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Diabetic wound and oxidative stress

Evy Sulistyoningrum*[1]

[1]Histology Department, Faculty of Medicine, Universitas Islam Indonesia, Jl. Kaliurang 14,5 Ngemplak, Sleman, Yogyakarta, Indonesia, 55584

EDITORIAL

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***Corresponding author:**
evy.sulistyoningrum@uii.ac.id

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International Diabetes Foundation (IDF) considers that diabetic foot disease needs special awareness since it becomes a clinical and substantial problem for diabetic patients and becomes a major economic burden to health systems worldwide.[1] Diabetic foot ulcers (DFU) are the most common occurring problems throughout the globe, with a global prevalence of 6.3%[2] and a startle recurrence rate of about 40 % within a year, 60% within 3 years, and 65% within 5 years.[3] Comprehensive treatment strategies are needed to circumvent limb amputation risk which is reported to happen every 20 s.[4] Therefore, DFU becomes an overwhelming complex crisis not only for patients but also for families and society.[5] The magnitude of the DFU problem remains vast with a dramatic increase in global diabetes prevalence from 451 million in 2017 to 693 million by 2045.[6]

A wound can be defined as a discontinuity of cellular, anatomical, and functional connection of a living tissue, which can be caused by various injuries including physical, chemical, thermal, microorganism, and immunological factors.[7] To restore its' structural and functional integrity, the tissue will encounter sequential phases with overlapping phases of wound healing including coagulation (hemostasis), inflammation, proliferation, and remodeling phases. In skin tissue, these processes require vast interaction of various cells from different compartments of the skin and its extracellular matrix components.[8] At normal conditions, the acute wound healing mechanism is highly efficient, lasting for about three weeks to result in a complete repair of both the epidermis and superficial dermis.[9]

The first phase, hemostasis, immediately starts upon injury resulting in the fibrin clot formation and constriction of blood vessels. Platelets, the fundamental contributor to hemostasis and coagulation, will be activated when encountering subendothelial connective tissue. Then it will express its receptors to interact with various proteins promoting adhesion to the blood vessel wall and will promote the formation of an insoluble clot (eschar). The eschar not only serves as a plug to prevent further bleeding but also prevents pathogen invasion and provides a scaffold for incoming immune cells and a source of cytokines and growth factors to recruit immunocompetent cells to migrate into the wound area.[10] Migration and extravasation of leucocytes to the site of the wound will induce an inflammatory reaction involving the release of inflammatory cytokines including interleukins (IL-1, IL6), Tumour Necrosis Factor-α (TNF-α), Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor-2 (FGF2). The leucocyte activity also involved many other factors including histamine, kinins, leukotrienes, proteases, acid hydrolases, nitrogen oxide, and reactive oxygen species. The inflammatory phase is tightly regulated to localize inflammation and prevent excessive tissue destruction.[9] The subsequent event following inflammation is the proliferative phase, to contract the injured tissue and reduces the wound area. Various cytokines and molecules such as Transforming Growth Factor-beta (TGF-β), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), and connective tissue growth factor (CTGF).[11] The fourth phase (remodeling phase), spans the entire process from the initial formation of fibrin clot to the formation of scar tissue. Principal contributors of the following two phases are fibroblasts, which are not only responsible for collagen and extracellular matrix synthesis, but also organize

all extracellular matrix components to enhance the mechanical strength of the healing wound.[9]

Chronic persistent hyperglycemia condition in diabetic patients and its associated complications have some pathologies which can lead to delayed wound healing mechanisms including: physical barrier disruption and risk for infection, high level of oxidative stress, peripheral neuropathy, microvascular complication, and suboptimal chronic inflammatory response.[12] Among those pathologies, oxidative stress nowadays becomes one of the major contributors to non-healing diabetic wounds. Reactive oxygen species (ROS) are fundamental regulators of several phases of wound healing; a balance of ROS generation and its scavenging system is required for efficient wound healing. Early stages of wound healing required low levels of ROS production to reduce local blood flow and to form a thrombus. In addition to initial platelet aggregation and leukocyte recruitment, the activation of keratinocytes and ECM remodeling is also stimulated by the early onset of ROS peak level. However, the redox imbalance, as a result of excessive ROS generation and the decrease of the antioxidant system, has been shown to be detrimental to the following stages of wound healing.[13]

In normal conditions, the generation of ROS is tightly regulated by ROS scavenging enzymes, such as superoxide dismutase, peroxidases (including catalases, phospholipid hydroperoxide, and glutathione peroxidase)[14] and also peroxiredoxins, as well as other antioxidants such as vitamin E and glutathione.[15] Elevated ROS levels can damage microvasculature of the peripheral nerves which can lead to dysfunction of sensory, motoric, and autonomic functioning of the nerve, and the subsequent effect of nerve damage increases the risk of developing a DFU.[10] Oxidative stress from ROS generation also leads to the sustained secretion of pro-inflammatory cytokines and activation of matrix metalloproteases (MMPs), and it also causes impairment of dermal fibroblast and keratinocyte function.[13]

Hyperglycemia condition can generate ROS via the hexosamine, polyol, protein kinase C, and AGEs (Advanced Glycation End-products) pathways.[12] The presence of AGEs in skin tissue will alter the architecture of the dermal structure and also trigger inflammation and ROS generation via their epidermal receptor RAGE (Receptor for Advanced Glycation End-products). The interaction of AGE and RAGE prevents hypoxia-inducible factors-1α (HIF-1α) transactivation and also VEGF and stromal-derived factor 1 (SDF-1) upregulation which lead to impairment of neovascularization.[10] Interaction of AGE and RAGE also contributes in impairment of wound contraction, prolongs the inflammatory response and damages extracellular matrix (ECM) proliferation.[16]

Clinical studies have reported evidence of a highly oxidizing environment in non-healing diabetic wounds. This condition which is associated with hyperglycemia and tissue hypoxia leads to delayed wound repair. Tissue oxidative stress may impair wound healing mechanism in diabetic patients through increased risk for skin injury, peripheral neuropathy, increased risk of ischemic lesions, and topical infection.[14] Better strategies on wound treatment focusing on oxidative stress control are mandatory to facilitate successive wound healing in diabetic patients, thereby reducing the unnecessary burden of amputation of this population.

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