, HDL, triglyceride, BUN, creatinine, AST, ALT, magnesium, calcium, phosphorus or thyroid function test results were excluded from the study.

Table 1. Restless Legs Syndrome Diagnostic Criteria

1.	An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs
2.	The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3.	The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4.	The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.

Table 2. IRLSS criteria

1.	Overall, how would you rate the RLS discomfort in you legs or arms? (4) Very severe (3) Severe (2) Moderate (1) Mild (0) None
2.	Overall, how would you rate the need to move around because of your RLS symptoms? (4) Very severe (3) Severe (2) Moderate (1) Mild (0) None
3.	Overall, how much relief of your RLS arm or leg discomfort do you get from moving around? (4) No relief (3) Slight relief (2) Moderate relief (1) Either complete or almost complete relief (0) No RLS symptoms and therefore question does not apply
4	Overall, how severe is your sleep disturbance from your RLS symptoms? (4) Very severe (3) Severe (2) Moderate (1) Mild (0) None
5	How severe is your tiredness or sleepiness from your RLS symptoms? (4) Very severe (3) Severe (2) Moderate (1) Mild (0) None
6	Overall, how severe is your RLS as a whole? (4) Very severe (3) Severe (2) Moderate (1) Mild (0) None
7	. How often did you have RLS symptoms? (4) Very often; six to seven days (3)often; four to five days (2) sometimes; two to three days (1) occasionally; one day or less (0) never
8	When you have RLS symptoms, how severe are they on an average day? (4) Very severe (This means 8 hours per 24 hour day or more.) (3) Severe (This means 3 to 8 hours per 24 hour day.) (2) Moderate (This means 1 to 3 hours per 24 hour day.) (1) Mild (This means less than 1 hour per 24 hour day.) (0) None
9	Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school, or work life? (4) Very severe (3) Severe (2) Moderate (1) Mild (0) None
10	How severe is your mood disturbance from your RLS symptoms–for example angry, depressed, sad, anxious, or irritable? (4) Very severe (3) Severe (2) Moderate (1) Mild (0) None

Statistical analysis

The SPSS 22 software program was used for the analysis of the data and the Kolmogorov-Smirnov test was used to determine the compliance of the quantitative data with a normal distribution. Student's t test was used for the data compliant with a normal distribution and the Mann-Whitney U test for the other data. The chi-square test was used for quantitative data. $p < 0.05$ was accepted as significant for all analyses.

Results

A total of 70 subjects consisting of 45 males and 25 females were included in our study. There were 8 smokers and 62 non-smokers. The mean age was 34.53±10.9 (17-61), the mean weight 95.33±17.7 kg (75-135) and the mean height 165.4±8.6 cm (148-187). The BMI range was 26 kg/m2 to 41 kg/m2 and the mean BMI was 33.33±5.6 kg/m2. Mean waist circumference value was 102.34±16.2 cm, and mean hip circumference 116.36±11.8 cm. The mean value for fat mass was 31.8±12.8 (7.1-62.5), fat-free mass (FFM) 56.3±11.3 kg (39.30-95.90), body water percentage (TBW) 41.2±8.3% (28.80-70.9%) and obesity duration 7.3±5.3 years (1-25) (Table 3).

Table 3. Variable Values

	Mean Value	Min-Max
Age	34.53±10.9	17-61
Weight (kg)	95.33±17.7	75-135
Height	165.4±8.6	148-187
BMI	33.33±5.6	26-41
Waist circumference	102.34±16.2	67-144
Hip circumference	116.36±11.8	83-144
Fat Mass	31.8±12.8	7.1-62.5
FFM	56.3±11.3	39.3-96.9
TBW	41.2±8.3	28.8-70.9
Obesity duration	7.3 ±5.3	1-25

RLS was found in 17 subjects in our study with 13 of these in the obese group and 4 in the non-obese group. No statistically significant difference was found between the obese and non-obese groups in terms of RLS incidence (p:0.165) and RLS severity (p:0.918).

There was also no significant relationship between hip circumference and the RLS presence (p:0.22) and severity (p:0.948), and also between waist circumference and the RLS presence (p:0.206) and severity (p:0.810). Again, no significant relationship was found between fat mass and the RLS presence (p;0.102) and severity (p:0.548); FFM and the RLS presence (p:0.698) and severity (p:0.980); and between TBW and RLS presence (p:0.565) RLS severity (p:0.978). The obesity duration did not create a significant change in the RLS presence (p:0.197) and severity (p:0.703) (Table 4). There was also no gender difference in RLS incidence in the population included in our study (p:0.926).

Table 4. Statistical Relationship Results

	RLS presence	RLS severity
Hip circumference	0.220 (p)	0.948 (p)
Waist circumference	0.206 (p)	0.810 (p)
Fat Mass	0.102 (p)	0.548 (p)
FFM	0.698 (p)	0.980 (p)
TBW	0.565 (p)	0.978 (p)
Obesity duration	0.197 (p)	0.703 (p)

Discussion

Obesity is now considered one of the most important preventable causes of disability in the world [11]. Increased BMI has also been found to increase the risk of developing RLS in a study conducted by Batool-Anwar et al. [12]. Similarly, obesity has been shown to progressively increase the frequency of RLS by Gao et al. [13]. Subjects diagnosed with RLS were found to have higher BMI measurements in a study conducted by Elwood et al. in 2006 [9].

Inadequate dopamine metabolism, sympathetic hyperactivity and chronic inflammation in the brain have been used in an attempt to explain the relationship between obesity and RLS [5,12].

The hypothalamic-pituitary-adrenal (HPA) system activation and inflammation usually caused by metabolic syndromes is one of underlying mechanisms of obesity increasing the risk of RLS development. Increased overnight HPA system activation was found in RLS patients in a study conducted in Germany. The physiological cortisol level was also found to be at its minimum when the RLS symptoms were maximally experienced [14]. It is therefore possible that the sleep disorder developing due to RLS may trigger HPA system activation and the RLS symptoms could also trigger HPA activation as a response to stress [15,16].

The best-proven biological abnormality in the pathophysiology of RLS is cerebral iron deficiency as shown in the cerebrospinal fluid and with magnetic resonance imaging methods and autopsy results [17]. Various studies have shown that serum iron levels were not significantly different between RLS patients and the control group, although CNS iron was lower in RLS patients. This is thought to be due to differences in iron absorption, transport of the iron from the blood-brain barrier, and intracellular iron regulation between the groups [18]. Systemic iron deficiency has been shown to cause a decrease in brain iron transport and consequently hypoxia and myelin loss [19], and obesity has been proven to cause a significant increase in the risk of systemic iron deficiency development [20]. Striatal dopamine D2 receptors have been shown to be lower in number in obese patients than in controls. Wang GJ et al. had documented a reduction in dopamine D2 receptors in morbidly obese subjects. PET was used for assess dopamine D2 receptor availability in striatum with brain glucose metabolism in ten morbidly obese subjects (BMI>40 kg/m2) and compared it to that in twelve non-obese controls. In obese subjects striatal D2 receptor availability was lower than controls and was positively correlated with metabolism in dorsolateral prefrontal, medial orbitofrontal, anterior cingulate gyrus and somatosensory cortices [21]. Iron serves as a cofactor of tyrosine hydroxylase which is a rate determinant in dopamine synthesis. Tyrosine hydroxylase function increases with iron deficiency and extracellular dopamine increases with an increase in tyrosine hydroxylase function, resulting in a decrease in the dopamine transporter and in the number of D2 receptors on the cell surface [22]. An increase in substantia nigra tyrosine hydroxylase and a decrease in the putamen D2 receptor level have been found in autopsy studies conducted on RLS patients [23].

A significant relationship was found between BMI and RLS in another conducted in the Korean population. This positive correlation was compliant with other studies and statistically significant in females but not in males [24].

Obesity and high cholesterol levels were found to significantly increase the risk for developing RLS in both genders after excluding age, ethnic origin, physical activity, smoking, alcohol use, antidepressant use, and a history of stroke-myocardial infarction or menopause, in a large-scale, prospective study conducted by De Vito et al. [25].

A total of 197,204 subjects were analyzed in 15 studies in a meta-analysis conducted by Song Lin et al. in 2018 and a significant relationship was found between obesity (BMI>30 kg/m2) and RLS ($p<0.001$) while being overweight (BMI 25-30 kg/m2) was found to increase RLS risk ($p<0.001$) [26].

RLS was shown to be more common in obese people but the result was not statistically significant in a study on 143 obese and 94 control subjects conducted by Yıldız D et al. in the Turkish population [27].

The RLS incidence was found to be high in the diabetic group in a study on 939 subjects from Iceland and another study on 998 subjects from a Swedish population in 2010 but no significant difference was present in the group with metabolic problems such as obesity, hypertension and cardiovascular disease and RLS was found to be 2 times more common in women from Iceland than in those from Sweden in this study [28].

No significant difference was found between obese and non-obese groups in terms of RLS incidence in our study, similar to the Iceland and Sweden population (p:0.165). Besides, unlike other studies in the literature, no gender difference was seen in the RLS incidence in both the obese (p:0.783) and non-obese groups (p:1.00).

Increasing waist circumference measurements were found to increase the RLS incidence progressively in a study conducted by Gao et al. [13]. Abdominal obesity was again found to increase risk of RLS incidence by 40-70% in a large-scale prospective study conducted by De Vito et al. [25]. However, no significant relationship was found between RLS incidence and waist circumference measurements (p:0.206) and obesity (p:0.16) in our study.

Although our study produced results that were similar to those from the populations from Iceland and Sweden, a large number of studies and meta-analyses have shown RLS incidence to increase in obesity. Our results may have been influenced by our small numbers of obese and control subjects.

Conclusion

The fact that obesity is a modifiable risk factor for RLS, which is a common movement disorder that decreases quality of life, is important in terms of preventive medicine. Although there are several views regarding the underlying mechanisms, the etiopathogenesis has not yet been elucidated. Further studies on a larger number of subjects may explain the relationship between obesity and RLS together with the etiopathogenesis.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
The authors declared that this study has received no financial support

Ethical approval
The Ethics Committee of Inonu University approved this study

Fatma Ebru Algul ORCID:0000-0003-0318-7571
Ayse Cikim Sertkaya ORCID:0000-0002-6068-8834
Sibel Altinayar ORCID:0000-0002-1126-0532

References

1. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4:101-19.
2. 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.
3. International Restless Legs Syndrome Study Group 2012. Revised diagnostic criteria. Available from http://irlssg.org/diagnostic -criteria/
4. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome (RLS) prevalence and impact: REST (RLS epidemiology, symptoms and treatment) general population study. Arch Intern Med. 2005;165:1286-92.
5. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome. Sleep Med. 2004;5:385-91.
6. Takaki J, Nishi T, Nangaku M, et al. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. Am J Kidney Dis. 2003;41:833-9.
7. Allen RP. Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. Am J Med. 2007;120:13-21.
8. Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. Lancet. 2001;357:354-7.
9. Elwood P, Hack M, Pickering J, et al. Sleep Disturbance, stroke and heart disease events: evidence from the Caerphilly cohort. J Epidemiol. Community Health. 2006;60:69-73.
10. Hargens TA, Kaleth AS, Edwards ES, et al. Assosiation between sleep disorders, obesity and exercise: a review. Nat Sci Sleep. 2013;5:27-35.
11. Wang Y, Beydoun MA. The obesity epidemic in the United States-gender, age, socioeconomic, racial/ethnic and geographic characteristics: a systematic review and meta-regression analysis. Epidemiol Rev. 2007;29:6-28.
12. Batool-Anwar S, Li Y, De Vito K, et al. Lifestyle factors and risk of restless legs syndrome: prospective cohort Study. J Clin Sleep Med. 12,187-94.
13. Gao X, Micheal A, Schwarzschild MD, et al. Obesity and restless legs syndrome in men and women. Neurology. 2009:72;1255-61.
14. Schilling C, Schredl M, Strobl P, et al. Restless legs syndrome: evidence for nocturnal hypothalamic-pituitary-adrenal system activaton. Mov Disord. 2010;25:1047-52.
15. Spath-Schwalbe E, Gofferje M, Kern W, et al. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. Biol Psychiatry. 1991;29:575-84.
16. Högl B. Circadian rhythms in restless legs syndrome. Sleep Med. 2006:7;209-10.
17. Early CJ, B Barker P, Horská A, et al. MRI-determined regional brain iron concentrations in early and late-onset restless legs syndrome. Sleep Med. 2006;7:458.
18. Allen R, Early C. Defining the phenotype of the restless legs syndrome using age-of-symptom-onset. Sleep Med. 2000;1:11-9.
19. Allen RP. Restless leg syndrome / Willis-Ekbom disease pathophysiology. Sleep Med Clin. 2015;10:207-14.
20. Zhao L, Zhang X, Shen Y, et al. Obesity and iron deficiency: a quantitative meta-analysis. Obes Rev. 2016:16;1081-93.
21. Wang GJ, Volkow ND, Logan J et al. Brain dopamine and obesity. Lancet. 2001;357:354-7.
22. Salas RE, Gamaldo CE, Allen RP. Update in restless legs syndrome. Curr Opin Neurol. 2010;23:401-6.
23. Concor JR, Wang XS, Allen RP, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. Brain 2009;132:2403-12.
24. Kim J, Choi C, Shin K, et al. Prevalence of restless legs syndrome and associated factors in the Korean adult population: the Korean Health and Genome Study. Psychiatry Clin Neurosciç 2005;59:350-3.
25. De Vito K, Yanping L, Batool-Anwar S, et al. Prospective study of obesity, hypertension, high cholesterol and risk of restless legs syndrome. Mov Disord. 2014:29;1044-52.
26. Lin S, Zhang H, Gao T, et al. The assosiation between obesity and restless legs syndrome: A systemic review and meta-analysis of observational studies. J Affect Disord. 2018;235:384-91.
27. Yıldız D, Buyukkoyuncu N, Kilic A, et al. Obesity: a possible risk factor for restless legs syndrome. Neurol Res. 2017;39:1044-8.
28. Benediktsdottir B, Janson C, Lindberg E, et al. Prevalence of restless legs syndrome among adults in Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. Sleep Med. 2010;11:1043-8.