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Understanding Biomarkers Involved in Healing Delay in Diabetic Wounds

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Abstract

Neuropathy and ischemia are the main disorders found in the ulceration underlying foot. The diabetic foot is the biggest complication of diabetes in the world. It estimates that 16 million of people in the carrying the United States of diabetes mellitus, about 15-20% will go to be hospitalized for complications of the diabetic foot. The inquiry concerning the physiopathologic alterations of the involved factors in the healing process of the carrier of diabetes mellitus and the complications generated for the vascular dysfunction still presents gaps. In this review, it was aimed to analyze the involved components in the tissue repair and its alterations in the diabetic patient. This is a descriptive study in which had analyzed articles indexed in the databases PUBMED and MEDLINE, in the period of 1930-2016. The study disclosed that some factors in the process of tissue regeneration, as the vascular endothelial growth factor and the fibroblast growth factor, could be altered to the hyperglycemic state. Moreover, the alterations of oxidative stress in special nitric oxide could influence negatively in the tissue repair.

Introduction

Understanding healing process

The steps of inflammation, proliferation and tissue remodeling that involves the physiological process of wound healing require, zzamong other issues, growth factors that act by stimulating chemotaxis, tissue proliferation, extracellular matrix formation and angiogenesis, as well as contraction and re-establishing the integrity cell [1].

It is known that diabetic patients show altered adherence, leukocyte chemotaxis, and opsonization. The cellular immune system has an inefficient and delayed response to noxious agents. Furthermore, no change of antioxidant systems and lower production of interleukin (IL-2), key points in the inflammatory process necessary for an effective immune response [2].

The process of healing by first intention occurs by the following mechanism: the blood spilled by the cutting form a clot that occupies the space between the edges of the wound and from the clot and the injured tissue, there are chemotactic factors and vasoactive promoting fluid exudation blood to the margins of the lesion and thus six hours after the wound, it is possible to observe the presence of phagocytes in the wound margins, and around 24 hours, the clot is already invaded by these cells, with a predominance of Polymorphonuclear (PMN) [3].

Fibroblast tissue wound margins become activated, proliferate, migrate toward the clot resorption and begin to synthesize the components of the Extracellular Matrix (ECM). The macromolecular network of the ECM consists of collagen, elastin, glycoproteins and proteoglycans, secreted by connective tissue cells such as fibroblasts and epithelial cells. All these components are in close contact with their cells and form one-dimensional gelatinous bed in which the cell involves [4].

Regarding the restoration of blood flow in damaged areas, the endothelium of thecapillaries adjacent sends shoots that grow into the clot to form new blood capillaries. This lost connective tissue is rich in blood capillaries and containing leukocytes and the extracellular matrix formed by thin collagen fibers (type III collagen), hyaluronic acid and a moderate number of proteoglycans are called granulation tissue. Grossly, this tissue as a pink color and grainy appearance [5].

Changes in blood viscosity in diabetic gifts this could negatively influence blood flows and thus in tissue repair. Hyperglycemia is a major risk factor for the development and progression of diabetic nephropathy. Hyperglycemia induces multiple cellular and molecular changes that presagethe development of renal vascular dysfunction [6].

Tissue Repair and Growth Factors

Some researchers like Grotendorst [7] and Broadley [8] demonstrated *in-vivo* and *in-vitro* models efficacy of growth factors in tissue repair and many of these studies correlated the factor Platelet-Derived Growth Factor (PDGF) the Fibroblast Growth Factor (FGF) and Epidermal Growth Factor (EGF) as decisive in the formation of granulation tissue, the latter being recommended therapeutic regeneration of wounds in diabetics [1].

The Vascular Endothelial Growth Factor (VEGF) is known stimulator of endothelial proliferation and has a central role in physiologic and pathologic angiogenesis [9]. Vriese andcols [10] tried to assess the role of VEGF in the pathophysiology of early renal dysfunctionin diabetes and demonstrated a possible mechanism by which hyperglycemia cause renal dysfunction, and thus VEGF could be useful as a therapeutic strategy for treatment of early nephropathy in diabetic patients.

Tsang et al [1] in a randomized double-blind study with 127 patients with diabetic foot and found a relative deficiency of some growth factors in chronic wounds in the diabetic foot, especially EGF and FGF and concluded that the use of EGF associated with PDGF could reduce the recovery time of these skin lesions.

Changes in Extracellular Matrix in the Diabetic State

The diabetic state is accompanied by alterations in Extracellular Matrix (ECM) in various tissues. The high level of blood glucose is considered as the main cause of the phenomenon and The Factor Of Growth Factor-b1 (TGFb1) is speculated to be the key mediator of matrixaccumulation.Schwartz, Keagy & Johnson [11] assessed the outcome of surgery for poplitealartery bypass hypothesized that individuals with diabetic foot ulcer could show changes inblood viscosity due to elevated levels of C-reactive protein and fibrinogen found in patientswith these wounds, compared to non-diabetics and non-diabetic patients with diabetic ulcers and these results re-inforce the propositions.

Tillett & Francis [12], who reported peaks of C-reactive protein and increased levels fibrinogen, serving as a biochemical response over this early acute response to a tissue repair process.This may ultimately be harmful and can lead an increased viscosity and thus potentially have an adverse effect on any attempt to bypass, that needs since the increased blood viscosity leads to a decrease in conduction the velocity of the essential cellular elements healing process, for example, platelets and polymorphonuclear cells.

Chikanza [13] et al suggested that cytokines produced by lymphocytes, macrophages, platelets, and monocytes are essential for deflagration an acute phasereaction. *In-vitro* studies suggest that cytokines and interleukins or Tumor Necrosis Factor (TNF) are the promoters of this reaction with tissue necrosis and inflammation.

Upchurch, Kegstand & Johnson [14] showed leukocyte and platelet dysfunction with membrane thickening and accelerated atherosclerosis in veins of small lumen in diabetic foot than non-diabetics, which would limit the blood supplies satisfactory in those areas, causing ischemic areas and that could eventually evolve into necrosis and ulceration.

Oxidative Stress Metabolism and Healing Process

Hyperglycemia increase ROS production, due to over production of superoxide by the mitochondrial electron-transport chain with decreased antioxidant defenses [15].

Increased mitochondrial oxidative stress was observed by mitochondria-specific superoxide indicator [16]. A study using a flow cytometric analysis revealed disruption of mitochondrial permeability and generation of oxidative stress in Endothelial Progenitor Cells (EPC) in hyperglycemic conditions [16].

Endothelial Progenitor Cells dysfunction could be critical for defective diabetic angiogenesis probably impaired nitric oxide signaling and increased oxidative stress, but the mechanisms underlying diabetic EPC dysfunction are still largely unknown [16].

Inflammatory processes can generate ROS and Reactive Nitrogen Species (RNS) like nitric oxide (NO•). However, nitric oxide may compete with oxygen in the iron-sulfur complex and copper centers in the respiratory chain and inhibit the mitochondrial ATP (adenosine triphosphate) synthesis [17].

Current Advances

Understanding healing process

A complex of biomarkers are involved in the healing process and the connection between these variables could be the key of understanding healing delay in Diabetic Wounds. For example, studies using a murine model diabetic observed that Angiopoietin-1 administration results in improved neovascularization dependent on these cells recruitment and has direct effects on wound re-epithelialization [18]. An Italian work analyzed wound biopsies from 75 patients with diabetic foot ulcers, shared in subgroups of Rapidly Healing (RH) and Non-Healing (NH) patients and identify serpin B3 strongly upregulated in RH *vs* NH wounds and they suggest that serpin B3 could be a biomarker of successful healing in diabetic patients [19]. A research using an injection of SDF-1α (SDF-1α, a homing the signal for recruiting Endothelial Progenitor Cells (EPC) to areas of neovascularization), engineered bone marrow-derived fibroblasts reported that SDF-1α-engineered cell-based therapy promotes diabetic wound healing by upregulating E-selectin expression leading to increased wound neovascularization [20]. Other study revealed that increased production of collagen was correlated with decreased oxidative and nitrosative stress in induced diabetic animals. The authors suggested that a certain level of oxidative stress is known to be required for the satisfactory induction of neovascularization in response to ischemia and damage tissue [21].

Some studies refer wounds will heal better in an environment that is adequately oxygenated according the principle that oxygen delivery to the wound will be impaired if tissue perfusion is adequate and suggests this therapy form [22-24], but the costs are not cheap. However, some alternative therapeutics have been showed positive results, like Ultrasound therapy [25-27], low-level laser therapy [28-31] and Electrostimulation [25,32-34]. However, it is important to note that successful treatment of wounds relies on monitoring, tissue perfusion and nutrition well managed.

Conclusion

Diabetes promotes itself, a high degree of entropy in biological systems. Humoral changesthat disrupt the extracellular matrix generate a degree of destabilization in the surroundingareas of hemostasis, which culminate with a high metabolic cost on the human body. Research in this area we should be focused on searching for external agents that promote areduction in energy cost for the diabetic patient and to stimulate an endogenous release of growth factors in tissue.

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