

INPLASY PROTOCOL

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None declared.

Prevalence of restless legs syndrome in diabetes mellitus: systematic review and meta-analysis of observational studies

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Review question / Objective: We conducted a review and meta-analysis of the available literature to evaluate the overall RLS prevalence in diabetes mellitus patients and compare the risk of RLS between diabetes mellitus patients and non-diabetic population.

Eligibility criteria: To be included in our review, eligible studies had to (1) be observational studies with cross-sectional, case-control or cohort designs analyzing RLS in diabetes mellitus patients; (2) diagnose RLS according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG); and (3) report point prevalence of RLS or sufficient data to calculate it.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 May 2021 and was last updated on 03 May 2021 (registration number INPLASY202150012).

INTRODUCTION

Review question / Objective: We conducted a review and meta-analysis of the available literature to evaluate the overall RLS prevalence in diabetes mellitus patients and compare the risk of RLS between

diabetes mellitus patients and non-diabetic population.

Rationale: Diabetes has become the most concerned health problem in the world. Chronic complications of diabetes, especially RLS, are often underdiagnosed. Severe restless legs syndrome can affect the

daily life of diabetic patients, reduce the quality of life, and even cause anxiety and depression in patients to form a vicious circle. It is particularly important to fully understand the prevalence of RLS in diabetic patients and to recognize the symptoms as early as possible, and then to give corresponding treatments.

Condition being studied: Restless legs syndrome (RLS) is a common neurological sensorimotor disorder characterized by uncomfortable sensations in the extremities and an overwhelming urge to move one's legs, especially in the evening and during periods of inactivity. First mentioned in 1672 by Willis, RLS was clinically described in the early 1940s by Ekbom, who coined and published the term "restless legs syndrome". As a consequence, the disease has also been called "Willis-Ekbom disease". The four minimal diagnostic criteria for RLS of the International Restless Legs Study Group (IRLSSG) were: 1. Desire to move the limbs usually associated with paresthesias/dysesthesias. 2. Motor restlessness. 3. Symptoms are worse or exclusively present at rest (i.e. lying, sitting) with at least partial and temporary relief by activity. 4. Symptoms are worse in evening/night. Although the pathophysiological pathways leading to RLS are still unknown, brain iron deficiency and dysfunction of the dopaminergic system appear to play a role. RLS can be secondary to various medical conditions, such as iron deficiency, rheumatoid arthritis, end-stage renal disease, obesity, and some physiological states such as pregnancy. However, the relationship between RLS and diabetes mellitus has not been deeply studied.

METHODS

Search strategy: The search string was ('restless legs syndrome', 'Willis-Ekbom disease', 'RLS') and ('diabetes mellitus', 'diabetes').

Participant or population: Diabetes mellitus patients (835,854).

Intervention: Restless legs syndrome.

Comparator: Non-diabetic population.

Study designs to be included: Observational studies.

Eligibility criteria: To be included in our review, eligible studies had to (1) be observational studies with cross-sectional, case-control or cohort designs analyzing RLS in diabetes mellitus patients; (2) diagnose RLS according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG); and (3) report point prevalence of RLS or sufficient data to calculate it.

Information sources: We searched the available literature in PubMed, Web of Science, and Embase databases.

Main outcome(s): The pooled prevalence of RLS among diabetes mellitus patients was 24% (95% CI 0.21-0.28; $P < 0.001$). For the comparison of RLS prevalence between diabetes mellitus patients and non-diabetic population, the random-effects model was again adopted because of the significant heterogeneity ($I^2 = 78.1\%$, $P < 0.001$). The pooled data revealed that patients with diabetes had a higher risk of RLS (OR 1.91, 95% CI 1.61-2.26; $P < 0.001$) than non-diabetic population.

Additional outcome(s): In subgroups divided by ethnicity, 16 studies included Asian patients (e1-e16) and 21 studies included non-Asian patients (e17-e31, e34-e36, e38-e40). The pooled estimates showed that the prevalence of RLS among diabetic patients was higher in Asia (27%, 95% CI 20%-34%; $P < 0.001$; $I^2 = 94.9\%$, $P < 0.001$) than outside Asia (23%, 95% CI 18%-27%; $P < 0.001$; $I^2 = 94.8\%$, $P < 0.001$). Four studies (e2, e4, e21, e36) evaluated the prevalence of RLS in both male and female diabetes patients. The prevalence of RLS was higher in female patients (23%, 95% CI 9%-37%; $P = 0.001$; $I^2 = 92.3\%$, $P < 0.001$) than in male patients (16%, 95% CI 8%-24%; $P < 0.001$; $I^2 = 74.0\%$, $P = 0.009$).

Data management: We use Excel to extract the original data and Endnote to manage the data.

Quality assessment / Risk of bias analysis: Each study was given a Newcastle-Ottawa Scale quality score. Publication bias was assessed using Egger's and/or Begg's tests.

Strategy of data synthesis: Heterogeneity among the included studies was evaluated using the Q test and quantified using I². An I² value below 25% was considered as homogeneity; 25% to < 50%, low heterogeneity; 50% to < 75%, moderate heterogeneity; and at least 75%, substantial heterogeneity. We planned to use a fixed-effects model to meta-analyze pooled data classified as homogeneous or of low heterogeneity, and a random-effects model for data classified as showing moderate or substantial heterogeneity. Publication bias was assessed using Egger's and/or Begg's tests.

Subgroup analysis: In subgroups divided by ethnicity, 16 studies included Asian patients (e1-e16) and 21 studies included non-Asian patients (e17-e31, e34-e36, e38-e40). The pooled estimates showed that the prevalence of RLS among diabetic patients was higher in Asia (27%, 95% CI 20%-34%; P < 0.001; I² = 94.9%, P < 0.001) than outside Asia (23%, 95% CI 18%-27%; P < 0.001; I² = 94.8%, P < 0.001). Four studies (e2, e4, e21, e36) evaluated the prevalence of RLS in both male and female diabetes patients. The prevalence of RLS was higher in female patients (23%, 95% CI 9%-37%; P = 0.001; I² = 92.3%, P < 0.001) than in male patients (16%, 95% CI 8%-24%; P < 0.001; I² = 74.0%, P = 0.009).

Sensitivity analysis: We performed a sensitivity analysis by omitting the individual studies one at a time to test the robustness of our findings.

Language: Only articles in English were included.

Country(ies) involved: China.

Other relevant information: None.

Keywords: diabetes mellitus; diabetes; restless legs syndrome; diabetic peripheral neuropathy; meta-analysis.

Dissemination plans: None.

Contributions of each author:

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