Journal of Pharmaceutical Research International

Volume 35, Issue 22, Page 20-40, 2023; Article no.JPRI.103829
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Association of Restless Legs Syndrome with Glycemic Control and Psychological Status in Adults with Type 2 Diabetes: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author EMA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SAA and NMMA managed the analyses of the study. Author SAA managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2023/v35i227414

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/103829

Systematic Review Article

Received: 01/06/2023
Accepted: 01/08/2023
Published: 21/08/2023

ABSTRACT

Background: Evidence is still lacking regarding the association of restless leg syndrome (RLS) on glycemic control and psychological status in diabetic patients.
Aims: To summarize the evidence regarding the association of RLS with glycemic control and psychological status in adults with type 2 diabetes.
Methods: The literature search compassed all English-published studies from inception till the 21st of May 2023 on the electronic databases of MEDLINE/PubMed, Cochrane Library, Web of Science,

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and ProQuest. The search terms included “Diabetes Mellitus, Type 2” AND "restless legs syndrome”. We created a narrative synthesis for the outcomes and pooling of the glycated hemoglobin (HbA1c) levels.
Results: Sixteen studies were included. Pooling of the HbA1c levels showed a lack of significant differences between the RLS+ve and RLS-ve groups. Seven out of eight studies showed a significant decrease in sleep quality. Three studies assessed the quality of life and found a marked decrease in RLS+ve patients. Two studies out of four found a significant association of RLS with depression, while the other two found a non-significant increase with RLS.
Conclusion: There is no evidence that RLS in type 2 diabetic patients is associated with poor glycemic control. The evidence suggests that RLS is associated with a reduction in sleep quality and quality of life. The evidence is inconclusive regarding the association of RLS with depression due to the low number of studies. Physicians should be aware of the associated disorders with RLS in diabetic patients and endeavour to identify and alleviate them.

Keywords: Glycemic control; depression; diabetes type 2; quality of life; restless legs syndrome; sleep quality.

1. INTRODUCTION

Restless legs syndrome (RLS) is a neurological, sensorimotor disorder. The syndrome is also known as Willis–Ekbom syndrome, named after Sir Thomas Willis and Ekbom who described this disorder [1]. The prevalence of RLS is very low in Asian populations (between 1% and 3%) [2], compared to the prevalence in Europe and North America (between 5% to 13%) [3]. The prevalence is higher in women than in men [4]. The prevalence of RLS tends to increase with age and in patients with several comorbidities [5]. Several diseases have been linked with RLS, including metabolic disorders (e.g., diabetes mellitus and iron deficiency), cardiovascular or renal disorders, autoimmune diseases (e.g., multiple sclerosis), neurodegenerative disorders (e.g., Parkinson's disease), inflammatory conditions, and depression [6].

Typical manifestations include uncomfortable sensations in the limbs and an urge to move the legs. The manifestations are usually experienced in the evening and during rest and disappear or decrease by movement [7]. Patients vary widely regarding the frequency as some patients may have less than one episode per year while others suffer daily. In addition, the severity of symptoms ranges from mild irritation to disabling manifestations. The onset of RLS peaks at about the age of 20 years and also at about 40 years. Patients who started suffering from RLS by the age of 40–45 years (early-onset RLS) tended to have a positive family history of RLS and a slowly progressing course. On the other hand, patients developing RLS after the age of 40–45 years (late-onset RLS) had a more rapid course and tended to suffer from multiple concomitant diseases [8].

The pathophysiology of RLS is still unclear. Some mechanisms have been proposed as the deficiency of brain iron and dysfunction of the dopaminergic system [9]. RLS may be primary (idiopathic) or secondary to other conditions such as iron deficiency, rheumatoid arthritis, end-stage renal disease, and pregnancy [10].

The International Restless Legs Study Group (IRLSSG) stated that the diagnosis of RLS depends on five diagnostic criteria that are: 1) a desire to move the limbs (usually associated with paresthesias/dysesthesias), 2) motor restlessness, 3) the presence or worsening of symptoms at rest (i.e., while lying or sitting) while relieved temporarily by activity, 4) worsening of symptoms in evening/night, and 5) these features are not solely accounted for as symptoms primary to another medical or a behavioural condition such as myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, or habitual foot tapping [11].

The RLS negatively impacts the quality of life (QOL) and psychological status. Severe RLS has been linked to depression and suicide [12]. Unfortunately, the diagnosis of RLS is often delayed due to poor awareness among physicians and a lack of knowledge among patients regarding which specialist can deal with these symptoms [13]. As RLS is typically a life-long disorder, proper long-term management for moderate-to-severe cases is necessary to reduce the socio-economic burden [4].

The RLS frequently manifests in diabetic patients [14]. Nevertheless, the relationship between RLS and DM still requires a more in-depth review to elucidate the factors that may contribute to the development of RLS in those patients. The present systematic review aimed to summarize the evidence regarding the association of restless legs syndrome with glycemic control and psychological status in adults with type 2 diabetes

2. MATERIALS AND METHODS

2.1 Methodology

This systematic review followed the principles of the conduction and reporting that are recommended by the Cochrane Handbook for Systematic Reviews of Interventions, version 6 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

2.2 The research Question

Is restless legs syndrome associated with glycemic control and psychological status in adults with type 2 diabetes mellitus?

2.3 Research aim and Objectives

This systematic review aimed to assess the potential association between RLS and both glycemic control and psychological status in adults with type 2 diabetes mellitus. The studied objectives included:

a) to assess the association of glycemic control with the presence and severity of RLS in adults with type 2 diabetes mellitus;
b) to evaluate the association of psychological status with the presence and severity of RLS in adults with type 2 diabetes mellitus.

2.4 Eligibility Criteria for the Studies

2.4.1 Inclusion criteria

This systematic review included observational studies whether cross-sectional or longitudinal in design (cohort or case-control studies) that were published in English from inception to the 21st of May 2023.

2.4.2 Participants

Patients with type 2 diabetes mellitus.

2.4.3 Comparisons

Between patients with RLS and those without and between different grades of RLS.

2.4.4 Exclusion criteria

Studies were excluded if conducted on animals, or if none of the studied comparisons was present. Excluded publication types were conference abstracts, protocols, reviews, and clinical guidelines. We also excluded duplicate reports.

2.5 Search Strategy

2.5.1 Electronic searches

We conducted the literature search on the electronic databases of MEDLINE/PubMed, Cochrane Library, Web of Science, and ProQuest. The search included all published articles from inception till the 21st of May 2023. The search took place during the period from the 7th of May 2023 to the 21st of May 2023. The search terms included “Diabetes Mellitus, Type 2” AND "restless legs syndrome”. The used search terms for each database along with the number of yielded search results are as follows: "Diabetes Mellitus, Type 2"[Mesh] AND ("restless legs syndrome"[MeSH Terms] OR ("restless"[All Fields] AND "legs"[All Fields] AND "syndrome"[All Fields]) OR "restless legs syndrome"[All Fields]) [PubMed, 45 studies]; "Diabetes Mellitus, Type 2"[Mesh] AND ("restless legs syndrome"[MeSH Terms] OR ("restless"[All Fields] AND "legs"[All Fields] AND "syndrome"[All Fields]) OR "restless legs syndrome"[All Fields]) [Cochrane library, one study]; "Diabetes Mellitus, Type 2” AND "restless legs syndrome"[All Fields] [WOS, 52 studies]; and "Diabetes Mellitus, Type 2” AND "restless legs syndrome"[All Fields] [ProQuest, 251 studies].

2.5.2 Other resources

The reference lists of the retrieved relevant records were searched for identifying other potentially eligible studies.

2.6 Selection of Studies

The first reviewer conducted the literature search on the electronic databases, followed by the evaluation of the titles and abstracts, then the obtaining of the full-text articles of potentially related studies, and finally the application of the eligibility criteria for inclusion in this review on

each study. The second reviewer reviewed the processes of search and study selection. Disputes between the first and the second reviewer regarding the selection or exclusion of studies were settled by referring to the third reviewer.

2.7 Data Extraction

Data extraction from the included studies was performed by the first reviewer using a standardized data sheet. Extracted data included: (a) the study characteristics (the study's country, design, eligibility criteria, sample size, and duration); (b) patients' characteristics (age, sex, duration of diabetes, and comorbidities); (c) RLS (prevalence and severity); (d) the glycemic control (glycosylated hemoglobin, fasting blood glucose, or random blood glucose), (e) psychological status of the patients (anxiety, sleep disorders, and quality of life). The second reviewer revised the extracted data to ensure the accuracy and clarity of the process. Disputes were resolved by consulting the third reviewer.

2.8 Measured Outcomes

2.8.1 Primary outcome

Glycemic control (glycosylated hemoglobin, fasting blood glucose, or random blood glucose) and psychological status (anxiety, sleep disorders, and quality of life).

2.8.2. Secondary outcomes

Secondary outcomes included the duration of diabetes and insulin intake in patients with restless leg syndrome.

2.9. Assessment of the Risk of Bias in Included Studies

We used the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies.

2.10. Data Synthesis

A narrative synthesis Table [18] was designed for each outcome to report the number of studies, the direction of effect, and the statistical significance. Review Manager (RevMan Version 5.4. The Cochrane Collaboration, 2020) was used for computing the standardized mean difference (SMD) for the level of glycosylated hemoglobin. The SMD is obtained by subtracting the mean for the RSL-ve group from the mean for the RLS+ve group and then dividing the result by the pooled standard deviation. A positive SMD indicated an increase in the level in the RLS+ve group relative to the RSL-ve group, while a negative SMD value indicated the reverse. Significant heterogeneity across the studies was determined at a Cochrane Chi-square test with a p-value<0.1 and an I^2 index ≥ 50%. The random-effects model was used as heterogeneity was significant [19]. A p-value<0.05 was selected for interpreting the comparisons between the RSL+ve and RSL-ve groups. The effect size for SMDs was classified as large ≥ 0.8; medium ≥ 0.5, small ≥ 0.2, negligible < 0.2 [20].

3. RESULTS

3.1 Results of Literature Search and Study Selection

The search of online databases yielded 338 records, out of which 34 records were excluded (29 duplicate records and five records published in languages other than English). The remaining 304 records underwent screening of the titles and abstracts, with the exclusion of 258 records because of the publication type (n =33), non-relevance (n = 223), and conduction on animals (n = 2). For the remaining 46 records, the full text was obtained and assessed for eligibility. All the retrieved 13 full-text records were eligible to be included in this systematic review. We excluded 32 studies(19 not containing an RLS-ve group, 11 lacking the comparisons of interest, and two in patients without type 2DM). Fourteen studies were eligible for inclusion in this systematic review. Screening of the reference lists of the retrieved articles identifies two other eligible studies. So, this review included sixteen studies [21]. Two of these published articles belonged to the same study [22], differing only in the reported outcomes (Fig. 1).

3.2 The Basic Characteristics of the Included Studies

Table 1 summarizes the basic characteristics of the included studies. Eleven studies were cross-sectional in design [23], while the remaining studies were case-control in design [24]. The studies were conducted in Canada [25], Brazil [26], Italy [22], the USA [27], Pakistan [28], Japan [29], the Kingdom of Saudi Arabia [30], Ecuador [31], Iran [32], Turkey [33], Sudan [34], and India [35]. The sample size varied widely across the

studies, and so was the prevalence of RLS+ve in the sample size. One study showed a very high prevalence of RLS among its sample [36]. The characteristics of the patients (age and sex), as well as the duration of type 2 DM, are summarized for each study.

3.3 The Assessment of the Risk of Bias in the Included Studies

Tables 2 and 3 summarize the assessment of the ROB in the included studies. As regards the cross-sectional studies, all studies clearly stated the research question and recruited the subjects selected from the same or similar populations. In addition, the outcome variables were clearly defined in all studies. In two studies, the population was not specified [37]. Six studies did not report the number of eligible subjects from whom the sample was drawn [38]. Only two studies justified their sample size. Two studies reported that the sample size was estimated but did not describe the parameters used for the calculation [36]. The remaining seven studies did not mention any calculation for determining the sample size [39]. Due to the nature of the cross-sectional design, all eleven studies were not able to elucidate whether RLS preceded the studies' outcomes or not, the exposure was assessed once only, and no follow-up was done (questions 6, 7, 10, and 13). The RLS was studied in the current systematic review as a binary categorical variable (present/absent), not as a spectrum of severity, so question eight in the checklist was non-applicable. All the studies reported using the 4-minimum requirements for the diagnosis of RLS by the IRLSSG group [11], except for one study [25]. None of the studies mentioned the blinding of the outcome assessors. Five only of the studies adjusted statistically for potential confounding variables [40], while the other six studies did not report any adjustments [41].

As regards the case control, all studies stated the research question clearly and specified the study population. The cases were well defined from the controls and so was the exposure in all studies. None of the studies justified the sample size. One study did not report how controls were selected [22]. One study recruited the controls from a population that could potentially differ from the cases [42]. One study reported that consequent cases were recruited (so randomization was not done) [22].

None of the studies reported that the exposure preceded the studied outcomes. Only one study reported the blinding of outcome assessors [22], while the other three did not [43]. Two studies did not perform matching or adjusting for confounding factors [44].

3.4 Results of Narrative Synthesis and Meta-Analysis

Table 4 displays the results of the studies regarding glycemic control and included the narrative synthesis. Ten studies reported the association between RLS and glycemic control [45].

Glycated hemoglobin (HbA1c) was reported in nine studies [46]. In four out of these nine studies, the RLS+ve group showed a non-significantly higher HbA1c level than the RLS-ve group [47], while two studies showed a significant increase [48]. Meanwhile, three studies showed a non-significantly lower HBA1c level in the RLS+ve group compared to the RLS-ve group [49].

Four studies assessed the levels of fasting blood sugar and/or random blood sugar. The blood sugar level was significantly elevated in the RLS+ve group in two studies [48] and non-significantly elevated in one study [36]. One study reported a non-significant decrease in the blood sugar level in the RLS+ve group [35].

Fig. 2 displays the pooling of the results of the studies regarding the levels of HbA1c in the RLS+ve and -ve groups. There was considerable heterogeneity among the studies when collectively analyzed (Chi = 31.02, $p<0.001$, I^2 = 77%); or when divided into a cross-sectional subgroup (Chi = 24.53, $p<0.001$, I^2 = 84%) and a case-control subgroup (Chi = 5.89, $p = 0.05$, I^2 = 66%); therefore, a random-effects model was used for pooling the results. The overall effect of pooling all the studies, regardless of their design, was a significant increase in HbA1c level in RLS+ve patients (SMD = 0.36, 95% CI: 0.04, 0.68, $p = 0.03$), which is small effect size. However, in the cross-sectional studies subgroup, the pooled SMD was 0.37 (95% CI: -0.09, 0.83), indicating a tendency to have an increased level in the RLS+ve patients, but did not reach statistical significance ($p=0.11$). The same conclusion was found by assessing the case-control subgroup separately (SMD = 0.32, 95% CI: -0.20, 0.083, $p = 0.23$). Sensitivity analysis was performed by excluding one study in which the mean HbA1c level in the RLS-ve group was much lower than the other studies. The sensitivity analysis showed a lack of

significant difference in each subgroup and the overall effect.

3.5 Sleep Quality and Disturbance

Table 5 shows the findings of nine studies regarding the association of RLS with sleep quality and excessive daytime somnolence (EDS) and included the narrative synthesis. Sleep quality was assessed mainly by Pittsburgh Sleep Quality Index (PSQI) and EDS was assessed by Epworth Sleepiness Score (ESS).

As regards sleep quality, seven studies showed significant deterioration in the RLS+ve patients compared to the RLS-ve group. One of these studies did not find a significant association on univariate analysis, but multivariate regression that adjusted for sex, marital status, body mass index, and triglycerides showed a significant association [32].

As regards EDS, two studies reported a significant increase in the RLS+ve group, while two other studies found a non-significant increase. Meanwhile, one study reported a non-significantly lower prevalence of EDS in the RLS+ve group compared to the RLS-ve group [31].

Pooling of the results of PSQI and ESS was not feasible due to the heterogeneity in the methods of reporting the results by the studies as the scales were sometimes reported as a numerical variable and sometimes as a categorical variable.

3.6 Psychological Status and Quality of Life

Table 6 shows the findings of five studies that assessed the psychological status and/or the quality of life in diabetic patients with and without RLS.

Quality of life was assessed in three studies using different tools, including the Medical Outcome Study 36-item Short Form (SF-36) and the EuroQol five-dimension questionnaire (EQ-5D-3L) [32]. The three studies showed a significant decrease in the quality of life in the RLS+ve group compared to the RLS-ve group.

Four studies have evaluated the association of RLS with psychiatric disorders. One study only estimated the prevalence of anxiety disorder, which was significantly higher in the RLS+ve group in both univariate and multivariate analyses. The four studies assessed the presence of depression using different methods, including clinical diagnosis, the Hamilton Depression Rating Scale, the Center for Epidemiologic Studies Depression Scale (CES-D) [27], and the Beck Depression Inventory (BDI II) [42]. Two studies found that the RLS was significantly associated with depression disorder, while the other two found higher scores of depression in the RLS+ve groups, suggesting a higher tendency to have the disorder, though the difference did not reach statistical significance.

Pooling of the results of the quality of life and psychological status was not feasible due to the low number of studies besides the heterogeneity in assessing the outcomes and reporting the results by the available studies.

4. DISCUSSION

4.1 Summary of the Main Findings

The prevalence of RLS increases in diabetic patients [14]. Evidence is still lacking regarding the association of restless leg syndrome (RLS) on glycemic control and psychological status in diabetic patients. The present systematic review was undertaken to summarize the evidence regarding the association of RLS with glycemic control and psychological status in adults with type 2 diabetes.

Sixteen studies were eligible for inclusion in this systematic review [21]. Eleven studies were cross-sectional in design [23], while the remaining studies were case-control in design [24]. The ratio of RLS+ve cases to RLS-ve subjects in the sample size varied considerably among the studies.

The results of individual studies were controversial regarding the association of RLS with glycemic control. The pooling of the levels of HbA1c from all studies showed first a significant increase with RLS. However, the sensitivity analysis showed a lack of statistical significance which conformed with the results of the subgroup analysis based on the study design. The RLS is assumed to cause considerable difficulty in initiating and maintaining sleep, resulting in the development of sleep disorder. The seriousness of prolonged sleep loss lies in the increased risk of morbidity (such as ischemic stroke and hypertension) and mortality. Accordingly, physicians following up with diabetic patients should identify and treat the symptoms of RLS to lower the risks of developing vascular disease and/or mortality.

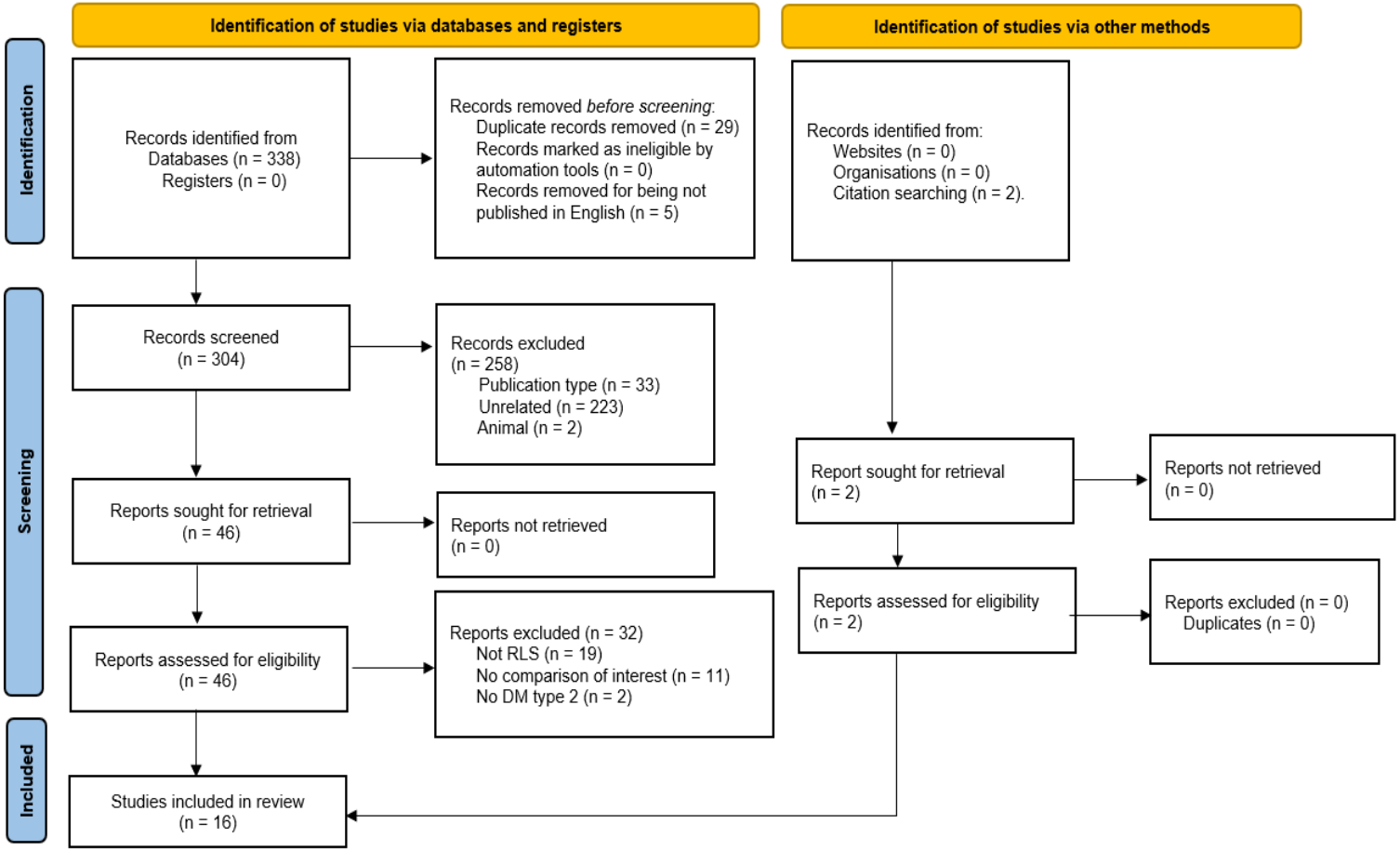

Fig. 1. The PRISMA flow chart diagram for the results of the literature search and study selection

Table 1. Characteristics of the included studies (n = 16)

Study	Study design	Country	Sample size (RLS+ve: RLS-ve)	Age (years) Mean ± SD	Sex (F%)	DM duration (years) Mean ± SD
Skomro 2001	Cross-sectional	Canada	14:44	RLS+ve: 58.1 ± 15.3 RLS-ve: 56.9 ± 14.4	RLS+ve: 43 RLS-ve: 52	RLS+ve: 9.7 ± 7.7 RLS-ve: 10.1 ± 8.1
Lopes 2005	Cross-sectional	Brazil	27:73	Total: 58.3 ± 12.3	Total: 73	Total: 9.8 ± 7.6
Merlino 2007 Merlino 2010	Case-control	Italy	22:102	RLS+ve: 64.2 ± 9.4 RLS-ve: 65.3 ± 8.5	RLS+ve: 64 RLS-ve: 30	Total: 12.3 ± 9.9
Cuellar 2008	Case-control	USA	18:21	RLS+ve: 59.5 ± 11.6 RLS-ve: 62.1 ± 10.8	RLS+ve: 55.6 RLS-ve: 57.1	NR
Daniele 2013	Case-control	Brazil	47: 153	RLS+ve: 53.2 ± 5.2 RLS-ve: 52.5 ± 5.8	RLS+ve: 72 RLS-ve: 54	RLS+ve: 11.4 ± 7.1 RLS-ve: 11.8 ± 7.6
Siddiqi 2015	Cross-sectional	Pakistan	67:53	RLS+ve: 56 ± 8.4 RLS-ve: 45 ± 8	RLS+ve: 50.5 RLS-ve: 40.3	NR
Harashima 2016	Cross-sectional	Japan	8:92	RLS+ve: 61.6 ± 13.6 RLS-ve: 65.4 ± 11.8	12.5% 41.3%	RLS+ve: 9.5 ± 4.9 RLS-ve: 12.2 ± 8.1
Mirghani 2016	Cross-sectional	KSA	126:174	F: 47.47 ± 1.04 M: 46.38 ± 0.88	Total: 56.3	NR
Arosemena Coronel 2017	Cross-sectional	Ecuador	134:156	Total: 64.08 [95% CI: 51.99-76.17]	Total: 71.3	1-5 years: 42.41% 5-10 years: 34.82% >10 years: 22.75%
Modarresnia 2018	Cross-sectional	Iran	41:169	Total: 54.89 ± 7.81	Total: 60.5	Total: 7.8 ± 4.89
Akın 2019	Cross-sectional	Turkey	90:228	Total: 60.9 ± 10.3	Total: 60.4	RLS+ve: 15.6 ± 6.7 RLS-ve: 13.7 ± 6.3
Bener 2019	Cross‐sectional	Turkey	199: 672	RLS+ve: 49.30 ± 13.67 RLS-ve: 50.63 ± 14.47	RLS+ve: 60.3 RLS-ve: 62.6	NR
Mirghani 2020	Case-control	Sudan	26: 54	RLS+ve: 53.92 ± 9.33 RLS-ve: 54.00 ± 6.89	RLS+ve: 76.9 RLS-ve: 55.5	NR
Pinheiro 2020	Cross-sectional	India	17: 193	RLS+ve: 60.8 ± 11.0 RLS+ve: 55.8 ± 13.6	RLS+ve: 23.6 RLS-ve: 33.7	Total: 10.52 Total: 8.14
Nawaz 2021	Cross-sectional	Pakistan	317:71	Age>40 RLS+ve: 82.7 RLS-ve: 80.3	RLS+ve: 60.3 RLS-ve: 23.9	NR

NR: not recorded

Table 2. The risk of bias assessment for the included studies based on the National Institutes of Health (NIH) quality assessment tool for the observational cohort and cross-sectional studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Skomro 2001	Yes	Yes	CD	Yes	No	No	No	NA	No	NA	Yes	NR	NA	Yes
Lopes 2005	Yes	No	Yes	Yes	No	No	No	NA	Yes	NA	Yes	NR	NA	Yes
Siddiqi 2015	Yes	Yes	CD	Yes	Yes	No	No	NA	Yes	NA	Yes	NR	NA	Yes
Harashima 2016	Yes	No	CD	Yes	No	No	No	NA	Yes	NA	Yes	NR	NA	No
Mirghani 2016	Yes	Yes	CD	Yes	No	No	No	NA	Yes	NA	Yes	NR	NA	No
Arosemena Coronel 2017	Yes	Yes	Yes	Yes	Yes	No	No	NA	Yes	NA	Yes	NR	NA	Yes
Modarresnia 2018	Yes	Yes	CD	Yes	CD	No	No	NA	Yes	NA	Yes	No	NA	Yes
Akın 2019	Yes	Yes	Yes	Yes	No	No	No	NA	Yes	NA	Yes	No	NA	No
Bener 2019	Yes	Yes	Yes	Yes	No	No	No	NA	Yes	NA	Yes	NR	NA	No
Pinheiro 2020	Yes	Yes	Yes	Yes	No	No	No	NA	Yes	NA	Yes	NR	NA	No
Nawaz 2021	Yes	Yes	CD	Yes	CD	No	No	NA	Yes	NA	Yes	NR	NA	No

Q1: Was the research question or objective in this paper clearly stated?; Q2: Was the study population clearly specified and defined?; Q3: Was the participation rate of eligible persons at least 50%?; Q4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?; Q5: Was a sample size justification, power description, or variance and effect estimates provided?; Q6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; Q7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; Q8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; Q9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q10: Was the exposure(s) assessed more than once over time?; Q11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q12: Were the outcome assessors blinded to the exposure status of participants?; Q13: Was loss to follow-up after baseline 20% or less?; Q14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?; CD: cannot determine; NA: not applicable.

Table 3. The risk of bias assessment for the included studies based on the National Institutes of Health (NIH) quality assessment tool for case-control studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Merlino 2007	Yes	Yes	NR	NR	Yes	Yes	No	NR	CD	Yes	Yes	No
Merlino 2010												
Cuellar 2008	Yes	Yes	NR	Yes	Yes	Yes	NR	NR	CD	Yes	NR	No
Daniele 2013	Yes	Yes	NR	Yes	CD	Yes	NR	NR	CD	Yes	NR	Yes
Mirghani 2020	Yes	Yes	NR	Yes	Yes	Yes	NR	NR	CD	Yes	NR	Yes

Q1: Was the research question or objective in this paper clearly stated and appropriate?; Q2: Was the study population clearly specified and defined?; Q3: Did the authors include a sample size justification?; Q4: Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?; Q5: Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?; Q6: Were the cases clearly defined and differentiated from controls?; Q7: If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?; Q8: Was there use of concurrent controls?; Q9: Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?; Q10: Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?; Q11: Were the assessors of exposure/risk blinded to the case or control status of participants?; Q12: Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?; CD: cannot determine; NA: not applicable.

Table 4. Assessments and results of glycemic control in the included studies (n = 10)

Study	Measures for assessing glycemic control	RLS+ve	RLS-ve	p-value
Skomro 2001	HbA1c (%)	7.6 ± 1.3	7.7 ± 1.8	0.88
Merlino 2007	HbA1c (%)	8.1 ± 1.4	7.7 ± 1.4	0.70
Cuellar 2008	HbA1c (%)	7.1 ± 1.5	7.4 ± 1.5	NS
Siddiqi 2015	RBS	250.5 ± 64.1	191 ± 72.3	0.00
	HbA1c (%)	9.4 ± 2.4	4.9 ± 4.5	0.00
Harashima 2016	HbA1c (%)	7.19 ± 0.56	7.45 ± 1.44	0.622
Mirghani 2016	HbA1c (%)	9.579 ± 0.1876	9.031 ± 0.5851	0.4370
Bener 2019	HbA1c (%)	7.89 ± 0.80	7.48 ± 0.88	0.001
	FBS (mmol/L)	7.45 ± 0.95	7.15 ± 0.89	0.024
Mirghani 2020	HbA1c (%)	10.04 ± 2.53	8.51 ± 1.62	0.077
Pinheiro 2020	RBS	173 ± 75	189 ± 94	0.15
	HbA1c (%)	8.87 ± 2	8.67 ± 2.4	0.28
Nawaz 2021	FBS >126 mg/dL N(%)	197/317 (62.2%)	36/71 (50.7%)	0.075

Study	Measures for assessing glycemic control	RLS+ve	RLS-ve	p-value
Summary	RBS >200 mg/dL N(%)	212/317 (66.9%)	46/71 (64.9%)	0.736
	HbA1c (%)	+ 4 NS + 2 S - 3 NS		
	RBS/FBS	+ 1 NS + 2 S -1 NS		

HbA1c: glycated hemoglobin; FBS: fasting blood sugar; NS: non-significant; RBS: random blood sugar; S: significant; + sign indicates an increased outcome in the RLS+ve group; - sign indicates decreased outcome in the RLS+ve group

Table 5. Assessments and results of sleep quality and disturbances in the included studies (n = 9)

Study	Measures for assessing Sleep quality & disturbances	RLS+ve	RLS-ve	p-value
Skomro 2001	Insomnia: difficulty with sleep onset or maintenance occurring at least 3 times per week.	72	43%	0.13
	EDS: ESS =>12	EDS: 72% ESS: 8.2 ± 6.5	EDS: 50% ESS: 4.8 ± 3.7	0.27 0.02
Lopes 2005	Quality of sleep: PSQI (=>6 poor sleepers)	RLS+ve had poorer general quality of sleep (P =0.02), longer sleep latency (P =0.000), shorter sleep duration (P =0.04), less sleep efficiency (P= 0.000), more use of sedatives (P = 0.000), and more diurnal dysfunction (P = 0.000)		
Cuellar 2008	Quality of sleep: PSQI (> 6 = poor sleepers).	Continuous: 12.9 ± 3.3 Poor sleep: 100.0%	6.7 ± 5.8 55.6%	0.002 0.050
	EDS: ESS= > 10	ESS: 10.3 ± 5.1	8.4 ± 6.0	0.051
Daniele 2013	Quality of sleep: PSQI ESS	19.6 ± 7.2 9.4 ± 6.3	12.3 ± 7.1 7.3 ± 5.3	<0.001 0.11
Siddiqi 2015	EDS: ESS>10	Disturbed sleep: 61.2% Daytime sleepiness: 59.7%	Disturbed sleep: 21.5% Daytime sleepiness: 12.1%	0.00 0.00
Arosemena Coronel 2017	EDS: ESS=>11	75/141 (53.2%)	90/149 (60.4%)	0.768
Modarresnia 2018	Quality of sleep: PSQI >5 Multivariate regression (adjusted for sex, marital status, body mass index, & triglycerides)	56.1% RLS: OR (95% CI): 2.793 (1.301–5.998)	63.3%	NR 0.008
Bener 2019	Good sleep quality: PSQI ≤5	Good: 20.1	Good: 29.6	0.024

Study	Measures for assessing Sleep quality & disturbances	RLS+ve	RLS-ve	p-value
	Average sleep quality: PSQI 6–8	Average: 36.7	Average: 30.2	
	Poor sleep quality: PSQI ≥9	Poor: 43.2	Poor: 40.2	
Pinheiro 2020	Quality of sleep: PSQI >11	5 ± 2.9	3.2 ± 2.4	0.01
Summary	Sleep Quality	+7 S + 1 NS		
	Excessive daytime sleepiness	+2 S +2 NS -1 NS		

EDS: excessive daytime somnolence; ESS: Epworth Sleepiness Score; PSQI: Pittsburgh Sleep Quality Index; NS: non-significant; S: significant; + sign indicates an increased outcome in the RLS+ve group; - sign indicates decreased outcome in the RLS+ve group

Table 6. Assessments and results of psychological status/quality of life in the included studies (n = 5)

Study	Measures for assessing psychological status/QoL	RLS+ve	RLS-ve	p-value
Merlino 2010	SF-36	RLS+ patients had significantly lower scores for general health (P=0.02), vitality (P<0.001), role limitations (P=0.002), mental health (P=0.01), and mental components summary (P=0.01).		
		Multivariate analyses confirmed that RLS was an independent predictor for vitality, role limitations, mental health, and mental components summary but not for general health		
	Clinical diagnosis of anxiety	22.7%	2%	0.002
	Multivariate analysis adjusted for body mass index	Multivariate logistic regression confirmed RLS as an independent predictor of anxiety (OR: 17.72, 95% CI: 2.63-72.34, p=0.003)		
	Hamilton Depression Rating Scale [HDRS]	31.8%	9.8%	0.01
	Multivariate analysis adjusted for sex, insulin treatment, number of comorbidities, & HbA1C levels	Multivariate logistic regression confirmed RLS as an independent predictor of depression (OR: 3.21, 95% CI: 1.07-11.23, p=0.04)		
Cuellar 2008	Depression: CES-D =>16	18.4 ± 9.1	12.1 ± 11.6	NS
Daniele 2013	SF-36	Functional capacity: 45.0 ± 26.9	56.8 ± 32.5	0.01
		50.8 ± 45.5	0.01	
		Physical limitation: 30.3 ± 37.2	59.4 ± 30.7	0.01
		46.1 ± 27.2	0.31	
		Pain: 41.5 ± 27.2	62.8 ± 25.3	0.14
		General health state: 41.5 ± 23.3	73.7 ± 30.0	0.04
		79.1 ± 36.9	0.002	

Study	Measures for assessing psychological status/QoL	RLS+ve	RLS-ve	p-value
		Vitality: 51.7 ± 24.6 Social aspects: 60.5 ± 32.5 Emotional limitations: 54.6 ± 43.6 Mental health: 60.3 ± 22.2	69.4 ± 23.9	0.08
	Beck Depression Inventory (BDI II): >=12 points	12.9 ± 9.2	9.2 ± 7.9	0.09
Modarresnia 2018	EuroQol five-dimension questionnaire (EQ-5D-3L) Multivariate Linear regression adjusting for sex, duration of DM, BMI, HbA1c, FBS, smoking, & insulin use	RLS: B(SE): −0.082 (0.03), P=0.007		
Bener 2019	Depression	20.6% OR (95% CI): 2.34 (1.53-3.61)	10.0%	0.001
Summary	Quality of life	+3 S		
	Anxiety	+1 S		
	Depression	+2 S +2 NS		

HbA1c: glycated hemoglobin; CES-D: The Center for Epidemiologic Studies Depression Scale; SF-36: Medical Outcome Study 36-item Short Form; NS: non-significant; S: significant; + sign indicates an increased outcome in the RLS+ve group; - sign indicates decreased outcome in the RLS+ve group

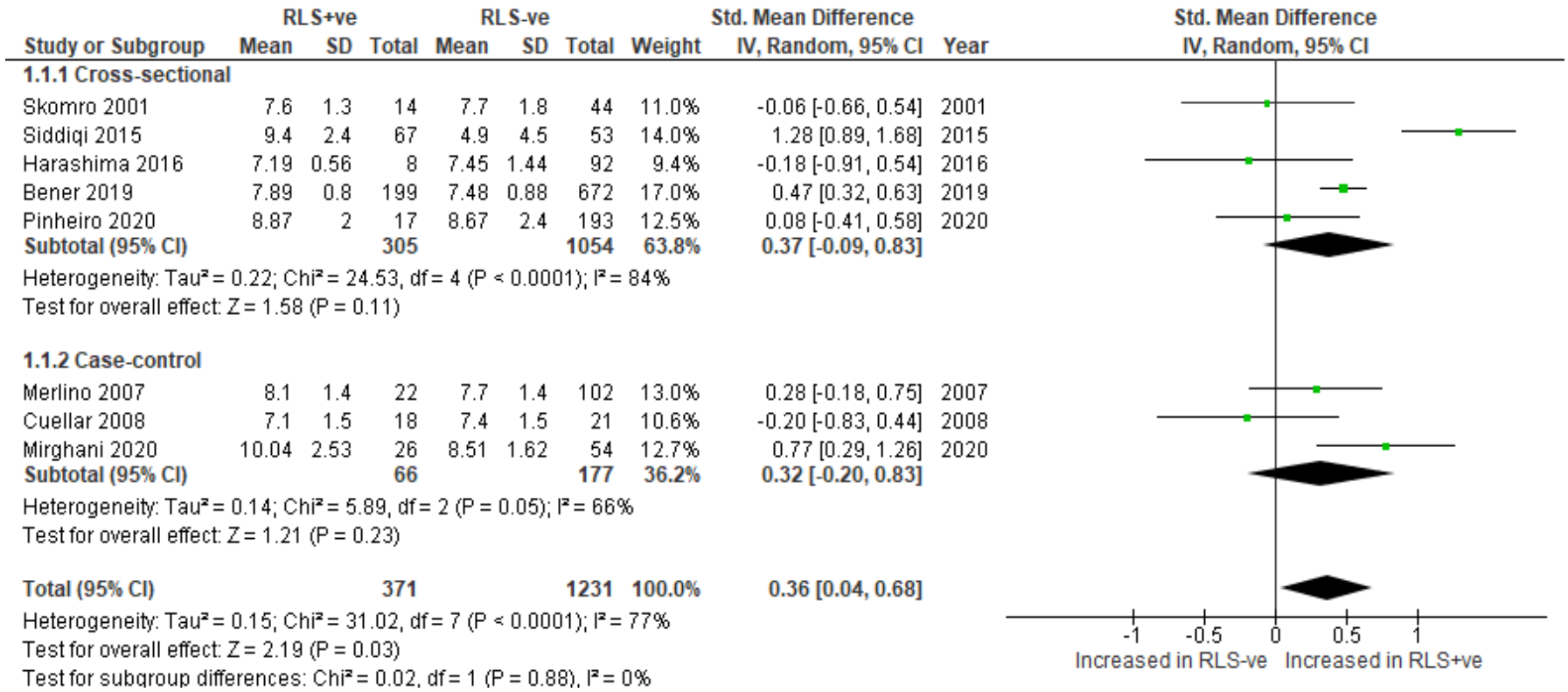

Fig. 2. Forest plot showing the comparison of glycated hemoglobin between patients with RLS and those without, with pooling of results

CI: confidence interval

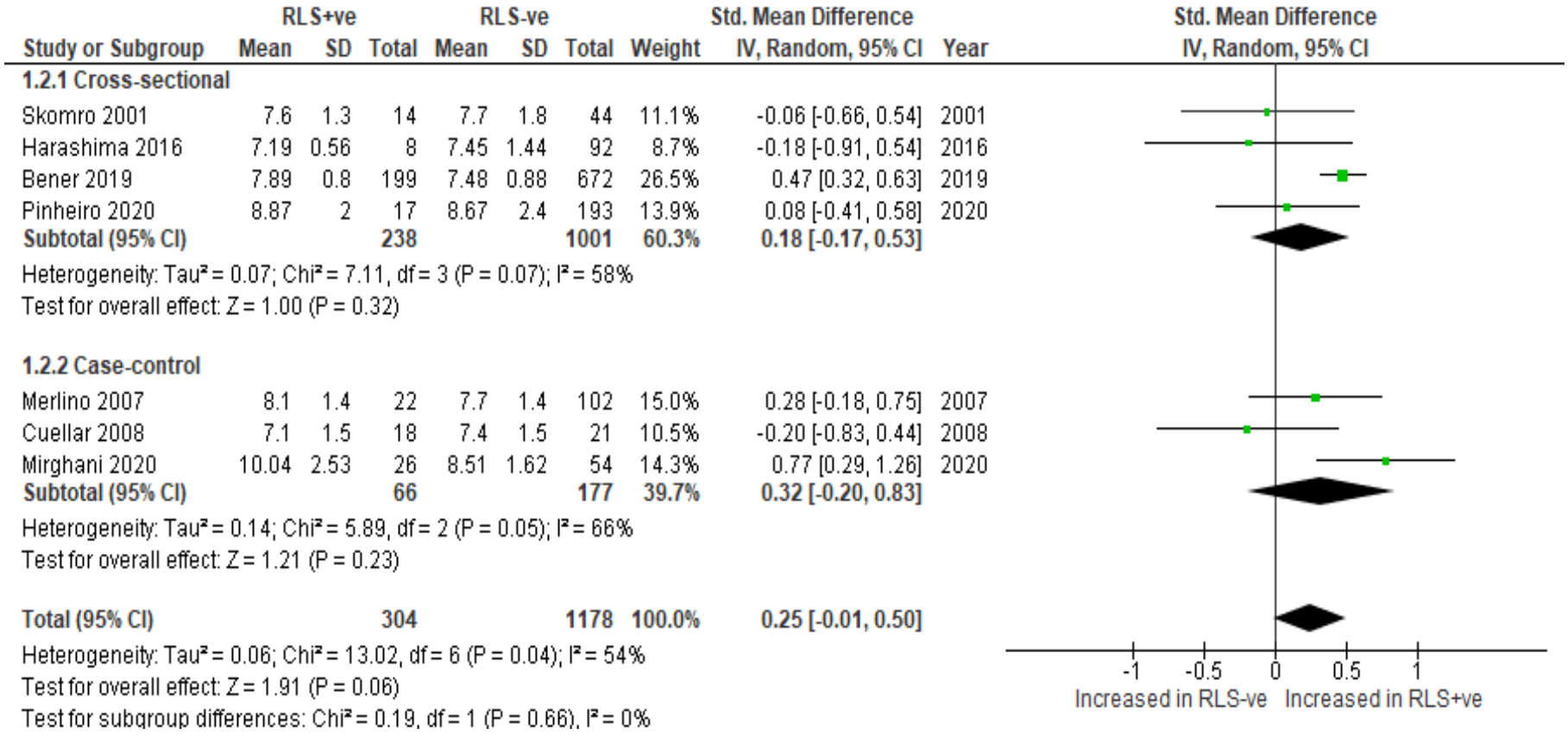

Fig. 3. Forest plot showing the comparison of glycated hemoglobin between patients with RLS and those without, with pooling of results after exclusion of the study by Siddiqi et al. (sensitivity analysis)

CI: confidence interval

All studies showed a reduction of sleep quality with RLS is associated with a reduction in sleep quality, which was statistically significant in seven out of eight studies.

Controversial results were also found among the studies regarding EDS, where two studies only reported a significant increase with RLS, another two studies showed a non-significant increase, and one study reported a non-significant decrease with RLS. diabetes itself is a risk factor that increases ESS. This controversy may be partially explained by the increased risk of EDS in diabetic patients who experience hypoglycemic episodes. Other confounding factors also exist in these studies as the older age of some participants may increase the likelihood of EDS [31].

Previous studies reported that RLS lowers the quality of life in the general population, affecting both physical and mental status. The quality of life was significantly impaired in the three studies that reported on the outcome.

Idiopathic RLS has been associated with anxiety and depressive disorders. There was an increase in the prevalence/scores of depression in the four studies that assessed the psychological status, but statistical significance was reached in two studies only. However, the other two studies did not conduct multivariate analysis which may have elicited significance by adjusting for the confounding variables. The proposed mechanism of RLS for affecting the psychological status is the impairment of sleep quality and daytime activities, which increase independently the risk for anxiety and depression. Meanwhile, RLS, anxiety, and depression can represent comorbid conditions that are caused by a common neurotransmitter abnormality.

The studied outcomes in the present systematic review are interlinked, and the clarification of the causal relationship is difficult, particularly as all studies did not confirm which variable preceded the other. Poor sleep quality and sleep disturbances are known to interfere with glycemic control and increase HbA1c levels. Poor sleep will also lead to EDS and impair the daytime activities including diet and exercise [27], thereby impairing more and more the patient's glycemic control. Sleepiness has been linked also with fatigue and depression. All these effects will interact to reduce the patient's quality of life.

4.2 Overall Completeness, Applicability, and Quality of the Evidence

Caution should be employed in interpreting the evidence from the current systematic review as the included studies showed a number of limitations. Most studies were cross-sectional in design, thus ascertaining the causal relationship between RLS and the studied outcomes was not feasible. Most studies did not justify their sample sizes, so the power of these studies to detect the hypothesized association is questionable. Selection bias is a concern, as most studies were ambiguous regarding the number of eligible patients from whom the cases were selected, and the methods of selection were not explained. In addition, only a few studies attempted to adjust for the potential confounding variables, so the results of most included studies could actually be attributed to other unadjusted factors. Another important source of potential bias is the assessment of sleep quality using PSQI which depends on the answers of the patients. This may result in under- or overestimation of the sleep quality. The use of a more objective tool is recommended such as polysomnography or actigraphy to reduce the ROB.

Detection bias is a concern also as most studies did not report whether the outcome assessors were blinded regarding the status of the participants. This may introduce a ROB in assessing the psychological status but is not likely to affect laboratory-measured outcomes as the levels of HbA1c and blood sugar. Only ten of the included sixteen studies reported measures of glycemic control in relation to RLS+ve and RLS-ve patients. This may suggest defective reporting and a risk of reporting bias, as measuring the level of glycemic control is essential in any studies reporting on the complications of DM.

Besides these limitations of the individual studies, there was considerable heterogeneity among the included studies. One reason was the difference in study design as some studies were cross-sectional and the other were longitudinal, and this was evident in the results of heterogeneity testing between the subgroups of study design. Meanwhile, other factors contributed to this heterogeneity as the Cochrane Chi-square test for heterogeneity was significant even within the subgroups of study design. These potential factors include the differences across the studies regarding the populations

from which the patients and cases were withdrawn as well as the duration of DM in the patients and the compliance of patients with treatment and regular follow-up. Although the age and sex of patients in most studies were comparable, variations in the healthcare systems in different countries could impact the level of glycemic control. The observed heterogeneity may impact the results of the current meta-analysis and thus the launching of high-quality studies with sufficient sample size is recommended to reduce heterogeneity in future similar meta-analyses.

The current systematic review also showed some limitations. The search was limited to studies published in English, but relevant studies might have been published in other languages. We found that the same outcome was assessed using different tools, which prevented the pooling of the individual study results. Even the results of the same tool were reported in different ways such as reporting the PSQI as a numerical variable or as a categorical variable. The results of funnel plot assessment did not suggest publication bias; however, the number of studies included in the meta-analysis (eight studies) was lower than that recommended for testing funnel plot asymmetry, as the power of tests in this case are too low to differentiate between chance and real asymmetry.

Regarding the generalizability of the results of meta-analysis, the reported patients' characteristics in most of the included studies were similar to those expected in patients suffering from the condition. Therefore, the findings can benefit patients with DM who are at risk to develop this complication.

5. CONCLUSION

There is no evidence that RLS in type 2 diabetic patients is associated with poor glycemic control. The evidence suggests that RLS is associated with a reduction in sleep quality and quality of life. The evidence is inconclusive regarding the association of RLS with depression due to the low number of studies. Physicians should be aware of the associated disorders with RLS in diabetic patients and endeavour to identify and alleviate them. We also recommend the conduct of prospective cohort studies to investigate the causal relationship between RLS and glycemic control and psychological status. Preferably, these studies should include newly diagnosed diabetic patients and perform regular, repeated measurements of glycemic control, manifestations of RLS, sleep quality, psychological status, and the overall QoL in order to establish the association between the exposure and outcomes. Glycemic control is better measured using glycosylated hemoglobin rather than using random or fasting blood sugar. Also, objective tools should be used to study the outcomes such as polysomnography or actigraphy for assessing the quality of sleep. Future studies should consider adjusting for potential confounding variables in analysing the results or employ propensity score matching to negate the baseline differences between the studied groups.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/103829