

World Journal of *Diabetes*

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REVIEW

- 1001** Non-coding RNAs: Role in diabetic foot and wound healing
Tang YB, Uwimana MMP, Zhu SQ, Zhang LX, Wu Q, Liang ZX
- 1014** Diabetic foot ulcer: Challenges and future
Yang L, Rong GC, Wu QN
- 1035** Keeping an eye on the diabetic foot: The connection between diabetic eye disease and wound healing in the lower extremity
Ramsey DJ, Kwan JT, Sharma A
- 1049** Diabetic foot ulcers: Classification, risk factors and management
Wang X, Yuan CX, Xu B, Yu Z
- 1066** Mesenchymal stem cell-derived exosomes: The dawn of diabetic wound healing
Wu J, Chen LH, Sun SY, Li Y, Ran XW

MINIREVIEWS

- 1096** Prehabilitation of overweight and obese patients with dysglycemia awaiting bariatric surgery: Predicting the success of obesity treatment
Cigrovski Berkovic M, Bilic-Curcic I, Mrzljak A, Canecki Varzic S, Cigrovski V
- 1106** Diabetic foot ulcers: A devastating complication of diabetes mellitus continues non-stop in spite of new medical treatment modalities
Akkus G, Sert M
- 1122** Hyperbaric oxygen therapy and chemokine administration - a combination with potential therapeutic value for treating diabetic wounds
Venkataseshan J, Viswanathan P
- 1131** The role of artificial intelligence technology in the care of diabetic foot ulcers: the past, the present, and the future
Pappachan JM, Cassidy B, Fernandez CJ, Chandrabalan V, Yap MH
- 1140** Single nucleotide variations in the development of diabetic foot ulcer: A narrative review
Hu YJ, Song CS, Jiang N

ORIGINAL ARTICLE

Observational Study

- 1154** Baseline moderate-range albuminuria is associated with protection against severe COVID-19 pneumonia
Bashkin A, Shehadeh M, Shbita L, Namoura K, Haiek R, Kuyantseva E, Boulos Y, Yakir O, Kruzel-Davila E

SYSTEMATIC REVIEWS

- 1168** Comparison of gliclazide *vs* linagliptin on hypoglycemia and cardiovascular events in type 2 diabetes mellitus: A systematic review

Mohan V, Wangnoo S, Das S, Dhediya R, Gaurav K

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Single nucleotide variations in the development of diabetic foot ulcer: A narrative review

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Abstract

Diabetes mellitus has become a global health problem, and the number of patients with diabetic foot ulcers (DFU) is rapidly increasing. Currently, DFU still poses great challenges to physicians, as the treatment is complex, with high risks of infection, recurrence, limb amputation, and even death. Therefore, a comprehensive understanding of DFU pathogenesis is of great importance. In this review, we summarized recent findings regarding the DFU development from the perspective of single-nucleotide variations (SNVs). Studies have shown that SNVs located in the genes encoding C-reactive protein, interleukin-6, tumor necrosis factor- α , stromal cell-derived factor-1, vascular endothelial growth factor, nuclear factor erythroid-2-related factor 2, sirtuin 1, intercellular adhesion molecule 1, monocyte chemoattractant protein-1, endothelial nitric oxide synthase, heat shock protein 70, hypoxia inducible factor 1 α , lysyl oxidase, intelectin 1, mitogen-activated protein kinase 14, toll-like receptors, osteoprotegerin, vitamin D receptor, and fibrinogen may be associated with the development of DFU. However, considering the limitations of the present investigations, future multi-center studies with larger sample sizes, as well as in-depth mechanistic research are warranted.

Key Words: Diabetic foot; Diabetic foot ulcer; Diabetic foot osteomyelitis; Single nucleotide variations; Narrative review

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Core Tip: The pathogenesis of diabetic foot ulcer (DFU) is complex and is associated with both extrinsic and intrinsic factors. Most previous studies have reported the roles of external factors in DFU development and have neglected internal factors. In this narrative review, we focused on single-nucleotide variations (SNVs), as a representative of host factors. We summarized recent findings regarding the relationships between genetic SNVs and susceptibility of different populations to DFU. Future multicenter investigations with larger sample sizes, as well as in-depth mechanistic research, are necessary to better recognize and understand the roles of SNVs in DFU pathogenesis.

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INTRODUCTION

Diabetes mellitus (DM), one of the most frequently encountered metabolic disorders, has become a global health problem and is considered a public health emergency[1]. The severity of DM is not only attributed to the disorder itself but also to its associated complications, influencing both life expectancy and quality of life[2]. DM-related complications affecting the lower extremities are common, complex, and costly ("3Cs"), with diabetic foot ulcer (DFU) being the most frequently recognized type[3]. It is estimated that the lifetime incidence of DF or DFU is approximately 15%–25% among patients with DM [4,5]. DFU remains one of the most challenging disorders for physicians to treat, with a high risk of infection, recurrence leading to limb amputation, and even death. Over half of DFUs are infected[6]; the incidence of DFU recurrence is 40% within 1 year and 65% within 3 years[3]. Despite various treatment strategies, approximately 20% of DFU patients with moderate and severe infections experience different levels of amputation[7,8]. According to a database analysis from the United Kingdom, the risk of death at 5 years for DFU patients was 2.5-fold greater than that for DM patients without DFU[9]. Additionally, treatment of DFU is costly, with nearly one-third of the estimated expenses for DM spent on DFU[10-12].

The great hazards of DFU necessitate a comprehensive understanding of its pathogenesis, aiming at increasing the cure rate, and decreasing the risks of infection, recurrence, and death. The progression of DFU is complex, with diabetic neuropathy (DN) and peripheral artery disease being the primary causes [13]. Multiple factors participate in the development of DFU; however, most previous studies have focused on environmental and controllable host factors. Recently, growing evidence has revealed that as a representative of host factors, single-nucleotide variations (SNVs) or single nucleotide polymorphisms are also involved in the development of DFU. This narrative review summarized current investigations regarding the roles of SNVs in the occurrence of DFU, thus providing new insights into the pathogenesis of DFU.

GENETIC SNVS INVOLVED IN DFU DEVELOPMENT

C-reactive protein

As an acute-phase response protein, C-reactive protein (CRP) levels increase in cases of tissue injury, infection, inflammation, and cancer[14,15]. Furthermore, it can be up to 1000 times the normal value in severe situations. A recent meta-analysis[16] indicated that the role of CRP is a promising biomarker for DFU infection evaluation. The CRP protein, encoded by the *CRP* gene, is located on chromosome 1q21-q23 and is 2.3 kb long[17]. Recent studies have reported that *CRP* genetic SNVs associated with the risk of developing DFU, including rs11265260, rs1800947, rs2794520, rs1130864, and rs3093059 (Table 1).

In a 2020 case-control study, Wang *et al*[17] investigated the potential influence of CRP SNVs, together with environmental factors, on the development of diabetic foot osteomyelitis (DFO) and prognosis of the patients with DFO. Altogether, 681 patients with DFO, 1053 patients without DFO, and 1261 healthy controls were included; and 11 CRP SNVs were analyzed. The results showed that rs11265260 (allele G), rs1800947 (allele G), rs2794520 (allele T), and rs1130864 (allele T) were linked to an increased risk to develop DFO in this Chinese cohort. Additionally, rs3093059 (allele C) showed a decreased risk. Furthermore, rs11265260 (allele G), rs1800947 (allele G), rs3093068 (allele G), and rs1130864 (allele T) were significant predictors of poor prognosis in these patients. Moreover, the GG and AG genotypes of rs11265260, the CG and GG genotypes of rs1800947, the TT genotype of rs3093059, and the CT and TT genotypes of rs113084 amplified the influences of smoking, alcohol consumption, cacostmia, and ulceration on progression from non-DFO to DFO. These outcomes imply that both

Table 1 Single nucleotide variations involving in the development of diabetic foot and its related complications

Ref.	Population or ethnicity	Total sample size (DF vs T2DM without DF) vs controls	Genes	SNVs reported	Potential influences of the SNVs on DF and DF related complications	Genotypes as risk or protective factors
Wang <i>et al</i> [17], 2020	Chinese	2995 (681 vs 1053 vs 1261)	<i>CRP</i>	rs11265260	Risk factor of DFO	GG + AG/GG
			<i>CRP</i>	rs1800947	Risk factor of DFO	GG + CG
			<i>CRP</i>	rs2794520	Risk factor of DFO	TT + CT/TT
			<i>CRP</i>	rs1130864	Risk factor of DFO	TT + CT/TT
			<i>CRP</i>	rs3093059	Protective factor against DFO	CC+CT/CC
Dhamodharan <i>et al</i> [23], 2015	Indian	515 (270 ¹ vs 139 vs 106)	<i>IL-6</i>	rs1800795	Protective factor against T2DM but not against DFU-DN	GC, CC
Erdogan <i>et al</i> [24], 2017	Turkish	204 (50 vs 35 vs 119)	<i>IL-6</i>	rs1800795	Risk factor of T2DM but not DFU	GG
Viswanathan <i>et al</i> [25], 2018	Indian	270 (without controls)	<i>IL-6</i>	rs1800795	Risk factor of severe wound infections	GC + CC
Dhamodharan <i>et al</i> [23], 2015	Indian	515 (270 ¹ vs 139 vs 106)	<i>TNF-α</i>	rs1800629	Risk factor of both T2DM and DFU-DN	GA, AA
				rs1800629	Risk factors of severe wound infections, ulcer grade of DF	GA + AA
Viswanathan <i>et al</i> [25], 2018	Indian	270 (without controls)	<i>TNF-α</i>	rs361525	Risk factor of ulcer grade of DF	GA + AA
Dhamodharan <i>et al</i> [23], 2015	Indian	515 (270 ¹ vs 139 vs 106)	<i>SDF-1</i>	rs1801157	Protective factor against T2DM and/or DFU-DN	GA, AA: T2DM; AA: DFU-DN
Viswanathan <i>et al</i> [25], 2018	Indian	270 (without controls)	<i>SDF-1</i>	rs1801157	Risk factors of severe wound infections and major amputations (foot/leg)	GA + AA
Amoli <i>et al</i> [34], 2011	Iranian	586 (247 vs 241 vs 98)	<i>VEGF</i>	rs699947	Protective factor against DFU	AA
Li <i>et al</i> [35], 2018	Chinese	288 (97 vs 88 vs 103)	<i>VEGF</i>	rs699947	Protective factor against DFU	AC, AA
Li[36], 2018	Chinese	229 (121 vs 108) (without healthy controls)	<i>VEGF</i>	rs2010963	Protective factor against DFU	CC
Teena <i>et al</i> [42], 2020	Indian	400 (100 vs 150 vs 150)	<i>NRF2</i>	rs35652124	Risk factors of DFU	TT
Teena <i>et al</i> [43], 2021	Indian	400 (100 vs 150 vs 150)	<i>NRF2</i>	rs182428269	Protective factor against T2DM and DFU	CC, CT
					Risk factor of T2DM and DFU	TT
Peng <i>et al</i> [45], 2018	Chinese	438 (142 vs 148 vs 148)	<i>SIRT1</i>	rs12778366	Protective factor against T2DM and DF	Allele C carriers
Cao <i>et al</i> [48], 2020	Chinese	430 (128 vs 147 vs 155)	<i>ICAM1</i>	rs5498	Protective factor against T2DM and DF	GG
			<i>ICAM1</i>	rs3093030	Protective factor against DF	CT + TT
Li[36], 2018	Chinese	229 (121 vs 108) (without healthy controls)	<i>MCP-1</i>	rs1024611	Risk factor of DFU	GG
Su <i>et al</i> [51], 2018	Chinese	400 (116 vs 135 vs 149)	<i>MCP-1</i>	rs1024611	Risk factor of DFU	AG, GG
Sadati <i>et al</i> [53], 2018	Iranian	257 (123 vs 134)	<i>eNOS</i>	eNOS Glu298Asp	Protective factor against	TT

		(without healthy controls)			DFU	
Erdogan <i>et al</i> [37], 2018	Turkish	182 (50 vs 57 vs 75)	eNOS	eNOS G894T	Risk factor of T2DM but not DFU	Not related to DFU onset
Zubair and Ahmad [58], 2018	Arabian	150 (50 vs 50 vs 50)	HSP-70	rs2227956	Risk factor of DFU	TT
					Protective factor of DFU	CC
Pichu <i>et al</i> [60], 2015	Indian	224 (79 vs 79 vs 66)	HIF-1 α	rs11549465	Risk factor of DFU but not T2DM	CT
Pichu <i>et al</i> [61], 2018	Indian	529 (199 vs 185 vs 145)	HIF-1 α	rs11549467	Risk factors of T2DM and DFU	GA
Pichu <i>et al</i> [65], 2017	Indian	906 (301 vs 305 vs 300)	LOX	rs1800449	Risk factor of DFU but not T2DM	AA
Mrozikiewicz-Rakowska <i>et al</i> [66], 2017	Polish	670 (204 vs 299 vs 167)	ITLN1	rs2274907	Risk factor of DF but not T2DM	TT
Meng <i>et al</i> [68], 2017	Scottish	3394 (699 vs 2695)	MAPK14	rs80028505	Risk factor of DFU	Not reported
Wifi <i>et al</i> [71], 2017	Egyptian	90 (30 vs 30 vs 30)	TLRs	rs5743836	Risk factor of DFU among T2DM patients	CT
Singh <i>et al</i> [70], 2013	Indian	255 (125 vs 130) (DFU vs healthy controls)	TLRs	rs4986790	Risk factor of DFU	AG/GG + AG
			TLRs	rs4986791	Risk factor of DFU	TT/CT/CT + TT
			TLRs	rs11536858	Risk factor of DFU	GG/AG/GG + AG
			TLRs	rs1927914	Risk factor of DFU	CC
			TLRs	rs1927911	Risk factor of DFU	CT/CT + TT
Nehring <i>et al</i> [72], 2013	Polish	877 (122 vs 293 vs 462)	OPG	rs2073617	Protective factor against DF among female patients	AG
			OPG	rs2073618	Risk factor of DF among T2DM patients	CC
Soroush <i>et al</i> [76], 2017	Iranian	212 (105 vs 107) (without healthy controls)	VDR	rs2228570	Risk factor of DFU among T2DM patients	TT + CT
Zhao <i>et al</i> [78], 2015	Chinese	300 (123 vs 97 vs 80)	FIB	rs6056	Risk factor of DF	CT, TT

¹This group of 270 patients included 191 patients with DFU-DN and 79 patients with DFU-peripheral vascular disease.

DF: Diabetic foot; T2DM: Type 2 diabetes mellitus; SNVs: Single Nucleotide Variations; DFO: Diabetic foot osteomyelitis; DFU-DN: Diabetic foot ulcer with diabetic neuropathy; CRP: C-reactive protein; IL-6: Interleukin-6; TNF- α : Tumor Necrosis Factor-Alpha; SDF-1: Stromal cell Derived Factor-1; VEGF: Vascular Endothelial Growth Factor; NRF2: Nuclear Factor Erythroid-2-related Factor 2; SIRT1: Sirtuin 1; ICAM1: Intercellular Adhesion Molecule 1; MCP-1: Monocyte Chemoattractant Protein-1; eNOS: Endothelial Nitric Oxide Synthase; HSP-70: Heat Shock Protein-70; HIF-1 α : Hypoxia inducible factor 1 alpha; LOX: Lysyl Oxidase; ITLN1: Intelectin 1 (Omentin); MAPK14: Mitogen-activated Protein Kinase 14; TLRs: Toll-Like receptors; OPG: Osteoprotegerin; VDR: Vitamin D receptor; FIB: Fibrinogen.

extrinsic and intrinsic factors participate in DFO pathogenesis, which may also affect patient prognosis. However, considering that this was a single-center study with a limited number of participants, future multicenter studies with larger sample sizes are necessary. Additionally, the potential effects of SNVs on plasma CRP levels still remain unclear. Previous studies have reported that several CRP SNVs such as rs1800947[18], rs1205[18,19], rs3091244[20] and rs3093059[21] might play a role in the development of diseases, partially *via* their influences on plasma CRP levels. Whether CRP SNVs influence CRP levels in patients with DFU requires further investigation.

Interleukin-6

Interleukin-6 (IL-6) is an important anti-inflammatory cytokine involved in the pathogenesis of type 2 diabetes mellitus (T2DM). Dysregulations of IL-6 and IL-6 signaling have been implicated in the etiology of autoimmune and inflammatory diseases, including T2DM[22]. One of the most frequently analyzed SNV sites is rs1800795; however, there is still a dispute regarding its role in the development of DFU (Table 1).

In 2015, Dhamodharan *et al*[23] reported a potential relationship between rs1800795 and susceptibility to DFU in an Indian population. The results revealed that the allele C of rs1800795 conferred significant protection against T2DM, but not against DFU. Similar outcomes were found in a Turkish population in

a study conducted by Erdogan *et al*[24]. It was observed that the G allele of rs1800795 is a risk factor for T2DM but not an independent risk factor for DFU. In 2018, Viswanathan *et al*[25] reported that compared with genotype GG, the mutant genotypes CC and CG of rs1800795 were linked to an elevated susceptibility to *Staphylococcus sp.*, *Proteus morganii*, and *Citrobacter diversus* related infections in DFU patients. This finding suggests a potential role of such an SNV in specific microbial infections. In addition, they also observed that patients with GC and CC genotypes had significantly lower IL-6 levels than those with GG genotype. This finding implies that such an SNV participates in the occurrence of severe wound infections among DFU patients, partly *via* its influence on serological IL-6 levels. A recent meta-analysis[26] focused on the potential relationship between rs1800795 and the risk of developing microvascular complications in T2DM patients. Based on a pooled analysis of 14 eligible studies, the authors concluded that rs1800795 was unrelated to susceptibility to microvascular complications of T2DM. As in this study[26], all relevant microvascular complications (diabetic nephropathy, retinopathy, and foot disease) and multiple ethnicities were included, these parameters were synthesized as a whole entity for analysis, both of which may lead to high heterogeneity, and thus, a high risk of bias to the outcomes.

Tumor necrosis factor- α

As part of the humoral immunity against infections, tumor necrosis factor (TNF) is involved in inflammatory responses and plays an important role in the pathogenesis of multiple infectious diseases. As one of the most prominent members of the TNF cytokine family, TNF- α is primarily secreted by macrophages, natural killer cells, lymphocytes, and neurons. Recently, increasing evidence has revealed that TNF- α SNVs are associated with the development of various inflammatory disorders, such as chronic osteomyelitis[27], coronavirus disease 2019[28], and severe sepsis[29]. Recent studies have also found that TNF- α SNVs (primarily rs1800629 and rs361525) are linked to the development of DFU (Table 1).

In a 2015 study, in addition to the IL-6 genetic SNV, Dhamodharan *et al*[23] and colleagues also noted that TNF- α SNVs rs1800629, but not rs361525, contributed to an increased risk of developing both T2DM and DFU-DN. In 2018, this group[25] also found that both rs1800629 and rs361525 were associated with severe microbial infections. Specifically, the genotypes GA and AA of rs1800629 displayed an elevated susceptibility to *Staphylococcus sp.*, *Proteus morganii*, and *Citrobacter diversus*-related infections. Genotypes GA and AA of rs361525 displayed an increased risk of developing *Proteus morganii*- and *Enterococcus sp.*-associated infections. In addition, rs1800629 and rs361525 were strongly correlated with ulcer grades. The potential influence of SNV genotypes on serological levels of inflammatory biomarkers was also examined. The authors noted that patients with GA and AA genotypes of rs1800629 had significantly lower levels of TNF- α and hsCRP than those with GG genotype[25]. Nonetheless, considering that the results were derived from two studies focusing on only one Indian population and by the same study group, future studies with different populations or ethnicities are warranted.

Stromal cell-derived factor-1

Stromal cell-derived factor-1 (SDF-1) is primarily responsible for homing and migration of endothelial progenitor cells and bone marrow-derived mesenchymal stem cells. It also plays a vital role in neovascularization[30]. Considering the pathophysiological changes in DFU, a potential role for SDF-1 is probable, and it is speculated that SDF-1 genetic SNVs may be linked to the development of DFU (Table 1).

The outcomes of a 2015 study[23] demonstrated that the allele A of SDF-1 SNV rs1801157 conferred protection against T2DM and DFU. Specifically, compared with the normal glucose tolerance (NGT) group, frequencies of the GA and AA genotypes were significantly lower in both T2DM and DFU-DN groups. In addition, the frequency of the AA genotype was significantly lower in the DFU-DN group than that in the NGT group. Multiple logistic regression analysis revealed that both genotypes displayed significant protection against T2DM. While the AA genotype alone had a protective effect against DFU-DN. Moreover, the mean glycated hemoglobin level of the AA genotype was the lowest among the three genotypes, with the highest high density lipoprotein (HDL) cholesterol level. This finding can help explain the protective effect of rs1801157 may be achieved partly *via* its influences on glycated hemoglobin and HDL-cholesterol. In a subsequent 2018 study[25], the mutant genotypes GA and AA of such an SNV site were found to be associated with an elevated risk of developing *Staphylococcus sp.*- and *Enterococcus sp.*-related infections. Additionally, this SNV was correlated with an elevated risk of major amputation, even after adjusting for confounding factors. Whether the limb can be preserved among DFU patients depends on multiple factors aside from SNVs. Thus, caution should be taken exercised in this conclusion. However, in this study[25], the authors failed to find any positive influence of SDF-1 SNV on the serum levels of the biomarkers analyzed.

Vascular endothelial growth factor

As a mitogen in vascular endothelial cells[31], vascular endothelial growth factor (VEGF) can induce collagenases and contribute to angiogenesis by clearing the matrix. This facilitates the migration and sprouting of endothelial cells[32]. VEGF regulates transforming growth factor- β and platelet-derived

growth factor during the wound healing in patients with DFU[33]. Recent studies have reported positive relationships between VEGF genetic SNVs and susceptibility to DFU in different populations (Table 1).

In 2011, Amoli *et al*[34] examined the potential relationship between VEGF SNVs rs25648 and rs699947, and susceptibility to DFU in an Iranian population. The results revealed that the frequency of the AA genotype of rs699947 was significantly lower in patients with DFU than in patients with diabetes without DFU. Additionally, the frequency of allele A was lower than that in the controls. These results propose that rs699947 may be a protective factor against DFU, with allele A and AA genotypes acting as protective factors. In 2018, Li *et al*[35] analyzed the potential role of VEGF SNVs rs699947 and rs13207351 in the pathogenesis of DFU in a Chinese Han cohort. They also found that allele A of rs699947 was distinctly correlated with a decreased DFU risk, with AC and AA acting as protective genotypes. However, no statistical differences were noted between rs13207351 and susceptibility to DFU in this Chinese cohort. In the same year, the same study team[36] analyzed the potential link between VEGF SNV rs2010963 and the risk of developing DFU. Specifically, the frequencies of the CC genotype and allele C of rs2010963 were lower among patients with DFU than among those with T2DM without DFU. This observation demonstrates the protective role of this particular SNV against DFU. In addition, patients with DFU with the CC genotype had significantly higher VEGF levels than those with the GG genotype. Thus, the protective effect of rs2010963 against DFU may be exerted partly *via* its influence on serological VEGF levels. In another 2018 study, Erdogan *et al*[37] analyzed the association between VEGF SNV rs3025039 and the risk of DFU development in a Turkish population. However, no significant associations were identified with either the risk of DFU development or susceptibility to T2DM. Considering the limited sample size of this study (50 DFU patients and 57 diabetic patients without DFU), the results should be interpreted with caution. Future studies with larger sample sizes are necessary.

Nuclear factor erythroid-2-related factor 2

Among diabetic patients, prolonged hyperglycemia, and oxidative stress lead to the generation of excessive reactive oxygen species (ROS). These factors contribute to endothelial dysfunction, vascular damage, and delayed wound healing[38]. In hyperglycemia, ROS levels are higher than the intrinsic antioxidant capacity. This leads to subsequent alterations in the extracellular matrix and delayed wound healing[39]. As a transcription factor, nuclear factor erythroid-2-related factor 2 (NRF2) can maintain cellular redox homeostasis and transcribe the antioxidant response element to offer endogenous protection to cells by combating ROS. Post-translational modifications of SNVs profoundly associated with diabetes have been investigated. SNVs in the regulatory motifs of the *NRF2* gene can affect its binding capacity and, thus, inhibit the transcription[40]. Epidemiological and genetic studies have indicated that NRF2 promoter SNVs in diseases are linked to oxidative stress. This indicates that NRF2 polymorphisms are genetically predisposed to disease susceptibility[41].

In a 2020 cross-sectional study conducted in an Indian population, Teena *et al*[42] examined the potential link between the NRF2 SNV rs35652124 and susceptibility to DFU. Results based on 400 participants demonstrated that the frequency of the TT genotype among the DFU patients (52%) was significantly higher than that among T2DM patients without DFU (23%) and NGT controls (12%). These observations suggest that the TT genotype might be associated with an increased risk of DFU development in both T2DM patients and healthy controls. In addition, compared with the wild CC genotype, patients with DFU with the TT genotype expressed significantly increased TNF- α and IL-6 levels but a significantly decreased IL-10 level. Increases in TNF- α and IL-6 and a decrease in IL-10 levels have been reported to slow the chronic wound healing process, especially under insulin resistance [42]. Therefore, one underlying mechanism by which NRF2 SNV rs35652124 participate in the development of DFU is through dysregulation of key genes involved in redox homeostasis and wound healing. In 2021, the same group[43] assessed the role of rs182428269 in the development of DFU in the same population. Similarly, they found that the frequency of the TT genotype of DFU subjects was the highest among the three groups (DFU patients *vs* T2DM patients without DFU *vs* NGT controls = 42% *vs* 20% *vs* 11.4%). These findings demonstrate that rs182428269 is linked to an increased susceptibility to DFU occurrence, with the TT genotype as a risk factor. Additionally, compared with the CC and CT genotypes, the expression of NRF2 was significantly decreased among the DFU subjects with the TT genotype. Thus, one potential mechanism of SNV in the development of DFU is that they may affect the expression of NRF2. Based on the outcomes of the two NRF2 SNVs studies discussed, it is speculated that dysfunction of NRF2 by SNVs might be helpful in discerning disease development and progression in T2DM.

Sirtuin 1

Sirtuin 1 (SIRT1), also known as NAD-dependent deacetylase sirtuin-1, is downregulated in patients with T2DM and is associated with oxidative stress[44]. Previous studies have indicated that SIRT1 SNVs might alter their expressions or functions and thus contribute to the development of different disorders, such as neural or vascular lesions. Recent studies have shown that SIRT1 SNVs are also involved in DFU development (Table 1).

In a 2018 case-control study, Peng *et al*[45] explored the influence of SIRT1 SNVs (rs12778366 and rs3758391) on DF susceptibility and severity in T2DM patients. Based on the outcomes of 142 DF patients, 148 T2DM patients without DF, and 148 healthy controls, they noted that the C allele of rs12778366 was correlated with reduced DF susceptibility compared to the healthy controls and T2DM patients. This study demonstrates that the allele C of rs12778366 might act as a protective factor against DF onset. Moreover, the authors noted that the DF patients displayed significant downregulation of SIRT1 expression compared to those of the T2DM patients and the healthy controls. However, no statistical differences were identified regarding SIRT1 expression among different genotypes of rs12778366. Therefore, the detailed mechanisms of SIRT1 SNVs in the pathogenesis of DF and T2DM require further investigation.

Intercellular adhesion molecule 1

Intercellular adhesion molecule 1 (ICAM1) is an important regulator of cardiovascular disorders and peripheral neuropathy in patients with diabetes[46]. It is a cell surface glycoprotein expressed in immune and endothelial cells[47]. ICAM1 is regulated by the *ICAM1* gene located at 19p13.2; its SNVs in exon regions may influence the protein expression or function. Recent studies have indicated that *ICAM1* genetic SNVs participate in DF development (Table 1).

In a 2020 study[48] comprising 128 DF patients, 147 T2DM patients, and 155 healthy controls, Cao *et al*[48] examined the potential correlations between ICAM1 SNVs rs5498 and rs3093030, and susceptibility toward DF. The results revealed that the GG genotype of rs5498 was distinctly correlated with a decreased risk of developing both T2DM and DF, with the mutant allele G acting as a protective factor. In addition, the authors analyzed the effects of ICAM1 SNVs on DF characteristics. Notably, they observed that DF patients with the GG genotype had a significantly higher levels of serum creatinine than those with the AA genotype. However, the potential reasons remain unclear. In addition to rs5498, they also reported that individuals with the rs3093030 allele T had a reduced susceptibility to DF. Thus, rs3093030 may also act as a protective factor against the onset of DF. As this study only compared outcomes from clinical data, further studies should be performed to investigate the detailed protective mechanisms.

Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (MCP-1), also known as chemokine (C-C motif) ligand 2, is a potent cytokine that activates monocytes, macrophages, and lymphocytes[49]. Abnormal expression of MCP-1 may contribute to complications related to angiogenesis and vascular functions in T2DM patients[50]. Recently, growing evidence has shown that *MCP-1* genetic SNVs may be linked to DFU occurrence (Table 1).

In the aforementioned 2018 study, apart from *VEGF* SNV rs2010963, Li[36] reported the potential role of *MCP-1* SNV rs1024611 in the development of DFU. The results revealed that, compared with T2DM patients, the frequencies of both the G allele and GG genotype were increased among DFU patients. These findings implied that such a variant might be a risk factor for DFU onset among patients with T2DM. Additionally, the expression level of MCP-1 in patients with DFU with the GG genotype was significantly higher than those with the AA genotype. In the same year, Su *et al*[51] reported the potential influence of rs1024611 on the development of DFU in another Chinese cohort. Similarly, they also found that the G allele was associated with an increased risk of DFU development. Furthermore, individuals with the AG and GG genotypes had a higher risk of developing DFU. Similar findings were also obtained in that the GG genotype of rs1024611 was correlated with enhanced MCP-1 expression. This is consistent with previous findings by Li[36] that demonstrated that *MCP-1* genetic SNV rs1024611 may exert its biological effects partially *via* its influence on peripheral MCP-1 expression level. Moreover, Su *et al*[51] also found that the GG genotype of rs1024611 was correlated with a significantly higher epidermal thickness. Additionally, a significantly lower dermal thickness among patients with DFU was noted compared to those of AA and AG genotypes. This reveals another potential mechanism of such an SNV in DFU occurrence.

Endothelial nitric oxide synthase

As a key cellular signaling molecule, nitric oxide (NO) is an effective vasodilator that leads to smooth muscle relaxation. NO triggers oxidative stress by increasing free radicals and plays an important role in the pathogenesis of microvascular complications related to diabetes[52]. NO is produced through the oxidation of L-arginine by nitric oxide synthase (NOS); endothelial nitric oxide synthase (eNOS) is one of the three NOS isoforms (NOS3). Several eNOS SNVs have been linked to the occurrence of different types of disorders, including DFU (Table 1).

In a 2018 study, Sadati *et al*[53] examined associations between eNOS SNV *Glu298Asp* and the risk of DFU development in an Iranian cohort. Outcomes derived from 123 patients with DFU and 134 patients with T2DM without DFU revealed that the frequency of allele T was significantly lower in patients with DFU than in T2DM controls, with TT displaying a lower frequency in patients with DFU. This implies that the T allele may be protective against DFU. The authors explored levels of ROS and the total antioxidant power of plasma among patients with different genotypes. However, no significant

relationships were observed between such an SNV and levels of the two indicators. In another study carried out in a Turkish population, Erdogan *et al*[37] analyzed the potential effect of the eNOS SNV G894T on DFU susceptibility. The results revealed that the G894T allele T was a risk factor for diabetes but not a risk factor for DFU. As mentioned previously, considering the limited sample size of this study, future studies with more participants should be conducted.

Heat shock protein-70

Heat shock protein (HSP)-70 protein responds to stress and wound repair. Previous experiments[54,55] have shown significantly delayed or attenuated responses of cutaneous wound-induced HSP-70 expression in diabetic animals. It also functions as a key molecule in pathways linked to inflammation. Meanwhile, excessive production of inflammatory cytokines has been implicated in the pathogenesis of DFU[56]. A recent study of 946 subjects indicated that HSP-70 genetic SNVs were strongly associated with renal complications in patients with T2DM in a South Indian population, demonstrating its possible role in T2DM and related complications.

Regarding the potential relationships between HSP-70 SNVs and DFU, a study[57] reported that HSP-70 SNVs were associated with the severity of DFU and surgical treatment outcomes. In 2018, Zubair and Ahmad[58] analyzed the potential role of HSP-70 SNV rs2227956 in the development of DFU in an Indian population. The results showed that a relatively higher frequency of the T allele was found among patients with DFU (7.3%) than among patients with T2DM (5.5%) and healthy controls (3.9%). The frequency of the TT genotype among patients with DFU was the highest (DFU *vs* T2DM *vs* healthy controls = 76% *vs* 44% *vs* 14%); and the frequency of the CC genotype among patients with DFU was the lowest (DFU *vs* T2DM *vs* healthy controls = 10% *vs* 30% *vs* 36%) among the three groups. This implies that the TT genotype may be a risk factor, whereas the CC genotype may be protective against DFU onset. Considering that only 150 participants were included (50 participants in each group), caution should be exercised in interpreting the findings.

Hypoxia inducible factor 1 alpha

Hypoxia inducible factor 1 alpha (HIF-1 α) is considered a leading cause of various chronic diseases, including diabetes. It is a key regulator of genes involved in cellular response to hypoxia[59]. Growing evidence has shown that HIF-1 α gene SNVs may be related to the development of DFU (Table 1).

In a 2015 study, Pichu *et al*[60] analyzed the potential link between HIF-1 α SNV rs11549465 and the risk of developing DFU in an Indian population. The results confirmed that the frequencies of the CT genotype in both patients with T2DM and patients with DFU were higher than those in healthy controls. However, a significant difference was only found among the patients with DFU. This suggests that the CT genotype might be a risk factor for DFU but not for T2DM. The outcomes of subsequent analyses demonstrated that HIF-1 α expression in patients with DFU was lower than that in patients with T2DM and healthy controls. In addition, patients with DFU with the CT genotype had a lower expression level of HIF-1 α than those with the CC genotype. This observation implied that reduced HIF-1 α expression might be associated with the development of DFU. In 2018, the same study[61] examined the role of HIF-1 α SNV rs11549467 in DFU occurrence. The frequencies of the GA genotype were significantly higher in patients with T2DM and DFU than in healthy controls. Thus, this genotype was considered a risk factor for both T2DM and DFU onset. Similar to their previous study[60], a decreased expression level of HIF-1 α was found among the patients with DFU compared to that in patients with T2DM and healthy controls. These findings suggest that HIF-1 α may play an important role in DFU pathogenesis. However, in-depth mechanistic studies are required.

Lysyl oxidase

Lysyl oxidase (LOX), an extracellular matrix-modifying enzyme, is associated with cell proliferation, metastasis, angiogenesis, and wound healing. Elevated expression of the LOX gene and accompanying cross-linked collagen fibrils in diabetic skin may lead to changes in tissue mechanical properties. These features are important for the regulation of tensile and elastic features of connective tissues[62,63]. LOX expression may be positively regulated by high glucose levels in diabetic skin[64]. LOX SNVs have also been associated with DFU development (Table 1).

In a 2017 case-control study, Pichu *et al*[65] analyzed the potential relationship between LOX SNV rs1800449 and susceptibility to DFU in an Indian population. The outcomes of 906 participants showed a significantly higher frequency of allele A among the DFU patients (42 %) than that among the controls (33%), with the AA genotype as a risk factor for DFU. Moreover, the LOX transcript level linked to the AA genotype among patients with DFU was significantly higher than that of the AA genotype among patients with T2DM and controls. This suggests that the increased expression of LOX may participate in the onset of DFU.

Intelectin 1

Intelectin 1 (ITLN1), also known as omentin, is encoded by the *ITLN1* gene located on the long arm of chromosome 1 (1q21.3)[66]. Mrozikiewicz-Rakowska *et al*[66] examined the potential role of rs2274907 in the development of DFU in a Polish population. Based on 670 individuals, they found that the T allele

was more frequent in the DF group than in the control group. Therefore, the TT genotype is a possible risk factor. In addition, this effect was sex-specific and observed in males (Table 1). Although the influence of such an SNV on the concentration of omentin in the DFU patients remains unclear, the authors introduced the underlying mechanisms regarding the protective effects of omentin on endothelium and smooth muscle cells for detail[66]. Omentin is able to stimulate NO production, leading to the endothelium-dependent vasodilation. In addition, omentin can also suppress the inflammatory response in endothelial cells by inhibiting the c-Jun N-terminal kinase activation *via* the AMP-activated protein kinase/eNOS signaling pathway. Furthermore, omentin decreases the adhesion of monocytes to endothelial cells by reducing expression of vascular cell adhesion protein-1 on the surface of monocytes as well as reducing the expression of intercellular adhesion molecule-1. Aside from endothelium, omentin also displayed an inhibitory effect on TNF- α -induced adhesion of monocytes in vascular smooth muscle cells of the rat. Nonetheless, the detailed mechanisms of ITLN1 SNVs in the development of DFU are still largely unknown and requires further research.

Mitogen-activated protein kinase 14

Mitogen-activated protein kinase 14 (MAPK14) targets a broad range of nuclear and cytosolic substrates that participate in a wide variety of cellular processes, such as proliferation, differentiation, apoptosis, transcription regulation, and development. It is a kinase involved in cellular responses to extracellular stimuli, such as pro-inflammatory cytokines or physical stress[67]. In a 2017 study, Meng *et al*[68] analyzed potential SNVs related to the development of DFU in a Scottish population. The results showed that rs80028505 was associated with increased susceptibility to DFU in a Scottish cohort (Table 1).

Toll-like receptors

Toll-like receptors (TLRs) superfamily members play a fundamental role in detecting invading pathogens or damage and initiating the innate immune system. Aberrant activation of TLRs exaggerates T cell-mediated autoimmune activation, causing unwanted inflammation and promoting DFU[69]. Recent studies have indicated that TLR SNVs are involved in DFU development (Table 1).

In a 2013 study, Singh *et al*[70] reported potential associations between TLR4 SNVs (rs4986790, rs4986791, rs11536858, rs1927911, and rs1927914) and susceptibility to DFU in an Indian population study. The results showed that these TLR4 SNVs correlated with an increased risk of developing DFU. They also reported 15 haplotypes with a frequency greater than 1%, and outcomes revealed that the haplotype ACATC displayed a strong association with DFU risk. In contrast, the haplotypes ATATC and ATGTT were noted to be protective against DFU. Furthermore, the authors also introduced two different models to predict the risk of DFU development. They proposed that the artificial neural network model was better than the multivariate linear regression model. In 2017, Wifi *et al*[71] analyzed the relationship between *TLR2* (rs3804100) and *TLR9* (rs5743836) SNVs and the risk of developing DF in an Egyptian population. The results suggest that rs5743836, rather than rs3804100, is associated with an elevated risk of DFU development among patients with T2DM. However, considering the limited number of eligible participants, cautious attitudes should be taken towards inferring the outcomes and conclusions.

Osteoprotegerin

Osteoprotegerin (OPG) plays a key role in the regulation of bone resorption and it belongs to the TNF superfamily. In a 2013 study, Nehring *et al*[72] examined the links between three SNVs (rs2073617, rs2073618, and rs3134069) located in the *TNFRSF11B* gene and the risk of DF development in a Polish population. The results showed that the C allele and CC genotype of rs2073618 were risk factors for DF onset in T2DM patients. For rs2073617, the mutant allele A and AG genotypes were protective against DF (Table 1).

Vitamin D receptor

Growing evidence has demonstrated that vitamin D receptor (VDR) SNVs are involved in the pathogenesis of several inflammatory disorders, such as fracture-related infection[73], tuberculosis[74], and periodontitis[75]. In a 2017 study, Soroush *et al*[76] analyzed the role of VDR SNV rs2228570 in the development of DFU in an Iranian population. The results showed that the frequencies of genotypes TT and TC among patients with DFU were significantly higher than those without DFU. This finding implies that such genotypes of this SNV present a risk factor to this cohort. In addition, they also evaluated the expression levels of oxidative stress indicators, thiobarbituric acid reactive substances (TBARS), and ferric-reducing ability of plasma (FRAP) among different genotypes of the SNV. The results showed that the median level of TBARS among patients with the TT and TC genotypes was significantly higher than that of the CC genotype. However, no statistical difference in FRAP levels between the two groups was noted. Nonetheless, no significant relationships were found between the genotypes and TBARS or FRAP levels among healthy controls. This suggests that one underlying mechanism of VDR SNV rs2228570 in DFU pathogenesis is partly *via* its influence on TBARS levels (Table 1).

Fibrinogen

Fibrinogen (FIB) and fibrin play important roles in multiple biological processes, including fibrinolysis, blood clotting, inflammation, wound healing, cellular and matrix interactions, and neoplasia. A recent study[77] confirmed the definitive role of FIB as a promising inflammatory marker in the discrimination of DFU. In a 2015 study, Zhao *et al*[78] investigated the correlation between *FIB* SNV rs6056 polymorphism and susceptibility towards DF in a Chinese population. Outcomes based on 300 subjects demonstrated that the mutant allele T, CT, and TT genotypes were risk factors for DF onset, following univariate logistic regression analysis. The TT genotype was associated with a relatively higher serological FIB level (Table 1).

LIMITATIONS AND FUTURE PERSPECTIVES

Increasing evidence has suggested that, in addition to extrinsic factors, intrinsic factors such as SNVs also participate in the development of DFU. However, these investigations had limitations. First, the sample sizes of most studies were limited; therefore, caution should be exercised regarding inferring relevant outcomes and conclusions. Second, most of the studies were conducted in Asian countries (*e.g.*, India, China, and Iran). To comprehensively evaluate the potential roles of SNVs in the pathogenesis of DFU, investigations focusing on different populations or ethnicities should be conducted in the future. Third, as the majority of the analyzed studies only reported preliminary findings based on case-control comparison outcomes, there is still a lack of in-depth research on mechanisms.

Based on these limitations, future studies should focus on two primary aspects. On the one hand, multi-center studies with larger sample sizes and diverse populations should be conducted. This will ensure a more accurate and comprehensive assessment of the potential roles of SNVs in the development of DFU. On the other hand, the detailed mechanisms should be investigated from different perspectives for SNVs with clinical significance.

CONCLUSION

Based on recent findings, SNVs located in the genes of *CRP* (rs11265260, rs1800947, rs2794520, rs1130864, rs3093059), *IL-6* (rs1800795), *TNF-α* (rs1800629, rs361525), *SDF-1* (rs1801157), *VEGF* (rs699947, rs2010963), *NRF2* (rs35652124, rs182428269), *SITR1* (rs12778366), *ICAM1* (rs5498, rs3093030), *MCP-1* (rs1024611), *eNOS* (Glu298Asp), *HSP-70* (rs2227956), *HIF-1α* (rs11549465, rs11549467), *LOX* (rs1800449), *ITLN1* (rs2274907), *MAPK14* (rs80028505), *TLRs* (rs5743836, rs4986790, rs4986791, rs11536858, rs1927914), *OPG* (rs2073617, rs2073618), *VDR* (rs2228570), and *FIB* (rs6056) may be important molecular players influencing the development and progression of DFU.

FOOTNOTES

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