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Beyond the wound: why diabetic foot is the "tip of the iceberg" of systemic disease

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Professor **Han Junfeng**, with a medical doctorate, holds the position of chief physician and serves as a doctoral supervisor. He earned his PhD in endocrinology and metabolism from Ruijin Hospital affiliated to Shanghai Jiao Tong University in 2006. In 2010, he was selected for the Excellent Young Talent Development Program at Shanghai Sixth People's Hospital, and in 2017, he was included in the Shanghai Talent Development Program. In 2019, he was awarded the "Research Physician" project under the Double Hundred Talent Program of Shanghai Jiao Tong University School of Medicine. His research has been funded by the National Natural Science Foundation of China in 2012, 2016, and 2021. As the first or corresponding author, he has published over 40 papers (including 30 SCI papers) in domestic and international journals. In 2012, he visited the University of Toronto in Canada as a senior visiting scholar, where he studied under Professor Michael Wheeler, an internationally renowned scholar in the field of pancreatic islet function. Clinical characteristics: (1) Clinical diagnosis and treatment of obesity and related metabolic diseases, as well as research on their pathogenesis; (2) Application of artificial intelligence in the management of diabetic foot.

Abstract: Diabetic foot ulcer (DFU) has traditionally been regarded as a localized wound problem, but emerging evidence indicates that it is essentially a focal manifestation of systemic metabolic-inflammatory-immune decompensation. Building upon the "cardio-renal-metabolic-foot" connection, this review further integrates the muscle-nutrition dimension and the psychological-cognitive dimension to systematically elaborate the multisystem hazards of DFU. Patients with DFU have a more than twofold increased risk of cardiovascular death; 40%-60% of them have comorbid chronic kidney disease, and declining renal function significantly elevates the risk of amputation. Sarcopenia and malnutrition constitute a double barrier to wound healing, forming a vicious cycle. The incidence of depression in patients with DFU is as high as 47%, and cognitive dysfunction is prevalent, yet these conditions have long been clinically overlooked. These dimensions mutually reinforce each other through mechanisms such as systemic inflammation, oxidative stress, endothelial dysfunction, and reduced behavioral adherence. Clinical management should shift from isolated wound care to multidisciplinary collaboration, with routine integration of sarcopenia assessment, nutritional screening, and psychological - cognitive support. Incorporating the muscle, nutritional, psychological, and cognitive dimensions into the systemic framework of DFU helps to more comprehensively understand the disease burden and optimize individualized treatment strategies.

Keywords: Diabetic foot ulcer; Cardiovascular disease; Chronic kidney disease; Metabolic abnormalities; Sarcopenia; Malnutrition; Psychology disorder; Cognitive dysfunction

Diabetic foot ulcer (DFU) represents the most severe and costliest complication of diabetes mellitus, affecting approximately 6.3% of the global adult diabetic population [1]. The 5-year mortality rate among patients with DFU has been reported to be as high as 50% [2]. Historically, research pertaining to DFU has long been concentrated on localized aspects, including wound healing, infection control, and limb salvage procedures. Nevertheless, accumulating clinical evidence and mechanistic investigations in recent years have progressively elucidated that DFU is not an isolated "foot disease" but rather a typical manifestation of systemic metabolic-inflammatory-immune decompensation localized to the lower extremity. The detrimental impact of DFU on patient health extends far beyond foot ulceration and amputation—the cardiovascular system, renal system, musculoskeletal system, and even psychological and cognitive functions are all subject to varying degrees of impairment.

In 2024, Lan *et al.* [3] proposed a four-dimensional framework encompassing the "cardio-renal-metabolic-foot" axis, systematically delineating the associations between DFU and cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic abnormalities. Compared with diabetic patients without DFU, those with DFU exhibit a more than 2-fold increased risk of cardiovascular mortality [4]; even among patients with neuropathic DFU in the absence of overt peripheral arterial disease, coronary atherosclerotic heart disease remains the most prevalent cause of death [5]. Furthermore, 40%–60% of patients with DFU are complicated by CKD [6]. DFU may share bidirectional pathophysiological linkages with cardiac and renal diseases, and DFU-related systemic

inflammation, infection, endothelial dysfunction, and oxidative stress may promote atherosclerosis, thrombosis, and myocardial dysfunction, thereby driving the initiation and progression of CVD [7-8]. However, the existing "cardio-renal-metabolic-foot" framework primarily concentrates on the cardiorenal system, with insufficient integration of the musculoskeletal system (sarcopenia, malnutrition), the nervous system (cognitive dysfunction), and the psychosocial dimension.

This review, building upon the "cardio-renal-metabolic-foot" framework, further incorporates the muscle-nutrition system and the psychological-cognitive system, and systematically elaborates on the epidemiological evidence, pathophysiological mechanisms, and corresponding clinical management strategies pertaining to each dimension.

1 Cardio-Renal-Metabolic-Foot Dimension: From Localized Ulceration to Systemic Vascular Injury

1.1 Cardiovascular Outcomes—DFU as an Independent Risk Factor for Cardiovascular Mortality

A robust and strongly positive association exists between DFU and cardiovascular mortality. Multiple systematic reviews, meta-analyses, and large-scale cohort studies have consistently demonstrated that patients with DFU are at an increased risk of cardiovascular death compared with diabetic patients without DFU, with a pooled risk ratio of approximately 2.5 [9-10]; concurrently, among the mortality profile of the DFU population, CVD has long ranked as the predominant cause, accounting for approximately 50% of all deaths, and exceeding 60% among those who died within the recent one-year period [11]. Moreover, DFU serves as an independent predictor of cardiovascular mortality, and its elevated risk is not only reflected in conventional risk factors but may also be accompanied by subclinical cardiac impairment [12].

The pathophysiological linkages between DFU and cardiovascular mortality are multilevel in nature. Firstly, the persistent systemic inflammatory response elicited by localized DFU and secondary infections promotes plaque instability through endothelial dysfunction, oxidative stress, and a prothrombotic state, directly driving the development and progression of myocardial infarction, stroke, and heart failure [13]. Secondly, the substantial burden of systemic atherosclerosis commonly observed in the DFU population (particularly when complicated by peripheral arterial disease) renders the coronary arteries and lower-extremity arteries simultaneous target organs of systemic atherosclerosis, thereby significantly increasing the risk of cardiovascular events and mortality [14-15]. Finally, diabetes-related microvascular pathology and autonomic neuropathy not only contribute to the development and delayed healing of foot ulcers but also obscure typical anginal symptoms, leading to delayed recognition of silent coronary ischemia and myocardial infarction, ultimately increasing the probability of sudden death and cardiovascular mortality [16]. In view of the strong association between DFU and cardiovascular mortality, along with its high proportional contribution to overall mortality, DFU should be regarded as a "warning signal" indicative of underlying or pre-existing CVD, necessitating active screening and management of CVD and its associated risk factors.

1.2 Renal Outcomes—Patients with End-Stage Kidney Disease Face the Risk of Amputation

The prevalence of chronic kidney disease (CKD) among the DFU population is as high as 40%, and a bidirectional deteriorating relationship exists between the two conditions. For patients with kidney disease, those with end-stage kidney disease (ESKD) receiving hemodialysis carry the highest risk of developing DFU, with a lower-extremity amputation risk approximately 10 times that of the general diabetic population. Compared with individuals having an estimated glomerular filtration rate (eGFR) ≥60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, patients with CKD stage 4 exhibit a 4-fold higher incidence of DFU and a more than 7-fold elevated risk of amputation; even a mild reduction in renal function (eGFR 30–<60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) is associated with an increased risk of new-onset DFU and amputation [17]. Furthermore, CKD aggravates the refractory nature of DFU, being correlated with decreased healing rates, increased ulcer recurrence, and elevated mortality risk [18]; conversely, DFU-related recurrent infections, systemic inflammation, hospitalizations, and perioperative exposures (contrast agents, antibiotics, fluid fluctuations, etc.) may precipitate acute kidney injury and drive the progression of CKD [19].

Mineral and calcium-phosphorus metabolic disturbances induced by CKD can lead to vascular calcification and a specific form of cutaneous calcification—calciphylaxis—giving rise to extremely challenging non-healing wounds [20]. Additionally, retention of CKD-related metabolites may exacerbate peripheral nerve injury; fluid retention, alterations in the renin-angiotensin system, oxidative stress, and a prothrombotic state may worsen peripheral vascular disease and ischemic ulceration; protein loss and metabolic derangements may result in hypoalbuminemia, impairing wound healing and promoting edema and circulatory disturbance; immune dysregulation may increase the risk of wound infection and prolong the inflammatory response, thereby facilitating chronic ulcer formation and attenuating tissue repair capacity [21-22].

Patients with DFU complicated by CKD present with multiple systemic and local comorbidities. The identification and treatment of pre-existing comorbidities such as anemia, hypoalbuminemia, immune dysfunction, and vascular calcification are of paramount importance for optimizing therapeutic outcomes in the management of the diabetic foot in the context of kidney disease.

2 The Muscle-Nutrition Dimension: A Neglected Determining Factor

2.1 Sarcopenia—From Local Foot Disease to Systemic Muscle Wasting

Sarcopenia is a geriatric syndrome characterized by age-related reductions in muscle mass, decreased muscle strength, and/or impaired physical performance. Sui et al. [23] proposed that sarcopenia and DFU share a bidirectional and mutually reinforcing relationship. Sarcopenia significantly increases the all-cause mortality risk in patients with DFU and is associated with impaired ankle-foot function, delayed ulcer healing, and an elevated risk of amputation. Sarcopenia serves as an independent risk factor for all-cause mortality in DFU patients; those with sarcopenia exhibit lower cumulative survival rates at 1, 3, and 5 years compared with those without sarcopenia [24]. Within the DFU population, sarcopenia is correlated with decreased ankle-foot function scores [25], as well as with higher ulcer incidence, higher Wagner grades, and increased amputation rates [26]. DFU is significantly associated with sarcopenia-related phenotypes (grip strength, difficulties in walking/standing up/climbing stairs, falls, lean body mass, etc.), and may accelerate the onset of sarcopenia beyond that induced by diabetes alone [27].

DFU-related vascular and neuropathic pathologies, ulcer infection, and chronic inflammation may promote muscle atrophy and strength decline through pathways involving hypoxia, microcirculatory disturbance, loss of neurotrophic support, and inflammation/oxidative stress; the pain, immobilization, and restricted mobility caused by DFU inevitably contribute to disuse muscle atrophy [23,28]. On the other hand, sarcopenia increases susceptibility to foot ulceration and infection by affecting gait stability and pressure distribution; it may also delay wound healing and exacerbate DFU progression by reducing tissue perfusion and metabolic capacity. Shared factors such as systemic inflammation, insulin resistance, and nutritional deficiencies (e.g., inadequate protein intake) further intensify both conditions, forming a vicious "DFU-sarcopenia" cycle [29-30].

Consequently, routine assessment tools for sarcopenia should be integrated into the clinical evaluation process for DFU patients. Proactive management, early detection, risk stratification, and timely intervention for sarcopenia are warranted. For DFU patients, resistance training, protein supplementation, and targeted therapeutic strategies may be employed to improve muscle function, reduce plantar pressure, and promote ulcer healing.

2.2 Malnutrition and Micronutrient Deficiencies — The Material Basis Predicament for Healing

Malnutrition and multiple micronutrient deficiencies, including zinc, magnesium, selenium, vitamin D, vitamin C, and vitamin A, are highly prevalent among DFU patients [31-33]. Deficiencies in protein and micronutrients can impair immune cell chemotaxis, phagocytic bactericidal activity, and antibody responses, thereby rendering infections more likely to occur and persist; they may also directly interfere with collagen cross-linking stability, fibroblast proliferation, and keratinocyte regeneration, causing wounds to remain arrested in the inflammatory phase and prolonging healing time [34]. The Controlling Nutritional Status (CONUT) score is a tool for assessing individual nutritional status. DFU patients exhibit higher CONUT scores compared with healthy controls and diabetic patients without foot ulcers, and the CONUT score is an independent factor associated with DFU severity [35]. Albumin is a marker reflecting systemic nutritional status, serving to maintain endothelial function, improve microcirculation, and attenuate inflammatory and oxidative damage; hypoalbuminemia is an independent risk factor for delayed healing of foot ulcers in diabetic patients [36]. Some studies have indicated that supplementation with zinc, magnesium, vitamin D, and vitamin A may improve ulcer dimensions such as length and width [37-38]. However, prospective studies have shown no association between micronutrient deficiencies and wound healing, suggesting that clinical attention should be directed toward identifying "whether a deficiency exists" rather than implementing indiscriminate supplementation [33].

Therefore, it is recommended that nutritional status be incorporated into the routine assessment of DFU, with nutritional risk screening and micronutrient testing performed particularly when healing is stalled. On the basis of standard therapy, targeted correction of identified deficiencies should be undertaken, establishing an individualized pathway of "screening—correction of deficiencies—nutritional support."

3 The Psychological-Cognitive Dimension: Wounds Beyond the Wound

3.1 Psychological Distress — The Evidence Gap Amid High Prevalence

The impact of psychological factors on DFU has long been marginalized in clinical practice; however, accumulating evidence in recent years has progressively underscored its importance. The prevalence of depression among patients with DFU is approximately 47%, and depression is associated with higher glycated hemoglobin (HbA1c) levels, a greater burden of comorbidities, and increased mortality; in a cohort study of patients with a first episode of DFU, a baseline diagnosis of depression was associated with a doubled risk of death at 5 years [39]. Nevertheless, whether depression directly affects DFU healing remains a subject of conflicting findings. A systematic review encompassing 11 studies revealed that approximately half of the studies suggested an association between depression and poor healing, whereas the other half did not detect a significant relationship, with overall evidence quality being limited [40]. Therefore, the relationship between psychological factors and wound healing may be more complex than previously assumed and should not be reduced to a linear causal model. The heterogeneity among existing studies in terms of definitions, measurement instruments, and follow-up

durations has substantially interfered with the consistency of results. Furthermore, patients with DFU commonly report anxiety, depression, and feelings of helplessness, the roots of which include deteriorating health, the long-term burden of disease management, fear of amputation, physical functional limitations, loss of independence, and a perceived sense of family burden [41].

The pathways through which psychological factors influence DFU outcomes include chronic stress activating the hypothalamic-pituitary-adrenal axis, leading to elevated cortisol levels, which in turn suppress the normal regulation of the inflammatory response and delay the healing process; simultaneously, depression and anxiety significantly reduce patient adherence to glycemic monitoring, foot care practices, offloading device usage, and medication regimens [42].

It is recommended that routine screening for depression and anxiety be incorporated into the assessment of DFU, with referral or integrated psychological support provided for high-risk individuals, and that high-quality, multicenter randomized controlled trials be conducted to validate these approaches.

3.2 Cognitive Dysfunction — A Seriously Overlooked Research Gap

Research on cognitive dysfunction in the field of DFU remains limited. Available evidence indicates that patients with active DFU require approximately twice the time to complete cognitive function assessments compared with diabetic patients without DFU, suggesting impairments in visuospatial/executive function and working memory; after adjustment for age, sex, diabetes duration, and educational level, prolonged completion time on cognitive assessment remained significantly associated with the risk of DFU occurrence [43]. Among DFU patients with comorbid cognitive dysfunction, 6-month healing rates are lower, healing time is prolonged, the proportion of major amputations is higher, and the rate of foot-related hospitalizations is elevated [44].

Based on the currently limited body of research, patients with DFU generally exhibit multi-domain cognitive impairment (particularly in executive function, memory, and reaction speed); cognitive dysfunction can significantly compromise complex foot care and self-management abilities, forming a vicious cycle of "insufficient cognitive resources—reduced adherence—worsening ulceration."

Therefore, performing routine brief cognitive screening at initial diagnosis and during follow-up of DFU to identify high-risk individuals, and implementing "de-escalated" educational and supportive measures (such as pictorial educational materials, family supervision, or remote reminders) for those with cognitive impairment, constitute important steps toward improving clinical outcomes in this population. This area may also represent the frontier with the greatest research value and interventional potential within the systemic framework of DFU.

4 Clinical Integration and Future Perspectives

In summary, DFU is not an isolated foot problem but rather a comprehensive manifestation of systemic decompensation. The siloed management approach confined to a single specialty is clearly insufficient. Multidisciplinary team (MDT) care for DFU spans multiple disciplines, including endocrinology, orthopedics, vascular surgery, podiatry, infectious diseases, nursing, and rehabilitation medicine, and its value is increasingly supported by robust evidence. A review published in *JAMA* summarizing 18 studies demonstrated that MDT care could reduce the risk of major amputation to approximately 40% of that observed with conventional care [45]. The 2025 edition of the *Practical guideline on the prevention and management of diabetic foot in China* also explicitly emphasizes that comprehensive assessment of vital organs including the heart, kidneys, and brain, along with MDT, constitutes the cornerstone of DFU diagnosis and management [46].

Future research should prioritize the following directions: (1) clinical integration and validation of sarcopenia assessment tools in DFU patients; (2) high-quality randomized controlled trials examining the effects of psychosocial interventions on DFU healing outcomes; (3) prospective cohort studies and systematic reviews investigating the association between DFU and cognitive dysfunction; and (4) multicenter real-world studies incorporating the muscle, nutritional, and psychological dimensions into multi-organ prognostic models for DFU.

In conclusion, the management of diabetic foot necessitates a paradigm shift—from "treating the wound" to "managing the whole patient." The incorporation of the muscle-nutrition and psychological-cognitive dimensions renders the "heart-kidney-metabolism-foot" framework more comprehensive. If clinical practice remains confined to wound care alone, the underlying multi-system pathological states may be overlooked, which would be tantamount to perceiving only the tip of the iceberg above the water surface.

Conflict of Interest None

References

[1] Pavithra T R, Kaliyaperumal R. Epidemiology, pathophysiology, and management of diabetic foot: a comprehensive review[J]. Foot (Edinb), 2026, 66: 102225.

[2] McDermott K, Fang M, Boulton A J M, et al. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers[J]. Diabetes Care, 2023, 46(1): 209-221.

[3] Lan N S R, Dwivedi G, Fegan P G, et al. Unravelling the cardio-renal-metabolic-foot connection in people with diabetes-related foot ulceration: a narrative review[J]. Cardiovasc Diabetol, 2024, 23(1): 437.

[4] Vlacho B, Bundó M, Llussà J, et al. Diabetic foot disease carries an intrinsic high risk of mortality and other severe outcomes in type 2 diabetes: a propensity score-matched retrospective population-based study[J]. Cardiovasc Diabetol, 2024, 23(1): 209.

[5] Rastogi A, Goyal G, Kesavan R, et al. Long term outcomes after incident diabetic foot ulcer: Multicenter large cohort prospective study (EDI-FOCUS investigators) epidemiology of diabetic foot complications study: Epidemiology of diabetic foot complications study[J]. Diabetes Res Clin Pract, 2020, 162: 108113.

[6] Vitale M, Orsi E, Solini A, et al. Association between age at diagnosis and all-cause mortality in type 2 diabetes: the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study[J]. Acta Diabetol, 2024, 61(9): 1107-1116.
[7] Wolf D, Ley K. Immunity and inflammation in atherosclerosis[J]. Herz, 2019, 44(2): 107-120.
[8] Bonnet J B, Sultan A. Narrative review of the relationship between CKD and diabetic foot ulcer[J]. Kidney Int Rep, 2022, 7(3): 381-388.
[9] Chin B Z, Lee P, Sia C H, et al. Diabetic foot ulcer is associated with cardiovascular-related mortality and morbidity–a systematic review and meta-analysis of 8062 patients[J]. Endocrine, 2024, 84(3): 852-863.
[10] Chen Lihong, Sun Shiyi, Gao Yunyi, et al. Global mortality of diabetic foot ulcer: a systematic review and meta-analysis of observational studies[J]. Diabetes Obes Metab, 2023, 25(1): 36-45.
[11] Chinese Diabetes Society, Chinese Society of Infectious Diseases, Chinese Society for Tissue Repair and Regeneration. Chinese guideline on prevention and management of diabetic foot (2019 edition) (IV)[J]. Chin J Diabetes Mellitus, 2019, 11(5): 316-327. **[In Chinese]**
[12] Farhan M, Patel T, Ahmed Shahbaz Ahmed S B, et al. Diabetic foot ulcer as an independent risk factor for cardiovascular mortality: a systematic review and meta-analysis with qualitative synthesis of cardiac biomarker evidence[J]. Cureus, 2026, 18(4): e106672.
[13] Lan N S R, Hiew J, Ferreira I, et al. Increased risk of major adverse cardiovascular events in patients with deep and infected diabetes-related foot ulcers[J]. Diabetologia, 2025, 68(2): 460-470.
[14] Gallagher K A, Mills J L, Armstrong D G, et al. Current status and principles for the treatment and prevention of diabetic foot ulcers in the cardiovascular patient population: a scientific statement from the American heart association[J]. Circulation, 2024, 149(4): e232-e253.
[15] Lan N S R, Hiew J, Chen P, et al. Medial arterial calcification of the foot arteries is associated with incident cardiovascular events or all-cause mortality in patients with diabetes-related foot ulceration[J]. Diabetes Res Clin Pract, 2026, 232: 113108.
[16] Monahan C T, Yammine H, Burnash S G, et al. High prevalence of silent, severe coronary ischemia in patients with diabetic foot ulcers[J]. J Vasc Surg, 2026, 83(1): 204-212.
[17] Tan T W, Caldwell B, Zhang Yi, et al. Foot and ankle care by podiatrists and amputations in patients with diabetes and kidney failure[J]. JAMA Netw Open, 2024, 7(3): e240801.
[18] Bonnet J B, Szwarc I, Avignon A, et al. Renal function is highly associated with podiatric risk in diabetic patients[J]. Clin Kidney J, 2023, 16(11): 2156-2163.
[19] Alkhami F, Rubin S, Borderie G, et al. Increased risk of renal events in people with diabetic foot disease: a longitudinal observational study[J]. Diabetes Metab, 2024, 50(4): 101536.
[20] Sandepudi K, Shah K V, Melnick B A, et al. Pathophysiology of wound development and chronicity in renal disease: a narrative review[J]. Int Wound J, 2025, 22(7): e70713.
[21] Liang Jiaru, An Hang, Hu Xuyang, et al. Correlation between chronic kidney disease and all-cause mortality in diabetic foot ulcers: evidence from the 1999-2004 national health and nutrition examination survey (NHANES)[J]. Front Endocrinol, 2025, 16: 1533087.
[22] Rastogi A, Gupta R, Ghosh J, et al. Renal foot in diabetes: implications for wound healing and solutions[J]. Adv Wound Care, 2026, 15(5): 325-347.
[23] Sui Yunpeng, Ma Ya, Zhou Kai, et al. A narrative review on the correlation between diabetic foot and sarcopenia[J]. Front Endocrinol, 2026, 17: 1711060.
[24] Yang Qin, Ni Xia, Zhang Yingxiao, et al. Sarcopenia is an independent risk factor for all-cause mortality rate in patients with diabetic foot ulcers[J]. Front Nutr, 2023, 10: 1097008.
[25] An Shujing, Kuang Weina, Hu Yonglu, et al. Association between sarcopenia and the foot-ankle function in type 2 diabetic foot ulcer[J]. Diabetol Metab Syndr, 2024, 16(1): 270.
[26] Cheng Qingfeng, Hu Jinbo, Yang Ping, et al. Sarcopenia is independently associated with diabetic foot disease[J]. Sci Rep, 2017, 7(1): 8372.
[27] Yin Heyang, Ma Yangping, Liu Xinyi, et al. Diabetes-related foot disease and sarcopenia-related traits: evidence from US and Chinese cohorts and Mendelian randomization[J]. Aging Clin Exp Res, 2026, 38(1): 92.
[28] Ahmad M, Mohamed A, Amiras D, et al. Sarcopenia in the foot on magnetic resonance imaging in patients with diabetes mellitus - a systematic review[J]. Clin Diabetes Endocrinol, 2024, 10(1): 31.
[29] Adhi Shree R, Nambi N, Radhakrishnan L, et al. Neutrophil migration is a crucial factor in wound healing and the pathogenesis of diabetic foot ulcers: insights into pharmacological interventions[J]. Curr Vasc Pharmacol, 2025, 23(2):98-112.
[30] Greenman R L, Panasyuk S, Wang Xiaoen, et al. Early changes in the skin microcirculation and muscle metabolism of the diabetic foot[J]. Lancet, 2005, 366(9498): 1711-1717.
[31] Apergi K, Dimosthenopoulos C, Papanas N. The role of nutrients and diet characteristics in the management of diabetic foot ulcers: a systematic review[J]. Int J Low Extrem Wounds, 2025, 24(3): 525-541.
[32] Kurian S J, Baral T, Unnikrishnan M K, et al. The association between micronutrient levels and diabetic foot ulcer: a systematic review with meta-analysis[J]. Front Endocrinol, 2023, 14: 1152854.
[33] Bechara N, Tehan P, Gunton J E. Prospective evaluation of vitamin C, vitamin D, and zinc deficiencies in patients with active foot ulceration[J]. Adv Wound Care, 2026, 15(2): 107-115.
[34] Wang Jie, Zhang Yan, Wang Qiong, et al. Establishment and evaluation of a novel tool based on inflammation-nutrition derived biomarkers for early diagnosis of diabetic foot ulcers[J]. Front Immunol, 2026, 17: 1794011.
[35] Nakamura H, Makiguchi T, Yamada Y, et al. Evaluation of CONUT score and serum zinc levels in patients with diabetic foot ulcers[J]. Int J Low Extrem Wounds, 2025: 15347346251326247.
[36] Lee S H, Kim S H, Kim K B, et al. Factors influencing wound healing in diabetic foot patients[J]. Medicina (Kaunas), 2024, 60(5): 723.
[37] Erdem H A, Yalçın N, Kaya A, et al. Vitabiotic: an alternative approach to diabetic foot[J]. Wound Repair Regen, 2024, 32(6): 890-894.
[38] Razzaghi R, Pidar F, Momen-Heravi M, et al. Magnesium supplementation and the effects on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial[J]. Biol Trace Elem Res, 2018, 181(2): 207-215.
[39] Pouwer F, Perrin B, Lavender A, et al. The quest for wellness: How to optimise self-care strategies for diabetic foot management?[J]. Diabetes Metab Res Rev, 2024, 40(3): e3751.
[40] Al-Smadi A M, Finlayson K, Andrew B, et al. The impact of depression on healing outcomes in people with diabetes-related foot ulcers: a systematic review[J]. Diabetes Res Clin Pract, 2025, 225: 112275.
[41] Hanlon M, McGuire B E, MacGilchrist C, et al. Beyond the wound: a scoping review of the psychosocial impact of diabetes-related foot ulcers[J]. Diabet Med, 2026, 43(4): e70243.
[42] Alasfour L, Alboloushi A, Kirwan E, et al. Mapping the evidence to determine the influence of stress, anxiety, and depression on wound healing in patients with diabetes-related foot ulcers: a scoping review[J]. J Tissue Viability, 2025, 34(3): 100935.
[43] Bechara N, Hawke F, Gunton J E, et al. Cognition and quality of life in patients with a diabetes-related foot ulcer[J]. J Tissue Viability, 2025, 34(3): 100913.
[44] Girgis C, Behme S, Holmes C, et al. Cognitive impairment is associated with poor diabetic foot ulcer outcomes[J]. Prim Care Diabetes, 2025, 19(5): 527-532.
[45] Armstrong D G, Tan T W, Boulton A J M, et al. Diabetic foot ulcers: a review[J]. JAMA, 2023, 330(1): 62-75.
[46] Chinese Burn Association, Yangtze River Delta Integrated Diabetic Foot Alliance, Editorial Committee of *Chinese Journal of Burns and Wounds*. Practical guideline on the prevention and management of diabetic foot in China (I)[J]. Chin J Burns, 2025, 41(11):1029-1049. **[In Chinese]**

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· 学术前沿 ·

超越创面：糖尿病足为何是全身性疾病的“冰山一角”

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韩峻峰教授，医学博士，主任医师，博士研究生导师。2006 年于上海交通大学附属瑞金医院内分泌代谢专业获得博士学位，2010 年入选上海市第六人民医院优秀青年人才培养计划，2017 年入选上海市人才发展计划。2019 年获得上海交通大学医学院双百人计划“研究型医师”项目。2012、2016、2021 年获得国家自然科学基金项目资助。目前作为第一作者或通信作者已在国内外期刊发表论文 40 余篇（SCI 论文 30 篇）。2012 年以高级访问学者赴加拿大多伦多大学进修，师从胰岛功能领域国际知名学者 Michael Wheeler 教授。临床特色：（1）肥胖及相关代谢性疾病的临床诊治及发病机制研究；（2）人工智能在糖尿病足管理中的应用。

摘要：糖尿病足溃疡（DFU）传统上被视为局部创面问题，但最新证据表明其本质是全身性代谢-炎症-免疫失代偿在局部的集中表现。本综述在“心-肾-代谢-足”四维框架基础上，进一步整合肌肉-营养维度与心理-认知维度，系统阐述糖尿病足溃疡的多系统危害。DFU 患者心血管死亡风险增加逾 2 倍；40%~60%的患者合并慢性肾脏病，且肾功能下降者截肢风险更高。肌少症与营养不良构成了愈合障碍的双重困境，形成恶性循环。DFU 患者抑郁症发生率高达 47%，且认知功能障碍普遍存在，却长期被临床忽视。各维度间通过全身性炎症、氧化应激、内皮功能障碍及行为依从性下降等机制相互强化。临床管理需从单一创面处理转向多学科协作，常规整合肌少症评估、营养筛查及心理认知支持。将肌肉、营养、心理与认知维度纳入 DFU 的全身性框架，有助于更全面地认识其疾病危害并优化个体化治疗策略。

关键词：糖尿病足溃疡；心血管疾病；慢性肾脏病；代谢异常；肌少症；营养不良；心理疾病；认知功能障碍
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Beyond the wound: why diabetic foot is the “tip of the iceberg” of systemic disease

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Abstract: Diabetic foot ulcer (DFU) has traditionally been regarded as a localized wound problem, but emerging evidence indicates that it is essentially a focal manifestation of systemic metabolic-inflammatory-immune decompensation. Building upon the “cardio-renal-metabolic-foot” connection, this review further integrates the muscle-nutrition dimension and the psychological-cognitive dimension to systematically elaborate the multisystem hazards of DFU. Patients with DFU have a more than twofold increased risk of cardiovascular death; 40%-60% of them have comorbid chronic kidney disease, and declining renal function significantly elevates the risk of amputation. Sarcopenia and malnutrition constitute a double barrier to wound healing, forming a vicious cycle. The incidence of depression in patients with DFU is as high as 47%, and cognitive dysfunction is prevalent, yet these conditions have long been clinically overlooked. These dimensions mutually

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reinforce each other through mechanisms such as systemic inflammation, oxidative stress, endothelial dysfunction, and reduced behavioral adherence. Clinical management should shift from isolated wound care to multidisciplinary collaboration, with routine integration of sarcopenia assessment, nutritional screening, and psychological-cognitive support. Incorporating the muscle, nutritional, psychological, and cognitive dimensions into the systemic framework of DFU helps to more comprehensively understand the disease burden and optimize individualized treatment strategies.

Keywords: Diabetic foot ulcer; Cardiovascular disease; Chronic kidney disease; Metabolic abnormalities; Sarcopenia; Malnutrition; Psychology disorder; Cognitive dysfunction

糖尿病足溃疡(diabetic foot ulcer, DFU)是糖尿病最严重、治疗成本最高的并发症,全球约有6.3%的成年糖尿病患者受其影响[1]。DFU患者的5年死亡率高达50%[2]。既往DFU相关研究长期聚焦于创面愈合、感染控制和保肢手术等局部层面。然而,近年的临床证据和机制研究正逐步揭示DFU并非孤立的"足部疾病",而是全身性代谢-炎症-免疫失代偿在足部的典型表现。DFU对患者健康的损害远不止于足部溃疡和截肢——其心血管系统、肾脏系统、骨骼肌肉系统乃至心理和认知功能均遭受着不同程度的侵蚀。

2024年Lan等[3]提出了"心-肾-代谢-足"四维框架,系统论述了DFU与心血管疾病(cardiovascular disease, CVD)、慢性肾脏病(chronic kidney disease, CKD)及代谢异常之间的联系。与无DFU的糖尿病患者相比,DFU患者的心血管死亡风险增加超过2倍[4];即使在无明显外周动脉疾病的神经病变性DFU患者中,冠状动脉粥样硬化性心脏病仍是其最常见的死因[5]。此外,40%~60%的DFU患者合并CKD[6]。DFU与心脏、肾脏疾病可能存在多向病理生理联系,DFU相关的全身性炎症、感染、内皮功能障碍和氧化应激可能促进动脉粥样硬化、血栓形成及心肌功能异常,并推动CVD发生和进展[7-8]。然而,现有"心-肾-代谢-足"框架主要聚焦于心肾系统,对骨骼肌肉系统(肌少症、营养不良)、神经系统(认知功能障碍)及心理社会维度的整合尚不充分。

本综述以"心-肾-代谢-足"四维框架为基准,进一步纳入肌肉-营养系统与心理认知系统,系统阐述每一维度的流行病学证据、病理生理机制及相应的临床管理对策。

1 心-肾-代谢维度:从局部溃疡到全身性血管损伤

1.1 心血管结局——DFU是心血管死亡的独立危险因素 DFU与心血管死亡之间存在明确且强相关的正向关联。多项系统评价、荟萃分析与大型队列研究均显示,DFU患者的心血管死亡风险较无DFU的糖尿病患者增加,合并风险比约为2.5[9-10];同时,DFU人群的死亡构成中,CVD长期稳居首位,约占全部死亡的50%,近1年内死亡的超过60%[11]。此外,DFU是心血管死亡的独立预测因子,其高风险不仅体现于传统危险因素,还可能伴随亚临床心脏损害[12]。

DFU与心血管死亡之间的病理生理联系是多层次的。首先,DFU局部与继发感染引发的持续性全身炎症反应,通过内皮功能障碍、氧化应激、促凝状态导致斑块不稳定,直接推动心肌梗死、卒中与心力衰竭的发生发展[13]。其次,DFU人群普遍存在的全身性动脉粥样硬化负荷(尤其合并外周动脉疾病时),使冠状动脉与下肢动脉同为系统性动脉粥样硬化的靶器官,从而显著增加心血管事件与死亡风险[14-15]。最后,糖尿病相关的微血管病变与自主神经病变,不仅促进足部溃疡的发生与难愈,还通过掩盖典型心绞痛症状导致隐匿性冠状动脉缺血与心肌梗死难以被及时识别,最终增加猝死与心血管死亡概率[16]。

鉴于DFU与心血管死亡的强关联及其高死亡构成比,DFU应被视为提示潜在或已存在CVD的"预警信号",需积极检测与管理CVD及其危险因素。

1.2 肾脏结局——终末期肾病患者面临截肢风险 DFU人群中CKD患病率高达40%,且两者之间还存在双向恶化关系。对于肾病患者而言,终末期肾病(接受血液透析治疗)者发生DFU的风险最高,下肢截肢风险是一般糖尿病患者的10倍;与估算肾小球滤过率(estimated glomerular filtration rate, eGFR)≥60 mL·min^{-1}·1.73 m^{-2}者相比,CKD 4期患者DFU的发生率升高了4倍,截肢风险则升高7倍以上;即使肾功能仅轻度下降(eGFR为30~<60 mL·min^{-1}·1.73 m^{-2}),亦与新发DFU及截肢风险升高相关[17]。此外,CKD加重了DFU的难治性,与DFU愈合率下降、溃疡复发率升高、死亡风险升高均相关[18];而DFU相关的反复感染、全身炎症、住院与围手术期暴露(造影剂、抗生素、容量波动等)可诱发急性肾损伤并推动CKD进展[19]。

CKD导致的矿物质和钙磷代谢紊乱可引起血管钙化和一种特殊的皮肤钙化形式——钙化防御,形

成极具挑战性的难愈合创面[20]。此外，CKD相关代谢物潴留可加重周围神经损伤；液体潴留、肾素-血管紧张素改变、氧化应激、促凝状态可加重外周血管病变与缺血性溃疡；蛋白丢失与代谢紊乱可致低白蛋白血症，影响创面愈合并促进水肿与循环障碍；免疫失调可增加伤口感染风险并延长炎症反应，促进慢性溃疡形成，减弱创面的修复能力[21-22]。

合并CKD的DFU患者伴有多种系统性和局部共病，识别并治疗已存在的贫血、低白蛋白血症、免疫功能障碍、血管钙化等共病，对于优化肾病足的治疗结局至关重要。

2　肌肉-营养维度：被忽视的决定性因素

2.1　*肌少症——从局部足病到全身肌肉萎缩*　肌少症是一种与增龄相关、以肌肉含量减少、肌肉力量下降和（或）躯体功能障碍为主要特征的老年综合征。Sui等[23]提出，肌少症与DFU之间存在双向且相互强化的关系。肌少症显著增加DFU患者的全因死亡风险，并与足踝功能受损、溃疡愈合延迟及截肢风险升高相关。肌少症是DFU患者全因死亡的独立风险因素，伴肌少症的DFU患者在1年、3年和5年的累积生存率均低于不伴肌少症的患者[24]。在DFU人群中，肌少症与足踝功能评分下降[25]相关，亦与足溃疡发生率、Wagner分级及截肢比例升高相关[26]。DFU与肌少症相关表型（握力、步行/起立/爬楼困难、跌倒、瘦体重等）显著相关，且可能较单纯糖尿病加速肌少症的发生[27]。

DFU相关的血管与神经病变、溃疡感染及慢性炎症可通过缺氧、微循环障碍、神经营养支持丧失与炎症/氧化应激等途径促进肌萎缩与肌力下降；DFU导致的疼痛、制动和活动受限不可避免地促进废用性肌萎缩[23, 28]。另一方面，肌少症通过影响步态稳定性和压力分布，增加足部溃疡和感染的易感性；也可通过降低组织灌注和代谢能力，延缓伤口愈合，加重DFU的进展。全身性炎症、胰岛素抵抗和营养缺乏（如蛋白质摄入不足）等共同因素进一步加剧了这两种状况，形成“DFU-肌少症”的恶性循环[29-30]。

因此，肌少症的常规评估工具应整合进DFU患者的临床评估流程。需主动管理、早期发现肌少症并进行风险分层与及时干预。对于DFU患者，可采取阻力训练、蛋白质补充以及针对性治疗，从而改善肌肉功能，减轻足底压力，促进溃疡愈合。

2.2　*营养不良与微量元素缺乏——愈合的物质基础困境*　DFU患者普遍存在营养不良与多种微量营养素缺乏，包括锌、镁、硒、维生素D、维生素C、维生素A等[31-33]。蛋白与微量营养素缺乏可以削弱免疫细胞趋化、吞噬杀菌与抗体反应，使感染更易发生并迁延；也可直接干扰胶原交联稳定、成纤维细胞增殖与角质形成细胞再生，使创面停滞于炎症期并延长愈合时间[34]。控制营养状态评分（Controlling Nutritional Status score，CONUT评分）是一种评估个体营养状态的工具。与健康对照人群及无足溃疡糖尿病患者相比，DFU患者CONUT评分更高，且CONUT评分是与DFU严重程度相关的独立因素[35]。白蛋白是反映机体营养状态的指标，可维持内皮功能、改善微循环并减轻炎症与氧化损伤；低白蛋白血症是糖尿病患者足部溃疡愈合延迟的独立危险因素[36]。有研究表明，补充锌、镁、维生素D、维生素A等可改善溃疡长度/宽度等指标[37-38]。但前瞻性研究显示，微量营养素缺乏与伤口愈合无关联，提示临床更应关注“是否存在缺乏”而非泛化补充[33]。

因此，建议将营养状态纳入DFU常规评估，尤其在愈合停滞时进行营养风险筛查与微量营养素检测。在标准治疗基础上，对明确缺乏者进行纠正，建立“筛查-纠正缺乏-营养支持”的个体化路径。

3　心理-认知维度：伤口之外的伤口

3.1　*心理困扰——高患病率下的证据裂谷*　心理因素在DFU中的影响长期被临床实践边缘化，但近年证据已逐渐凸显其重要性。DFU患者抑郁症发生率约为47%，且抑郁症与更高的糖化血红蛋白（glycated hemoglobin，HbA_{1c}）水平、更多并发症及更高死亡率相关；在首发DFU队列研究中，基线时确诊抑郁症与5年死亡风险翻倍相关[39]。然而，对于抑郁症是否直接影响DFU愈合，现有研究结果存在矛盾。一项纳入11项研究的系统综述显示，约半数提示抑郁症与愈合不良相关，另一半未发现显著关联，总体证据质量有限[40]。因此，心理因素与创面愈合之间的关系可能比想象中更为复杂，不应简化为线性因果模型。现有研究在定义、测量工具和随访时间上的异质性对结果一致性产生了实质性干扰。此外，DFU患者普遍报告焦虑、抑郁与无力感，其根源包括健康恶化、长期管理负担、对截肢的恐惧、身体功能受限、独立性丧失及家庭负担感[41]。

心理因素对DFU的影响路径包括慢性压力激活下丘脑-垂体-肾上腺轴，皮质醇升高，进而抑制炎症反应的正常调控，延迟愈合进程；同时，抑郁和焦虑显著降低患者对血糖监测、足部护理、减负装置使用

和用药依从性[42]。

建议在DFU评估中常规筛查抑郁、焦虑，并对高危个体进行转诊或整合心理支持，并开展高质量、多中心随机对照试验加以验证。

3.2　*认知功能障碍——被严重忽视的研究空白*　认知功能障碍在DFU领域研究有限。现有研究表明，活动性DFU患者完成认知功能评估的时间约为无DFU糖尿病患者的2倍，提示视空间/执行功能与工作记忆受损；校正年龄、性别、糖尿病病程与教育水平后，认知功能评估完成时间延长仍与DFU发生风险显著相关[43]。合并认知功能障碍的DFU患者6个月愈合率更低、愈合时间更长，发生高位截肢的比例更高，且足部相关住院比例更高[44]。

基于目前有限的研究，DFU患者普遍存在多域认知受损（尤其执行功能、记忆、反应速度）；认知功能障碍会显著削弱复杂足部护理与自我管理能力，形成“认知资源不足—依从性下降—溃疡恶化”的恶性循环。

因此，在DFU初诊与随访中常规进行简易认知筛查，识别高风险个体，并对合并认知功能障碍者采取“降阶化”教育与支持（图文化教育材料、家庭监督或远程提醒等），是改善该群体临床结局的重要步骤，也可能是DFU全身性框架中最具研究价值和干预潜力的前沿阵地。

4　临床整合与展望

综上所述，DFU不是孤立的足部问题，而是全身性失代偿的综合表现。单一专科的孤岛式管理显然力不从心。DFU多学科诊疗（multi-disciplinary team，MDT）横跨内分泌科、骨科、血管外科、足病科、感染科、护理和康复医学等多个领域，其价值正在获得越来越坚实的证据支持。一篇发表于*JAMA*的综述汇总18项研究显示，MDT相对常规方式可使大截肢风险降低至约原来的40%[45]。2025年版《中国糖尿病足防治实践指南》中亦明确强调，对患者心、肾、脑等重要脏器的全面评估以及MDT是DFU诊疗的基石[46]。

未来研究应优先关注以下方向：（1）肌少症评估工具在DFU患者中的临床整合和验证；（2）心理社会干预对DFU愈合结局的高质量随机对照试验；（3）DFU与认知功能障碍之间关联的前瞻性队列研究和系统综述；（4）将肌肉、营养和心理维度整合进DFU多器官预后模型的多中心真实世界研究。

总而言之，糖尿病足的管理需要范式转换——从“治疗创面”走向“管理全身”。肌肉-营养、心理-认知等维度的加入则使“心-肾-代谢-足”框架更加完整。若临床实践仅局限于创面处理，则可能忽视其背后的多系统病理状态，无异于只看到冰山浮于水面的一角。

利益冲突　无

参考文献

[1] Pavithra TR, Kaliyaperumal R. Epidemiology, pathophysiology, and management of diabetic foot: a comprehensive review [J]. Foot, 2026, 66: 102225.
[2] McDermott K, Fang M, Boulton AJM, et al. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers [J]. Diabetes Care, 2023, 46(1): 209-221.
[3] Lan NSR, Dwivedi G, Fegan PG, et al. Unravelling the cardio-renal-metabolic-foot connection in people with diabetes-related foot ulceration: a narrative review [J]. Cardiovasc Diabetol, 2024, 23(1): 437.
[4] Vlacho B, Bundó M, Llussà J, et al. Diabetic foot disease carries an intrinsic high risk of mortality and other severe outcomes in type 2 diabetes: a propensity score-matched retrospective population-based study [J]. Cardiovasc Diabetol, 2024, 23(1): 209.
[5] Rastogi A, Goyal G, Kesavan R, et al. Long term outcomes after incident diabetic foot ulcer: multicenter large cohort prospective study (EDI-FOCUS investigators) epidemiology of diabetic foot complications study Epidemiology of diabetic foot complications study [J]. Diabetes Res Clin Pract, 2020, 162: 108113.
[6] Vitale M, Orsi E, Solini A, et al. Association between age at diagnosis and all-cause mortality in type 2 diabetes: the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study [J]. Acta Diabetol, 2024, 61(9): 1107-1116.
[7] Wolf D, Ley K. Immunity and inflammation in atherosclerosis [J]. Circ Res, 2019, 124(2): 315-327.
[8] Bonnet JB, Sultan A. Narrative review of the relationship between CKD and diabetic foot ulcer [J]. Kidney Int Rep, 2022, 7(3): 381-388.
[9] Chin BZ, Lee P, Sia CH, et al. Diabetic foot ulcer is associated with cardiovascular-related mortality and morbidity-a systematic review and meta-analysis of 8062 patients [J]. Endocrine, 2024, 84(3): 852-863.
[10] Chen LH, Sun SY, Gao YY, et al. Global mortality of diabetic foot ulcer: a systematic review and meta-analysis of observational studies [J]. Diabetes Obesity Metabolism, 2023, 25(1): 36-45.
[11] 中华医学会糖尿病学分会，中华医学会感染病学分会，中华医学会组织修复与再生分会. 中国糖尿病足防治指南（2019版）（Ⅳ）[J]. 中华糖尿病杂志，2019，11(5): 316-327.
[12] Farhan M, Patel T, Ahmed Shahbaz Ahmed SB, et al. Diabetic foot ulcer as an independent risk factor for cardiovascular mortality: a systematic review and meta-analysis with qualitative synthesis of cardiac biomarker evidence [J]. Cureus, 2026, 18(4): e106672.
[13] Lan NSR, Hiew J, Ferreira I, et al. Increased risk of major adverse cardiovascular events in patients with deep and infected diabetes-related foot ulcers [J]. Diabetologia, 2025, 68(2): 460-470.
[14] Gallagher KA, Mills JL, Armstrong DG, et al. Current status and principles for the treatment and prevention of diabetic foot ulcers in the cardiovascular patient population: a scientific statement from the American Heart Association [J]. Circulation, 2024, 149(4): e232-e253.
[15] Lan NSR, Hiew J, Chen P, et al. Medial arterial calcification of the foot arteries is associated with incident cardiovascular events or all-cause mortality in patients with diabetes-related foot ulceration [J]. Diabetes Res Clin Pract, 2026, 232: 113108.

[16] Monahan CT, Yammine H, Burnash SG, et al. High prevalence of silent, severe coronary ischemia in patients with diabetic foot ulcers [J]. J Vasc Surg, 2026, 83(1): 204-212.
[17] Tan TW, Caldwell B, Zhang Y, et al. Foot and ankle care by podiatrists and amputations in patients with diabetes and kidney failure [J]. JAMA Netw Open, 2024, 7(3): e240801.
[18] Bonnet JB, Szwarc I, Avignon A, et al. Renal function is highly associated with podiatric risk in diabetic patients[J]. Clin Kidney J, 2023, 16(11): 2156-2163.
[19] Alkhami F, Rubin S, Borderie G, et al. Increased risk of renal events in people with diabetic foot disease: a longitudinal observational study[J]. Diabetes Metab, 2024, 50(4): 101536.
[20] Sandepudi K, Shah KV, Melnick BA, et al. Pathophysiology of wound development and chronicity in renal disease: a narrative review[J]. Int Wound J, 2025, 22(7): e70713.
[21] Liang JR, An H, Hu XY, et al. Correlation between chronic kidney disease and all-cause mortality in diabetic foot ulcers: evidence from the 1999-2004 national health and nutrition examination survey (NHANES)[J]. Front Endocrinol, 2025, 16: 1533087.
[22] Rastogi A, Gupta R, Ghosh J, et al. Renal foot in diabetes implications for wound healing and solutions[J]. Adv Wound Care, 2026, 15(5): 325-347.
[23] Sui YP, Ma Y, et al. A narrative review on the correlation between diabetic foot and sarcopenia [J]. Front Endocrinol, 2026, 17: 1711060.
[24] Yang Q, Ni X, Zhang YX, et al. Sarcopenia is an independent risk factor for all-cause mortality rate in patients with diabetic foot ulcers [J]. Front Nutr, 2023, 10: 1097008.
[25] An SJ, Kuang WN, Hu YL, et al. Association between sarcopenia and the foot-ankle function in type 2 diabetic foot ulcer[J]. Diabetol Metab Syndr, 2024, 16: 270.
[26] Cheng QF, Hu JB, Yang P, et al. Sarcopenia is independently associated with diabetic foot disease[J]. Sci Rep, 2017, 7: 8372.
[27] Yin HY, Ma YP, Liu XY, et al. Diabetes-related foot disease and sarcopenia-related traits: evidence from US and Chinese cohorts and Mendelian randomization[J]. Aging Clin Exp Res, 2026, 38: 92.
[28] Ahmad M, Mohamed A, Amiras D, et al. Sarcopenia in the foot on magnetic resonance imaging in patients with diabetes mellitus - a systematic review[J]. Clin Diabetes Endocrinol, 2024, 10: 31.
[29] Asunama ASR, Nambi N, Radhakrishnan L, et al. Neutrophil migration is a crucial factor in wound healing and the pathogenesis of diabetic foot ulcers: insights into pharmacological interventions[J]. Curr Vasc Pharmacol, 2025, 23(2): 98-112.
[30] Greenman RL, Panasyuk S, Wang XE, et al. Early changes in the skin microcirculation and muscle metabolism of the diabetic foot [J]. Lancet, 2005, 366(9498): 1711-1717.
[31] Apergi K, Dimosthenopoulos C, Papanas N. The role of nutrients and diet characteristics in the management of diabetic foot ulcers: a systematic review[J]. Int J Low Extrem Wounds, 2025, 24(3): 525-541.
[32] Kurian SJ, Baral T, Unnikrishnan MK, et al. The association between micronutrient levels and diabetic foot ulcer: a systematic review with meta-analysis[J]. Front Endocrinol, 2023, 14: 1152854.
[33] Bechara N, Tehan P, Gunton JE. Prospective evaluation of vitamin C, vitamin D, and zinc deficiencies in patients with active foot ulceration[J]. Adv Wound Care, 2026, 15(2): 107-115.
[34] Wang J, Zhang Y, et al. Establishment and evaluation of a novel tool based on inflammation-nutrition derived biomarkers for early diagnosis of diabetic foot ulcers [J]. Front Immunol, 2026, 17: 1794011.
[35] Nakamura H, Makiguchi T, Yamada Y, et al. Evaluation of CONUT score and serum zinc levels in patients with diabetic foot ulcers[J]. Int J Low Extrem Wounds, 2025 15347346251326247.
[36] Lee SH, Kim SH, Kim KB, et al. Factors influencing wound healing in diabetic foot patients[J]. Medicina, 2024, 60(5): 723.
[37] Erdem HA, Yalçın N, Kaya A, et al. Vitabiotic an alternative approach to diabetic foot[J]. Wound Repair Regeneration, 2024, 32 (6): 890-894.
[38] Razzaghi R, Pidar F, Momen-Heravi M, et al. Magnesium supplementation and the effects on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial[J]. Biol Trace Elem Res, 2018, 181(2): 207-215.
[39] Pouwer F, Perrin B, Lavender A, et al. The quest for wellness: How to optimise self-care strategies for diabetic foot management?[J]. Diabetes Metabolism Res, 2024, 40(3): e3751.
[40] Al-Smadi AM, Finlayson K, Andrew B, et al. The impact of depression on healing outcomes in people with diabetes-related foot ulcers: a systematic review[J]. Diabetes Res Clin Pract, 2025, 225: 112275.
[41] Hanlon M, McGuire BE, MacGilchrist C, et al. Beyond the wound: a scoping review of the psychosocial impact of diabetes-related foot ulcers[J]. Diabet Med, 2026, 43(4): e70243.
[42] Alasfour L, Alboloushi A, Kirwan E, et al. Mapping the evidence to determine the influence of stress, anxiety, and depression on wound healing in patients with diabetes-related foot ulcers: a scoping review[J]. J Tissue Viability, 2025, 34(3): 100935.
[43] Bechara N, Hawke F, Gunton JE, et al. Cognition and quality of life in patients with a diabetes-related foot ulcer[J]. J Tissue Viability, 2025, 34(3): 100913.
[44] Girgis C, Behme S, Holmes C, et al. Cognitive impairment is associated with poor diabetic foot ulcer outcomes[J]. Prim Care Diabetes, 2025, 19(5): 527-532.
[45] Armstrong DG, Tan TW, Boulton AJM, et al. Diabetic foot ulcers: a review[J]. JAMA, 2023, 330(1): 62.
[46] 中华医学会烧伤外科学分会,长三角一体化糖尿病足专病联盟,《中华烧伤与创面修复杂志》编辑委员会. 中国糖尿病足防治实践指南(Ⅰ)[J]. 中华烧伤与创面修复杂志,2025,41(11): 1029-1049.

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