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REVIEW ARTICLE

Quality of Life and Increasing Role of Biomarkers in Diagnosis, Prognosis and Prediction of Diabetic Foot Ulcer

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ABSTRACT:

Diabetic foot ulcer (DFU) is a long term serious complication associated with diabetes and is defined as the ulceration in diabetic patients caused due to peripheral neuropathy and peripheral arterial disease of lower limbs. It is one of the major and leading causes of lower extremity amputations and increased morbidity. Increased podiatric pressure, abnormal glycemic parameters and many other causes leads to healing and non- healing ulcers in diabetic patients. Quality of life in DFU patients vary depending upon the stages of ulcers and duration of ulcers. DFU patients with healed ulcer will have higher quality of life than the patient with non- healed and chronic ulcers. Health related quality of life decreased progressively with the poor healing of wounds. In current scenario biomarkers are playing a major role in drug discovery, preclinical pharmacological studies, clinical trials and post marketing studies.The general biomarker discussed in this review are transforming growth factor, procalcitonin, calprotectin, cystatinC, Osteoprotegerin-1, edothelin- 1, CXCL-6, CXCL-12, Epithelial neutrophil activator, hypoxia inducible factor-1, Growth factors, Nitric oxide, Stem progenitor cell, Matrix metalloproteinase, Fibrinogen and Serpin B3. These above mentioned biomarkers are gaining importance in current scenario thus reducing morbidity and mortality rate.

KEYWORDS: Diabetic foot ulcer, Biomarkers, Diagnosis, Prognosis, Prediction, Healing and Non- healing ulcers.

INTRODUCTION:

Diabetic foot ulcer (DFU) is a long term serious complication associated with diabetes and is defined as the ulceration in diabetic patients caused due to peripheral neuropathy and peripheral arterial disease of lower limbs. The prevalence of DFU is nearly about 4-10% in the general diabetic population. 5% of most diabetic populations leads to diabetic foot ulcers with 15% risk of development of complications and increased risk factors [1-3].

Global prevalence of DFU is found to be around 6%[4] where the extremity amputation of DFU in now increasing with great global variability [5]. The most increased prevalence rate was found in North America (13%) in comparison to Oceania (3%) and 7.2% and 5.5% is the prevalence rate of DFU in Africa and Asia respectively. 5.1% was the observed prevalence rate in Australia and 16.6% in Belgium. Prevalence rate in India was 11.6% [6]. Biomarker recently plays a very important role in the diagnosis, prognosis and prediction of many diseases where DFU can also be diagnosed and treated with the use of biomarkers avoiding amputations and reduces morbidity and mortality rate. This review focuses mainly on the novel and emerging biomarkers till date identified in diabetic foot ulcer.

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QUALITY OF LIFE IN DIABETIC FOOT ULCER PATIENTS: Health related quality of life decreased progressively with the poor healing of wounds [7]. DFU has a great impact on quality of life and it is proved that poorer quality of life was found in patients with increased diabetic ulceration [8]. There are many factors of DFU leading the patients to poorer quality of life such as body weight, nutritional status, and lifestyle modifications.Compared with normal weight (18.5 < BMI < 25kg/m2) patients, over weight and obese diabetic patients were 2.12 times and 2.65 times more likely to develop Diabetic foot ulcer [9]. Malnutrition is very common among DFU patients leading to poor prognosis suggesting that nutrition plays a key role in quality of life in DFU patients[10]. Poorer glycemic control, peripheral neuropathy, hypertension, poor podiatric care leads to increased risk of DFU suggesting that effective intervention in life style modifications will have improved quality of life in DFU patients [11].

INCREASING ROLE OF BIOMARKERS IN DFU:
Biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention"[12]. In current scenario biomarkers are playing a major role in drug discovery, preclinical pharmacological studies, clinical trials and post marketing studies. The general biomarker discussed in this review are transforming growth factor, procalcitonin, calprotectin, cystatinC, Osteoprotegerin-1, edothelin- 1, CXCL-6, CXCL-12, Epithelial neutrophil activator, hypoxia inducible factor-1, Growth factors, Nitric oxide, Stem progenitor cell, Matrix metalloproteinase, Fibrinogen and Serpin B3. These above mentioned biomarkers are gaining importance in current scenario thus reducing morbidity and mortality rate.

DIAGNOSTIC BIOMARKERS:

TRANSFORMING GROWTH FACTOR BETA-1 (TGF-β1) AND miRNA:
TGF induces (ECM) extracellular matrix secretion and also implicate its role in morphological, proliferative and differential changes of many cells including osteocytes. TGF β1 was prominently decreased in amputated limbs and ulcerative limbs of DFU patients.Comparing miRNA and TGF-β1 therein exist an inverse relationship between them representing negative correlation [14]. In another study it shows in certain DFU patients, decreased rate of production of approximately 67% resulted in increased inflammation and delayed healing of wounds. Here novels methods used in analysis TGF levels was by three independent factors such as: logTGFβ1 levels, incipient DNF (log MAU) and age [13] [14]. Categorical diagnosis of DFU can be analyzed by TGF-β1 and it also has independent correlations with diabetic neuropathy.

PROCALCITONIN:
Procalcitonin is the precursor of the hormone calcitonin which is a 116- amino acid protein precursor [16-19]. According to some authors PCT is more accurate than C- reactive protein [15]. A study conducted with measurement of PCT, ESR, CRP, WBC and the obtained values represent that both the CRP and PCT levels were high in Infected Diabetic Foot Ulcer (IDFU) patients than Non-Infected Diabetic Foot Ulcer (NIDFU). The obtained PCT levels were variable and it depends upon the factors such as site and extension of infection. PCT thus show a maximum area under curve value and was statistically significant in relation with infection [20]. On combination with respective CRP levels in patients along with PCT, it proves to be a promising diagnostic biomarker for DFU thus differentiating infected and non- infected ulcers [21].

CALPROTECTIN:
Calprotectin is a 37k-Da calcium- and zinc – binding protein and it represents the neutrophilic inflammation [22]. In assessment using wound exudates high protease levels resist the use of other biomarkers, where calprotectin plays a major role as marker [23].

CYSTATIN:
Cystatin C is a cysteine protease inhibitor which induces infection by influencing immune response. In a study conducted with 30,329 patients it was found that elevated cystatin C levels was found in association with long term community acquired sepsis irrespective of GFR, albumin-creatinine ratio and CRP levels [24]. In a study conducted with 102 T2DM subjects with peripheral neuropathy, both the cystatin C levels and albumin creatinine ratio was increased in peripheral neuropathy patients in comparison with non peripheral neuropathy patients, but statistical significance was found with albumin- creatinine ratio. This study shows albumin- creatinine ratio is more sensitive biomarker than cystatin C [25]. In a study conducted to analyze the relationship between cystatin C and DPN with 937 patients it was found that high cystatin levels was closely associated with DPN and can be used as a potential diagnostic biomarker [26]. Another study also shows that cystatin C levels showsstrong linear correlation with Wagner classification system but the related mechanisms needs to be evaluated [27]. Cystatin C levels of > 1.35mg/L proves to show a 6 fold increased risk of incurable diabetic foot infection in a Chinese population and also it plays a major role in peripheral retinopathy. It shows more response and is likely associated with chronic complications [28].

PREDICTIVE BIOMARKERS:

OSTEOPROTEGERIN (OPG) AND ENDOTHELIN-1(ET-1):

Endothelin is a protein reported to have the effect of contractility fibroblast necessary for wound closure and skin reconstitution. Both these two compounds are finding its role as potent predictive biomarkers in recent studies of DFU. As reported by earlier studies increase in ET-1 was found in many diabetic patients while OPG plays its role in atherogenesis of blood vessels [29-32] and increased in its expression was found to be associated with micro- and macroangiopathy [33]. In a study conducted with 40DFU patients the levels of CBC, differential count, levels of HbA1C, creatinine, lipid profile, FBG, marker of endothelial dysfunction (ET-1) and marker of vascular calcification (osteoprotegerin/ OPG) where two measurements conducted in association with stages of healing process such as inflammatory phase and proliferative phase. According to this study the OPG levels has a positive correlation with wound healing in response to simvastatin drug [29]. It was also reported that OPG helps the endothelial cells from entering the process of apoptosis and play a major part in angiogenesis of rats [34].

CXCL-6:

Chemokine (c-x-cmtif) ligand (CXCL-6) is a cytokine involved in CXC chemokine family and it is also so called as chemotactic protein 2(GCP-2). Healing of wound is a complex processs involving homeostasis, inflammation, proliferation, angiogenesis and remodeling [35][36]. Cytokines are playing a major role in the process of wound healing- angiogenesis and thus delayed or impaired wound healing can be analyzed by assessment of levels of cytokines. [37] A study shows that the wound exudates of CXCL-6 cytokine concentrations shows a significant difference between non- healing (NH) and rapidly healing (RH). CXCL-6 levels were high in RH group than in NH group. The molecular process involved in effects of CXCL-6 associated with DFU remains unclear and yet to be investigated.

EPITHELIAL NEUTROPHIL ACTIVATOR (ENA-78):

Epithelial neutrophil activator, encoded by CXCL-5 is a chemotactic factor inducing neutrophilic degranulation and release myeloperoxidase and reactive oxidative species, a chemokine having both neutrophil attractor and activator function [38]. A reported study with diabetic foot ulcer rapid healing (RH) patients and non-healing (NH) patients. Resulted biomarker after the elimination of traditional confounding risk factors ENA -78 found in wound exudates is an independent early predictor of wound healing in DFU patients [39]. As stated in other studies ENA-78 activate monocytes by platelets- dependent action and shows angiogenesis and hence ENA-78 helps in wound healing at inflammatory phase [40-42].

PROGNOSTIC BIOMARKER:

MATRIX METALLOPROTEINASES (MMPs): Both MMPs and TIMPs are produced by cells involved in wound healing process and their concentration varies depending upon the stage of healing and the location of wound. Increased levels of MMPs and decreased levels of TIMPs shows the poor and slow healing process and the ulcer failing to heal on treatment [43][44]. Many clinical signs are found to be present in the wound exudates of DFU and increased levels of MMP-9 shows the inflammation and poor healing rate of ulcers. Nearly 5 fold decrease in the levels of MMP-9 was found in good healers which are not found in poor healers.[45].

CONCLUSION:

Biomarkers are now becoming and gaining importance in various aspects of medical treatments. In DFU biomarkers should be used in all aspects including diagnosis, prognosis and prediction of treatment in order to minimize the risk of morbidity. This current review projects the novel and emerging biomarkers in the terms of DFU and creating a new insight for the DFU management.

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