Review Article

The Role of Adiponectin in Diabetic Peripheral Neuropathy: A Systematic Review and Meta-Analysis

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Keywords

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is a prevalent microvascular consequence of diabetes with a complex etiology. Adiponectin, an adipokine with anti-inflammatory and neuroprotective properties, has been implicated in DPN, but its significance remains unclear due to conflicting findings. The objective of this systematic review is to assess the association between circulating adiponectin levels and the risk of DPN in individuals with diabetes.

Methods: We did a systematic literature search in PubMed, Scopus, and CINAHL for studies investigating adiponectin levels in diabetes patients with and without DPN. A meta-analysis was done to evaluate the pooled mean difference in adiponectin levels between patients and controls. Study quality was rated using the Joanna Briggs Institute's critical appraisal tool.

Results: The systematic review comprised 13 studies with 3,337 participants. Meta-analysis of 4 studies (920 participants) indicated no significant difference in adiponectin levels between DPN patients (n=418) and controls (n=502) (pooled mean difference 0.01, 95% CI: -0.24 to 0.26, p=0.94), with strong heterogeneity (I^2=59%). Subgroup analyses were not possible due to inadequate data. Risk of bias was generally low, with 7 studies graded as good quality.

Conclusions: Our findings imply that circulating adiponectin levels are not linked with the risk of DPN in diabetes. However, the substantial heterogeneity among studies underscores the need for more well-designed prospective studies to explain the role of adiponectin in DPN etiology.

Introduction

Diabetes is a debilitating metabolic disorder associated with both macro and microvascular complications. Long-term microvascular complications of diabetes include peripheral neuropathy which is clinically impacted with numbness and lack of sensation thereby resulting in poor quality of life [1].

The global prevalence of diabetes is indeed a significant health concern, which is estimated to be around 9.3% [2]. Furthermore, it is alarming that approximately 40.3% of diabetic patients develop Diabetic Neuropathy (DNP), highlighting the serious impact of diabetes on nerve health and overall well-being [3].
The lack of sensation in Diabetic Neuropathy (DNP) is a significant concern because it can lead to unnoticed peripheral injuries, particularly in the feet, ultimately resulting in foot ulcers. If not properly managed, these ulcers can become severe and may ultimately necessitate amputation.

The various mechanisms involved in the pathogenesis of DM include hyperglycemia, insulin resistance, oxidative stress, and inflammation. Adiponectin is an adipokine involved in various metabolic and physiological function [4]. Insulin sensitivity, inflammation, energy regulation, and lipid metabolism are all impacted by adiponectin [5]. Both beta cells and immune cells express adiponectin receptors, thereby indicating its potential to influence immunological activity in diabetes[6]. The anti-inflammatory role of adiponectin is found to improve insulin sensitivity, which is suggestive of its role in delaying the progression of diabetes.

Moreover, adiponectin exhibits neuroprotective effects in various neurological disorders such as Alzheimer's, depression, and stroke [7]. In DNP, the neurons that are affected are predominantly sensory in nature [8]. Interestingly, adiponectin pathway activation is observed to be neuroprotective for somatosensory neurons in diabetic animal models, suggesting that it may play a role in reducing the neuropathy associated with diabetes [9,10].

The literature presents inconsistencies regarding the significance of adiponectin in relation to its serum level in DNP. Some studies have reported elevated blood adiponectin levels in DNP patients whereas others have shown either reduced or no discernible difference, suggesting a more nuanced relationship that needs additional study. In fact, because of inconsistent research results, the function of adiponectin in diabetic neuropathy (DNP) is still up for discussion. This variation emphasizes the need for a more thorough investigation to determine the specific role of adiponectin in DNP.
The primary objective of this systematic review is to evaluate the association between circulating adiponectin levels and the risk of DNP in diabetic patients. In this study, both systematic review and meta-analysis were performed to establish the association between serum adiponectin levels and the risk of DPN.

Methods

The systematic review followed the guidelines outlined by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol was registered on PROSPERO (Registration ID: CRD42024504656).

Selection Procedure

The objective of this systematic review and meta-analysis was to evaluate the association between adiponectin levels and diabetic peripheral neuropathy. The inclusion criteria were as follows: 1. Observational studies (cohort studies, case-control studies, cross-sectional studies) investigating the association between adiponectin levels and diabetic peripheral neuropathy, 2. Studies involving participants diagnosed with diabetic peripheral neuropathy, confirmed through appropriate clinical assessments, neuropathy scoring systems, nerve conduction studies, or other established diagnostic methods as specified in individual studies; 3. Studies reporting adiponectin levels (measured in blood/serum/plasma) in diabetic patients with and without peripheral neuropathy or compared to healthy controls, 4. Studies providing data to calculate measures of effect (e.g. mean differences, odds ratios) and associated measures of variance, 5. Studies published in the English language. The exclusion criteria were: 1. Reviews, case reports, editorials, letters, and commentaries, 2. Animal or preclinical studies, 3. Studies not assessing or reporting adiponectin levels in relation to diabetic peripheral neuropathy; 4. Studies with insufficient data to extract adiponectin levels or effect sizes, 5. Duplicate publications or studies with overlapping datasets.

Search Strategy

A comprehensive literature search was conducted in PubMed, Scopus, and CINAHL databases from inception to March 2024 to identify relevant studies. Our search strategy utilized a combination of keywords related to "adiponectin" and "diabetic neuropathy" (Table 1). Additionally, bibliographies of included studies were manually screened for any missed relevant citations. Only studies published in the English language were considered.

Table 1: Search strategy.

Database	Search Terms
Pubmed	(“adiponectin”[MeSH Terms] OR “adiponectin”[All Fields] OR “adiponectin s”[All Fields] OR “adiponectine”[All Fields] OR “adiponectins”[All Fields] OR “AdipoQ”[All Fields] OR “Acrp30”[All Fields]) AND (“diabetic neuropathies”[MeSH Terms] OR (“diabetic”[All Fields] AND “neuropathies”[All Fields]) OR “diabetic neuropathies”[All Fields] OR (“diabetic”[All Fields] AND “neuropathy”[All Fields]) OR “diabetic neuropathy”[All Fields] OR ((“diabete”[All Fields] OR “diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields] OR “diabetes”[All Fields] OR “diabetes insipidus”[MeSH Terms] OR (“diabetes”[All Fields] AND “insipidus”[All Fields]) OR “diabetes insipidus”[All Fields] OR “diabetic”[All Fields] OR “diabetics”[All Fields] OR “diabets”[All Fields]) AND (“peripheral nervous system diseases”[MeSH Terms] OR (“peripheral”[All Fields] AND “nervous”[All Fields] AND “system”[All Fields] AND “diseases”[All Fields]) OR “peripheral nervous system diseases”[All Fields] OR (“peripheral”[All Fields] AND “neuropathy”[All Fields]) OR “peripheral neuropathy”[All Fields])))
Scopus	(TITLE-ABS-KEY-AUTH (adiponectin OR adipoq OR acrp30) AND TITLE-ABS-KEY-AUTH (diabetic AND neuropathy OR diabetic AND peripheral AND neuropathy))
CINAHL	Boolean/Phrase: (adiponectin OR adipoq OR acrp30) AND (diabetic AND neuropathy OR diabetic AND peripheral AND neuropathy) ; Expanders: Apply equivalent subjects; Language: English

Screening and Data Extraction

Studies identified from the database searches underwent an initial screening by two independent reviewers based on titles and abstracts. Potentially relevant studies then had their full texts reviewed for eligibility using the CADIMA tool version 2.2.3. Any disagreements were resolved by consultation with a third reviewer.

Data from the included studies was extracted by two independent reviewers into a standardized form, with discrepancies resolved by consensus or a third reviewer. Extracted data included participant demographics, study characteristics, adiponectin levels, and outcomes related to diabetic peripheral neuropathy.

Quality Assessment

The quality of included studies and risk of bias were evaluated using the Joanna Briggs Institute’s critical appraisal checklist for cross-sectional studies. A risk of bias summary and graph were generated using RevMan 5.4 software.

Data Analysis

Meta-analysis was performed using RevMan 5.4 software. For dichotomous outcomes, risk ratios (RR) with 95% confidence intervals (CI) were calculated. Continuous outcomes were pooled and expressed as mean differences (MD) using the inverse variance method and a random-effects model with 95% CIs.

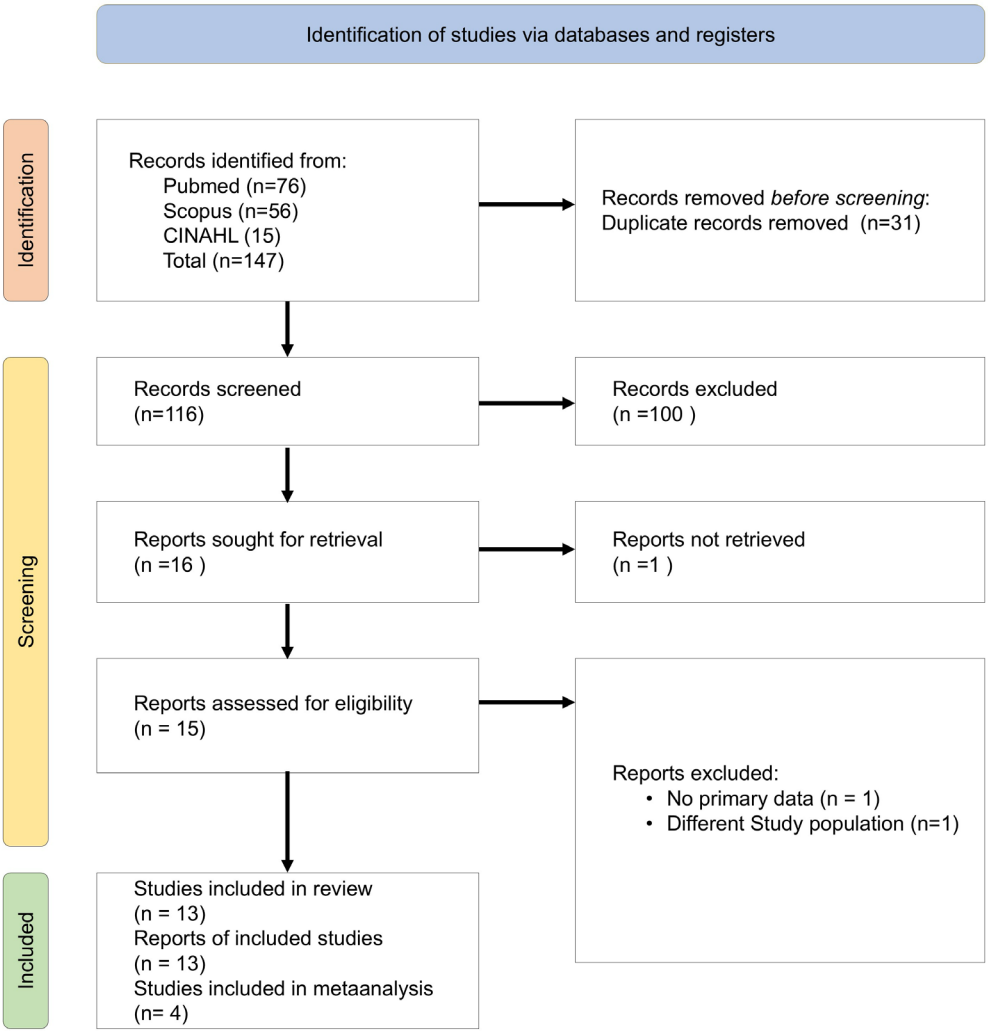
Heterogeneity across studies was assessed using Cochran’s Q statistic and the I^2 index. Based on heterogeneity levels, either a fixed-effect or random-effects model was employed. Subgroup analyses were not performed due to lack of sufficient data. Sensitivity analysis was performed using R software.

Results

Study Selection

The database searches initially identified 147 records and finally 116 records were screened after removing duplicates. Following screening of titles and abstracts, 15 articles underwent full-text review. Finally, 13 studies which met the eligibility criteria were included in the systematic review and 4 studies were included in meta-analysis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Figure 1: PRISMA flow chart.



PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study Characteristics

The basic characteristics of the 13 included studies are presented in Table 1. The studies were conducted across various countries including China, India, Japan, Korea, Spain, and Germany. The total sample size was 3,337 participants.

The included studies were cross-sectional (n=10), case-control (n=2), randomized controlled trial (n=1), and an experimental study (n=1). The age of participants in the included studies ranged from 39.7 to 72 years. The duration of diabetes ranged from 1 to 20 years across studies. Diagnosis of diabetic peripheral neuropathy was established using different methods such as neuropathy symptom scores, neurological examinations, nerve conduction studies, current perception threshold testing, and vibratory perception threshold. (Table 2)

Adiponectin Levels

Table 3 summarizes the reported adiponectin levels in cases (diabetic peripheral neuropathy) and controls (non-neuropathy or healthy) across the included studies. While some studies found significantly higher adiponectin levels in neuropathy cases compared to controls, others reported no difference or lower levels in cases.

Table 1: Basic characteristics of included studies.

Study	Country	Population	Duration of diabetes	Diabetic Peripheral Neuropathy score/Nerve conduction study
Qing Sun et al, 2020 [11]	China	Chinese patients with type 2 diabetes	Median 10 years for non-DPN group, 16 years for DPN group	Not reported
Mohanraj PS et al, 2024 [12]	India	Individuals aged 35 to 65 years with type 2 diabetes mellitus	1 to 20 years	Neuropathy symptom score (NSS), diabetes neuropathy examination (DNE) score, and nerve conduction studies
Zhi-Yong Ji et al, 2015 [13]	China	Type 2 diabetes patients with and without diabetic peripheral neuropathy, and healthy controls.	Not reported	Patients with diabetic peripheral neuropathy had clinical manifestations of acroparesthesia or motor nerve involvement, reduced degree of deep and superficial sensation, and reduced sensory nerve conduction velocity (SCV) and motor nerve conduction velocity (MNCV).
Ken Satoh et al, 2023 [14]	Japan	Patients with type 2 diabetes	Reported in years (Median values - Non-obese group: 5 years, Obese group: 8 years)	Not reported
R. Pradeepa et al., 2014 [15]	India	South Indian type 2 diabetic subjects	Reported in years (Without microvascular complications: 3.5 ± 4.5 years, With microvascular complications: 6.4 ± 6.2 years)	Neuropathy was diagnosed if vibratory perception threshold (VPT) of the great toe using biothesiometry exceeded ≥20 V.
Chan-Hee Jung et al, 2014 [16]	Korea	Patients with type 2 diabetes	6.2 ± 5.2 years	Diabetic peripheral neuropathy was diagnosed using the Michigan Neuropathy Screening Instrument, neurological screening examinations, and current perception threshold test.

Study	Country	Population	Duration of diabetes	Diabetic Peripheral Neuropathy score/Nerve conduction study
J. M. González-Clemente et al, 2005 [17]	Spain	Subjects with type 1 diabetes mellitus	14 years	Not reported
H. Usta Atmaca et al, 2017 [18]	Not reported	Type 2 diabetes mellitus patients with peripheral neuropathy	Not reported	Patients were diagnosed with diabetic neuropathy using electromyography (EMG)
Chan-Hee Jung et al., 2012 [19]	Korea	Type 2 diabetic patients	6.1 ± 5.0 years (mean ± SD)	Not reported
Christophe E.M. De Block et al, 2005 [20]	Not reported	Type 1 diabetic patients without nephropathy	19 ± 11 years	Electromyographic examination with nerve conduction velocity tests, including motor (peroneal and tibial) and sensory (sural) nerves, H-reflexes, and F-waves. Neuropathy severity was graded.
C. Herder et al, 2015 [21]	Germany	People aged 61-82 years with Type 2 diabetes from the population-based KORA F4 study.	Median duration since diagnosis was 3 years for those without polyneuropathy and 8 years for those with polyneuropathy.	Not reported. The presence of clinical diabetic sensorimotor polyneuropathy was defined as bilateral impairment of foot vibration perception and/or foot pressure sensation.
Umapathy Dhamodharan et al, 2015 [22]	Not reported	T2DM subjects with and without diabetic foot ulcer	Not reported	Not reported
Ágnes Molnár et al, 2022 [23]	Not reported	Type 2 diabetes mellitus patients with distal sensory polyneuropathy	10.3 ± 3.7 years (patients with neuropathy), 10.9 ± 4.1 years (controls)	Current perception threshold (CPT) measured by Neurometer®

*Data are presented as mean ± SD or median (range).

Table 2: Details of the included Study.

Study	Sample size	Mean Age, years	Gender distribution	Design
Qing Sun et al, 2020 [11]	219 total, with 98 cases and 121 controls	Median 58 years for non-DPN group, 62.5 years for DPN group	48.8% male in non-DPN group, 43.9% male in DPN group	Cross-sectional study
Mohanraj PS et al, 2024 [12]	86 participants, with 43 cases and 43 controls	Cases (with neuropathy): 54.5 ± 11 years Controls (without neuropathy): 53.1 ± 8.7 years	Cases: 23 females (53%) Controls: 19 females (44%)	Cross-sectional study
Zhi-Yong Ji et al, 2015 [13]	With 90 Cases (DPN group) & 90 Controls (NDPN group), and 90 healthy controls (NC group).	DPN group: 54.1 ± 5.6 years, NDPN group: 54.9 ± 5.1 years, NC group: 53.5 ± 5.0 years.	DPN group: 46 males, 44 females. NDPN group: 50 males, 40 females. NC group: 40 males, 50 females.	Case-control study.
Ken Satoh et al, 2023 [14]	94 patients (197 non-obese, 197 obese)	Not reported (Median age - Non-obese group: 55 years, Obese group: 54 years)	Non-obese group - 98 males, 99 females; Obese group - 104 males, 93 females	Cross-sectional study
R. Pradeepa et al., 2014 [15]	Total 487 diabetic subjects (With cases of microvascular complications: 266, Without microvascular complications: 221)	Without microvascular complications: 45.7 ± 9.5 years, With microvascular complications: 54.7 ± 11.1 years	Not explicitly reported	Cross-sectional study
Chan-Hee Jung et al, 2014 [16]	With Cases & Controls: 153 total patients, 87 with neuropathy (cases), 66 without neuropathy (controls)	52.5 ± 10.0 years	100 men (65.4%), 53 women (34.6%)	Cross-sectional study
J. M. González-Clemente et al, 2005 [17]	With Cases = 36, Controls = 84	With DPN = 28.03 ± 7.15, Without DPN = 27.17 ± 6.35	38.9% women in DPN group, 54.8% women in non-DPN group	Cross-sectional study
H. Usta Atmaca et al, 2017 [18]	23 cases with type 2 diabetes and peripheral neuropathy, 21 healthy controls	56.1 ± 6.6 years for cases, 36.3 ± 7.5 years for controls	Cases - 20 females, 3 males; Controls - 20 females, 1 male	Randomized, double-blind, placebo-controlled, prospective study

Study	Sample size	Mean Age, years	Gender distribution	Design
Chan-Hee Jung et al., 2012 [19]	Total 142 patients (94 males, 48 females), with cases of cardiac autonomic neuropathy (CAN)	52.4 ± 10.0 years	94 males (66.2%), 48 females (33.8%)	Cross-sectional study
Christophe E.M. De Block et al, 2005 [20]	592 (Cases and controls not specified)	41 ± 12 years	324 men, 268 women	Cross-sectional study
C. Herder et al, 2015 [21]	47 cases with polyneuropathy, 168 controls without polyneuropathy.	Around 71-72 years in both groups.	59% male in those without polyneuropathy, 66% male in those with polyneuropathy.	Cross-sectional study.
Umapathy Dhamodharan et al, 2015 [22]	Sample Size: Total = 515 NGT/Control = 106 T2DM without DFU = 139 T2DM with neuropathic DFU (DFU-DN) = 191 T2DM with PVD (DFU-PVD) = 79	NGT = 39.7 ± 8.4 T2DM = 49.0 ± 9.9 DFU-DN = 58.6 ± 8.5 DFU-PVD = 59.5 ± 8.5	NGT (M/F) = 56/50 T2DM (M/F) = 80/59 DFU-DN (M/F) = 125/66 DFU-PVD (M/F) = 56/23	Cross-sectional study
Ágnes Molnár et al, 2022 [23]	30 cases with neuropathy, 32 controls without neuropathy	61.97 ± 8.09 (cases), 64.37 ± 6.52 (controls)	9 males/21 females (cases), 10 males/22 females (controls)	Experimental study with 6-week aerobic exercise intervention

Table 3: Details of intervention used and Study outcome.

Study	Comparison group	Adiponectin level	Outcome	Dropout	Measures of DPN
Qing Sun et al, 2020 [11]	Non-DPN patients	Median 8.13 mg/ml for non-DPN group, 9.63 mg/ml for DPN group	Serum adiponectin levels were positively associated with diabetic peripheral neuropathy.	Not reported	Presence of common DPN symptoms and abnormal neurological screening tests.
Mohanraj PS et al, 2024 [12]	Type 2 diabetes mellitus patients without neuropathy	Cases (with neuropathy): 3.3 ± 1.2 µg/mL Controls (without neuropathy): 3.6 ± 1.2 µg/mL	No significant difference in adiponectin levels between cases and controls. Adiponectin showed no significant association with diabetic peripheral neuropathy.	Not reported	Neuropathy symptom score (NSS), diabetes neuropathy examination (DNE) score, nerve conduction studies
Zhi-Yong Ji et al, 2015 [13]	Non-diabetic peripheral neuropathy (NDPN) group and healthy normal controls (NC group).	Serum levels of adiponectin were markedly reduced in the DPN group compared to NDPN and NC groups.	The study found that the T allele in +45T/G and +276G/T polymorphisms of the adiponectin gene was associated with an elevated risk of diabetic peripheral neuropathy in type 2 diabetes patients, likely by down-regulating adiponectin serum levels.	Not reported.	Clinical manifestations, reduced sensory and motor nerve conduction velocities.
Ken Satoh et al, 2023 [14]	Non-obese (BMI 20-25 kg/m2) vs Obese (BMI ≥32 kg/m2) patients with type 2 diabetes	Reported (Median values - Non-obese group: 3.00 µg/mL, Obese group: 2.36 µg/mL)	Association of adiponectin levels with microvascular complications (retinopathy, nephropathy, neuropathy)	Not reported	Defined as presence of two of the following - diminished Achilles tendon reflex, inability to sense vibration, symptoms of distal neuropathy.
R. Pradeepa et al., 2014 [15]	Subjects with and without microvascular complications (retinopathy, nephropathy, neuropathy)	Geometric mean reported Without microvascular complications: 5.3 µg/mL With microvascular complications: 6.1 µg/mL With diabetic retinopathy: 6.8 µg/mL Without diabetic retinopathy: 5.5 µg/mL With neuropathy: 6.5 µg/mL Without neuropathy: 5.6 µg/mL	Association of serum adiponectin with diabetic microvascular complications (retinopathy, nephropathy, neuropathy)	Not reported	Vibratory perception threshold using biothesiometry

Study	Comparison group	Adiponectin level	Outcome	Dropout	Measures of DPN
Chan-Hee Jung et al, 2014 [16]	Patients without neuropathy	Not reported specifically	The mean levels of adiponectin were significantly higher in patients with neuropathy compared to those without neuropathy.	Not reported	Michigan Neuropathy Screening Instrument, neurological examinations, current perception threshold test
J. M. González-Clemente et al, 2005 [17]	Subjects with type 1 diabetes without diabetic neuropathy	Median (IQR) With DPN = 9.19 (7.61-18.53) mg/l Without DPN = 13.34 (10.01-16.23) mg/l	The study found an association between diabetic neuropathy and increased plasma levels of soluble TNF-α receptors (sTNFR1 and sTNFR2), indicating activation of the TNF-α system, independent of glycemic control and cardiovascular risk factors.	Not reported	Peripheral neuropathy assessed by MNSI questionnaire and neurological examination. Cardiovascular autonomic neuropathy assessed by heart rate variability tests.
H. Usta Atmaca et al, 2017 [18]	Healthy controls	9.3 ± 2.7 ng/mL for cases, 11.6 ± 3.4 ng/mL for controls	600 mg/day alpha lipoic acid treatment for 6 weeks did not improve metabolic parameters or adiponectin levels in type 2 diabetes patients.	Not reported	Electromyography
Chan-Hee Jung et al., 2012 [19]	Patients with CAN compared to patients without CAN	With CAN: 4185 ± 3615 ng/mL, Without CAN: 3138 ± 3010 ng/mL	Higher serum adiponectin levels were associated with increased risk for presence of cardiac autonomic neuropathy (CAN).	Not reported	Cardiac autonomic neuropathy assessed by Ewing's protocol and heart rate variability parameters.
Christophe E.M. De Block et al, 2005 [20]	Normal-weight (BMI < 25 kg/m2) vs. overweight (BMI ≥ 25 kg/m2) patients	Reported, but no difference between patients with or without neuropathy	Prevalence of retinopathy and neuropathy in overweight vs. normal-weight patients	Not reported	Electromyography with nerve conduction studies
C. Herder et al, 2015 [21]	People with Type 2 diabetes without polyneuropathy.	Median total adiponectin level was 6746 ng/ml in those with polyneuropathy and 7894 ng/ml in those without polyneuropathy.	The study investigated the association between serum omentin levels and polyneuropathy.	Not reported.	Clinical assessment of bilateral foot vibration perception and pressure sensation impairment.
Umapathy Dhamodharan et al, 2015 [22]	NGT/Control group	NGT: 536.0 (0.1-1787) ng/mL T2DM: 528.6 (6.2-1255) ng/mL DFU-DN: 524.0 (63.3-1641) ng/mL DFU-PVD: 453.5 (164.9-1078) ng/mL	Association of IL-6, TNF-α and SDF-1 polymorphisms with diabetic foot ulcer	Not reported	Vibration perception threshold

Study	Comparison group	Adiponectin level	Outcome	Dropout	Measures of DPN
Ágnes Molnár et al, 2022 [23]	Age and gender-matched type 2 diabetes patients without neuropathy	6.91 ± 3.32 µg/mL (cases before exercise), 7.09 ± 3.88 µg/mL (cases after exercise), 6.89 ± 3.32 µg/mL (controls)	Physical activity increased FGF21 levels in cases, which correlated with improvement in CPT values (severity of neuropathy).	Not reported	Current perception threshold (CPT) by Neurometer®

Meta-Analysis

A meta-analysis was conducted to investigate the association between adiponectin levels and diabetic peripheral neuropathy. The meta-analysis included 4 studies with a total of 920 participants, comprising 418 cases and 502 controls. Using a random-effects model, the pooled mean difference in adiponectin levels between cases and controls was 0.01 (95% CI: [-0.24, 0.26]), which was not statistically significant (p = 0.94). However, substantial heterogeneity was observed across the included studies (I^2 = 59%, p = 0.06). The random-effects model was chosen due to the moderate level of heterogeneity, as it accounts for potential variability in treatment effects across studies. The overall meta-analysis results suggest that there is no significant difference in adiponectin levels between individuals with diabetic peripheral neuropathy and controls, but the findings should be interpreted with caution given the substantial heterogeneity among the included studies (Figure 2). Both visual inspection of the funnel plot and Egger's test did not indicate potential publication bias (Figure 3).

Figure 2: Forest Plot.

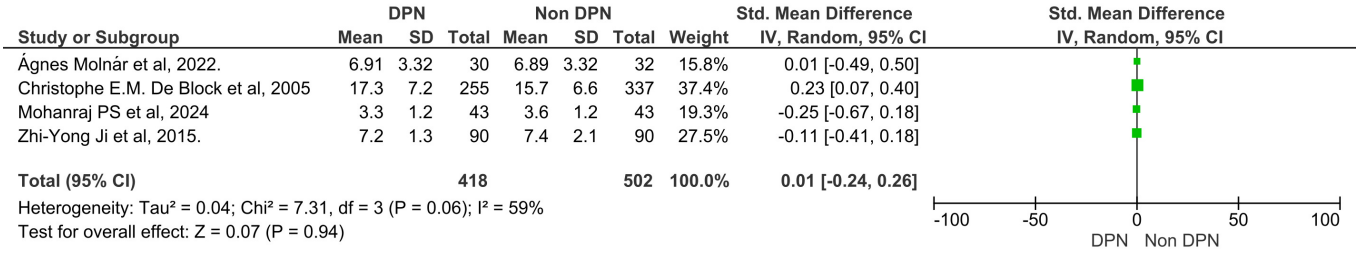
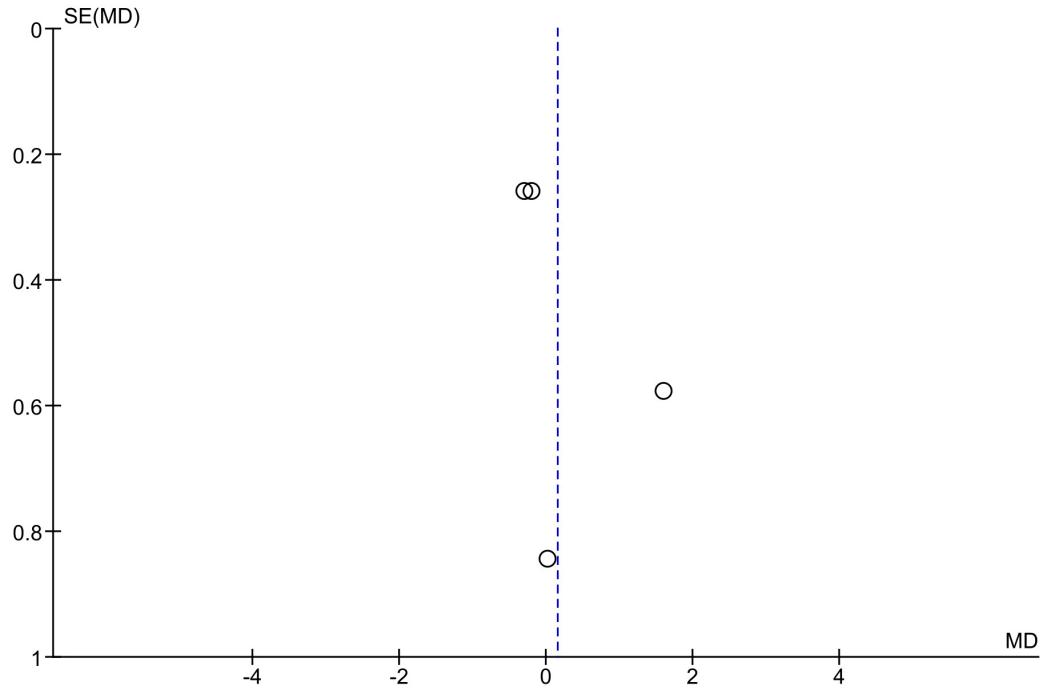


Figure 3: Funnel Plot.



Subgroup analyses could not be performed due to the limited number of studies and variability in reporting of data.

Quality Assessment

The risk of bias assessment for the included studies is summarized in Figure 4 and 5. The main potential sources of bias were related to non-random sampling, lack of blinding of outcome assessors, and unclear handling of missing data in some studies. Overall, 7 studies were judged to be of high quality, while 5 had some concerns regarding risk of bias. Despite the identified potential biases, the majority of the included studies were considered of high quality, enhancing the overall reliability of the study findings.

Figure 4: Risk of Bias Graph.

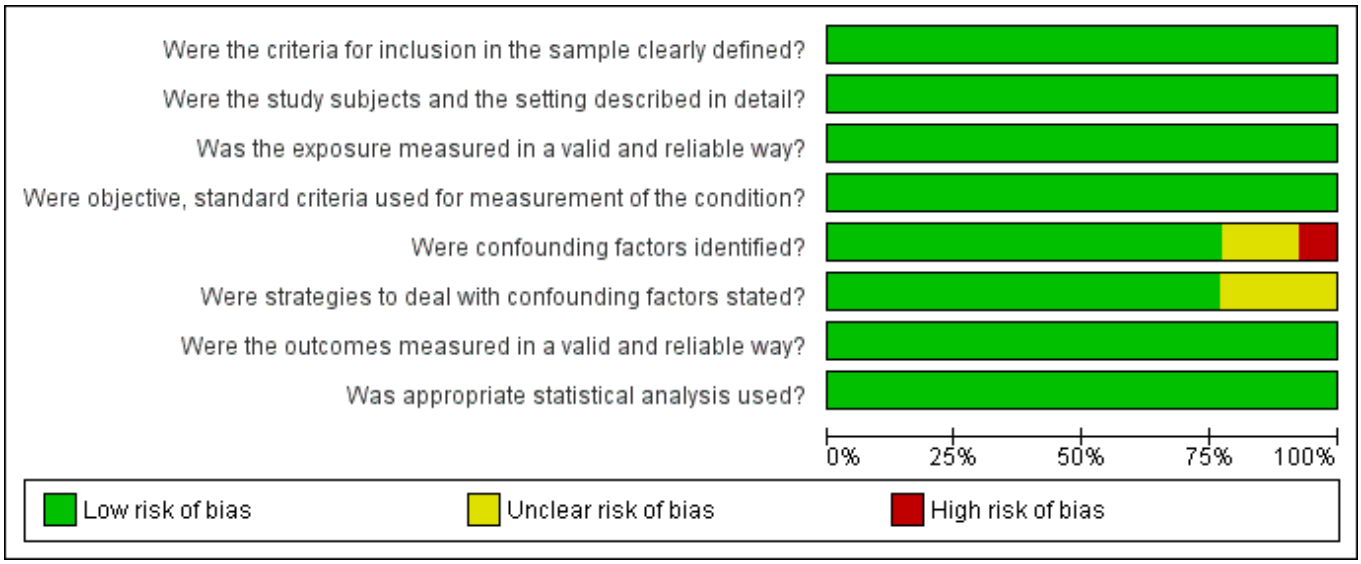
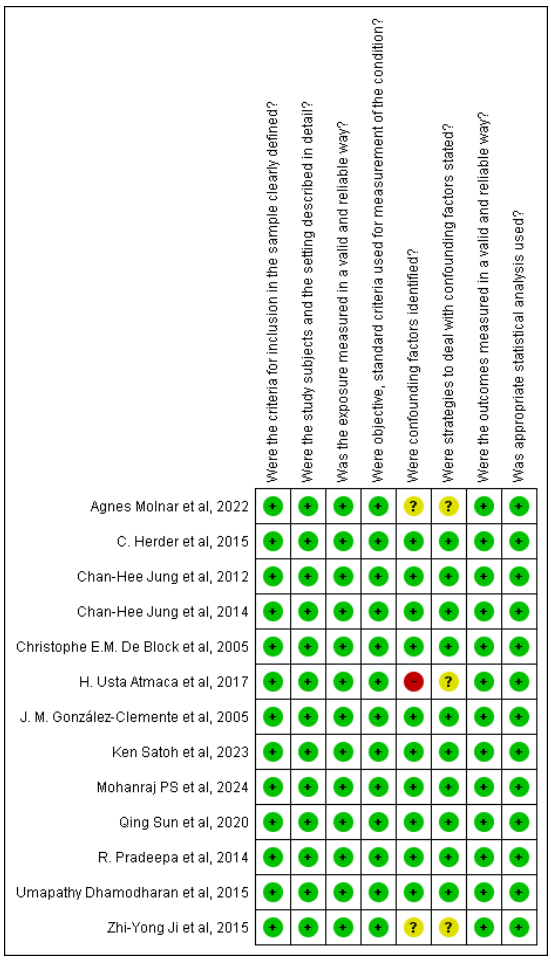


Figure 5: Risk of bias Summary.



Sensitivity Analysis

During our sensitivity analysis, we deliberately excluded individual studies in a systematic manner to evaluate their influence on the overall pooled effect size and the degree of heterogeneity observed. Despite these exclusions, our findings suggest that there were no significant alterations to the combined estimate or the level of variability. The use of the meta-analytical method, specifically the inverse variance method and the restricted maximum-likelihood estimator for tau^2, ensured the reliability of our findings. Thus, our analysis indicates that the overall conclusion about the effect size and heterogeneity stays consistent irrespective of the various instances of study exclusion.

Table 4: Sensitivity analysis.

Study excluded	SMD	95%-CI	p-value	tau^2	I^2
Ágnes Molnár et al (2022)	-0.00	[-0.31, 0.30]	0.99	0.05	72%
Christophe E.M. De Block et al (2005)	-0.13	[-0.34, 0.09]	0.25	0.00	0%
Mohanraj PS et al (2024)	0.08	[-0.17, 0.33]	0.55	0.03	55%
Zhi-Yong Ji et al (2015)	0.05	[-0.26, 0.36]	0.76	0.04	57%
Pooled estimate	0.01	[-0.24, 0.26]	0.94	0.04	59%

Meta-analytical method: - Inverse variance method - Restricted maximum-likelihood estimator for tau^2

Additional Analyses

Several studies also reported on additional outcomes related to adiponectin levels and diabetic complications. These are summarized below: Qing Sun et al. found that higher adiponectin was associated with increased risk of cardiovascular autonomic neuropathy in addition to peripheral neuropathy. Pradeepa et al. reported higher geometric mean adiponectin levels in patients with diabetic retinopathy (6.8 µg/mL) and nephropathy compared to those without microvascular complications. The study by Dhamodharan et al. found no significant differences in adiponectin across groups with type 2 diabetes, with or without neuropathic diabetic foot ulcers. Molnar et al. showed that a 6-week aerobic exercise intervention increased adiponectin levels in patients with distal sensory polyneuropathy, which correlated with improved current perception threshold (neuropathy severity).

Discussion

In this study, systematic review along with metanalysis were performed in order to assess an association between serum adiponectin levels and risk of DPN in diabetes.

On doing a thorough literature search, 13 studies reported adiponectin levels in diabetes, where comparison was done between individuals with and without DPN. Among which, four studies reported an increased level of adiponectin in DPN. However, on the contrary three other studies have reported reduced levels of adiponectin and the remaining six studies have mentioned no significant difference.

When it comes diabetes mellitus, DPN is the most prevalent neuropathic condition associated with it [24]. Lack of peripheral sensation results in unnoticed multiple injuries, intense distressing neuropathic pain, poor wound healing and ulceration, terminating to amputation of the lower limb.

DPN involves multiple aetiology. However, the exact mechanism of its development is still un resolved. The various pathways involved could be summated as disruptions in the pathways associated with hyperglycaemia, dyslipidaemia, oxidative stress-induced microvascular problems, neuronal inflammation, mitochondrial damage, and cell death. Since the pathophysiology of diabetes involves insulin resistant and inflammation, presence of Adiponectin's receptor on beta cells and immune cells is suggestive of a crucial role of adiponectin in its pathogenesis[4]. Furthermore, adiponectin has been linked to ameliorate insulin resistance, subclinical inflammation, and has neuroprotective effects in individuals with diabetes [7]. Adiponectin via AMPK pathway is found to improve diabetic neuropathy by targeting pathways of oxidative stress and anti-oxidants in animal models of diabetes [25]. Therefore, it has a promising role in the pathophysiology of DPN.

One of the most extensively studied pathogenesis of DPN is inflammation. Interestingly, the role of adiponectin is both anti-inflammatory as well as neuroprotective. Other adipokine such as leptin, enhances production of pro-inflammatory cytokines like TNF and IL-6, assisting inflammatory process and stimulating macrophages there by leading to neuropathic pain[26]. Studies where adiponectin levels were increased in DPN are suggestive that this rise in levels could be secondary in nature, in response to reduced inflammation [11,16,17,19].

Understanding the primary function of adiponectin in the pathophysiology of DPN is aided by the evidences in animal models with DPN, knockouts of the protein stimulate the MAPK pathway, resulting in hyperalgesia [27]. Additionally, Adiponectin via AMPK pathway enhances several pathways associated with oxidation, metabolism, insulin sensitivity, inflammatory response and cell survival [28]. Further, AMPK activation is found to be beneficial improving diabetic neuropathy in animal models by targeting oxidative stress [25]. Interestingly, adiponectin receptor agonist is found to be neuroprotective in diabetic neuropathy and has potential future in treatment of DPN [29]. These data support the conclusions of several investigations that have shown that DPN has lower levels of adiponectin [13,14,18].

There have been reports of both elevated and lowered adiponectin levels, which may have an impact on the pathophysiology of DPN. Its precise function is unclear, though. Consequently, it was necessary to carry out a thorough analysis. After doing this meta-analysis, we discovered that, in a diverse population, there were no appreciable differences in adiponectin levels between instances of diabetes with and without diabetic peripheral neuropathy.

Our findings imply that adiponectin might not have a role in the etiology of diabetic peripheral neuropathy. However, given the ethnic heterogeneity, chronicity of the condition (DPN is a long-term consequence of diabetes), age group disparities in the research population, and the impact of standard treatment, these results should be interpreted cautiously.

This study employs a thorough and meticulous methodology to investigate the potential role of adiponectin as a novel biomarker, which may prove useful in the future for diagnostic and prognostic purposes, as well as serving as a therapeutic targeting of diabetic peripheral neuropathy. However, this study comes with certain limitations, with medication being prime factor in almost all the studies. Levels of adiponectin are found to be reduced in newly diagnosed cases of diabetes [30]. Nonetheless, it has been discovered that taking metformin increases adiponectin levels [31]. Given that DPN is a long-term side effect of diabetic drugs, it is possible that it will influence the results of most investigations. Further, this study included both type 1 and type 2 diabetes which can have an impact on generalizability of the study results.

Additionally, study design of the studies included in this meta-analysis were mostly either cross-sectional or case control in nature, which could lead to bias since not all confounding variables were taken into account. Furthermore, the heterogeneity observed across studies, particularly in adiponectin levels, is a notable limitation. Although we addressed this using a random-effects model and sensitivity analysis, it may still affect the robustness of our findings. Lastly, the inclusion of studies focusing on other neuropathy-related complications (e.g., cardiac autonomic neuropathy) may introduce bias. While these studies were included for discussion purposes and excluded from the meta-analysis, their inclusion underscores the need for standardized diagnostic criteria and reporting in future research. Therefore, additional prospective cohort studies can provide more precise relationship between serum adiponectin and the risk of DPN in individuals with diabetes.

Conclusion

Based on our systematic review and meta-analysis of multiple studies, we find no correlation between adiponectin levels and the heightened risk of diabetic peripheral neuropathy (DPN) in individuals with diabetes. Despite variations across studies, our systematic review provides a comprehensive overview, underscoring the necessity for further investigation to clarify adiponectin's exact role in the development of DPN.

Conflict of Interests

The authors declare that they have no conflict of interest regarding the publication of this article.

Ethical Approval

This systematic review and meta-analysis utilized publicly available data and did not involve direct research on human participants or animals. Therefore, no ethical approval was required.

Credit Author Statements

Aniruddha Sen: Conceptualization, Methodology, Data Collection, Formal Analysis, Writing – Original Draft.

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Vinoth Rajendran: Data Curation, Statistical Analysis, Writing – Review & Editing.

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Srinivas Nagaram: Validation, Writing – Review & Editing.

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