

# Gender differences in diabetic neuropathy in the Japanese population:

## A literature review

Naomi Oshiro (Faculty of Health Sciences, Kyorin University, xj6n@ks.kyorin-u.ac.jp, Japan)

Yuko Tsumagari (Faculty of Health Sciences, Kyorin University, yuko-tsumagari@ks.kyorin-u.ac.jp, Japan)

Yaoko Iwasaki (Faculty of Health Sciences, Kyorin University, iwasaki@ks.kyorin-u.ac.jp, Japan)

### Abstract

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus, affecting over 30 % of patients. In Japan, where the prevalence of diabetes is notably high—especially among older adults—addressing DPN has become a clinical priority. However, little is known about gender-specific differences in DPN manifestation, progression, and self-care behaviors within the Japanese context. This study aimed to examine gender differences in DPN-related factors by reviewing Japanese literature, to inform more personalized intervention strategies. A systematic literature search was conducted using Ichushi Web and CiNii Articles up to September 2024. Inclusion criteria were studies involving patients with DPN, original articles, full-text availability, and a focus on gender differences. A total of 19 studies were selected and analysed based on participant characteristics, study design, outcome measures, and reported gender-based findings. Male patients demonstrated higher rates of smoking, alcohol use, and sarcopenia associated with DPN, while female patients showed stronger engagement in self-care practices and a higher prevalence of dyslipidemia in postmenopausal stages. Nerve conduction patterns varied by gender but were also influenced by anatomical factors. Subjective symptom reporting was more prominent in females, suggesting possible gender-related biases in symptom recognition. This review highlights significant gender-based trends in DPN risk factors and symptom expression among Japanese patients. These findings suggest the need for gender- and age-specific rehabilitation strategies, including targeted muscle preservation programs for males and enhanced educational interventions for females, especially during menopausal transitions.

### Key words

diabetes, diabetic neuropathy, gender differences, clinical features, literature review

### 1. Introduction

In Japan, the number of individuals with diabetes is estimated to be approximately 10 million, with a national prevalence of 12 %. This rate increases to over 30 % among those aged 60 years and older, which is higher than the global average of 10.5 % (Magliano and Boyko, 2022; Ministry of Health, Labour and Welfare, 2022). Given the continuing aging of the population, the prevalence is expected to rise further.

Diabetic neuropathy, a common complication of diabetes, affects more than 30 % of individuals with the disease (Survey Research Group of Japan Physicians Association, 2001b). This condition can impair sensory, motor, and autonomic nerve functions (Kamiya et al., 2024). In clinical practice, rehabilitation interventions—particularly exercise therapy and lifestyle guidance—are commonly applied in response to muscle weakness, especially in the feet and lower limbs.

In Japan, the prevalence of diabetes among males is nearly 1.8 times higher than that in females (17.5 % vs. 9.8 %) (Magliano and Boyko, 2022; Ministry of Health, Labour and Welfare, 2022), a trend consistent with global data (Survey Research Group of Japan Physicians Association, 2001b). The higher risk in males is attributed to lifestyle factors such as

smoking and alcohol consumption (Okuyama and Terauchi, 2013), as well as biological mechanisms; testosterone increases insulin resistance, while estrogen enhances insulin sensitivity (Okuyama and Terauchi, 2013). Conversely, females are more susceptible to gender-specific complications such as gestational diabetes and the worsening of menopausal symptoms (Kasahara et al., 2018). Since exercise increases insulin sensitivity through skeletal muscle activation (Sugita et al., 2018), males with greater muscle mass may have an advantage in glycemic control. These differences highlight the need for gender-specific risk management strategies.

With the rapid growth of the aging population, it is crucial to understand gender-related characteristics in diabetic complications to improve quality of life (QOL) and promote healthy life expectancy among affected individuals. In this study, we conducted a literature review focusing on gender differences in diabetic neuropathy in Japan to identify clinical characteristics and potential considerations for the development of rehabilitation intervention strategies tailored to the specific clinical presentation of each gender.

### 2. Participants and methods

#### 2.1 Literature selection criteria

We conducted a literature review focusing on diabetic peripheral neuropathy (DPN) in Japan with attention to gender-based differences. Eligible studies met the following inclusion

criteria: (1) the study population included individuals diagnosed with diabetic neuropathy, (2) the study addressed gender or gender differences in any aspect of DPN, (3) the article was an original research paper (not a review or commentary), and (4) the full-text was accessible for review.

Initial screening was based on titles and abstracts to determine eligibility. In cases where eligibility could not be clearly judged, the articles were included for full-text review. In the secondary screening phase, full-texts were examined to extract details about participants, study design, evaluation methods, and reported gender differences.

## 2.2 Search Strategy

To comprehensively collect data on gender differences in diabetic neuropathy, we searched two major Japanese academic databases: Ichushi Web (Japan Medical Abstracts Society, n.d.) and CiNii Articles (National Institute of Informatics, n.d.). The search was conducted up to September 2024, using the following search string (translated for clarity):

(Diabetic neuropathy [MeSH or AL]) AND (Sex factors [MeSH or AL] OR Gender difference [AL]) AND (Article type: Original article)

The search terms and strategy were developed through discussion among three occupational therapy researchers with 20, 21, and 23 years of clinical experience, respectively, to ensure methodological validity. Each researcher independently assessed article eligibility, and final inclusion was determined through consensus discussion.

The search was performed on September 19, 2024, yielding 43 articles from Ichushi Web, which included 5 duplicates found in CiNii Articles. After removing duplicates, 43 unique articles remained.

In the first screening, 34 articles were selected. In the second screening, full-texts of these 34 articles were reviewed, resulting in the final inclusion of 19 studies that met all eligibility criteria (see Figure 1).

Detailed information on the included studies is provided in Table 1, including participant characteristics, study design, and evaluation measures.

## 3. Results

Among the 19 selected articles, most studies were cross-sectional studies ( $n = 17$ ), with only 2 cohort studies (see Table 1).

### 3.1 Outcome measures

The outcome measures used in the reviewed study were the following objective measures (see Table 1): (1) Basic demographic data (e.g., gender, age, height, weight, smoking/alcohol habits, diabetes duration, history, BMI) ( $n = 19$ ), (2) Biochemical parameters (e.g., serum and urinary creatinine) ( $n = 9$ ), (3) DPN-specific indicators (e.g., Achilles tendon reflex, pain/numbness, vibration sense) ( $n = 14$ ), and (4) Physical function (e.g., grip strength, skeletal muscle mass, the Short Physical Performance Battery) ( $n = 4$ ). Subjective evaluations were assessed using the Self-Efficacy Scale for Diabetes Self-Care (SESD), the Exercise Self-Efficacy Scale for Diabetes Self-Care (ESESD), the Foot Care Confidence Scale Japanese Version (J-FCCS), and the Summary of Diabetes Self-Care Activities Measure Japanese Version (J-SDSCA) ( $n = 2$ ). All studies collected basic patient information and medical history. Following this, quantitatively examined gender differences in nerve damage using nerve conduction velocity of motor and sensory nerves were 8 studies.

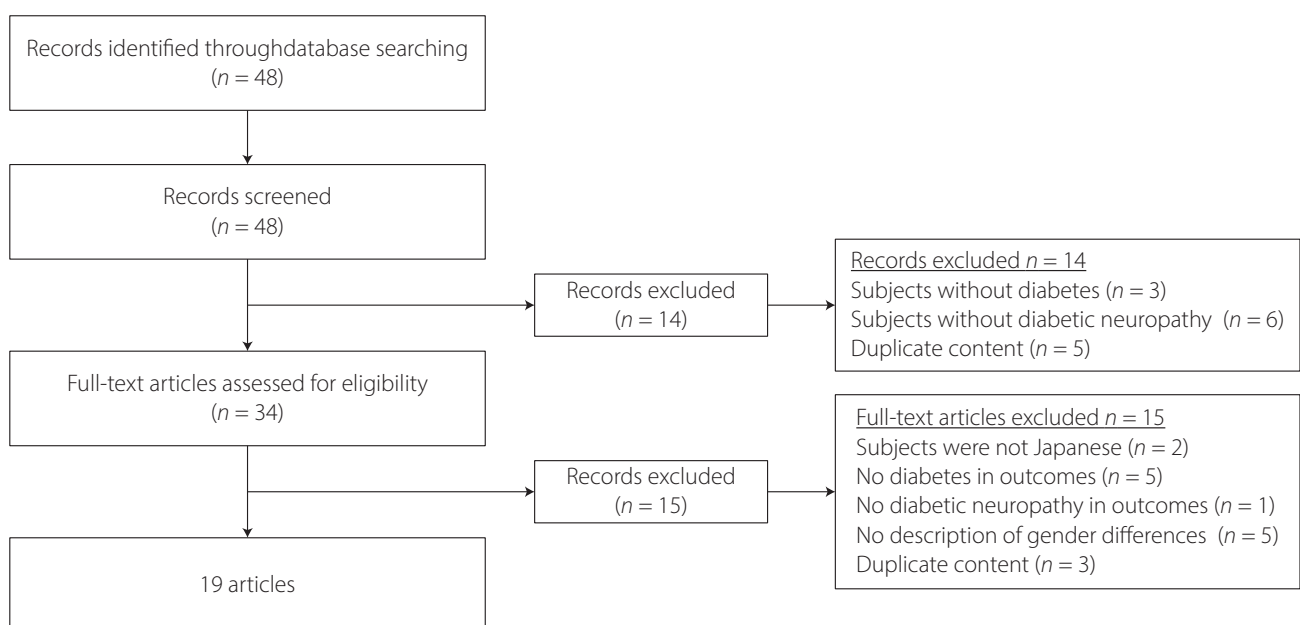


Figure 1: Identified studies from literature search and screening process

### 3.2 Gender differences

Several gender differences were observed across various clinical parameters (see Table 2). In males, higher values were reported for smoking and alcohol consumption histories, longer duration of diabetes (particularly in those under 60 years) (Kashima et al., 2023; Tajima et al., 2015; Survey Research Group of Japan Physicians Association, 2001a), and greater prevalence of myocardial infarction and diabetic neuropathy (Oshima, 2010; Tajima et al., 2015; Survey Research Group of Japan Physicians Association, 2001a). Although the association between diabetic neuropathy and lifestyle factors such as smoking and alcohol consumption was inconsistent across studies, the prevalence of diabetic complications, including nephropathy and retinopathy, showed no significant gender difference (Survey Research Group of Japan Physicians Association, 2001a). Biochemical parameter findings indicated that HbA1c and triglyceride levels were higher in males (Kataoka et al., 2013; Tajima et al., 2015). Furthermore, several studies reported higher prevalence of diabetic neuropathy, reduced nerve conduction velocity, ulnar nerve impairment, diminished sensory perception, and increased incidence of lower limb amputation in neuropathy-related assessments (Hasegawa et al., 2019a; 2019b; Kataoka et al., 2013; Oshima, 2010; Survey Research Group of Japan Physicians Association, 2001a). Physical function was also more impaired, with a higher prevalence of sarcopenia, reduced ankle range of motion, and decreased knee extensor strength observed in male patients (Kashima et al., 2023; Matsui et al., 2019; Seno et al., 2011; Survey Research Group of Japan Physicians Association, 2001a).

In contrast, female patients exhibited higher body mass index (BMI), with this trend being particularly prominent in older age groups (Hasegawa et al., 2016; Hasegawa et al., 2017a; Kawase et al., 2010; Tajima et al., 2015). Biochemical data indicated that the prevalence of hyperlipidemia and hypertension was higher in females; however, age-specific data were not consistently available (Kataoka et al., 2013; Oshima, 2010; Tajima et al., 2015; Survey Research Group of Japan Physicians Association, 2001a). Regarding neuropathy, females more frequently reported sensory disturbances such as pain and numbness and showed elevated perception thresholds in the upper limbs (Seno et al., 2011; Yokoyama et al., 2020). Additionally, decreased nerve conduction velocity and signs of median nerve impairment were also observed (Hasegawa et al., 2002; Hasegawa et al., 2008; Hasegawa et al., 2016; Hasegawa et al., 2017a, 2017b; Hasegawa et al., 2019a; 2019b). In terms of physical function, a decline in maximum walking speed was more commonly noted among female patients (Kashima et al., 2023).

The relationship between subjective evaluation and gender differences is as follows. Among male patients with diabetes, those with higher levels of self-efficacy tended to

engage more frequently in foot care behaviors (Maeda et al., 2019). In female patients, higher scores on the Evaluation Scale for Empowerment in Self-care among Diabetics (ESED) were associated with better performance on the Short Physical Performance Battery (SPPB) (Imasato et al., 2024; Maeda et al., 2019). Additionally, females with a longer history of diabetes education or those who had received guidance on diet and self-care were more likely to practice actual self-care behaviors (Imasato et al., 2024).

### 4. Discussion

This review revealed notable gender-based differences across several domains related to diabetic peripheral neuropathy (DPN) in Japan. According to the 2023 report by the Japanese Ministry of Health, Labour and Welfare, the rates of alcohol consumption were higher in males (14.1 %) than in females (9.5 %), although the rate among females has significantly increased over the past decade. Conversely, smoking rates have declined for both genders, currently standing at 25.6 % in males and 6.9 % in females (Ministry of Health, Labour and Welfare, 2023). These lifestyle behaviors clearly exhibit gender differences, but their trends vary across age groups. Accordingly, the impact of smoking and alcohol use on the development of DPN appears complex (Survey Research Group of Japan Physicians Association, 2001b) and not solely attributable to biological gender. Furthermore, while these behaviors are known risk factors for diabetes onset, the reviewed studies did not show consistent evidence linking them to increased DPN risk by gender.

Nerve conduction studies showed reduced velocities in both genders with diabetes. Ulnar nerve involvement was more common in males, while median nerve dysfunction predominated in females. These patterns may reflect anatomical differences—such as a larger humerus in males and narrower carpal tunnels in females—rather than diabetes-specific pathophysiology, suggesting the observed gender differences may not be directly attributable to DPN.

BMI tended to decline with age in males, despite higher baseline muscle mass. This may be due in part to longer diabetes duration among male patients who are often diagnosed at a younger age. Chronic hyperglycemia is known to contribute to weight loss and muscle atrophy; a trend observed in previous research on type 1 diabetes (Kalyani et al., 2014; Kishi et al., 2023). Notably, the association between DPN and sarcopenia was significant in males but not in females. These findings suggest that males may be more susceptible to DPN-related muscle deterioration, even though females are generally perceived as more vulnerable to frailty.

Importantly, gender differences are not static and may shift across life-stages. Therefore, age-specific and gender-sensitive rehabilitation intervention strategies should be considered when addressing diabetes-related complications.

Table 1: List of selected articles including participant characteristics, study design, and evaluation measures

ID	Author	Research design	Number of subjects	Outcome measures				Subjective evaluations
				Basic demographic data	Biochemical parameters	DPN-specific indicators	Physical function	
1	Ayaka Imasato et al. (2024)	cross-sectional study	33 DM (21 M, 12 F >40 y)	Gender, age, height, weight, BMI, DM education history, family role, family history, nutritional guidance history, DR	HbA1c, eGFR	DPN-t, Subjective symptoms (+/-)	Grip strength, SMM, Sarcopenia (+/-), SPPB	SES, ES-ESD
2	Kensaku Kashima et al. (2023)	cross-sectional study	119 T2DM patients (68 M, 51 F)	Gender, age, height, weight, BMI, Comorbidities, DM duration, smoking history, alcohol consumption, DPN diagnosis (+/-), insulin history, exercise habits	FPG, HbA1c, TC, TG, LDL-C, HDL-C, AST, ALT, UN, Cre, eGFR	N/A	Grip strength, Knee extension strength, Balance, 10m gait speed, COFST, Sarcopenia (+/-), SMM	N/A
3	Hiroki Yokoyama et al. (2020)	cross-sectional study	2,745 with DPN (1,705 M, 1,040 F)	Gender, age, BMI, smoking status, alcohol consumption, DM duration, medical history, DPN diagnosis (+/-)	S-Cr, U-Cr, HbA1c, LDL-C, HDL-C, TG, SBP, eGFR	Bilateral spontaneous pain, Hypoesthesia (pin/temperature), Leg perception	N/A	N/A
4	Nobumasa Matsui et al. (2019)	cross-sectional study	M-DM (50-69 y): 28, M-DM (30-49 y): 14, F-DM (50-69 y): 10, M-HC (50-69 y): 10	Gender, age, weight, BMI, DM duration, DPN diagnosis (+/-)	HbA1c	Monofilament, MCV	ROM (ankle joint/ metatarsophalangeal joint/subtalar joint)	N/A
5	Osamu Hasegawa et al. (2019)	cohort study	3,240 DM (1,931 M, 1,309 F)	Gender, age, height, weight, BMI, DM duration	N/A	DPN-t, PNI-R, MCV, CMAI, SNI	N/A	N/A
6	Osamu Hasegawa et al. (2019)	cross-sectional study	3,229 DM (1,916 M, 1,313 F)	Gender, age, DM duration	N/A	CMAI, SNI, PNI-R	N/A	N/A
7	Kayoko Maeda et al. (2019)	cross-sectional study	100 T2DM patients (69 M, 41 F)	Gender, age, BMI, DM duration, DM complications, foot care instruction, smoking status	HbA1c	Subjective symptoms (+/-)	N/A	J-SDSCA, J-FCCS
8	Osamu Hasegawa et al. (2017)	cross-sectional study	2,490 DM (1,468 M, 1,022 F)	Gender, age, BMI, DM duration	N/A	CMAI, SNI, PNI-R	N/A	N/A
9	Osamu Hasegawa et al. (2017)	cross-sectional study	2,718 DM (1,609 M, 1,109 F)	Gender, age, DM duration	N/A	CMAI, SNI, PNI-R	N/A	N/A
10	Osamu Hasegawa et al. (2016)	cross-sectional study	2,438 DM (1,27 M and 99 F <40 y, 1315 M and 897 F >40 y)	Gender, age, height, weight, BMI, DM duration	HbA1c	CMAI, SNI, PNI-R	N/A	N/A

11	Naoko Tajima et al. (2015)	cohort study	5,944T2DM patients (3,575M, 2,369F)	Gender, age, height, weight, BMI, DM duration, comorbidities, family history of DM, regular alcohol, smoker	HbA1c, FPG, PPPG, LDL-C, HDL-C, non-HDL-C, TG, Cre, eGFR, Alb	N/A	N/A	N/A
12	Hiroaki Kataoka et al. (2013)	cross-sectional study	111DM (58M, 53F)	Gender, age, height, weight, BMI, DM duration, exercise habits(aerobic/resistance)	HbA1c, TC, TG, LDL-C, HDL-C	Subjective symptoms(+/-), DPN-t	Muscle mass (Upper/lower limb)	N/A
13	Shinichiro Seno et al. (2011)	cross-sectional study	1,658HC (1,024M, 634F), 829DM (477M, 352F)	Gender, age, DM (+/-)	N/A	Sensory thresholds (forearm/tarsal/Achilles tendon)	N/A	N/A
14	Kanako Kawase et al. (2010)	cross-sectional study	109T2DM (50M, 59F)	Gender, age, BMI, DM duration, DM treatment, DPN diagnosis (+/-)	HbA1c, FBG, CPR	MCV, SCV	N/A	N/A
15	Seiichi Oshima (2010)	cross-sectional study	4,165DM (2,394M, 1,771F)	Gender, age, DM duration, drug treatment, comorbidities, lifestyle modification, exercise, medication, DPN diagnosis (+/-)	FPG, HbA1c	N/A	N/A	N/A
16	Osamu Hasegawa et al. (2008)	cross-sectional study	737DM (443M, 294F)	Gender, age, height, weight, BMI, DM duration	N/A	CMAI, SNI, PNI-R	N/A	N/A
17	Yoshio Goto et al. (2001)	cross-sectional study	12,821DM (6,714M, 6,107F)	Gender, age, BMI, smoking history, alcohol consumption, DM duration, DM treatment duration, drug treatment, comorbidities	FPG, HbA1c	N/A	N/A	N/A
18	Kiyoshi Takekuma et al. (2002)	cross-sectional study	924HC (472M, 452F), 1001IR (286M, 515F), 149DM (92M, 57F)	Gender, age, BMI, BP, alcohol consumption	FPG, HbA1c, FPI, TC, TG, HDL-C	CPT test	N/A	N/A
19	Osamu Hasegawa et al. (2002)	cross-sectional study	46HC (19M, 27F), 63DM (37M, 26F)	Gender, age, BMI, DM duration	N/A	CMAI, SNI	N/A	N/A

Notes: "Number of subjects" = DM, diabetes mellitus; M: Male; F: Female; Y: years of age; T2DM, type 2 DM; DPN, diabetic peripheral neuropathy; HC, Healthy Control; IR, Insulin Resistance. "Basic demographic data" = BMI, body mass index; DR, Diabetic retinopathy. "Biochemical parameters" = FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; UN, urea nitrogen; Cre, Creatinine; SBP, Systolic blood pressure. "DPN-specific indicators" = DPN-t, Achilles reflex, Vibration test, Monofilament; MCV, motor nerve conduction velocity; PNI-R, polyneuropathy index-revised; CMAI, CMAP index; CMAP, compound motor action potential (median nerve/ ulnar nerve/ fibular nerve/ tibial nerve/ fibular nerve); SNI, SNAP index; SNAP, sensory nerve action potential (median nerve/ ulnar nerve/ fibular nerve/ tibial nerve); CPT, Current Perceptual thresholds. "Physical function" = SMM, Skeletal Muscle Mass; SPB, Short Physical Performance Battery (balance, gait, Stand Up Test); COFST, Closed-eye One-leg Standing Test; ROM, range of motion. "Subjective evaluations" = SED, Self-Efficacy Scale for DM Self-Care; ESED, The Exercise Self-Efficacy Scale for DM Self-Care; J-SDSCA, The Summary of Diabetes Self-Care Activities Measure; J-FCCS, Foot Care Confidence Scale. Comorbidities category: hyperlipidemia/hypertension/myocardial infarction/cerebrovascular disease/dyslipidemia/stroke/myocardial infarction retinopathy/nephropathy/lower limb neuropathy/coronary artery disease/carotid intima/arteriosclerosis obliterans/skin diseases/ leg amputation. Bold and Underlined: parameters of statistically significant differences.

Table 2: Outcome measures with gender differences identified

	Items significant in “males”	Items significant in “females”
Basic demographic data	<ul style="list-style-type: none"> <li>• Smoking history [2, 17]</li> <li>• Alcohol consumption history [2, 11, 17]</li> <li>• History of diabetes [10, 11]</li> <li>• BMI (young adults) [10]</li> <li>• History of cerebrovascular disease [11]</li> <li>• Myocardial infarction [11, 15, 17]</li> </ul>	<ul style="list-style-type: none"> <li>• Diabetes education history [1]</li> <li>• BMI [8, 10, 11, 14]</li> <li>• History of diabetes (older age group) [10]</li> <li>• Family history of diabetes [11]</li> <li>• Aerobic exercise [12]</li> </ul>
Biochemical parameters	<ul style="list-style-type: none"> <li>• HbA1c (younger age group) [10]</li> <li>• TG (triglycerides) [11, 12]</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperlipidemia [11, 12, 15, 17]</li> <li>• Hypertension [11, 15, 17]</li> <li>• HbA1c (older age group) [10]</li> </ul>
DPN-specific indicators	<ul style="list-style-type: none"> <li>• Prevalence [5, 15]</li> <li>• Factors affecting lower limb muscle mass [12]</li> <li>• Leg amputation [17]</li> <li>• Perception threshold [13]</li> <li>• Hypersensitivity related to insulin resistance [17]</li> <li>• Decreased nerve conduction velocity /Ulnar neuropathy [5, 6, 8, 9, 10, 16, 19]</li> </ul>	<ul style="list-style-type: none"> <li>• Painful DPN [3]</li> <li>• Raised threshold of perception in upper extremity [13]</li> <li>• Decreased nerve conduction velocity /Median neuropathy [5, 6, 8, 9, 10, 16, 19]</li> </ul>
Physical function	<ul style="list-style-type: none"> <li>• Sarcopenia [2]</li> <li>• Decreased grip strength and knee extension muscle strength [2]</li> <li>• Decreased ankle joint range of motion [4]</li> </ul>	<ul style="list-style-type: none"> <li>• Decrease in maximum walking speed [2]</li> </ul>
Self-efficacy	<ul style="list-style-type: none"> <li>• Positive correlation between self-efficacy and foot care behavior [7]</li> </ul>	<ul style="list-style-type: none"> <li>• Positive correlation between SPPB and diabetes self-care exercise self-efficacy scale [1]</li> <li>• Positive correlation between diet and foot care instruction and self-care behaviors [7]</li> </ul>

Notes: [ ] indicates corresponding literature number (ID) in Table 1. BMI, body mass index; DPN, diabetic peripheral neuropathy.

While male patients may experience greater physiological deterioration, female patients demonstrated higher health awareness. Females were more likely to have a history of diabetes education and were more engaged in dietary management and foot care. Although data were limited, this suggests that greater receptiveness to education in females may contribute to improved self-care behaviors. However, females over the age of 40 are at an increased risk of dyslipidemia, likely due to hormonal changes associated with menopause. Estrogen is thought to have a neuroprotective and metabolic regulatory role, and its decline may elevate the risk of neurodegeneration and metabolic syndrome (Hirai, 2024; Okuyama and Terauchi, 2013). Thus, a comprehensive evaluation of hormonal transitions and lifestyle factors in postmenopausal females is essential, and targeted preventive strategies for this group may be especially important in Japanese clinical practice.

Additionally, gender differences in symptom perception should be given attention. Females may be more sensitive to neuropathic symptoms such as numbness or pain due to lower sensory thresholds, while males may underreport symptoms due to differences in help-seeking behavior or social norms. These differences may contribute to underdiagnosis or mischaracterization of DPN and should be considered in clinical assessments.

However, one limitation of this study is the predominance

of cross-sectional research designs. In long-term cases of diabetes, not only do symptoms change over time, but aging-related hormonal fluctuations also occur, which are difficult to capture using cross-sectional approaches. Furthermore, changes in social conditions—such as population aging and the increasing participation of female empowerment—may not be adequately reflected. To develop future rehabilitation programs that consider gender differences, it is essential to conduct longitudinal studies that track changes in diabetic neuropathy symptoms over time.

Although the majority of included studies were cross-sectional research designs, the identification of gender-specific trends highlights the need for tailored interventions in future clinical trials. Rehabilitation programs that address muscle preservation in males and enhance self-care and lifestyle management in females—particularly around menopause—should be developed and rigorously evaluated to improve long-term outcomes in individuals with diabetes.

## 5. Conclusion

This review suggests that male patients with diabetic neuropathy may face a greater risk of muscle atrophy and functional decline. While female patients tend to be more health-conscious and responsive to self-care interventions, hormonal changes after menopause may predispose them to additional complications such as dyslipidemia. These find-



ings highlight the importance of considering gender-specific characteristics in clinical interventions and preventive strategies for diabetic neuropathy in aging populations.

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