Submitted: 01 November, 2023 Accepted: 01 December, 2023 Published: 30 January, 2024 DOI:10.22514/jomh.2024.002

SYSTEMATIC REVIEW

JOMH Journal of Men's Health

Gender difference as the risk of diabetic foot ulcers in T2DM patients: a meta-analysis

Xiaogang Hu[1,†], Runfang Kang[2,†], Ling Chen[1,*], Xiaopeng Hu[3]

[1]Department of Geriatric, Lishui Second People's Hospital, 323000 Lishui, Zhejiang, China
[2]Department of Integrated Traditional Chinese and Western Medicine Surgery, Lishui Second People's Hospital, 323000 Lishui, Zhejiang, China
[3]Department of Pharmacy, Huangshi Fifth People's Hospital, 435000 Huangshi, Hubei, China

***Correspondence**
chenling3110101@126.com
(Ling Chen)

† These authors contributed equally.

Abstract

To investigate the gender difference as a risk factor of diabetic foot ulcer (DFU) in diabetes mellitus type 2 (T2DM) patients. The online databases including China National Knowledge Infrastructure (CNKI), Wanfang, China Biomedical Literature, PubMed, Embase, Web of Science, and Cochrane Library were searched. The retrospective and prospective studies published on the gender difference as risk factor of DFU were accessed from the databases and analyzed by the STATA software. Two prospective and 7 retrospective studies involving 4399 DFU patients were included. The results exhibited that being male (odd ratio (OR) = 1.74, 95% Confidence interval, confidence interval (CI): 1.55–1.96, $p = 0.0001$) was a statistically significant risk factor of DFU in T2DM patients. Other risk factors were the age of >60 years (OR = 3.12, 95% CI: 2.16–4.49, $p = 0.0001$), smoking (OR = 4.32, 95% CI: 3.13–5.68, $p = 0.0001$), hypertension (OR = 2.18, 95% CI: 1.39–3.87, $p = 0.0001$), cerebrovascular event (OR = 2.16, 95% CI: 1.88–3.98, $p = 0.0001$), coronary artery disease (OR = 1.16, 95% CI: 1.05–1.96, $p = 0.0001$), chronic renal failure (OR = 2.21, 95% CI: 1.54–2.79, $p = 0.001$), and Glycosylated hemoglobin (HbA1c) ≥7 (OR = 3.56, 95% CI: 2.27–4.43, $p = 0.001$). Furthermore, insulin treatment was the protective factor of DFU in male (OR = 0.66, 95% CI: 0.38–0.93, $p = 0.001$) and female (OR = 0.44, 95% CI: 0.27–0.83, $p = 0.003$) T2DM patients. Male, age >60 years, smoking, hypertension, coronary artery disease, chronic renal failure, and HbA1c ≥7 were the risk factors of DFU in T2DM patients. The publicity and awareness regarding these risk factors should be strengthened in the future clinical practice. Regular screening of high-risk groups be carried out for early detection and treatment.

Keywords

Gender difference; Risk factor; Diabetic foot ulcers; Meta-analysis

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease [1]. The incidence and disease burden of DM have been on the rise globally in recent years [2]. As per the statistics of International Diabetes Alliance in 2019, the number of adult diabetes patients has exceeded 463 million worldwide which account for ~6% of world's population [3]. Risk factors of T2DM include high blood sugar, high blood pressure, abnormal lipid profile, overweight and obesity, and familial inheritance [2, 3]. Diabetic foot (DF) is a disease of blood vessels and nerves in the foot of diabetic patients which lead to insufficient blood supply, paresthesia, ulceration and infection symptoms. Muscles and bones may get affected in severe cases to cause tissue necrosis and amputation. DF is thus the most serious complication of diabetes, and about 1/3 of diabetes patients possess infection risk [4]. Diabetes foot ulcer (DFU) may occur as the disease progresses [5]. Some patients need amputation because of the deterioration in their condition which can lead to death. DFU recurrence rate is high that can reach to above 50% in three years and affect the patient's life quality [6]. The prevention and treatment of diabetic skin injury and DFU is thus important.

DFU occurrence and development are affected by the factors such as peripheral neuropathy, peripheral artery disease, and local tissue infection [7]. However, the effect of gender difference on DFU has not been studied. Therefore, a meta-analysis was conducted to assess the gender difference as risk factor to DFU.

2. Methods

2.1 Databases search strategies

The online databases including CNKI, Wanfang Database, China Biomedical Literature Database, PubMed, Embase, Web of Science, and Cochrane Library were searched. The retrospective as well as the prospective studies published on gender difference as the risk factor of DFU were accessed from the databases. The search period ranged from the database inception date to 30 December 2022. The retrieval mode was constructed by combining the subject word and free word.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) Observational studies including case-control and cohort studies; (2) The subjects were diabetes and DFU patients; (3) Risk factor analysis involving DFU; and (4) Outcome indicators defined as the risk factors that might lead to DFU.

Exclusion criteria: (1) Replicate studies or the studies on same population; (2) Studies having incomplete and uncomplimentary data; (3) Low quality research with quality assessment score <7; and (4) Graduation thesis, review and conference proceedings.

2.3 Literature screening and data extraction

The literature screening and data extraction were independently conducted by the two researchers followed by cross-checking of results. They consulted a third researcher in case of disagreement. The literature screening process involved the reading of title and excluding the irrelevant literature; then reading the abstract and full text to judge the data integrity; and finally deciding for its inclusion. Data extraction included the name of first author, publication year, study location, study type, total sample size, sample size of groups, gender and DFU risk factors.

2.4 Quality assessment of included studies

The case-control and cohort studies included herein were evaluated by the Newcastle-Ottawa Scale (NOS) as per the standard of evidence-based medicine [8].

2.5 Statistical analysis

The extracted data were processed and analyzed by STATA SE 12.0 software (Beijing Huanzhong Ruichi Technology Co., LTD, Beijing, China). The secondary classification variables were expressed *via* odds ratio (OR) and 95% confidence interval (CI), and the continuous variables as mean difference (MD) and 95% CI. $p < 0.05$ and the 95% CI containing 0 indicated the statistically significant differences. p value (inspection level $\alpha = 0.1$) and I^2 judged the heterogeneity among included studies. The heterogeneity had no significance at $p > 0.1$ and $I^2 \leq 50\%$, and the fixed effect model was selected for data analysis. The heterogeneity was significant at $p < 0.1$ and $I^2 > 50\%$, where the random effect model was employed to analyze the data.

3. Results

3.1 Baseline characteristics of included studies

A total of 10,464 literature studies were obtained according to the search strategy. Nine studies [9–17] were finally included after following the established screening process. There were 2 prospective and 7 retrospective studies with sample size of 4399. The basic characteristics and quality evaluation results of 9 included studies are given in Table 1.

3.2 Gender difference in DFU risk

All included studies reported the association between gender and DFU risk. Meta-analysis in fixed-effect model ($I^2 = 7.1\%$, $p = 0.376$) revealed that male was a statistically significant independent risk factor of DFU (OR = 1.74, 95% CI: 1.55–1.96, $p = 0.0001$).

3.3 Risk factors of DFU in males and females

Nine included studies reported the risk factors of DFU in males and females (Fig. 1). Results exhibited that age >60 years (OR = 2.11, 95% CI: 1.48–3.34, $p = 0.0001$), smoking (OR = 3.12, 95% CI: 2.57–4.25, $p = 0.0001$), hypertension (OR = 1.89, 95% CI: 1.16–3.12, $p = 0.0001$), coronary artery disease (OR = 1.43, 95% CI: 1.13–2.18, $p = 0.0001$), chronic renal failure (OR = 1.47, 95% CI: 1.16–2.18, $p = 0.0001$), and HbA1c ≥7 (OR = 2.87, 95% CI: 1.38–3.49, $p = 0.001$) were the risk factors of DFU in T2DM patients. Furthermore, the insulin treatment (OR = 0.45, 95% CI: 0.22–0.87, $p = 0.0001$) was the protective factor of DFU in T2DM patients (Fig. 2).

3.4 Risk factors of DFU in male T2DM patients

Six included studies reported the association between DFU and the risk factors in male T2DM patients. Results depicted that the age >60 year (OR = 3.12, 95% CI: 2.16–4.49, $p = 0.0001$), smoking (OR = 4.32, 95% CI: 3.13–5.68, $p = 0.0001$), hypertension (OR = 2.18, 95% CI: 1.39–3.87, $p = 0.0001$), cerebrovascular event (OR = 2.16, 95% CI: 1.88–3.98, $p = 0.0001$), coronary artery disease (OR = 1.16, 95% CI: 1.05–1.96, $p = 0.0001$), chronic renal failure (OR = 2.21, 95% CI: 1.54–2.79, $p = 0.001$), and HbA1c ≥7 (OR = 3.56, 95% CI: 2.27–4.43, $p = 0.001$) were the risk factors of DFU in male T2DM patients (Fig. 3). The insulin treatment (OR = 0.66, 95% CI: 0.38–0.93, $p = 0.001$) was the protective factor of DFU in male T2DM patients (Fig. 3).

3.5 Risk factors of DFU in female T2DM patients

Seven included studies reported the relationship between DFU and the risk factors in female T2DM patients (Fig. 4). The meta-analysis results exhibited that the age >60 years (OR = 2.11, 95% CI: 1.36–3.58, $p = 0.001$), cerebrovascular event (OR = 1.84, 95% CI: 1.32–3.27, $p = 0.002$), chronic renal failure (OR = 2.21, 95% CI: 1.54–2.79, $p = 0.001$), and HbA1c ≥7 (OR = 3.12, 95% CI: 2.68–4.14, $p = 0.0001$) were the risk factors of DFU in female T2DM patients (Fig. 4). The insulin treatment (OR = 0.44, 95% CI: 0.27–0.83, $p = 0.003$) was the protective factor of DFU in female T2DM patients (Fig. 4).

4. Discussion

The chronic and refractory skin injuries such as diabetes foot ulcers (DFU) have become a health problem affecting the diabetes patients life quality [18]. Prevention and treatment of DFU is a multidisciplinary process [19]. Understanding the DFU risk factors and taking in-time prevention and treatment measures can improve the patients prognosis [20]. Rismayanti

TABLE 1. Characteristics of the 9 included studies.

Study ID	Study type	Country	Age (yr, Mean ± SD)	Sample size	Male/Femal	DM duration	Follow-up	NOS Score
Lin 2010	Retrospective	China	68.42 ± 12.18	90	47/43	15 yr	NR	8
Akinci 2011	Prospective	Turkey	60.20 ± 8.87	165	109/56	15 yr	6.0 yr	7
Aziz 2011	Prospective	Singapore	59.80 ± 10.25	100	51/49	>5 yr	2.0 yr	8
Saltoglu 2015	Retrospective	Turkey	61.30 ± 9.73	455	310/145	15 yr	6.0 mon	7
Ferreira 2018	Retrospective	Portugal	68.26 ± 11.47	479	294/185	10 yr	1.0 yr	8
Peled 2019	Retrospective	Israel	63.22 ± 8.46	418	311/107	NR	NR	8
Aziz 2020	Retrospective	Austria	68.87 ± 11.49	858	442/416	NR	2.0 yr	7
Gandhi 2021	Retrospective	USA	56.50 ± 9.18	981	527/457	10 yr	1.0 yr	8
Jiang 2022	Retrospective	China	60.35 ± 12.38	853	369/484	10 yr	1.0 yr	8

DM: Diabetes mellitus; NOS: Newcastle-Ottawa Scale; SD: Standard deviation; NR: Not reported.

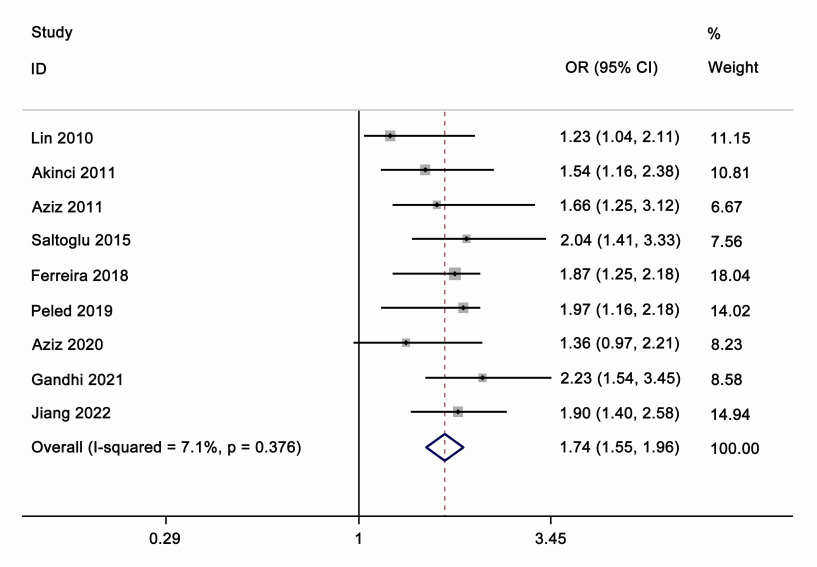

FIGURE 1. Meta-analysis of gender difference in the DFU risk. OR: odds ratio; CI: confidence interval.

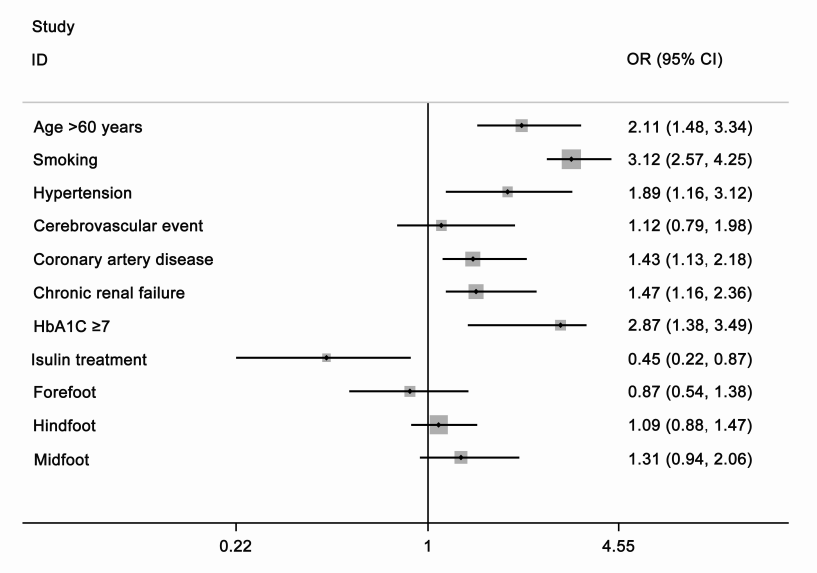

FIGURE 2. Meta-analysis of DFU risk factors in males and females. OR: odds ratio; CI: confidence interval; HbA1c: Glycosylated hemoglobin.

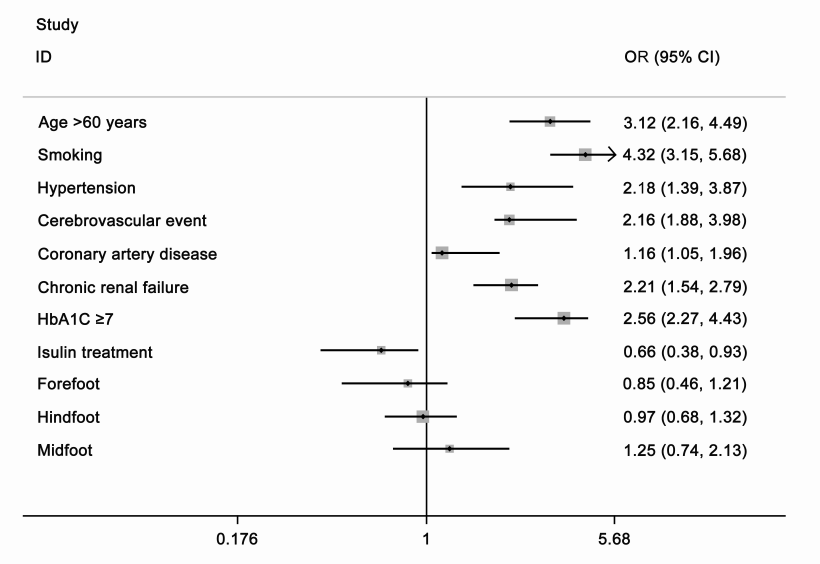

FIGURE 3. Meta-analysis of DFU risk factors in male T2DM patients. OR: odds ratio; CI: confidence interval; HbA1c: Glycosylated hemoglobin.

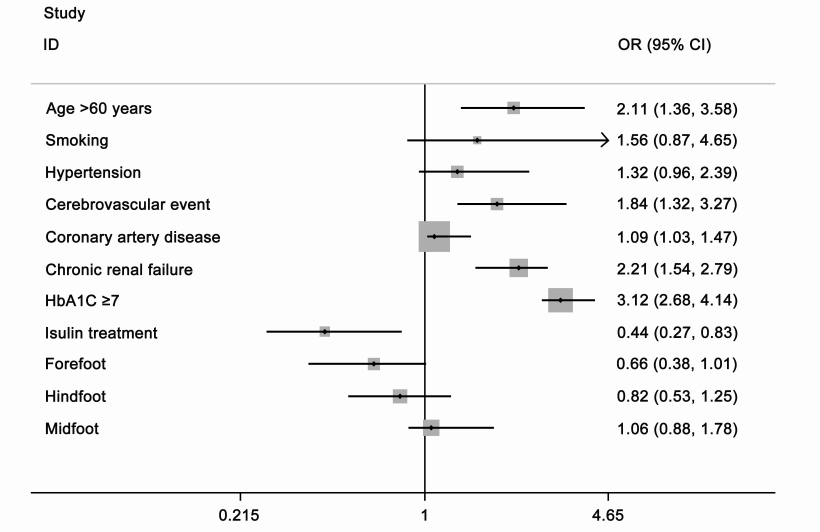

FIGURE 4. Meta-analysis of DFU risk factors in female T2DM patients. OR: odds ratio; CI: confidence interval; HbA1c: Glycosylated hemoglobin.

et al. [21] show that 5% to 8% DFU patients need amputation which seriously affects their health and life quality. It is imperative to take timely measures for preventing and controlling DFU in diabetes treatments [22]. Therefore, in-depth research on DFU risk factors, and active intervention can prevent and/or delay the DFU occurrence. Several studies have involved empirical evaluations which lack high-quality evidence [23].

The meta-analysis results reveal that being male is an independent risk factor of DFU in T2DM patients. The gender difference may also be a risk factor of DFU. So, more attentive protection and treatment of DFU are required in gender specific T2DM patients. Other risk factors including age >60 years, smoking, hypertension, cerebrovascular event, coronary artery disease, chronic renal failure, and HbA1c ≥7 are linked to DFU in male T2DM patients. The insulin treatment is the protective factor of DFU in male and female T2DM patients.

The diabetic males are more prone to develop DFU than diabetic females. The male patients are at high risk of DFU as well as of amputation, *i.e.*, 1.39 to 1.77 times higher than in female patients [24]. It is found herein that the most male diabetic patients have DFU compared to the females. Estrogen in the women can protect blood vessels [5]. Men compared to women do more physical work because of their social roles. Men feet are thus more vulnerable to trauma [25]. Male patients have high proportion of smoking where tobacco damages the blood vessels and increases the vascular diseases around diabetes [26]. The average weight of men is higher than that of women, and thus the higher foot pressure which may increase the DFU risk in diabetic patients [27, 28].

The male, age >60 years, smoking, hypertension, coronary artery disease, chronic renal failure, and HbA1c ≥7 are the risk factors of DFU in T2DM patients, and the insulin treatment

is a protective factor for DFU. The recognized risk factors include genetic factors, obesity, insufficient physical activity, diet, pregnancy, reproductive history, early life nutritional status, socioeconomic status, smoking, alcohol consumption, and hypertension which require further comparisons and studies.

This study has some limitations. Firstly, the studies included in this meta-analysis are mainly retrospective with limited sample size. Only 2 articles have the prospective studies. Secondly, the demonstration of risk factors is not comprehensive because of quality of original research which may affect the level of evidence and extrapolation of results. Therefore, high-quality random controlled trails are required for more accurate conclusions.

5. Conclusions

Male, age >60 years, smoking, hypertension, coronary artery disease, chronic renal failure, and HbA1c $\geq$7 are the risk factors of DFU in T2DM patients, and the insulin treatment is a protective factor for DFU. This demonstrates that the publicity and awareness pertaining to these risk factors must be strengthened in future clinical practice. Moreover, regular screening of high-risk groups is necessary for early detection and timely treatment.

AVAILABILITY OF DATA AND MATERIALS

Authors declare that all the data supporting the findings of this study are available within the paper and any raw data can be obtained from corresponding author upon request.

AUTHOR CONTRIBUTIONS

XGH—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. LC, RFK and XPH—supervised the data collection; analyzed the data, interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Yang Y, Luan Y, Feng Q, Chen X, Qin B, Ren K, *et al*. Epigenetics and beyond: targeting histone methylation to treat type 2 diabetes mellitus. Frontiers in Pharmacology. 2022; 12: 807413.

[2] Shojima N, Yamauchi T. Progress in genetics of type 2 diabetes and diabetic complications. Journal of Diabetes Investigation. 2023; 14: 503–515.

[3] Khunti K, Mathieu C, Torbeyns B, Del Prato S, Heine R, Colhoun H, *et al*. Diabetes registries and high-quality diabetes care. The Lancet Diabetes & Endocrinology. 2023; 11: 70–72.

[4] Dao L, Choi S, Freeby M. Type 2 diabetes mellitus and cognitive function: understanding the connections. Current Opinion in Endocrinology, Diabetes & Obesity. 2023; 30: 7–13.

[5] Bekele F, Chelkeba L. Amputation rate of diabetic foot ulcer and associated factors in diabetes mellitus patients admitted to Nekemte referral hospital, western Ethiopia: prospective observational study. Journal of Foot and Ankle Research. 2020; 13: 65.

[6] Wang C, Mai L, Yang C, Liu D, Sun K, Song W, *et al*. Reducing major lower extremity amputations after the introduction of a multidisciplinary team in patient with diabetes foot ulcer. BMC Endocrine Disorders. 2016; 16: 38.

[7] Eneroth M, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. Journal of Diabetes and its Complications. 1999; 13: 254–263.

[8] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology. 2010; 25: 603–605.

[9] Lin C, Hsu L, Chen C, Yeh J, Sun J, Lin C, *et al*. C-reactive protein as an outcome predictor for percutaneous transluminal angioplasty in diabetic patients with peripheral arterial disease and infected foot ulcers. Diabetes Research and Clinical Practice. 2010; 90: 167–172.

[10] Akinci B, Yener S, Yesil S, Yapar N, Kucukyavas Y, Bayraktar F. Acute phase reactants predict the risk of amputation in diabetic foot infection. Journal of the American Podiatric Medical Association. 2011; 101: 1–6.

[11] Aziz Z, Lin WK, Nather A, Huak CY. Predictive factors for lower extremity amputations in diabetic foot infections. Diabetic Foot & Ankle. 2011; 2: 7463.

[12] Saltoglu N, Yemisen M, Ergonul O, Kadanali A, Karagoz G, Batirel A, *et al*. Predictors for limb loss among patient with diabetic foot infections: an observational retrospective multicentric study in Turkey. Clinical Microbiology and Infection. 2015; 21: 659–664.

[13] Ferreira L, Carvalho A, Carvalho R. Short-term predictors of amputation in patients with diabetic foot ulcers. Diabetes & Metabolic Syndrome. 2018; 12: 875–879.

[14] Peled S, Pollack R, Elishoov O, Haze A, Cahn A. Association of inpatient glucose measurements with amputations in patients hospitalized with acute diabetic foot. The Journal of Clinical Endocrinology & Metabolism. 2019; 104: 5445–5452.

[15] Aziz F, Reichardt B, Sourij C, Dimai H, Reichart D, Köhler G, *et al*. Epidemiology of major lower extremity amputations in individuals with diabetes in Austria, 2014–2017: a retrospective analysis of health insurance database. Diabetes Research and Clinical Practice. 2020; 170: 108477.

[16] Gandhi SK, Waschbusch M, Michael M, Zhang M, Li X, Juhaeri J, *et al*. Age- and sex-specific incidence of non-traumatic lower limb amputation in patients with type 2 diabetes mellitus in a U.S. claims database. Diabetes Research and Clinical Practice. 2020; 169: 108452.

[17] Jiang M, Gan F, Gan M, Deng H, Chen X, Yuan X, *et al*. Predicting the risk of diabetic foot ulcers from diabetics with dysmetabolism: a retrospective clinical trial. Frontiers in Endocrinology. 2022; 13: 929864.

[18] Borderie G, Foussard N, Larroumet A, Blanco L, Barbet-Massin M, Ducos C, *et al*. Diabetic retinopathy relates to the incidence of foot ulcers and amputations in type 2 diabetes. Diabetes/Metabolism Research and Reviews. 2023; 39: e3605.

[19] Sharma R, Sharma SK, Mudgal SK, Jelly P, Thakur K. Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of controlled clinical trials. Scientific Reports. 2021; 11: 2189.

[20] Ramachandran V, Mohanasundaram T, Karunakaran D, Gunasekaran M, Tiwari R. Physiological and pathophysiological aspects of diabetic foot

ulcer and its treatment strategies. Current Diabetes Reviews. 2023; 19: e031122210617.

[21] Rismayanti IDA, Nursalam, Farida VN, Dewi NWS, Utami R, Aris A, *et al*. Early detection to prevent foot ulceration among type 2 diabetes mellitus patient: a multi-intervention review. Journal of Public Health Research. 2022; 11: 2752.

[22] Li Y, Ju S, Li X, Li W, Zhou S, Wang G, *et al*. Characterization of the microenvironment of diabetic foot ulcers and potential drug identification based on scRNA-seq. Frontiers in Endocrinology. 2022; 13: 997880.

[23] Raghav A, Tripathi P, Mishra BK, Jeong GB, Banday S, Gautam KA, *et al*. Mesenchymal stromal cell-derived tailored exosomes treat bacteria-associated diabetes foot ulcers: a customized approach from bench to bed. Frontiers in Microbiology. 2021; 12: 712588.

[24] Jifar WW, Atnafie SA, Angalaparameswari S. A review: matrix metallopeptidase-9 nanoparticles targeted for the treatment of diabetic foot ulcers. Journal of Multidisciplinary Healthcare. 2021; 14: 3321–3329.

[25] Rathnayake A, Saboo A, Malabu UH, Falhammar H. Lower extremity amputations and long-term outcomes in diabetic foot ulcers: a systematic review. World Journal of Diabetes. 2020; 11: 391–399.

[26] Crawford F, Chappell FM, Lewsey J, Riley R, Hawkins N, Nicolson D, *et al*. Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model. Health Technology Assessment. 2020; 24: 1–198.

[27] Haycocks S, Cameron R, Edge M, Budd J, Chadwick P. Implementation of a novel mHealth application for the management of people with diabetes and recently healed foot ulceration: a feasibility study. Digital Health. 2022; 8: 20552076221142103.

[28] Rovers FJ, Van Netten JJ, Busch-Westbroek TE, Aan de Stegge WB, Bus SA. Adherence to at-home monitoring of foot temperatures in people with diabetes at high risk of ulceration. To be published in The International Journal of Lower Extremity Wounds. 2022. [Preprint].

How to cite this article: Xiaogang Hu, Runfang Kang, Ling Chen, Xiaopeng Hu. Gender difference as the risk of diabetic foot ulcers in T2DM patients: a meta-analysis. Journal of Men's Health. 2024; 20(1): 1-6. doi: 10.22514/jomh.2024.002.