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SYSTEMATIC REVIEW AND META-ANALYSIS OPEN ACCESS

Molecular Inflammatory, Oxidative Stress, and Angiogenic Pathways in Diabetic Foot Ulcer Pathogenesis: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Diabetic foot ulcer (DFU) is a serious health condition in diabetes mellitus and a primary reason of non-traumatic amputations of lower-limb worldwide. This study was intended to investigate the combined effect of inflammation, oxidative stress, and pathological angiogenic pathways in DFU. Methods: The extensive literature search included the use of PubMed, Web of Science, Google Scholar, and Scopus, from 2019 to 2025. Researches based on human subjects with DFUs were incorporated when they have quantitative data of inflammatory, oxidative stress or angiogenic biomarkers. Studies conducted in animal, or in vitro studies, and those without quantitative data were excluded. Funnel plot symmetry and Newcastle-Ottowa scale (NOS-adapted) was used to determine publication bias and risk of bias respectively. Results: Total seven studies fulfilled the inclusion criteria and meta-analyses were done in terms of a random-effects inverse-variance model. DFU pooled analyses showed significantly higher tumor necrosis factor-alpha (TNF-α) (SMD = 3.52; 95% CI: 2.22-4.83, p = 0.0001) and malondialdehyde (MDA) (SMD = 3.07; 95% CI: 1.67-4.48, p = 0.0001) levels in DFU when compared with controls whereas, the pooled analyses of vascular endothelial growth factor (VEGF) suggested similar pattern between the compared groups (SMD = 0.39; 95% CI: - 3.41 to 4.19, p = 0.84). Substantial heterogeneity was found (I^2 > 90%). There was moderate risk of bias among the included studies and certainty of evidence was also moderate according to GRADE assessment. Conclusion: High TNF-α and MDA concentrations could be utilized as molecular predictors for risk stratification by DFU and the severity of the disease.

Keywords: Diabetic Foot, Diabetes Mellitus, Wound Healing, Inflammation, Oxidative Stress, Angiogenesis, Tumor Necrosis Factor-alpha, Vascular Endothelial Growth Factor, Malondialdehyde

Diabetic foot ulcer (DFU) is a highly devastating and common side effect of diabetes mellitus, which follows a complex association of peripheral neuropathy, ischemia, abnormally impaired immune responses, impaired wound healing, and infection [1,2]. On a global scale, it is still a major cause of non-traumatic amputations of lower limbs [3]. DFUs are associated with chronic metabolic dysregulation, vascular impairment, and changes in the tissue repairing [4]. Despite the high level of wound management and protection against infections, the healing outcomes still need improvement.

DFU pathogenesis is mainly driven by inflammation that is linked to sustain mobilization of pro-inflammatory pathways and a disequilibrium between inflammatory and resolving mediators [5]. Higher cytokine concentrations including tumor necrosis factor-alpha (TNF-α) and interleukins lead to slower wound healing, extracellular matrix degradation, and prone infection [6]. Simultaneously, hyperglycemia results in excessive generation of reactive oxygen species due to oxidative stress causing lipid, protein and DNA damage, and associated biomarkers such as malondialdehyde are linked to ulcer severity [7,8]. Moreover, angiogenesis has a significant role in wound healing since an incapacitated neovascularization restrict the oxygen supply and nutrients to the affected area [9].

Angiogenic factors including VEGF, bFGF and sFlt-1, in case of dysregulation, interfere with granulation, tissue formation and epithelialization [10,11]. These pathways have been examined independently, but their association and how they work together to influence each other is still under-reported. The proposed study aimed to contribute in comprehending the cumulative impact of inflammatory, oxidative stress, and angiogenic mechanisms on DFU pathogenesis and provided evidence-based therapy guidance based on biomarkers.

Methodology

The study followed the PRISMA 2020 guidelines [12].

Data Sources: Databases such as PubMed, Web of Science, Google Scholar, and Scopus were searched thoroughly. All the pertinent studies that were published between 2019 and the December 2025 were included in the search. Besides, reference lists from eligible records were manually screened to find relevant studies.

Search Strategy: To identify DFU and related molecular pathways, a representative search strategy was used containing both MeSH and free-text terms. The Boolean operators were used to combine concepts of search, including (("diabetic foot ulcer" OR "DFU") AND ("inflammation" OR "inflammatory markers" OR "TNF-alpha" OR "IL-6") AND ("oxidative stress" OR "malondialdehyde" OR "MDA") AND ("angiogenesis" OR "VEGF" OR "bFGF" OR "sFlt-1").

Eligibility Criteria: Studies involving comparative analysis of patients suffering from DFU and diabetic patients without ulcers and/or healthy controls and reporting quantitative measure of inflammatory, oxidative stress, or angiogenic molecular markers and extractable outcome data (mean ± standard deviation, effect estimates or adequate raw data) were included. Excluded studies were case reports, editorials, reviews, abstracts of conferences, animal or in vitro researches, non-comparative studies, articles that could not contain extractable quantitative data and those that were not published in English.

Study Selection: The titles and abstracts of each identified study was screened by two independent reviewers. Eligibility criteria were applied and studies with full-text access were selected. In case of conflict between the two reviewers, decision was made by a third reviewer.

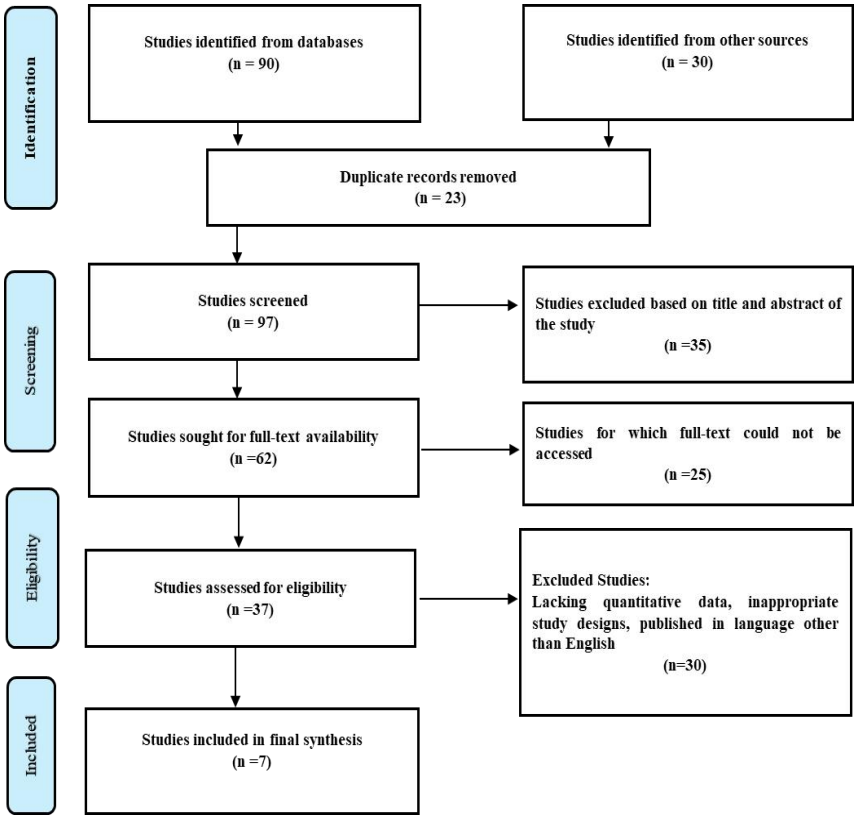

Figure 1: PRISMA Flow Diagram

Data Extraction: The standardized form was used by two independent reviewers to extract the data. The extracted information included name of the author, publication year, name of country where research had been conducted, design of the study, sample size, characteristics of the participants, molecular markers measured, type of biological sample used, outcomes measured, and key findings. In cases where data were missing or not clear, respective authors were contacted. In case of no response, missing values were estimated based on the available summary statistics, no imputation was done for completely missing data.

Outcome: The primary outcome was to evaluate the differences in levels of angiogenic marker, inflammatory marker, and oxidation stress marker in DFU and control groups. The secondary outcome was to establish the association between the levels of molecular markers and the DFU severity, the presence of infection, wound healing, and prognosis.

Statistical Analysis: MetaAnalysisOnline tool was used to perform statistical analysis and to generate forest plots by using a random-effect model with an inverse-variance approach, as required by the study design [13]. The results were reported in standardized mean differences (SMDs) and 95% confidence intervals (CI). The p-value was set at less than 0.05, whereas I^2 statistics was calculated to measure heterogeneity and any value above 50% was assumed to represent high heterogeneity. In instances where meta-analysis was not applicable due to study heterogeneity or inadequate data, the synthesization of results was done in a narrative manner.

Quality and Bias Assessment: Newcastle-Ottawa Scale (NOS)-adapted was utilized by two independent reviewers to analyze the risk of bias among observational studies [14]. In addition to the areas of selection, comparability, and outcome assessment, control of confounders was analyzed separately to ensure reporting clarity. The general quality of evidence was assessed through GRADE approach [15]. The publication bias of outcomes incorporated in the meta-analysis was analyzed by funnel plots. Funnel plots were generated using the effect sizes against the standard errors [16].

Results

An extensive search of the identified electronic databases and additional sources retrieved 120 records on molecular inflammatory, oxidative stress, or angiogenic pathways involved in the pathogenesis of DFU. After the removal of 23 duplicate records, titles and abstracts of studies were filtered based on relevancy and 35 studies were further eliminated. The full-text were not retrieved for 25 articles and the rest of the articles were then evaluated on eligibility criteria, leading to inclusion of seven studies in the qualitative analysis and quantitative analysis when feasible. A PRISMA flow diagram for the systematic process of study selection was provided in Figure 1. The selected studies had been published between 2019 and 2025 from India, China, Japan, Iraq, and Egypt. The study designs included were hospital-based case-control studies, cross sectional observational, retrospective comparative studies and a randomized controlled trial. Sample sizes ranged from 32 to 189 participants per cohort of DFU patients, diabetic patients with no ulcers, and healthy controls. A summary of the study design, methodological characteristics and key findings of the included studies was shown in Table 1.

Table 1. Study Design, Methodological Characteristics and Key Findings of the Included Studies

Study & Year	Country	Study Design	Sample Size (DFU / Diabetes / Control)	Molecular Markers Assessed	Outcomes Measured	Key Findings
Al-Khalidi et al., 2025 [17]	Iraq	Hospital-based case–control	90 (30 DFU, 30 diabetes without ulcer, 30 healthy control)	IL-10, IL-18, TNF-α, bFGF	Serum biomarker levels	Elevated TNF-α, IL-18; reduced IL-10 and altered bFGF
Wang et al., 2025 [18]	China	Observational cohort (infection-based comparison)	144 (70 infection, 74 non-infection)	TNF-α, IL-6, IFN-γ	Infection severity, prognosis	Inflammatory cytokines increased with infection severity and prognosis
Guo et al., 2025 [19]	India	Retrospective comparative study	80 (40 control, 40 MRDO-DFU patients)	Inflammatory markers, VEGF	Inflammatory indices, VEGF, wound healing, bacterial clearance,	Reduced inflammation, improved VEGF, faster healing, shorter hospitalization
Dhamodharana et al., 2019 [20]	India	Randomized controlled trial	32 (HBO:15, Non-HBO:17)	Nrf2, EGF, VEGF, PDGF, FGF-2, CXCL10, eNOS, nitrite	Tissue biomarker levels, angiogenesis	HBO enhanced antioxidant defense, angiogenesis, and tissue repair
Nyamadzawo et al., 2025 [21]	Japan	Cross-sectional observational	44 diabetics (with DFU) + 32 non-diabetics	Urinary MDA	DFU severity, oxidative stress	Urinary MDA correlated strongly with DFU severity
Sangeeta et al., 2025 [22]	India	Cross-sectional observational	189 (Control:63, Pre-ulcer:63, Ulcer:63)	IL-6, TNF-α, CRP, MDA, MMP-9, VEGF, ICAM-1	Biomarker levels, peripheral neuropathy, PAD	Inflammation and oxidative stress increased across disease stages
Abd El-Khalik et al., 2020 [23]	Egypt	Case–control	60 (30 DFU, 30 diabetic without DFU) + 20 healthy controls	sFlt-1, VEGF, AOPPs, MDA, Total thiol, TNF-α	Biomarker levels	Inflammation, oxidative stress elevated; angiogenic imbalance present

Abbreviations: *AOPPs = Advanced Oxidation Protein Products, ALBC = Antibiotic-Loaded Bone Cement, AUC = Area Under the Curve, bFGF = Basic Fibroblast Growth Factor, CRP = C-Reactive Protein, CXCL10 = C-X-C Motif Chemokine Ligand 10, DFU = Diabetic Foot Ulcer, DM = Diabetes Mellitus, EGF = Epidermal Growth Factor, eNOS = Endothelial Nitric Oxide Synthase, FGF-2 = Fibroblast Growth Factor-2, HBO = Hyperbaric Oxygen (therapy), ICAM-1 = Intercellular Adhesion Molecule-1, IFN-γ = Interferon Gamma, IL-6 = Interleukin-6, IL-10 = Interleukin-10, IL-18 = Interleukin-18, MDRO-DFU = Multidrug-Resistant Organism-Associated Diabetic Foot Ulcer, MDA = Malondialdehyde, MMP-9 = Matrix Metalloproteinase-9, NPWT = Negative Pressure Wound Therapy, Nrf2 = Nuclear Factor Erythroid 2–Related Factor 2, PAD = Peripheral Arterial Disease, PDGF = Platelet-Derived Growth Factor, rs = Spearman's Rank Correlation Coefficient, sFlt-1 = Soluble Fms-Like Tyrosine Kinase-1, TNF-α = Tumor Necrosis Factor Alpha, VEGF = Vascular Endothelial Growth Factor*

Overall, the studies have assessed a wide range of molecular biomarkers, including inflammatory markers (i.e., TNF-α, IL-6, IL-18, IL-10, CRP), markers of oxidative stress (malondialdehyde [MDA], total thiol, urinary MDA), angiogenic and endothelial biomarkers (VEGF, sFlt-1, bFGF, PDGF, EGF). Generally, the qualitative synthesis revealed coherent evidence of up-regulation of inflammatory stress and oxidative stress biomarkers in DFU patients versus diabetic patients without ulcers and healthy controls, and an abnormal angiogenic signaling, involving VEGF and its inhibitors. Dhamodarana et al.[20], was the only RCT-based study among the selected articles, therefore data was only utilized for narrative synthesis. The meta-analysis comprised six articles to determine the interconnection among inflammatory, oxidative stress, and angiogenic pathways of DFU by quantifying the concentrations of TNF-α, MDA, and VEGF, respectively. A total of three articles that measured VEGF levels were analyzed to create a forest plot. Total 133 participants were in the experimental/DFU group and 123 participants were in the healthy control group. A pooled analysis based on a random-effects inverse-variance model did not find significant difference between two cohorts (SMD = 0.39; 95% CI: -3.41 to 4.19, p = 0.84). Significant heterogeneity was found with I^2 = 99%, suggesting a significant difference in the magnitude and direction of the effect sizes presented by the studies (Figure 2).

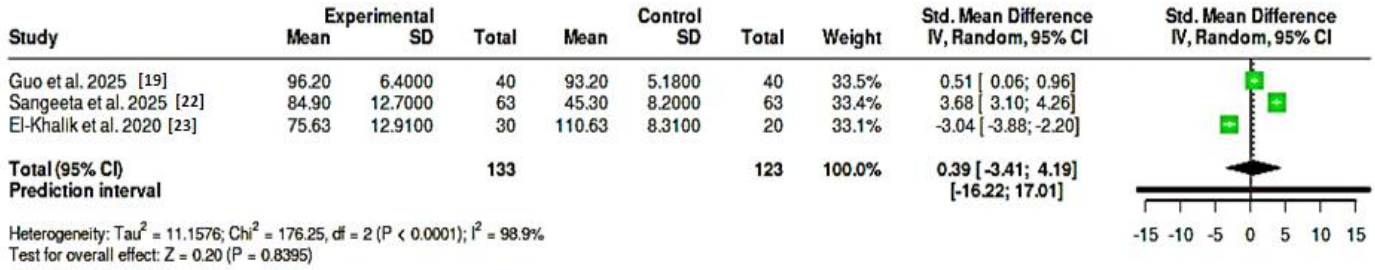

Figure 2. Forest plot of Vascular Endothelial Growth Factor (VEGF) levels in diabetic foot ulcer (DFU) patients versus healthy controls

A total of 4 studies comprising of 193 DFU patients and 187 control subjects were combined for TNF-α analysis. The results indicated that the level of TNF-α in DFU patients was considerably greater than in controls (SMD = 3.52, 95% CI = 2.22 - 4.83), and the effect was statistically significant ($p < 0.05$). There existed a level of pronounced heterogeneity the $I^2 = 94.7\%$, ($p < 0.01$) which might be referring to inter-study variations in population, disease severity and methods of assessing biomarkers (Figure 3).

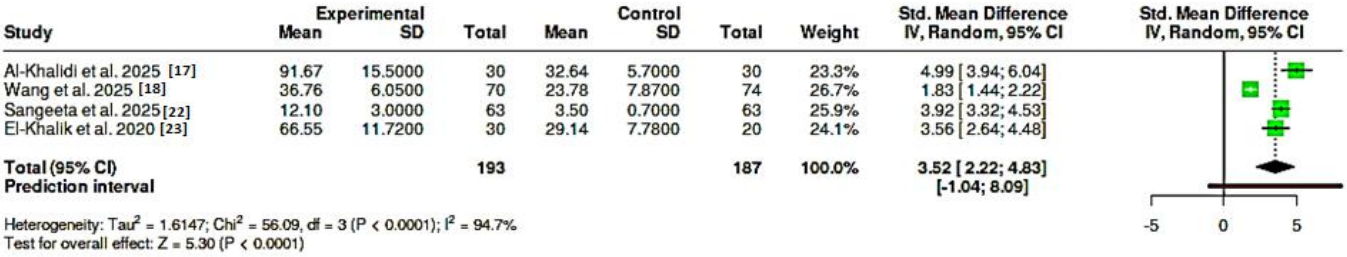

Figure 3. Forest plot of Tumor Necrosis Factor-Alpha (TNF-α) levels in diabetic foot ulcer (DFU) patients versus healthy controls

There were 3 studies that evaluated oxidative stress in terms of MDA levels including 114 DFU patients and 151 controls including healthy controls and diabetic patients without ulcers. The combined outcomes showed a statistically significant increase in MDA levels in DFU patients (SMD = 3.07; 95% CI: 1.67-4.48, $p < 0.05$). Heterogeneity was found to be high ($p < 0.01$) with the I^2 value being 93.6% indicating that there was a significant methodological and clinical variation in the included studies (Figure 4).

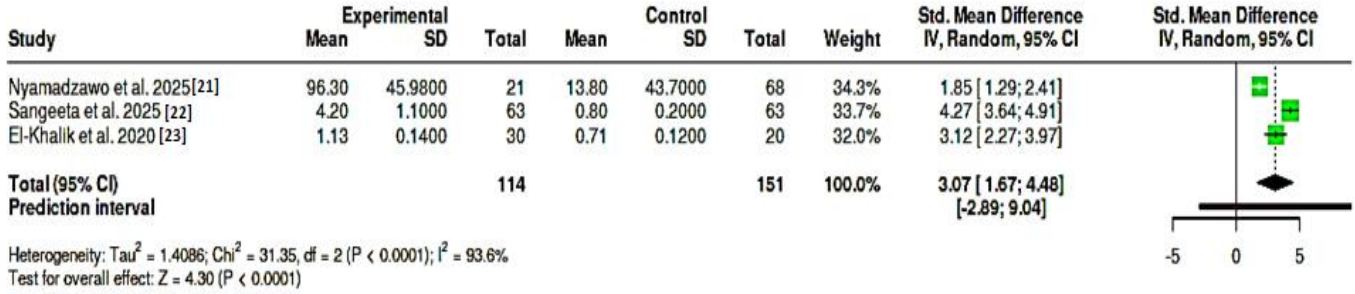

Figure 4. Forest plot of Malondialdehyde (MDA) levels in diabetic foot ulcer (DFU) patients versus controls (healthy controls/diabetic patient without ulcer)

Heterogeneity between studies were examined using a subgroup analysis. TNF-α was found to be the most reliable inflammatory cytokine to differentiate among DFU, non-ulcerated diabetes and healthy controls, with the levels rising proportionately to the severity of the ulcer, as well as to infection. Strong and reproducible correlations between oxidative stress as indicated by high MDA and presence of DFU indicated its pivot position in tissue injury and disease progression. Angiogenic processes were also stage-specific: VEGF was either elevated at the early or pre-ulcerative stage but functionally invalid in the late DFU, where it was involved in impaired wound healing.

Secondary subgroup analyses revealed that profiles of these biomarkers varied based on clinical severity, prognosis, and the stage of therapy. A combination of inflammatory markers, where TNF-α, had high discriminatory ability in adverse outcomes in infected DFUs but oxidative stress markers, were high at advance stages of the disease. The interventional subgroups showed that clinical outcomes were significantly influenced by the type of pathway involved. For example, treatment aimed at antioxidant and angiogenic responses, including higher surveillance of the VEGF activity, was linked to a greater wound healing and recovery, endorsing the prognostic and therapeutic value of these molecular signatures. The pooled estimates proved to be robust as shown in sensitivity analyses. In VEGF-based studies, no effect on exclusion of individual studies was observed, suggesting an overall stable finding. Among TNF-α related studies, the elimination of Wang et al.[18] led to slight decrease of the heterogeneity ($I^2 = 53.6\%$), whereas, in MDA-relevant studies, upon exclusion of Nyamadzawo et al.[21], the heterogeneity decreased to 77.8% without altering the overall direction of effect. The potential risk of bias was evaluated by using the proper tools as per the study design as shown in Table 2. Moderate risk of bias was observed for most of the observational studies and RCTs with potential risk of bias.

Table 2: Risk of Bias Assessment of Included Studies

Risk of Bias Assessment of Included Observational Studies Using NOS-Adapted Domains					
Study	**Selection**	**Comparability**	**Outcome / Exposure**	**Confounding**	**Overall Risk**
Al-Khalidi et al., 2025 [17]	🟢 Clear case-control definition	🟡 Age/sex matched only	🟢 Validated ELISA in duplicates	🟡 Limited adjustment	🟡 Minor limitations in confounding control
Wang et al., 2025 [18]	🟢 Clear criteria for inclusion/exclusion	🟡 Grouping by infection status	🟢 Standardized ELISA, ROC analysis	🟡 Partial adjustment	🟡 Overall moderate confidence
Guo et al., 2025 [19]	🟡 Retrospective design	🟡 Unclear Baseline comparability	🟢 Objective lab outcomes	🔴 Limited confounder control	🟡–🔴 One domain showed high risk
Nyamadzawo et al., 2025 [21]	🔴 Purposive sampling, pilot study	🟡 Unclear Grouping	🟢 Validated assays	🔴 Repeated measures treated as independent	🔴 Multiple high-risk domains
Sangeeta et al., 2025 [22]	🟢 Clear group definitions	🟢 Well-defined exclusion criteria	🟢 Blinded lab analysis	🟡 No multivariable modeling	🟡 Minor confounding concerns
El-Khalik et al., 2020 [23]	🟢 Clear group definitions	🟢 Matched groups	🟢 ELISA + molecular validation	🟡 Moderate	🟢–🟡 Slight limitations in confounding control

Risk of Bias Assessment of Included Randomized Controlled Trial Using Cochrane RoB-2 tool								
Study	**Random sequence generation**	**Allocation concealment**	**Blinding of participants & personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**	**Overall risk**
Dhamodharana et al., 2019 [20]	Unclear risk (method not described)	Unclear risk (concealment not reported)	High risk (no sham intervention)	Unclear risk (assessor blinding unclear)	Low risk (complete outcome data)	Low risk (outcomes prespecified)	Unclear risk (small sample size)	Moderate

🟢 = *Low risk of bias,* 🟡 = *Moderate risk of bias,* 🔴 = *High risk of bias,* 🟡–🔴 = *Moderate to High,* 🟢–🟡 = *Low-to moderate risk. Overall, a moderate to high risk of bias was observed in the included studies.*

TNF-α, MDA, and VEGF were also assessed for the publication bias by using funnel plots. The visual examination of the funnel plots of the three biomarkers did not imply asymmetry, suggesting no significant publication bias. Due to limited number of studies in each plot Egger's test was not performed and statistical inference was not established. Overall, the funnel plot findings showed no evidence of publication bias between the selected studies of the three molecular markers as shown in Figure 5. According to the GRADE assessment, the overall certainty of evidence was moderate in the case of TNF-α and MDA and moderate to low in the case of VEGF.

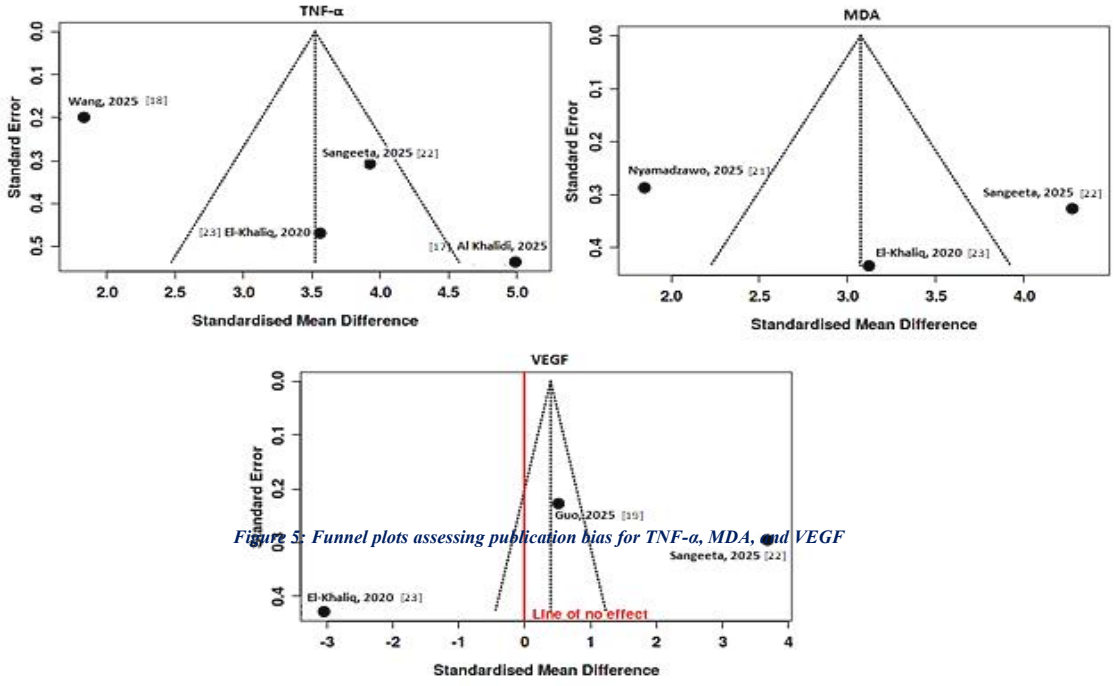

Figure 5: Funnel plots assessing publication bias for TNF-α, MDA, and VEGF

Discussion

This study reviewed the molecular markers of inflammatory, oxidative stress and angiogenic pathways that are involved in differential expression among DFU patients, non-ulcerative diabetic patients and healthy controls. Levels of TNF-α were considerably higher among DFU patients, reflecting it was a major mediator of persistent inflammation, endothelial dysfunction, and failure of extracellular matrix remodeling [24,25]. These findings are in concomitant with other experimental and clinical studies which suggested long-term TNF-α activity in chronic wounds [26]. Moreover, the extended period of inflammation interfered with cell migration (fibroblasts), collagen formation, and angiogenic competence [27-29]. TNF-α levels had been

found to be similar in all infected DFU and ischemic ulcers and was linked with severity of the disease and poor healing [30,31]. Although there was heterogeneity among studies, the results demonstrated the stability of the direction and strength of effect of TNF-α as a potential molecular marker of the DFU pathology.

The finding of oxidative stress as an independent and concomitant initiator of DFU chronicity was also observed. The elevated levels of MDA in the included studies reflected the overproduction of lipid peroxidation and the inefficiency of redox homeostasis in ulcerated tissue [32,33]. These results are in accord with the earlier reports that claimed association between hyperglycemia-induced reactive oxygen species generation and endothelial damage, decreased bioavailability of nitric oxide and microvascular dysfunction of diabetic wounds [34-36]. Positive correlation of MDA with ulcer severity revealed that oxidative damage is a major enhancer of inflammatory damage and tissue necrosis [37,38]. Conversely, angiogenic signaling did not play any considerable role in DFU as suggested by insignificant difference in the VEGF-based pooled results between the DFU and control patients. This contradiction was supported by existing literature which reported that VEGF expression in DFUs is strongly circumstantial [39,40]. Early/pre-ulcerative stages could be at least compensatory with upregulation of VEGF, however, advanced ulcers were characterized by functional angiogenic failure, receptor resistance, ischemia, as well as inhibitory agents including tyrosine kinase-1 [41,42]. Together, these results suggested that chronic inflammation with oxidative stress promote the development of ulcers and unregulated angiogenesis inhibits tissue healing [43].

This review had several limitations. The included studies were mostly observational, which restricted causal inference. The heterogeneity was high because of the variations in the populations of patients, severity of ulcers, infection level and the methods used to identify biomarkers. Confounder adjustment variability and a single time point measurement of biomarkers only decreased comparability. Also, the use of English-language publications and lack of protocol registration may have led to selection and reporting bias. The prospective multicenter studies with standardized biomarker assays and longitudinal sampling should be prioritized in future, to better capture the dynamics of the disease. A combination of multi-omics framework for inflammatory, oxidative stress, and angiogenic markers could streamline risk stratification and prognosis of DFU. These methods would allow biomarker-informed, personalized therapies against inflammation, redox plasticity and vascular pathology.

Conclusion

This meta-analysis and systematic review indicated that diabetic foot ulcer pathogenesis was linked to chronic inflammatory process and oxidative stress as revealed by the stable increase of the TNF-α and MDA concentrations. The uncontrolled angiogenic signaling was another aspect that led to wound healing impairments indicating the necessity of combining molecular interventions to enhance risk stratification and specific therapeutic interventions in the management of DFU.

Acknowledgement

None

Conflict of Interest

None

Grant Support & Funding Source

None

Authors' Contribution

NA, FA contributed significantly. MA, EEK and KU participated equally as per ICMJE. All authors gave their final approval to publish this article.

Ethical Statement

Not applicable for this study design

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