E-ISSN: 3068-5052
Journal of Regenerative Medicine & Biology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

A Review of Inflammation and the Role of Pro and Anti-Inflammatory Cytokines in Diabetes and Chronic Diabetic Ulcers

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Citation: Sengupta P, et al. A Review of Inflammation and the Role of Pro and Anti-Inflammatory Cytokines in Diabetes and Chronic Diabetic Ulcers. J Reg Med Biol Res. 2025;6(3):1-6.

https://doi.org/10.46889/JRMBR.2025/6301

Received Date: 04-09-2025

Accepted Date: 22-09-2025

Published Date: 29-09-2025

Abstract

Diabetic ulcers, especially foot ulcers, represent a significant clinical and socioeconomic burden, due to impaired wound healing driven by chronic inflammation. In contrast, reduced levels of IL-10 and TGF-β further exacerbate poor healing outcomes therefore highlighting the crucial interplay between pro and anti-inflammatory cytokines. Also, advanced glycation and lipoxidation end-products, oxidative stress and immune dysregulation amplify tissue injury and impair cellular defence mechanisms.

In the formation of advanced protein glycosylation reactions, hyperglycaemia, along with oxygen-free radicals, is also a contributing factor to the non-healing of ulcers. Advanced glycation end products or AGE products, are implicated in various diabetic complications and inflammation. Another less characterized synthetic end product is advanced lipoxidation end product or ALE, which is implicated in the increased expression of cyclooxygenase-2, MCP-1, IL-6 and eight dysfunction. In fact, even keratinocytes, microvascular endothelial cells, excessive production of free oxygen radicals and NO are also involved in cytokine dysregulation and non-healing of diabetic ulcers.

Together, these alterations result in chronic, non-resolving wounds characteristic of DFUs. Understanding these inflammatory mechanisms will help to shed light on the pathophysiology of impaired healing but also identifies potential biomarkers and therapeutic targets for improving DFU management. The following review highlights the complex interplay of pro- and anti-inflammatory cytokines, chemokines and growth factors that disrupt the normal wound-healing cascade in diabetic patients. High levels of TNF-α, IL-1β, IL-6, CRP and other mediators contribute to persistent low-grade inflammation, impaired fibroblast function, excessive extracellular matrix degradation and delayed angiogenesis.

Keywords: Diabetic Ulcers; Diabetic Foot Ulcers; Chronic; Inflammation; Inflammatory Cytokines; Chemokines; Pro-Inflammatory Cytokines; Anti-Inflammatory Cytokines; Wound

Inflammation in Diabetes

Most patients with diabetic foot ulcers, poor healing is linked to high levels of certain inflammatory biomarkers such as C-reactive protein and several pro-inflammatory cytokines, including Tumour Necrosis Factor α (TNFα), Granulocyte-Colony Stimulating Factor (G-CSF) and Interleukin (IL)-1 β, IL-2 and IL-6. These markers have been persistently found to be in elevated levels in diabetic patients even before the development of ulcers, suggesting they might not be the sole drivers of ulcer formation but can negatively impact the wound healing process. Further, secretion of MMP-9, tissue Plasminogen Activator (tPA) and PTPB1 impedes the activity of growth factors crucial for tissue repair. Conversely, growth factors such as Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF) and TGF-α can promote healing when present in adequate

concentrations [1-4].

Matrix metalloproteinases expressed in chronic wounds cause a functional breakdown of the extracellular matrix [5]. In one study, macrophages isolated from mice with diabetic wounds have exhibited a lower response to remove dead and pathogenic cells, resulting in prolonged inflammation [6].

Further, a state of chronic low-grade inflammation is a common pathological manifestation in diabetes type 2 diabetes mellitus. A previous study reported that the levels of IL-1α, IL-6 and IL-4 were elevated acutely during hyperglycaemia in both type 1 and type 2 diabetes [7].

In patients with metabolic syndrome, as in those with diabetes, peripheral inflammation, characterized by the release of leukocytes and pro-inflammatory mediators, is an important phenomenon, particularly in relation to glucose levels and neutrophil dysfunction. In T2DM, Th1, IL-6 and TNF-α dominate over the regulation of Th2 cells and their cytokine production, such as IL-4 and IL-10 [8].

Inflammation in Diabetic Wound Healing

DFUs primarily arise from diabetic neuropathy and peripheral artery disease, either independently or in combination, leading to microvascular complications, biomechanical abnormalities, increased morbidity and heightened susceptibility to infections [9,10]. Selvin, et al., reported that each 1% rise in haemoglobin A1c is associated with a 26% higher risk of developing peripheral artery disease [11]. Similarly, Zubair, et al., demonstrated that patients with diabetic foot ulcers exhibit elevated levels of IL-6, hsCRP and TNF-α, alongside reduced concentrations of adiponectin [12]. Normally, the different pro-inflammatory cytokines involved immediately after a wound in both humans and animals are IL-1α, IL-1β, IL-6, IL-12 and TNF-α [13]. Chemokines secreted from keratinocytes, such as CXCL1, CXCL5 and CXCL8, also play an important role in the upregulation of pro-inflammatory cytokines during wound healing. Their induced expression stimulates the synthesis of neutrophils, leukocytes, monocytes and macrophages, which are then directed to the wound site to remove foreign materials. These chemokines also induce the proliferation of epithelial stem cells and mesenchymal stem cells [14-16].

Impairment in diabetes wound healing is due to the presence of fewer early inflammatory cells and an increased number of neutrophils and macrophages in the later stages, which are related to alterations in chemokine and growth factor expression. Tumour Necrosis Factor-α (TNF-α), a major pro-inflammatory factor, stimulated the keratinocytes and the fibroblasts to release growth factors during the first 12 to 24 hours post-wound formation, followed by the proliferating phase, where the Tumour Necrosis Factor-α (TNF-α) returns to normal or baseline levels. Further, at the wound site, the neutrophils and macrophages all bind to specific proteins of the ECM and bring in about the phagocytic activity for removing the foreign bodies as mentioned before and help in the synthesis of chemokines, chemoattractant, growth factors and cytokines to form a granulation or a connective tissue through several signaling cascades. These help in the migration of the endothelial cells, fibroblasts and the stem cells from the adjacent dermis. Therefore, this phase becomes crucial as collagen and ECM proteins are synthesized, playing a significant role in the interplay between inflammation and repair through cell influx. This process is highly conserved and is tightly regulated, requiring a self-limited inflammatory response for proper wound healing [16,17]. However, in the case of diabetic wounds, high levels of Tumour Necrosis Factor-α (TNF-α) are observed due to impaired fibroblast proliferation, resulting in the inhibition of angiogenesis, differentiation, migration and apoptosis [18].

TNF-α's main source is macrophages; however, it can also be produced by adipose tissue, neurons, mast cells and lymphocytes [19,20]. In combination with IL-1β and IL-6, it can stimulate the acute-phase response, act as a potent neutrophil chemoattractant and stimulate the classical activation of macrophages. *In-vitro*, TNF-α also stimulates apoptosis of fibroblasts, keratinocytes and endothelial cells [21,22]. STZ-injected diabetic rats displayed significantly higher levels of serum TNF-α by day 4 post-wounding. Diabetic patients have also shown a significant upregulation in serum TNF-α during high blood glucose events compared with a relatively little change observed in normal patients [23]. Additionally, TNF-α has been observed to be elevated in the serum of obese patients [24]. Acute hyperglycaemia appears to trigger a much stronger upregulation of TNF-α in people with diabetes, lending further credence to the overall chronic inflammatory state seen in this disease.

Pro- and Anti-Inflammatory Markers

IL-1β

It is an important pro-inflammatory cytokine that is activated via the caspase-1 cleavage in the secretory lysosome after caspase-1 activation by the NALP3 inflammasome. It is produced by blood monocytes and tissue macrophages, stimulating the inflammatory process by increasing the mobilization of leukocytes from the bone marrow and the secretion of acute-phase proteins from the liver [25,26]. It is believed that obese patients have a sustained release of this IL-1 Beta from the adipose tissue and can have a broad effect on the distribution of the IL-1 receptor. Elevated levels of IL-1β have been implicated in the development of insulin resistance and aberrant wound healing in diabetes [27]. In cases of human foot ulcers, there has also been an increased level of IL-1 beta, which has been found to decrease as the wound heals properly [28].

IL-2

IL-2, a pro-inflammatory cytokine, plays a crucial role in the wound healing process. It is usually present in the early stages of wound healing and guides the T-cell proliferation. Apart from orchestrating the immune response, IL-2 also modulates the release of cytokines and growth factors and stimulates the production of TH1 cells. These TH1 cells secrete Interferon-γ (IFN-γ), which boosts wound healing. Along with IFN-α, IL-2 also promotes angiogenesis and the proliferation of endothelial cells, which are required for revascularization and tissue healing [29]. During the early stages of inflammation in wound healing, IL-2 levels reach a peak level and progressively declines down by around day 14. This downregulation plays an important role in the wound healing process. Elevated IL-2 concentrations, present both locally and systemically, support the early recruitment of immune effector cells such as macrophages and neutrophils. As healing advances, IL-2 levels subsequently decrease, likely influenced by T-regulatory cell signaling which helps in resolving inflammation also [29].

IL-6

It is another class of pro-inflammatory cytokine secreted by the T lymphocytes and the macrophages and is critical in host defence [30]. Visceral fat, also known as adipose tissue, is a significant reservoir of IL-6, which stimulates the release of acute-phase proteins from the liver, promotes the production of neutrophils in the bone marrow and supports the proliferation of B lymphocytes. It also influences the recruitment of leukocytes through the release of IL-8 and MCP-1 from endothelial cells [31]. In diabetes, insulin resistance, hyperglycaemia and beta-cell inflammation are all associated with increased levels of IL-6 [31,32]. Blood glucose concentration and wound chronicity have a strong direct relationship with the increased IL-6 expression in diabetic foot ulcers and their blocking has been shown to successfully reduce inflammation and heal chronic wounds [33].

C-Reactive Protein

C-reactive protein can upregulate adhesion molecules expressed on endothelial cells and increase the release of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α. As CRP is regulated transcriptionally by IL-6 and IL-1β, it can result in a cyclic amplification of inflammation. Both Type 1 and Type 2 diabetic patients have significantly elevated CRP in their plasma [34,35].

Diabetic patients with diabetic foot ulcers also display significantly higher CRP in their serum when compared with wounded non-diabetic patients or diabetics without foot ulcers and CRP levels were significantly lower for those diabetic patients with healed ulcers [36]. This indicates the potential of CRP as a clinical biomarker for diabetic foot ulcer healing.

IL-10

It is one of the few anti-inflammatory cytokines secreted mainly by the T helper cells, regulatory T-cells, macrophages and dendritic cells [37,38]. Human diabetic foot ulcers have shown a decrease in the expression of IL-10 cytokines, particularly in the keratinocytes and at the wound margins [39]. The expression of this anti-inflammatory cytokine is quite low in diabetic wounds, which might be implicated in the development of chronic non-healing wounds.

TGF-β

TGF-β functions as a chemoattractant for neutrophils and monocytes during the early stages of diabetic wound healing and also stimulates monocyte-to-macrophage differentiation, fibroblast proliferation and extracellular matrix synthesis [40]. Immediately after injury, it is secreted by platelets, keratinocytes, resident macrophages and fibroblasts [41]. As such, TGF-β experiences a

biphasic expression during normal wound healing that peaks within a few hours and again at 5 days post-injury [42]. In a rat model of type 2 diabetes mellitus, TGF-β reduction was associated with delayed wound healing and impaired fibroblast migration [43]. Similarly, in diabetic foot ulcer patients, there has been a decrease in the TGF-β level and its receptor, which is associated with delayed wound closure [44]. The concentration of this cytokine in patients with Type 2 diabetes and chronic ulcers also correlates with decreased matrix metalloproteinase activity and an increase in tissue inhibitors of matrix metalloproteinases [45]. Thereby, it can be concluded that delay in diabetic wound healing is attributed to lower levels of TGF-β.

Discussion

Both type I and type II diabetes are characterized by sustained hyperglycaemia and a chronic elevation of pro-inflammatory mediators, creating an environment that induces and perpetuates inflammatory responses, leading to a chronic inflammatory state. However, this condition is a low-grade inflammation and the hyperglycaemic background leads to impaired cellular defence mechanisms [3]. In normal wound healing, where inflammation occurs in an orderly, sequential manner, in patients with T2DM and ulcers, the immune reaction appears to be prolonged and ineffective in nature, with a reduction in chemotactic and phagocytic activity [17]. The above evidence highlights the important role of dysregulated inflammation in the pathogenesis and persistence of DFUs. The levels of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-2, IL-6 and CRP are consistently up-regulated in diabetic patients, often preceding ulcer formation and contribute to impaired fibroblast activity, excessive extracellular matrix degradation and delayed angiogenesis. On the other hand, reduced concentrations of anti-inflammatory cytokines such as IL-10 and TGF-β exacerbate the imbalance, creating a prolonged inflammatory milieu that hinders progression into the proliferative and remodeling phases of wound healing. Upregulation of matrix metalloproteinase activity, accumulation of advanced glycation and lipoxidation end-products, oxidative stress and immune dysfunction, further disrupt the wound healing process and impair repair responses. These findings emphasize that DFUs are molecularly driven by a complex interplay of inflammatory mediators, chemokines and growth factors whose imbalance sustains chronic, non-resolving wounds. A clearer understanding of these molecular and cellular mechanisms is the key to understanding the pathophysiology of chronic diabetic wound healing along with the identification of potential biomarkers and therapeutic targets.

Conclusion

Wound healing in diabetic patients is profoundly influenced by a sustained pro-inflammatory environment, characterized by up regulation of different cytokines, dysregulated chemokines, oxidative stress and impaired cellular repair responses. Acute inflammation is a part of healing process, however, in diabetes its persistence becomes a barrier to wound repair. Reduced anti-inflammatory cytokines, growth factors further disrupts this balance, underscoring the need for immunomodulatory therapies and restore growth factor activities and address metabolic dysfunctions. Further research is required to translate these mechanisms into interventions that would accelerate healing and risk of amputation.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

Not applicable.

Funding

None.

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