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Prevalence of diabetic neuropathy in nonalcoholic fatty liver disease (NAFLD) patients: A systematic review and meta-analysis

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Abstract

Nonalcoholic fatty liver disease (NAFLD) refers to the uncontrolled accumulation of triglyceride (TG) in the liver when the person has no other liver disease etiologies. Among all causes of neuropathy, diabetic neuropathy is the most common one worldwide, and it causes notable morbidity and increases mortality. The prevalence of diabetic neuropathy and NAFLD has been demonstrated in few studies. This study aims to summarize existing data estimating peripheral diabetic neuropathy prevalence among sonographically detected NAFLD patients. We searched PubMed, Scopus, Web of Science, and Google scholar for articles in the English language up until October 2021 for the clinical trials of diabetic neuropathy in NAFLD patients and used the articles for a systematic review and meta-analysis. Seven studies (6,918 patients with type 2 diabetes mellitus (T2DM)) were involved. The prevalence of diabetic neuropathy among T2DM patients with ultrasound (US) detected-NAFLD was 0.48 (95% CI= 0.31-0.65, I^2= 99.01%), however it was not significantly different from patients without NAFLD (OR=1.02, 95% CI= 0.89-1.17. p=0.748, I^2=81.6%). The prevalence of diabetic neuropathy among T2DM patients with NAFLD is not significantly different from patients without NAFLD.

Keywords: NAFLD, Diabetes Mellitus, neuropathy

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) refers to the uncontrolled accumulation of TG in the liver when the person has no other liver disease etiologies, for example, use of medications which induce steatosis, chronic viral hepatitis and substantial alcohol consumption.[1] It is particularly defined by steatosis presence in more than five percent of hepatocytes in spite of no

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alcohol consumption.[2] NAFLD is actually the most common underlying cause of advanced cryptogenic cirrhosis[3] and is the most common chronic liver disease around the world.[4] NAFLD global prevalence is approximately 24% currently, i.e, highest in the Middle East and South America (32% and 31% respectively) followed by Asia, the USA, and Europe (27%, 24% and 23% respectively).[5] According to WHO global report, diabetes prevalence is nearly 8.5% among the global population or 422 million persons.[6] Among patients with diabetes 70 to 80 percent develop NAFLD.[7,8]

Among all causes of neuropathy, diabetic neuropathy is the most common worldwide, and approximately affect half of patients with diabetes.[9,10] It causes notable morbidity, increases mortality and impairs life quality.[11,12] Indeed, about 25 percent of health care budget for diabetes in the US is spent on diabetic neuropathy.[13] Diabetic neuropathy usually refers to clinically different disorders which affect the nervous system, i.e, with diverse clinical courses, phenotypes and anatomic features. The common basic pathophysiology is a result of hyperglycemic condition and microangiopathy.[14] Distal sensorimotor symmetric neuropathy-attributable to microvascular and metabolic alterations- is the most common form; however, most of body systems may be affected due to autonomic nerves involvement.[15] The lifetime diabetic neuropathy incidence is nearly 45% in patients with type II diabetes and approximately 54% to 59% in patients with type I diabetes[16] with approximately one out of four patients experiencing pain.[17] Various epidemiological studies have increasingly claimed that there is a correlation between NAFLD and other metabolic disorders. For instance, the mortality related to cardiovascular disease (CVD) in the NAFLD patients is higher than liver-related mortality.[18]

Supposing CVD is one of the most common type II diabetes chronic complications and NAFLD prevalence in type II diabetes patients is nearly threefold that among general population[7,19], various epidemiological studies have been conducted to clarify the relationship between diabetes neuropathy and NAFLD.[20] However, just a small number of studies have comprehensively evaluated the correlation of NAFLD with peripheral diabetic neuropathy in the individuals with type II diabetes and have published conflicting results.[21-26] Considering this, this study aims to summarize existing data estimating peripheral diabetic neuropathy prevalence among sonographically detected NAFLD patients.

METHODS

Search strategy

A systematic search was conducted in PubMed, Scopus, Web of Science, and Google scholar for articles in the English language up until search date (October 2021). Our search terms were as follows: ((((“Non-alcoholic Fatty Liver Disease” [Mesh]) OR (“Nonalcoholic Fatty Liver Disease”[Title/Abstract]) OR (“Nonalcoholic Fatty Liver Disease”[Title/Abstract]) OR (NAFLD[Title/Abstract]) OR (“Fatty Liver, Nonalcoholic”[Title/Abstract]) OR (“Liver, Nonalcoholic Fatty”[Title/Abstract]) OR (“Nonalcoholic Steatohepatitis”[Title/Abstract]) OR (“Steatohepatitis, Nonalcoholic”[Title/Abstract]) OR (NASH[Title/Abstract]))) AND (((“Diabetes Mellitus, Type 2” [Mesh]) OR (T2DM[Title/Abstract]) OR (“Type 2 Diabetes”[Title/Abstract]) OR (“Type 2 Diabetes Mellitus”[Title/Abstract])))) AND ((((“Microvascular complications”[Title/Abstract]) OR (Microangiopathy[Title/Abstract]) OR (“Diabetic Neuropathy”[Mesh]) OR (“Neuropathies, Diabetic”[Title/Abstract]) OR (“Neuropathy, Diabetic”[Title/Abstract]) OR (“Diabetic Autonomic Neuropathy”[Title/Abstract]) OR (“Autonomic Neuropathies, Diabetic”[Title/Abstract]) OR ((“Microvascular complications”[Title/Abstract]) OR (Microangiopathy[Title/Abstract]) OR (“Diabetic Neuropathy”[Title/Abstract]) OR (“Neuropathies, Diabetic”[Title/Abstract]) OR (“Neuropathy, Diabetic”[Title/Abstract]) OR (“Diabetic Autonomic Neuropathy”[Title/Abstract]) OR (“Autonomic Neuropathies, Diabetic”[Title/Abstract]) OR (“Autonomic Neuropathy, Diabetic”[Title/Abstract]) OR (“Diabetic Autonomic Neuropathies”[Title/Abstract]) OR (“Neuropathies, Diabetic Autonomic”[Title/Abstract]) OR (“Neuropathy, Diabetic Autonomic”[Title/Abstract]) OR (“Diabetic Neuralgia”[Title/Abstract]) OR (“Diabetic Neuralgias”[Title/Abstract]) OR (“Neuralgias, Diabetic”[Title/Abstract]) OR (“Diabetic Neuropathy, Painful”[Title/Abstract]) OR (“Diabetic Neuropathies, Painful”[Title/Abstract]) OR (“Neuropathies, Painful Diabetic”[Title/Abstract]) OR (“Neuropathy, Painful Diabetic”[Title/Abstract]) OR (“Painful Diabetic Neuropathies”[Title/Abstract]) OR (“Painful Diabetic Neuropathy”[Title/

Abstract]) OR ("Neuralgia, Diabetic"[Title/Abstract]) OR ("Symmetric Diabetic Proximal Motor Neuropathy"[Title/Abstract]) OR ("Asymmetric Diabetic Proximal Motor Neuropathy"[Title/Abstract]) OR ("Diabetic Asymmetric Polyneuropathy"[Title/Abstract]) OR ("Asymmetric Polyneuropathies, Diabetic"[Title/Abstract]) OR ("Asymmetric Polyneuropathy, Diabetic"[Title/Abstract]) OR ("Diabetic Asymmetric Polyneuropathies"[Title/Abstract]) OR ("Polyneuropathies, Diabetic Asymmetric"[Title/Abstract]) OR ("Polyneuropathy, Diabetic Asymmetric"[Title/Abstract]) OR ("Diabetic Mononeuropathy"[Title/Abstract]) OR ("Diabetic Mononeuropathies"[Title/Abstract]) OR ("Mononeuropathies, Diabetic"[Title/Abstract]) OR ("Mononeuropathy, Diabetic"[Title/Abstract]) OR ("Diabetic Mononeuropathy Simplex"[Title/Abstract]) OR ("Diabetic Mononeuropathy Simplices"[Title/Abstract]) OR ("Mononeuropathy Simplex, Diabetic"[Title/Abstract]) OR ("Mononeuropathy Simplices, Diabetic"[Title/Abstract]) OR ("Simplex, Diabetic Mononeuropathy"[Title/Abstract]) OR ("Simplices, Diabetic Mononeuropathy"[Title/Abstract]) OR ("Diabetic Amyotrophy"[Title/Abstract]) OR ("Amyotrophies, Diabetic"[Title/Abstract]) OR ("Amyotrophy, Diabetic"[Title/Abstract]) OR ("Diabetic Amyotrophies"[Title/Abstract]) OR ("Diabetic Polyneuropathy"[Title/Abstract]) OR ("Diabetic Polyneuropathies"[Title/Abstract]) OR ("Polyneuropathies, Diabetic"[Title/Abstract]) OR ("Polyneuropathy, Diabetic"[Title/Abstract])))

The references of the selected articles were further screened to figure out relevant articles. We used EndNote version X9 for literature management.

The protocol of our study was registered on PROSPERO. PROSPERO 2021 CRD42021291096 available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021291096

Inclusion and exclusion criteria

Two authors (MG. Kashanizadeh, M Poudineh) screened the titles and abstracts of the articles for the eligibility for inclusion individually followed by screening the full text of the selected articles. Disagreements were resolved by the final ruling of a third author (N Deravi). The authors were not blinded to the list of authors, institutions, or journals while selecting studies or extracting data. Studies were included if they fulfilled the following criteria:1) Diabetic patient diagnosed with diabetic neuropathy2) Both retrospective and prospective observational studies with a sample size greater than five patients 3) NAFLD was diagnosed with ultrasonographic imaging (ultrasound, computer tomography, magnetic resonance imaging, or spectroscopy).

Studies were excluded if any of these criteria were unmet and/or: 1) reviews, case reports, comment editorial and case series less than 5 patients 2) studies with incomplete data 3) Other causes of NAFLD including alcohol consumption (≥140 g/week in women and ≥ 210 g/week in man) and viral hepatitis were excluded according to standard guidelines. 4) studies were not written in English. 5) partially overlapping patients. 6) non-human studies. Our analysis in this review is in accordance with PRISMA guidelines (Moher *et al*., 2009). Duplications were identified and the recent ones were included.

Quality assessment

Cochrane risk of bias tool and Risk of Bias in Non-Randomized Studies of Interventions (https://jbi.global/critical-appraisal-tools) were used by two authors (SH. Yaghoobpoor and M. Rahmanian) independently to assess the risk of bias for randomized controlled trials (RCTs) and quasi-experimental non-RCTs, respectively. Studies were included if they have a score of less than four which is considered a low risk of bias. If there were any discrepancies, it would be resolved by a third author (G Erabi).

Statistical analysis

The aim of this study is to assess the relationship between NAFLD and diabetic neuropathyin patients with type 2 diabetes. Meta-analytic pooling was performed using the inverse variance method to calculate weights. Pooled incidences with 95 % confidence intervals (CIs) were obtained using Der Simonian-Laird random-effects modeling. Subgroup meta-regression analysis was performed based on patients' mean/median /age (>65 or ≤ 65 years), imaging modality (MRI or CT/MRI), the origin of publication (Europe, USA, or Asia), single/ multi-center design, and patients in ICU (reported or not reported). Likelihood ratio tests were used to compare the random-effects models in subgroup analysis. Between-study heterogeneity was calculated by using the $\chi 2$ statistics for pooled estimates ($P < 0.05$, indicating significant heterogeneity) and the Higgin's inconsistency index (I 2), where I 2 values of

0%–40%, 30 %–60 %, 50%–90%, and 75%–100% indicated insignificant, moderate, substantial, and considerable heterogeneity, respectively. Publication bias was evaluated using funnel plots and Egger's test, with a *P*-value < 0.1 indicating significant bias.

Publication bias-adjusted pooled incidences were also calculated via the trim-and-fill method, where agreement between the unadjusted and adjusted pooled incidences and estimates may indicate little publication bias. All statistical meta-analyses were performed using R (v.3.6.1, R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Study selection

Through search of databases, we initially identified 126 studies, among which, we removed 21 studies because of duplication. After title-abstract screening, 83 other articles were excluded. After full-text screening of the 22 remaining articles, finally 7 studies(25, 27-32) were found eligible to be included in our meta-analysis (Figure 1).

Characteristics of included studies

Totally, 6918 patients with type 2 diabetes mellitus

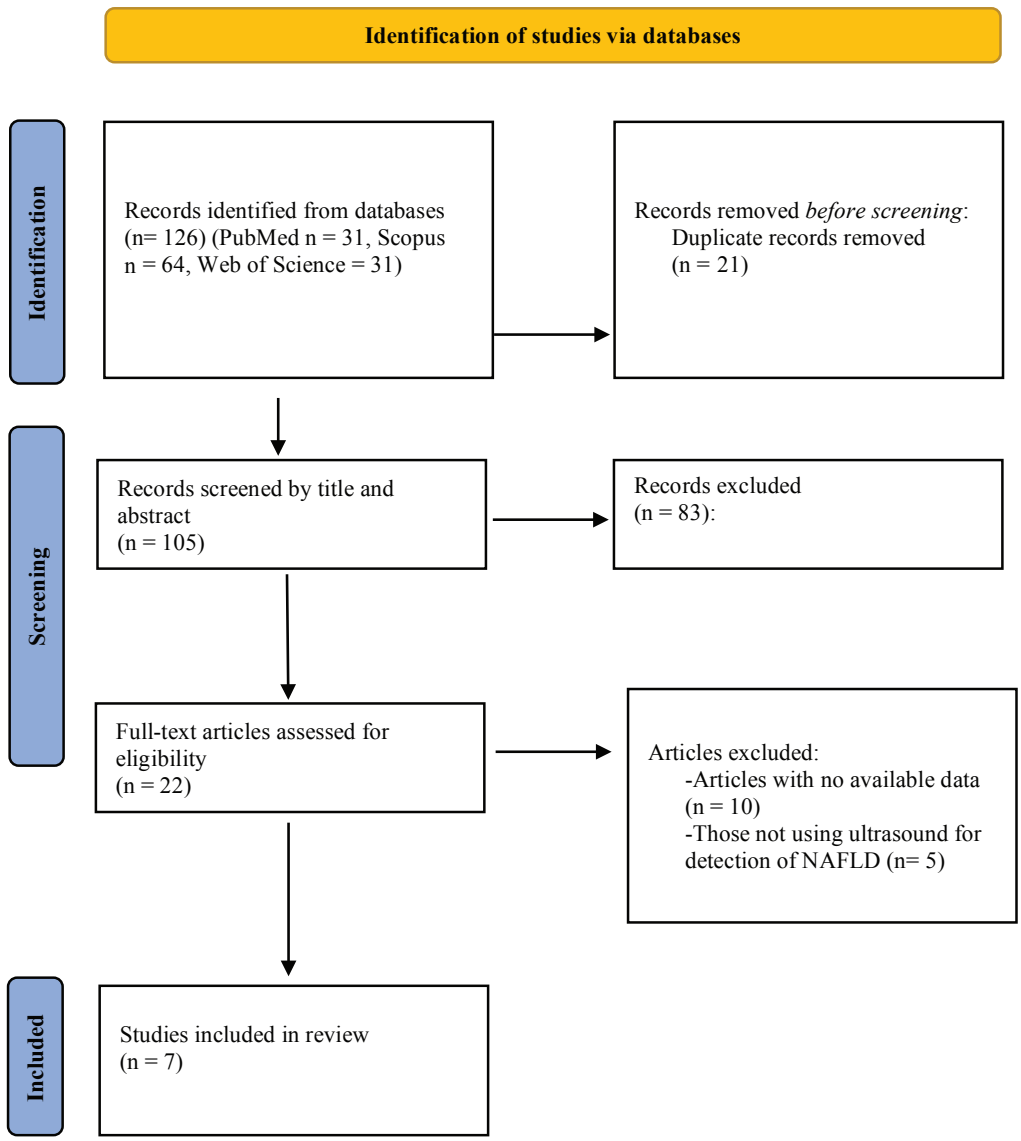

Figure 1. Prisma flow diagram

(T2DM) were involved in the included studies. Fifty-two percent of the patients' population were male. As both males and females were involved in all of the included studies, we cannot rule out the gender role. Number of T2DM patients with ultrasonography- diagnosed NAFLD was 2872 among the total population. (Table 1)

Pooled prevalence of diabetic neuropathy among T2DM patients with NAFLD

The reported prevalence rate of diabetic neuropathy among T2DM patients with NAFLD, diagnosed by ultrasonography, among the included studies ranged from 0.10(28) to 0.80. The pooled prevalence of diabetic neuropathy among T2DM patients with NAFLD was 0.48 (95% CI= 0.31-0.65, I^2= 99.01%). (Figure 2)

Prevalence of neuropathy among T2DM patients with NAFLD was not significantly different from those without (OR=1.02, 95% CI= 0.89-1.17. p=0.748, I^2=81.6%). (Figure 3)

Publication bias

In order to evaluate the publication bias, we conducted Eager test. This test demonstrated no signs of publication bias among the included studies (p= 0.29).

DISCUSSION

Several studies have assessed the prevalence of diabetic neuropathy among T2DM patients with NAFLD, detected by ultrasonography (US). The present study systematically combined the results of those studies. The major finding of our meta-analysis was that the pooled the prevalence of diabetic neuropathy among T2DM patients with US detected-NAFLD was 0.48. However, prevalence of neuropathy among T2DM patients with NAFLD was not significantly different from patients without NAFLD.

The relationship between NAFLD and diabetic microvascular complications has only been established through association studies, and the cause-effect correlation is still unclear. In patients with T2DM, NAFLD has been proposed as an independent predictor of diabetic nephropathy and diabetic retinopathy[33], although the link with diabetic polyneuropathy is less obvious. The early stages of NAFLD are often asymptomatic, with abnormal liver tests such as increased plasma alanine aminotransferase (ALT), aspartate transaminase (AST), and/or gamma-glutamyltransferase (GT) being discovered by accident.[34] However, because liver enzymes change in NAFLD patients, they are not commonly used as diagnostic or severity markers.[35-37] As a result, imaging modalities such as ultrasound are commonly used as a first-line diagnostic step in evaluating hepatic steatosis, owing to its safety, availability, and low cost.[38] According to Greco *et al*.[39] it is evident that diabetic patients should have a hepatic ultrasonography examination to detect NAFLD early.

The pathogenetic link between DPN and NAFLD, is still being debated. On the one hand, the metabolic asset that leads to NAFLD is widely regarded as one of the major risk factors for diabetic polyneuropathy. Furthermore, in addition to the recognized metabolic correlates, enhanced release of some pathogenic mediators from the liver, including advanced glycation end-products, reactive oxygen species, C reactive protein, IL-6, and TNF-α could be potential molecular mediators connecting NAFLD and diabetic polyneuropathy, similar to diabetic retinopathy and chronic kidney disease.[40]

Data suggests that pathological risk factors for both peripheral neuropathy and NAFLD development are identical. Several studies have shown the importance of factors apart from glucose management in the evolution of diabetic peripheral neuropathy. Insulin resistance and dyslipidemia are two of these factors, both of which are considered to have a role in the evolution of NAFLD. While good glycemic control has been demonstrated to delay the onset of diabetic peripheral neuropathy in type 1 diabetes[14], this impact has been less well evidenced in T2DM. Furthermore, unlike type 1 diabetes, peripheral neuropathy can be found in up to 20% of newly diagnosed type 2 diabetes patients and can occur in the pre-diabetic condition.[9,41-43] Recent research into the etiology of both peripheral neuropathy and NAFLD suggests that the two conditions may be linked. Age, height, HbA1c, and diabetes duration are all traditional risk factors for high vibration perception threshold (VPT) as a measure of distal sensorimotor polyneuropathy (DSP) in the same way that NAFLD has been linked to traditional cardiovascular risk factors like hypertension, obesity, smoking, and elevated triglyceride levels, elevated VPT has been linked to traditional cardiovascular risk factors like obesity, hypertension, smoking, and high triglyceride levels, in addition to a history of cardiovascular disease.[44]

Dyslipidemia is known to be linked to peripheral neuropathy by affecting both on

TABLE 1: A summary of the studies on the prevalence of diabetic neuropathy in nonalcoholic fatty liver disease (NAFLD) patients

Title of Article	Doi	Author (year)	Country	Study design	Total population and type of diabetes	Number of patients with neuropathy	Number of patients with NAFLD	Prevalence of NAFLD in patients with diabetic neuropathy	Prevalence of neuropathy in patients with NAFLD	Sex (both male and female number and percent)	Odd ratio 95% confidence interval	Neuropathy diagnosis	NAFLD diagnosis	Re-frence	Critical Appraisal
Prevalences of diabetic retinopathy and nephropathy are lower in Korean type 2 diabetic patients with non-alcoholic fatty liver disease	10.1111/jdi.12139	Kim (2014)[24]	Korea	Cross-sectional	929 T2DM	450	588		47.2%	Males, 489 (52.6%) Females, 440 (47.4%)	0.440 (0.255–0.759)	Nerve conduction velocity testing, the current perception threshold test, or the presence of typical symptoms and compatible findings on neurological examinations or a history of treatment for neuropathy.	US	(27)	6/8
Association of non-alcoholic fatty liver disease with diabetic microvascular and macrovascular complications in South Indian diabetic subjects	10.4103/0973-3930.70861	Viswa-nathan (2010)[28]	South India	Cross-sectional	2161 T2DM	58	156		27.5%	Male, 1187 (55%) Female, 974 (45%)	5.89, 95% (2.1–16.2)	Biothesio-metry	US	(28)	8/8
Association between non-alcoholic fatty liver disease and diabetes-related microvascular complications: A retrospective cross-sectional study of hospitalized patients.	10.1016/j.eprac.2021.02.004	Wen (2021)[29]	China	cross-sectional	1982 T2DM	1298	1181		66%	Males, 1016 (52.7%) Females, 966 (47.3%)	1.012 (0.805-1.274)	Clinical medical records	US	(29)	8/8
Significant liver fibrosis, as assessed by fibroscan, is independently associated with chronic vascular complications of type 2 diabetes: A multicenter study.	10.1016/j.diabres.2021.108884	Miko-lasevic (2021)[30]	Croatia	cross-sectional	442 T2DM	164	206		51.5%	Males, 209 (47.3%) Females, 233 (52.7%)	4.45 (1.15–16.1)	clinical examination and/or electromyo-graphy	FibroScan	(30)	7/8

Title of Article	Doi	Author (year)	Country	Study design	Total population and type of diabetes	Number of patients with neuropathy	Number of patients with NAFLD	Prevalence of NAFLD in patients with diabetic neuropathy	Prevalence of neuropathy in patients with NAFLD	Sex (both male and female number and percent)	Odd ratio 95% confidence interval	Neuropathy diagnosis	NAFLD diagnosis	Re-frence	Critical Appraisal
Liver fibrosis by FibroScan® independently of established cardiovascular risk parameters associates with macrovascular and microvascular complications in patients with type 2 diabetes	10.1111/liv.14274	Lombardi (2020)[31]	Italy	cross-sectional	394 T2DM	24	83		13%	Males, 210 (53.4%) Females, 184 (46.6%)	2.4 (0.02-319.6)	diagnostic tests (i.e., electro-myography and clinical examination	US, Fibro-Scan, and NFS	(31)	7/8
An association of large-fibre peripheral nerve dysfunction with non-invasive measures of liver fibrosis secondary to non-alcoholic fatty liver disease in diabetes	10.1016/j.jdiacomp.2015.06.015	Williams (2015)[25]	Australia	Cross-sectional	456 T2DM	364	358		80%	Males 270 (59.2%) Females 186 (40.8%)	2.22 (1.24–3.98)	VPT	US	(25)	8/8
Importance of non-invasive liver fibrosis scores for mortality and complications development in individuals with type 2 diabetes	10.1016/j.jdiacomp.2021.107879	Leite (2021)[32]	Brazil	Cross-sectional	554 T2DM	185	300		67.7%	Males, 218 (39.4) Females 336 (60.6%)	0.96 (0.80–1.16)	Physical examination	US and NFS	(32)	8/8
Assessment of the relationship between non-alcoholic fatty liver disease and diabetic complications	10.1111/jdi.12518	Yan (2016)[49]	China	Cross-sectional	212 T2DM	67	143		46.85	Males 120 (56.6%) Females 92 (43.4%)		Physical examination	Ultra-sonography		6/8

Abbreviations:
NFS: NAFLD fibrosis score; US: ultrasonography; VPT: vibration perception threshold.

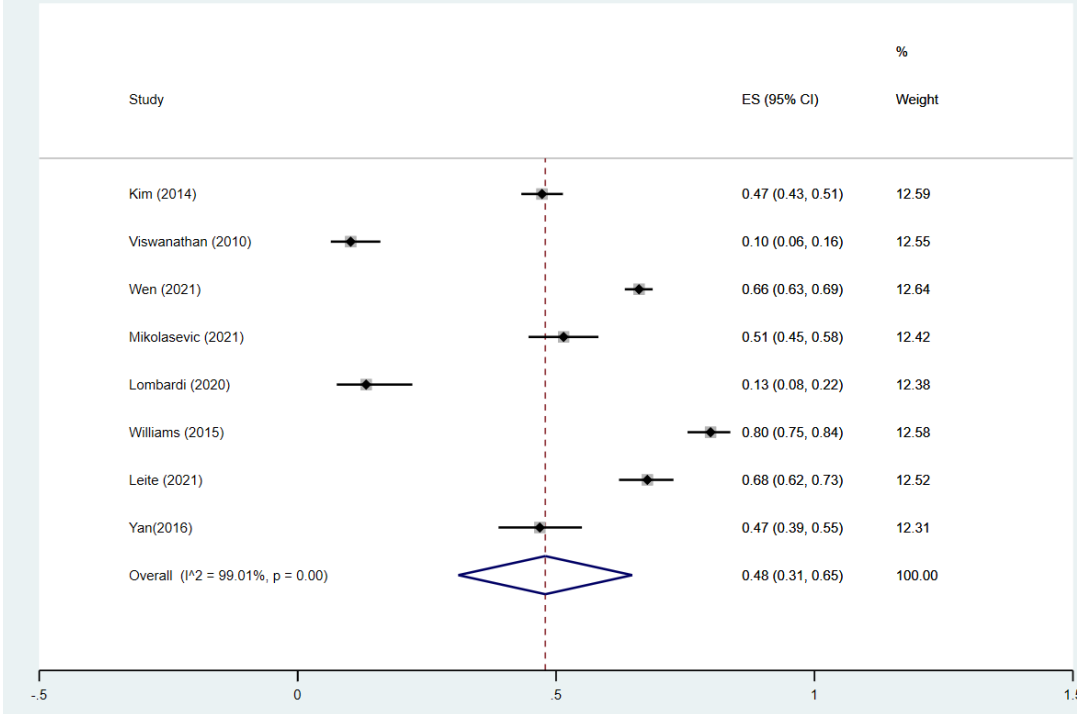

Figure 2. Forest plot showing the overall diabetic neuropathy prevalence in T2DM patients with NAFLD.

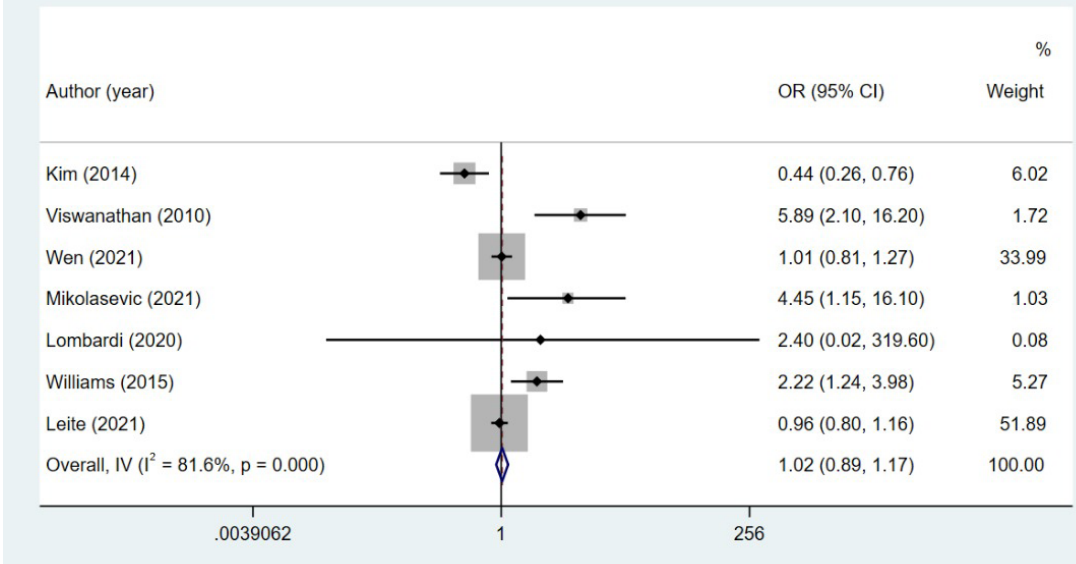

Figure 3. Forrest plot comparing diabetic patients with and without NAFLD regarding the prevalence of diabetic neuropathy, given as odds ratio.

neuronal cells both directly through free fatty acids lipotoxicity and indirectly by activating a systemic inflammatory cytokine cascade and intensifying insulin resistance.[45-48] Insulin resistance could also play a part in the development of peripheral neuropathy, explaining why it is so common in people with pre-diabetes[42] and why insulin sensitisers, such as metformin and thiazolidinediones, could decrease the occurrence of diabetic peripheral neuropathy compared to insulin or insulin secretagogues, after adjusting for differences in glycemic control.[47]

A meta-analysis study by Greco *et al*.[39] They showed that DPN prevalence was significantly higher in T2DM patients with NAFLD. This could be because of not limiting the NAFLD diagnosis method to ultrasonography, as they included studies using ultrasound, composite non-invasive biomarkers, or ultrasound elastography for NAFLD diagnosis. In studies by Mikolasevic *et al*.[30], Viswanathan *et al*.[28], Lombardi *et al*.[21], a significantly higher prevalence of diabetic neuropathy was reported among T2DM patients with NAFLD than those without. Although, according to our results, prevalence of diabetic neuropathy among T2DM patients with NAFLD was not significantly different from those without. Similar to our findings, Kim *et al*.[24] did not find significant difference. This could be explained as patients with NAFLD may have intact b-cell activity, which results in more stable glycemic management and a reduction in microvascular consequences. Also, there was the possibility that the shorter duration of diabetes and relatively younger age of patients with NAFLD compared to those without NAFLD may have contributed to a lower prevalence of diabetic complications. Additionally, patients with NAFLD, who had higher BMI and insulin resistance, may have been urged to change their lifestyles more intensely by increasing their exercise and nutrition regimens. As a result, they could have attained comparable glycemic control faster than individuals who did not have NAFLD, which may be connected to a lower incidence of diabetes complications.[24]

It is believed that the severity of NAFLD may have a part in the development of comorbidities.[39] Liver biopsy is the gold standard method for detecting NAFLD severity in terms of steatosis quantity, necro-inflammation, and fibrosis, but it is not suited for large-scale screening because of invasiveness and expense.[10] Several new non-invasive approaches, such as composite biomarkers, ultrasound elastography, and magnetic resonance, have shown to be effective in determining the severity of NAFLD and have been advocated for broad usage in clinical practice. As there were not enough papers assessing NAFLD severity, it was impossible to conduct a reliable analysis of such data. Future research should look into whether the severity of NAFLD can anticipate the development of diabetic polyneuropathy.

There were several limitations in our study. First, since this is a meta-analysis, causal relationships could not be determined. Second, we discovered significant variation among research, limiting the applicability of our findings. Third, there was a low number of studies eligible for inclusion in our meta-analysis. Finally, differences in country and geographic origin among studies could be a source of heterogeneity, which should be taken with caution and confirmed by additional studies. The good feature of our study was the homogeneity of studies in the method used for diagnosis of NAFLD, which was restricted to ultrasonography.

To conclude the prevalence of diabetic neuropathy in NAFLD patients was 0.48 (95% CI= 0.31-0.65, I^2= 99.01%), but it was not significantly different from patients without NAFLD (OR=1.02, 95% CI= 0.89-1.17. p=0.748, I^2=81.6%).

DISCLOSURE

Ethics: Institutional Review Board approval not applicable

Data availability: Data is available upon request from corresponding author.

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Conflicts of interest: None

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