An Update on the Potential Inflammatory and Oxidative Biomarkers for the Early Assessment of Diabetic Foot Ulcer: A Review

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ABSTRACT

Diabetic foot ulcers (DFUs) has been identified as most chronic diabetes complications, contributing to raise morbidity and increased healthcare expenses and exaggerated risk of limb amputation. Early diagnosis is quite important to prevent the progressive development of DFUs and to reduce the disability, mortality rate and hospitalization. Severe inflammation has been recognized as major key pathogenic feature of DFU; however role played by inflammation on the DFU diagnosis remain unclear. In recent years, inflammatory and oxidative biomarkers facilitate a non-invasive strategy for the early assessment of diabetic foot ulceration. Various inflammatory and oxidative biomarkers such as interleukins, tumor necrosis factor and C-reactive protein have been widely used as biomarkers for the assessment of DFUs. In this review article, advanced inflammatory and oxidative biomarkers that can facilitate accurate early assessment of DFU will be discussed in detail. Studies which include detailed discussion regarding the evaluation of diagnostic and comparative efficacy of inflammatory and oxidative biomarkers wee included in this manuscript.

Keywords: Limb amputations, biomarkers, interleukins, Tumor necrosis factor,

Abbreviations

DM- Diabetes mellitus

DFU-Diabeic foot ulcer

MMP-9- Matrix metalloproteinase-9

ICAM-1- Intracellular adhesion molecule-1

CRP- C-reactive protein

PCT- Procalcitonin

NIDFU - Non-infectious diabetic foot ulcer

IDFU -infectious diabetic foot ulcer

WDFU- Without diabetic foot ulceration\

ECM- extracellular matrix

IL- interleukins

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TNF- Tumor necrosis factor

BAFF -B-cell activating factor

ROS- reactive oxygen species

INTRODUCTION

Diabetes mellitus (DM) is characterized by severe hyperglycemia resulting from severe abnormalities in secretion of insulin or utilization. [1] WHO reported that worldwide, around 589 million people (20-79 years) are living with diabetes and it is suggested that by 2045, around 853 million people will suffer from diabetes. [2-3] Inappropriate control of DM can be responsible for severe chronic diabetes complications. Furthermore, at the initial DM diagnosis, certain severe complications are seen in patients present with DM. [4] Diabetic foot ulcer (DFU) incidence is seen in 15-25% of diabetic patients, while major causes of morbidity and mortality are DFU and chronic amputation. [5]

Multiple factors, such as peripheral neuropathy, severe inflammation, degradation of extracellular matrix (ECM), oxidative stress and ischemia are involved in DFUs pathogenesis. [6] Conventional diagnostic strategies are majorly depend on clinical assessments, which often assess ulcers in initial stages, reducing the effectivness of therapeutic interventions. In the prediction of disease severity, prevention and, early clinical diagnosis, a huge clinical role has been played by the biomarkers. Furthermore, a huge role has been played by biomarkers in the development of new therapeutic targets or assessment of therapeutic interventions. The DFU progression can be assessed from inflammatory and oxidative targets associated with the DFU pathogenesis. Considering this, there is a huge demand for the development of non-invasive, promising biomarkers that are associated with potential of identifying the individuals at high risk for DFUs. [7]

A significant link exists between pathophysiological mechanisms involved in the progression of DFUs and inflammatory biomarkers including tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and C-reactive protein, as suggested by findings of recent studies [8,9] However, their clinical application in the early assessment of DFUs remain unexplained. Evaluation of procalcitonin (PCT) has been conducted as a significant biomarker for the assessment of early infection in DFUs, but study findings demonstrates that it facilitates limited sensitivity in the detection of DFUs in the early-stage. [10]

A major role in the progression of DFUs has been played by various oxidative stress biomarkers like intracellular adhesion molecule-1 (ICAM-1), vascular endothelial growth factor and malodialdehyde. These markers demonstrate underlying pathophysiological processes like vascular impairment and lipid peroxidation involved in the progression of foot ulcers. During tissue remodeling and wound healing, a significant role in the ECM degradation has been played by matrix metalloproteinase-9 (MMP-9), a zinc-dependent endopeptidase. [11m]

Pathophysiological Changes in Dfu

The pathophysiological variations in DFU are associated with many diseases like foot deformity, sepsis, inflammatory cytokines and peripheral vascular disease. [12,13] A major factor is that induction of foot ulcer has not been induced by these risk factors. Among diabetic patients present with poor glycemic control, nerve fibre induced damage through various pathological mechanisms has been observed e.g protein kinase C formation, e.g formation of protein kinase C, generation of glycosylation end products and severe inflammation. [14] As a result, lesions in sensory, motor and autonomic nerves are induced by peripheral neuropathy, which has emerged as a major reason behind diabetic foot ulceration and responsible for around 78% of diabetic lesions. Limited joint mobility or neuropathy-induced foot deformity leads to callus formation at the pressure spot. Local pressure is elevated due to the formation of callus tissue, which when combined with undiagnosed repetitive lesions can cause local tissue injury, ulceration, inflammation and tissue death. The clinical incidence of atherosclerosis is seen higher in DM patients which leads to arteriosclerosis, endothelial hyperplasia, and thickened capillary basement membrane. These all risk factors influence the supply of blood to the arteries, resulting in ischemia in the surrounding tissues ischemia, which further potentiates the risk of progression of DFUs. [15]

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Wound Healing and Dfu

Physiological processes consist of four major events: overlapping phases: inflammation, coagulation, migration and remodeling are involved in the wound healing process. Orderly progression of these phases has been seen in patients present with acute wounds which leads to timely wound healing. However, severe inflammation is seen at the wounded site in non-healing chronic wounded tissues in the inflammatory phase. [16] In wounded tissues, macrophages have emerged as the major producers of pro-inflammatory cytokines in a continuous inflammatory state.

In diabetes, macrophage function is altered due to various mechanisms like recruitment of moniocytes to the wounded tissues, reduction in Phagocytosis. In its late stage, the function of fibroblasts and keratinocytes is also influenced in diabetes resulting in damage to the wound epithelial cells [17] Findings of experimental research reports and clinical evidence suggested that orderly progress in the steps involved in wound healing in DFU and other types of severe wounds is not seen unlike the linear wound healing in acute injury. [18] Delayed healing of wounded tssues in DM patients is seen due to alteration in more than 100 physiological factors like deposition of ECM, accumulation of collagen, granulation tissue amount, fibroblast migration and proliferation, epidermal nerve quantity, bone healing and balance between ECM components deposition ,and their remodeling by MMPs.

Dfu Biomarkers- Inflammatory Biomarkers

Procalcitonin

Liver, lungs, kidneys and Thyroid C cells released Procalcitonin (PCT) which consists of 116 amino acid works as a calcitonin percursor that plays a crucial role in the investigation of infection as a biomarker. [19] Umapthy *et.al* conducted a clinical study with the objective of investigating PCT efficacy in the diagnosis of DFU in which 185 patients present with T2DM (Type 2 diabetes mellitus) were included. [20] Patients were divided into three major groups in this study in which T2DM without DFU, T2DM patients present with noninfected DFU and T2DM present with infectious DFU. Blood analysis findings report demonstrate that PCT might act as a biomarkers for the diagnosis of patients present with DFUs. In addition to this, concentration of PCT in the peripheral circulation was linked with cytokines 17 level and T-helper-1-cells. Massara et.al [21] conducted another study in which 15 DM patients present with NIDFU (Non-infectious diabetic foot ulcer) and 15 with IDFU (infectious diabetic foot ulcer) were enrolled. Findings of the study suggested that in comparison to NIDFU, PCT and CRP level were reported significantly higher in IDFU group. Furthermore, higher efficiency of PCT level was seen in the differentiation of NIDFU from IDFU. Park et.al [22] suggested that the level of CRP and PCT was significnatly linked to the DFU infection severity. On the other hand, Korkmaz et.al [23] conducted a study in which 38 NIDFU patients and 38 IDFU patients and 43 patients with WDFU (without diabetic foot ulceration) were enrolled. Findings of the study suggested that in comparison to NIDFU, levels of ESR , fibrinogen, interleukin, CRP and WBC were seen higher om IDFU patients. During the NIDFU and IDFU assessment, no significant effect of PCT has been seen, while high AUCROC value (0.998; $P < 0.001$), value of serum CRP was seen. Based on the recent evidence, fibrinogen and serum Interleukin-6 (IL-6) are emerged as the major two inflammatory biomarkers for IDFU differentiation. Certain results suggested that in comparison to patients present present with mild DFU infection, the PCT predictive effect is low but highly effective in patients present with severe IDFU.

Pentraxin-3

At the inflammatory site, pantraxin-3 (PTX) is a soluble pattern recognition receptor, produced by fibroblasts, granulosa cells, endothelial cells, adipocytes, mesangial cells and mononuclear phagocytes. Considering this, its elevated level may suggest severe inflammation at the vascular site. In the endothelial wall, a huge concentration of PTX-3 is released at the inflammatory region which acts as an endothelial regulator in the thrombosis and ischemic vascular disease and inhibit restenosis and angiogenesis. [24, 25] Ozer et.al [26] suggested that for the diagnosis of IDFU, PTX-3 acts as a valid biomarker. In this study, 45 healthy controls, 45 WDFU patients and 60 IDFU patients were enrolled. On the basis of clinical severity, IDFU patients were randomly divided into three subgroups: severe, moderate and mild. In the study findings, a negative correlation of the level of plasma PTX-3 with glucose was seen and in all three IDFU subgroups, both PTX-3 and glucose levels were statistically

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different. Furthermore, in patients present with mild, severe, and moderate IDFU, no significant variations in the levels of ESR and CRP was seen. Takashi et.al [27] demonstrates the positive association of PTX-3 with diabetes and glycosylated hemoglobin. Serum level of PTX-3 is increased due to chronic hyperglycemia, which may demonstrate that blood glucose level was responsible for the positive regulation of PTX-3. To conclude, recent clinical evidence regarding PTX-3 as a significant biomarker of vascular inflammation is still limited, more studies are needed to demonstrate its efficacy.

C-Reactive Protein

CRP has emerged as a major element of inflammatory reactions which level may rise to more than 1000-folds due to tissue destruction or infection. Considering it, it is used as a biomarker in the diagnosis of inflammation and acute-phase infection. Recently, due to its huge clinical value in the clinical and pathological lab, it has been recognized as a major biomarker for various cardiovascular conditions. Recent findings of research studies in various diseases and associated conditions demonstrated the CRP role in therapeutic and research tool. Findings of studies suggested that a rise in the level of CRP is linked with diabetes.[28,29] Acute DFU and its progression were associated with a marked rise in the level of cytokines, chemokines and proteins, as suggested by

Weight et.al [30] In 175 WDFU patients and 282 patients with acute DFU , blood analysis was conducted and study findings demonstrates that elevated level of CRP, fibrinogen and IL-6 was seen in acute DFU patients in comparison to WDFU patients.

CRP concentration of 56 amputess present with gangrene and DFU before and after surgery was studied by Metineren et.al.[31] Findings of a retrospective study suggested that within 2 weeks after surgery, 42% of 56 patients died within 2 weeks. The rise in mortality was suggested by preoperative/postoperative CRP ≤ 1.5 ($P < 0.001$), this rise in the serum CRP level was a key marker of mortality. In DFU patients, two factors, CRP and old age were promising prognostic factors.

Interleukin

Blood monocytes and tissue macrophages produced interleukins (IL) which are major cytokines play significant role in immune system activvity-adaptive and innate. IL are released onto target cells by infected body which bind to the signals produced by target cells and activate them, altering cell behaviour. In patients present with DFU, ILs level rise along with delayed wound healing, and development of insulin resistance. [32-34]

21 DM patients without DFU, 21 health volunteers and 20 patients with acute DM were enrolled in study conducted by Sabuncu et.al [35] Findings of blood sample analysis suggested that in comparison to healthy individuals, DFU patients and DM patients with DFU, IL-18 level was quite high. However, these findings have not demonstrate that if the IL-8 level elevation was the consequence or cause of DFU. More research studies are needed to demonstrate the IL-18 role within diabetic ulcers. Further, Weighelt et.al [36] suggested that in comparison to diabetic patients without diabetic foot, level of IL-6 patients present with acute DFU was high. Findings by Kolumam et.al [37] also suggested that during the normal wounds healing, upregulation of IL-20 subfamily cytokines was seen and diabetic muce wound healing could also be raised by various interleukins such as IL-24 and IL-22. Out of all, IL-22 could potentiate the blood vessels healing through various mechanisms like synthesis of granulation tissue, epithelialization, thereby potentiating healing of diabetic foot wounds.

Tumor Necrosis Factor

Tumor necrosis factor (TNF-alpha) alpha has emerged as a major inflammatory regulator and a cellular signaling protein detected as a crucial factor in the cytokines network. TNF-alpha act as a major member of the TNF family that is produced by T-cells, macrophages and monocytes, could influence various biological pathways including apoptosis, angiogenesis, migration and molecular process of adhesion. The crucial function of TNF-alpha is to regulate the activity of the immune system through the B cells, macrophages and B cells activation, therefore potentiating the cytokines and cell adhesion molecules expression. Furthermore, in wound healing, the role of TNF-alpha is evident by its marked expression in vascular endothelial cells. TNF-alpha has been suggested to have an indirect angiogenic effect, depending upon the production of secondary mediators e.g

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vascular endothelial growth factor. However, it is quite challenging to understand the TNF-alpha dual angiogenesis role under different pathological conditions. To conclude, TNF-alpha dysregulation has also associated with various human inflammatory diseases in addition to various malignant tumors. [38]

40 NIDFU patients and 44 IDFU patients were selected in a study conducted by Dhamodharan et al. During the process of chronic wound healing process, multiplexed blood-based cytokine immunoassay was utilized to assess blood levels of CRP and BAFF (B-cell activating factor) In the findings, it was seen that in comparison to CRP, AUCROC for BAFF (0.89; [95 % CI: 0.73–1.0]) was higher. Furthermore, a positive correlation of CRP levels with B-cell activating factor (BAFF) level was seen, and a negative association of IL-10 family cytokines and interferon family cytokines with IL-6 receptor family was observed. [39] Table 1 demonstrates the various inflammatory biomarkers that can be utilized for diagnosis of DFU at an early stage.

Role Of Oxidative Stress in The Pathogenesis of Diabetic Foot Ulcers

Oxidative stress play a crucial role in the continous development of diabetic wounds which creates a microenvironment with chronic inflammation. Advanced glycation end product synthesis is potentiated by severe hyperglycemia in patients which attach to the receptors to activate various signaling pathways that rises the reactive oxygen species (ROS) synthesis. [40] Furthermore, electron leakage in the electron transport chain and mitochondrial dysfunction s induced by hyperglycemia further raise the levels of ROS. Neutrophils and macrophages are activated by chronic inflammation in foot ulcers which produce ROS while engulfing pathogenic microorganisms and clearing necrotic debris. In addition to this, severe impairment in antioxidant system functions is observed in patients present with diabetes, resulting in impaired ability of the ROS scavenging system of body. Excessive synthesis of ROS leads to destruction of cellular function and integrity by oxidation of lipids, proteins and DNA, therefore altering physiological wound healing process. DNA bases are also oxidized by ROS, causing cellular dysfunctioning and mutations. Oxidative stress also raises insulin resistance, a major critical factor involved in the wound healing process. Various stress kinases enzymes such as JNK, are activated by excessive oxidative stress which inhibit insulin signaling. Furthermore, pro-inflammatory cytokines and nuclear factor Kappa B activation are induced by the ROS which further raises the pro-inflammatory mediators such as IL-6 and TNF-alpha release. In patients present with diabetes, significant increase in the level of these mediator which are closely linked to insulin resistance and delayed physiological events involved in the wound healing process.

Biomarkers of Oxidative Stress

Proteins

In vitro studies suggested that ROS interacts with certain amino acids. Excessive production of free radicals induces diabetic hyperglycemia which causes oxidative degeneration and protein glycation. Various biomarkers such as fructosamine levels and glycated hemoglobin can be utilized to estimate the extent of protein glycation. Nonenzymatic glycation can also be responsible for severe changes in activity and structure of antioxidant protein enzymes.[41] The conversion of L-tyrosine to 3,3 -di tyrosine can be catalyzed by the myloperoxidase enzyme which is a crucial biomarker to assess protein oxidation, as suggested by the findings of in vitro studies. [42]

Lipids

Severe alterations in the lipid profile of the body are induced by DM increasing the susceptibility of cells towards lipid peroxidation. [43] Findings of experimental studies suggested that free radicals majorly attack the polyunsaturated fatty acid due to the presence of double bonds. [44] Fatty acids are produced by lipid hyperperoxides through intermediate free radical processes that lead to the synthesis of highly toxic lipid radicals. [45] Lipid peroxidation has been recognized as a major biomarker of oxidative stress which has emerged as the most significant area of research. [46] Due to severe lipid peroxidation, malondialdehyde is produced which can be utilised to investigate lipid peroxidation after undergoing reaction with thiobarbituric acid. [47]

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Vitamins

Vitamins have emerged as a significant part of the biological system as a crucial role in various biochemical mechanims has been played by them. Vitamin A, C and E work as antioxidants due to their strong potential to detoxify the free radicals Toxicity is also raised by these vitamins by generating pro-oxidants in certain pathological conditions. Diabetes leads to either potentiate or reducing the level of Vitamin E in body. However, conflicting findings suggest the vitamin E deleterious effect on diabetes-induced vascular abnormlaties. . [48]

Glutathione

Severe alterations in enzymes activity glutathione reductase and glutathione peroxidase are induced by diabetes. Peroxides are metabolized to water by these enzymes present in the cellular membrane which further leads to the conversion of glutathione disulfide back into glutathione.. [48] Any alterations in their concentration will potentiate the risk of oxidative stress and cellular injury.

Catalase

Hydrogen peroxide metabolism is regulated by Catalase that can induce severe damage to RNA, DNA and lipids in excessive concentration. Hydrogen peroxide is converted catalytically into oxygen and water by CAT. Beta cells of the pancreas produce excessive ROS by undergoing oxidative stress in the case of catalase deficiency. [49] During the assessment of functional changes induced by hyperglycemia, endothelial cell gene expression fingerprint, production of hydorgen peroxide, and mitochondrial membrane polarization demonstrate that synthesis of hydrogen peroxide Is modulated by hyperglycemia.

Superoxide Dismutase

The First line of defense is provided by superoxide dismutase against ROS induced cell injury by potentiating the superoxide proportion which act as the primary ROS involved in oxygen metabolism to molecular oxygen and oxygen to peroxide.. [50]

DISCUSSION

DFUs has emerged as a major diabetes mellitus complication, contributing to prolonged hospitalizations, increased morbidity and increased risk of limb amputation. DFU underlying pathophysiology is quite complex, involving oxidative stress, endothelial dysfunctioning, severe inflammation and degradation of ECM. A central crucial role in DFUs pathogenesis has been played by inflammation, contributing to influencing wound healing and increasing risk towards infection. IL-6 acts as a major regulator in the inflammatory pathway modulating release of cytokines and immune cell activation. [51] TNF-alpha level rises have also been linked with poor healing of wounded tissue due to its role in modulating apoptosis and disturbing the functioning of fibroblast. Out of all inflammatory biomarkers, highest diagnostic accuracy was seen with CRP, underscoring its significance as a promising screening tool for the assessment of DFUs progression. CRP acts as a reliable biological indicator of progression of inflammatory processes in diabetic patients due to its potential to work as an acute-phase reactant generated in response to tissue injury and inflammation. Various pathways involved in vascular and metabolic disturbances have been initiated by chronic hyperglycemia that potentiates systemic inflammation.

Oxidative stress is produced due to elevated blood glucose, which further potentiate pro-inflammatory signaling pathways and lead to upregulation of various cytokines like TNF-α. and IL-6. These inflammatory mediators are involved in leukocyte adhesion, microvascular injury and endothelial dysfunctioning all of which disturb the process of immune regulation and tissue. Furthermore, wound-healing cascade is disrupted by prolonged inflammation which distrubs the process of angiogenesis, collagen production and fibroblast functioning. (53

However, potential role of oxidative and inflammatory biomarkes has been established, their major role in guiding the therapeutic intervention methods such as angiogenic therapies, anti-inflammatory and antioxidant shoukd be explored in future clinical trials

CONCLUSION AND FUTURE PRESEPECTIVES

It is quite important to conduct research studies on DFU biomarkers with multiple approaches considering the rise in diabetes and its complication incidence worldwide. In the past few years, significant progression has been seen in understanding the therapeutic and management strategies involved in the treatment of diabetic foot ulceration. Biomarkers of DFUs have emerged as the representative of pathogenetic mechanisms involved in the progression of the DFUs which can facilitate better understanding of DFU, improving prevention of disease, early clinical assessment, and prediction of disease progression. Oxidative and inflammatory biomarkers can be utilized for early identification of DFU after future research strategies from bench to bedside, leading to appropriate management and thus reducing the risk of trauma of amputation. In various fields, research on disease biomarkers continues to progress. Various factors that are linked with validation, relevance, consistency, and potential clinical callaboration of clinical outcomes should be taken into consideration. New clinical insights into DFU prevention and treatment can be suggested on the basis of positive findings of research based upon DFU biomarkers which is still in its initial phases and continuous progression. However, potential role of oxidative and inflammatory biomarkes has been established, their major role in guiding the therapeutic intervention methods such as angiogenic therapies, anti-inflammatory and antioxidant shoukd be explored in future clinical trials

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Table 1: Various inflammatory biomarkers that can be utilized for diagnosis of DFU at an early stage

Potential biomarker	Clinical utility	Clinical potential in the identification of DFU
PTX-3	Soluable pattern recognizition receptor, which directly demonstrates vascular inflammation.	A clinical biomarker for the assessment of IDFU disease progression facilitating decision regarding amputation. (24)
PCT	Precursor of Calcitonin, play a significant role in the assessment of bacterial infection as a biomarker.	A significant clinical biomarker for the diagnosis of IDFU mild and severe stages and differentiation of teomyelitis and soft tissue infections. (19)
CRP	Plasma protein, a crucial element of inflammatory reactions.	Grade 1 and Grade 2 ulcers can be differentiated by this biomarker and furthermore, it can also be utilized for the confirmation of infection. (28)
TNF-alpha	Cell signaling protein and inflammatory regulator	A potential clinical biomarker for the IDFU AND NIDFU differentiation. (38)
IL-18	mainfestation of immune dysfunctioning and inflammatory cascade	A significant biomarker for the DFU diagnosis.
IL-24. IL-20, IL-24	Potentiates repair of wounded tissue in DM by increasing pro-healing functions of keratinocytes	can be utilized for DFU patients therapeutic benefits by potentiating the DFU healing process.