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Obesity, Diet, and Risk of Restless Legs Syndrome

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ABSTRACT

The restless legs syndrome (RLS) is a common movement disorder, characterized by an almost irresistible urge to move the legs in the evening or at rest. According to recent estimates, it affects ~5–15% of adults and often has a substantial impact on sleep, daily activities, and quality of life. Although genetic susceptibility has been shown to play an important role in the pathogenesis of RLS, there is evidence supporting possible environmental causes of RLS. In this review, we focus on obesity and dietary factors, including iron, B vitamins, vitamin E, vitamin C, and magnesium, as these factors are modifiable. Both clinical and epidemiology studies suggest that obesity and dietary factors could be risk factors for RLS. However, previous studies are limited by small sample sizes and retrospective or cross-sectional designs that preclude conclusions regarding causality. Therefore, further prospective studies examining the relation between obesity, diet, and the risk of developing RLS should be a priority.

Keywords: Obesity, diet, risk factor, restless legs syndrome, iron deficiency, homocysteine

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INTRODUCTION

Restless legs syndrome (RLS) is a neurological disorder characterized by an almost irresistible urge to move the legs [1, 2]. RLS is the most common movement disorder, affecting approximately 5–15% of the general population [1–3], with a substantial impact on sleep, daily activities, and quality of life [4]. It has been shown that approximately 50% of RLS patients reported an inability to fall asleep and 61% reported disturbed or interrupted sleep [5], which may result from an urge to move as well as from related sensory symptoms in the legs, which are worse at night and while at rest [1].

Cross-sectional studies have shown that subjects with RLS have a significantly higher prevalence of depression, diabetes, cardiovascular disease, and a lower mental health score than subjects without RLS [6–11]. RLS sufferers also have a reduced quality of life compared with the general population, which is comparable with that experienced by those with other serious chronic medical conditions, such as type 2 diabetes mellitus, chronic obstructive pulmonary disorder, or depression [5]. Among patients with endstage renal disease, RLS was associated with increased mortality [12].

It has been suggested that RLS is associated with both genetic and non-genetic factors. More than 50% of RLS patients have a positive family history of this condition [2]. Two recent genome-wide association studies provided strong evidence of the association of genetic variations with RLS [13, 14]. Additionally, non-genetic factors such as age, female sex, pregnancy, iron deficiency, and other lifestyle factors have also been suggested to play an important role in RLS [1, 2, 6]. In this review, we focus on the potential roles of obesity and diet on RLS risk because both are modified factors.

OBESITY AND RLS

The unfavorable role of obesity on dopamine status in the central nervous system (CNS) has been demonstrated by several human and animal studies. A case–control study showed that obese individuals (n=10, body mass index (BMI) >40 kg/m^2) had a significantly lower striatal dopamine D_2 receptor availability than controls ($P<0.01$) [15]. These findings were supported by observations from animal studies where obese rats had lower D_2 dopamine receptors [16, 17].

Moreover, in obese individuals, D_2 receptor levels have been shown to be inversely associated with BMI (r=0.84) [15]. Genetic studies have shown a link between obesity and variants of dopamine metabolism-related genes, such as Taq 1, monoamine oxidase A, and monoamine oxidase B [18, 19]. Vascular abnormality resulting from obesity could be an alternative mechanism underlining the possible association between obesity and RLS. Cardiovascular diseases have been shown to be positively associated with RLS [20]. A recent study showed that

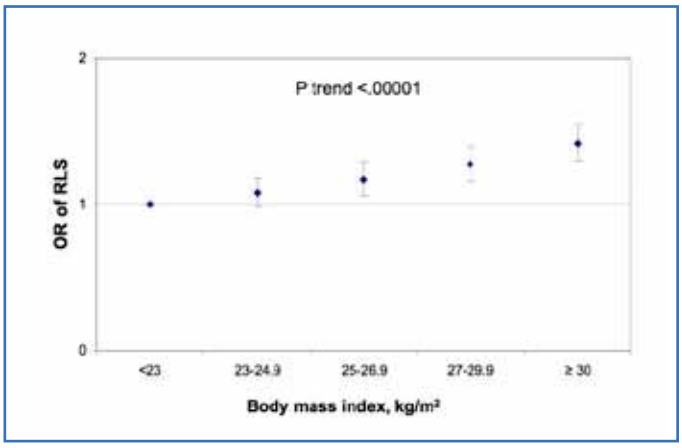

Figure 1. Adjusted OR (95% CI) of RLS according to body mass index in the Health Professionals Follow-up Study and the Nurses' Health Study II [25], adjusting for age, ethnicity, smoking status, physical activity, use of antidepressants, the Crown–Crisp phobia index, and presence of stroke, hypertension, or myocardial infraction (each of them, yes/no)

enhanced external counterpulsation treatment significantly improved the RLS symptoms [21].

Several epidemiologic studies have examined the cross-sectional relationship between obesity and RLS. Most of these studies [11, 22, 23], but not all [24], have reported significant positive associations. Among 1803 men and women aged 18 years or older, Phillips *et al* found that each increase of 5 kg/m^2 BMI was associated with a 31% increased likelihood of having RLS [22]. In another cross-sectional study conducted in five European countries (n=18 890), crude odds ratio (OR) for RLS was 1.22 (95% CI 1.0 to 1.5) for BMI of >27 vs 20–25 kg/m^2 [11]. In a Korean population (n=9939), Kim *et al* found a significant association between BMI and RLS among women (OR=1.2 for BMI >25 vs ≤25 kg/m^2) but not among men (OR=1.1) [23]. In contrast, in a case–control study including 103 RLS cases and 103 control subjects (mean age 43 years for both groups) living in Mersin, Turkey, Sevim *et al* reported a similar mean BMI between the two groups (mean BMI 25.8 kg/m^2 for both groups) [24]. One possible interpretation for failure to find significant associations between BMI and RLS could be the small sample size.

We have been conducting analyses to examine the cross-sectional association between obesity and RLS in two ongoing US cohorts: the Health Professional Follow-up Study (23 575 men, mean age 67 years) and the Nurses' Health Study II (65 872 women, mean age 50 years) free from diabetes and arthritis (**Figure 1**) [25]. Information on RLS was assessed using a set of standardized questions recommended by the International RLS Study Group. Multivariate OR for RLS was 1.42 (95% CI 1.3 to 1.6; *P* trend <0.0001) for subjects with BMI >30 vs <23 kg/m^2 and 1.60 (95% CI 1.5 to 1.8; *P* trend<0.0001) for highest vs lowest waist circumference quintiles. BMI in early adulthood (age 18–21 years) and weight gain were also positively associated with the prevalence of RLS (*P* trend <0.01 for both). These preliminary results suggest a possible role of obesity in RLS. However, this observation needs to be replicated in other populations with different cultural backgrounds and lifestyles.

DIETARY FACTORS AND RLS

Iron Status

Since 1945, when Ekbom first proposed that RLS could be secondary to iron deficiency [26], the role of iron in the pathology of RLS has been investigated intensively. Serological studies have observed a lower ferritin or a higher transferrin concentration, indicating a decreased iron sufficiency, in serum or cerebrospinal fluid (CSF) among RLS patients, relative to control subjects [27–31]. These findings have been supported by imaging studies. Using magnetic resonance imaging (MRI), it has been shown that RLS patients have a significantly lower iron concentration in brain, as assessed by an "iron index", than control subjects [32, 33]. Further studies observed that RLS severity was inversely associated with serum ferritin levels [34, 35]. Clinical trials provide further evidence of a possible causal relationship between iron and RLS: supplementation of iron, either orally [34, 36] or intravenously [30, 37], resulted in significant improvement in RLS symptoms. However, it remains unclear whether dietary iron content at normal intake level is associated with RLS risk or progression. Iron could influence CNS dopamine status via several mechanisms. Iron deficiency may decrease dopamine synthesis, as iron is a cofactor of tyrosine hydroxylase. Animal studies have shown that iron deficiency reduced dopamine transporters and subsequently reduced dopamine uptake [38, 39].

Because serum ferritin and transferrin concentrations are affected by several factors, such as inflammation and diet, in addition to body iron stores, the observed associations between these biomarkers and RLS could be confounded. This limitation could be overcome by the use of the history of blood donation as a marker of body iron levels. Because body iron stores can be reduced greatly through regular blood donation, the contrast between regular blood donors and non-donors with a similar distribution of other RLS risk factors provides a direct and powerful test of the hypothesis that depletion of body iron stores increases the risk of RLS. Few studies have examined RLS status among blood donors. In a small hospital-based cross-sectional study (n=109), patients with repeated blood donation (≥5 times in their lifetime) were five times more likely to have RLS and/or periodic limb movement in sleep (PLMS) than those without repeated blood donation (OR=5.1) [40]. A similar positive association between blood donation and RLS was observed in a case–control study with 64 iron deficiency anemic and 256 non-anemic control subjects in an Indian population [41]. A cross-sectional study

reported a high prevalence of RLS among blood donors (15% and 25% for men and women respectively; n=946) [42]. This study also reported significant associations between the presence of RLS and red cell distribution width, a marker of iron deficiency, but not with dietary iron intake [42]. In a small retrospective clinical study of eight blood donors with RLS, six RLS cases were found to have an onset at about the same time as or after blood donations [43]. However, these results should be interpreted with caution because of small sample size and the potential recall and selection bias associated with a retrospective design.

B Vitamins

The role of folate and vitamin B12 in RLS has been suggested since the 1970s. In a series of clinical studies of folate and RLS [44–47], Botez *et al* observed that (1) RLS patients generally had low plasma, red blood cell, and CSF folate concentrations; (2) RLS symptoms were temporarily improved immediately after administration of vitamin B12 as assessed by the Schilling test; and (3) RLS was responsive to folic acid therapy. Further, in a randomized clinical trial by Botez and Lambert [47], one group of 11 pregnant women received a multivitamin tablet daily containing 0.5 g of folic acid, B12, and iron, whereas the other group (n=10) received the same multivitamin without folic acid. These women were followed up to the 13th, 22nd, and 35th weeks of pregnancy and 6 weeks after delivery. At the end of the trial, only 1 out of 11 women developed RLS in the folic acid group relative to 8 out of 10 in the control group (P=0.002). Similarly, a small cohort study including 45 pregnant women found that those with RLS had lower plasma folate concentrations during preconception and at each trimester than subjects without RLS [48].

Folate is important for the generation of dopamine in the CNS [49]. Folate and S-adenosyl-methionine, which is modulated by folate and B12, influence the synthesis of CNS tetrahydrobiopterin, which is essential in the conversion of tyrosine to L-dopa through tyrosine hydroxylase [50, 51]. Interestingly, tetrahydrobiopterin has a circadian change, which parallels the pattern seen in RLS symptoms. A study including 30 RLS cases and 22 control subjects showed that tetrahydrobiopterin levels decreased significantly during the night among RLS patients, but not among control subjects [52].

Abnormalities in folate and B12 metabolic function result in elevated homocysteine concentration, which may also have a direct role in the pathogenesis of RLS because of its toxic effect on dopaminergic neurons. In an animal model of Parkinson's disease (PD), folate deficiency and elevated homocysteine significantly sensitized dopaminergic neurons to a subtoxic dose of MPTP [53]. Homocysteine also has a neurotoxic effect by activating the N-methyl-D-aspartate receptor, leading to cell death [54, 55], or may be converted into homocysteic acid, which also has an excitotoxic effect on neurons [54, 56]. Further, elevated homocysteine is associated with cardiovascular and renal disease, which have been found to co-occur with RLS. In a case–control study including 97 RLS patients and 92 healthy control subjects, Bachmann *et al* reported that RLS patients tended to have higher serum homocysteine concentrations relative to control subjects (11.7 vs 11.0 μmol/L), but the difference was not significant [57].

Magnesium

A small case–control study showed that RLS patients had a lower serum magnesium concentration relative to control subjects [58]. Oral or intravenous administration of magnesium has been shown to relieve RLS symptoms [59, 60]. However, a recent case–control study including 11 RLS cases failed to find a significant difference for serum and CSF magnesium concentrations between cases and control subjects [61]. Magnesium inhibits N-methyl-D-aspartate receptors, which could be involved in RLS through the activation and production of inflammatory mediators [62]. Magnesium serves as a calcium antagonist because of their chemical similarity [63]. Reduction in magnesium–calcium competition due to magnesium deficiency may lead to muscle cramping [64]. This could confound the observed association between magnesium and RLS. However, to our knowledge, no study has examined whether dietary intake of magnesium is associated with RLS risk or progression.

A possible association between intake of antioxidants, such as vitamin E, and vitamin C and RLS has been suggested by some studies [3, 65, 66]. However, there have been no studies specifically examining whether long-term intake of such antioxidants influences RLS risk or progression.

Summary

As reviewed above, both clinical and epidemiological studies support the notions that obesity and nutritional inadequacy could be modifiable risk factors for RLS. However, these studies are limited by their cross-sectional design, small sample size, and failure to adjust for several important cofounders. Therefore, further prospective studies examining the relation between obesity, diet, and the risk of developing RLS should be a priority. Further, potential interaction between these factors and genetic susceptibility would also be of interest to explore in future studies. Understanding the roles of obesity and diet in RLS will not only improve our understanding of the etiology of RLS but could potentially help to pursue new treatment and prevention strategies.

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