Vegf : structure, biological activities, regulations and roles in the healing of diabetic ulcers

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Review Article

VEGF: structure, biological activities, regulations and roles in the healing of diabetic ulcers

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ABSTRACT

Diabetic ulcer patients can be hampered their ulcer healing process. The condition is caused by hyperglycemia and accumulation of advanced glycation end-products (AGEs) that can cause interference with VEGF and its receptors and signaling pathways. The VEGF core region is formed by a cystine bond motif with 8 invariant cystine residues in inter and intramolecular disulfide bound to the end of the central 4-stranded at each monomer with a side-by-side antiparallel orientation. VEGF stimulates angiogenesis in three dimensions, causing the encounter of microvascular endothelial cells, penetration into collagen gels and forming capillary-like structures. Regulation of VEGF gene expression through: (1) hypoxia; (2) cytokines and (3) differentiation and transformation. VEGF stimulates wound healing through several mechanisms such as collagen deposition, angiogenesis and epithelialisation.

Keywords: Diabetic ulcers, Regulations, Roles, Structure, VEGF

INTRODUCTION

Diabetic ulcer patients can be hampered their ulcer healing process.[1] Many reports are associated with diabetic foot ulcer patients (DFU) who do not recover after 12 weeks of treatment, however ulcers generally resolve naturally within 2 or 5 weeks after treatment.[2] Results of studies in the United States reported that DFU can be cured between 24% and 31% with a standard care.[3]

The fundamental stages of the wound healing process include: hemostasis, inflammation, repair, which includes cell replication and extracellular matrix synthesis (ECM) as well as tissue remodeling.[4] The most interesting stage of this process is in the proliferation phase, because this phase determines the success of wound closure. In this phase is characterized by angiogenesis or neovascularization, so that wound will successfully healed.[5-8] The acceleration of wound healing is often associated with angiogenesis.[9] Angiogenesis or neovascularization is mediated by several growth factors, which is the vascular endothelial growth factor (VEGF).[5-8,10-12] Vascular endothelial growth factor is secreted by keratinocytes on the wound`s edges.[13]

Diabetic ulcers suffer from hyperglycemia and accumulation of advanced glycation end-products (AGEs), which may cause growth factor disorders such as VEGF and its receptors, signalling pathways,

interfering with endothelial proliferation, migration and recruitment of endothelial progenitor cells (EPCs) and bone marrow redemption.[14] In addition, the presence of infection in diabetic ulcers can occur angiogenesis disorders, so it can cause wound healing disorders.[15] VEGF is a cytokine that regulates some endothelial cell biological activity, increases the production of vasodilatation mediators and vascular permeability as well as chemotaxis agents.[10,16,17] One of the mediators of VEGF, namely: nitric oxide, increases the collagen deposition in diabetic foot ulcers and restores endothelial function to improve neural conduction and tissue oxygenation. Recombinant VEGF has been used in experimental wound diabetes both in vivo and in vitro.[18]

Structure and biological activities

Vascular endothelial growth factor is a signal protein that occurs naturally in the body, stimulates vasculogenesis and angiogenesis.[19] The VEGF family currently consists of 7 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and PIGF. The core region is formed by a cystine bond motif with 8 invariant cystine residues in inter and intramolecular disulfide bound to the end of the central 4-stranded at each monomer with a side-by-side antiparallel orientation. The VEGF-A gene consists of 8 exons that appear on 7 amino acid isoforms 121, 145,148,165,183,189,206 and one amino acid isoform 110 as a result of proteolytic release. VEGF-B consists of 2 amino acid isoforms 167 and 186. VEGF-C and VEGF-D, are released proteolytically from each proprotein. All of these VEGF members take great care of their homologous domains encoded by exon 1-5.[19]

VEGF known that has many important biological activities. VEGF is a powerful mitogen (ED50 2-10 pm) for microvascular and macrovascular endothelial cells obtained from arteries, veins and lymphatics, but has no mitogen activity for other cell types. VEGF stimulates angiogenesis in three dimensions: it causes encounters of microvascular endothelial cells, penetration into collagen gels, and forms capillary-like structures. VEGF causes vascular (sprouting) blood vessel growth, strong angiogenic response, promotes expression of serine proteases uro-kinase-type and tissue-type plasminogen activators (PA) and also PA inhibitor 1 (PAI-1) in microvascular endothelial cells, to maintain the balance of proteolytic processes. VEGF increases the expression of interstitial collagenase metaloproteinase. The presence of concurrent effects on collagenase and plasminogen activator by VEGF, this would establish a prodegradation environment for the migration and growth of endothelial cells. This environment is an important element of the cellular process chain that bridges cell invasion and network remodeling, as a constant proangiogenic activity of VEGF. VEGF is also known as a vascular permeability factor that promotes vascular leakage. With increased microvascular permeability, this is a very important stage of angiogenesis associated with tumors and wounds. The main function of VEGF in the angiogenesis process is to induce leakage of plasma proteins, resulting in the formation of extravascular gel fibrin, a substrate for penetration and growth of endothelial cells and tumor cells. The long-term number and physiology of microvascular driven by VEGF is, in particular, determined by the microenviroment host rather than the stimulus that initiates angiogenesis itself.[20]

Receptor

VEGF has 3 receptors, namely VEGFR-1 (Flt-1/fms-like-tyrosine kinase-1), VEGFR-2 (KDR/Flk-1/fetal liver kinase-1) and VEGFR-3 (Flt-4) each receptor has 7 immunoglobuline-like domains in the extracellular domain.16,17 Flt-1 has the highest affinity to rhVEGF165, whereas its affinity Flk-1/KDR is slightly lower, VEGF-C/VRP binds with high affinity with Flt-4.21 VEGF receptors shown in Figure 1.[16]

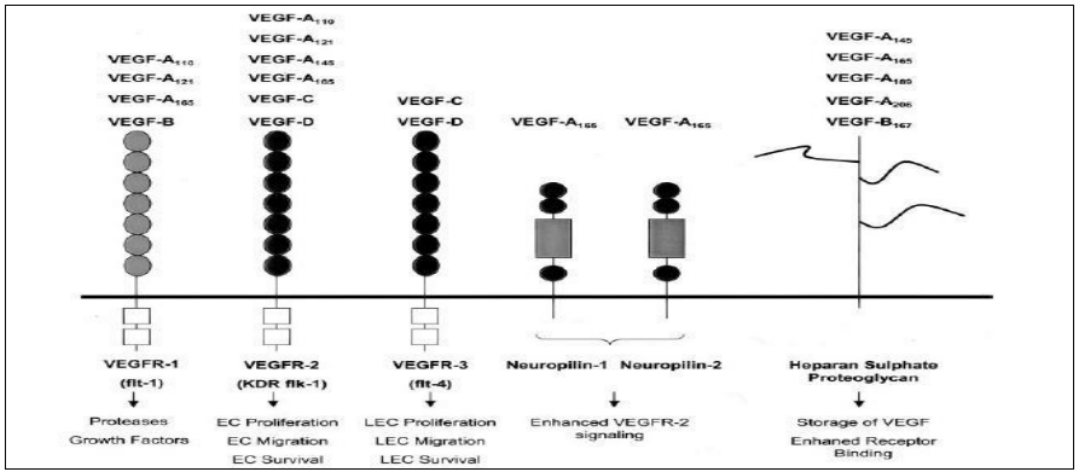

Figure 1: Receptor VEGF.

Regulation of gene expression

Regulation of VEGF gene expression trough:

Hipoxia

Oxygen pressures have a major role in the regulation of VEGF gene expression both in vitro and in vivo.[20] Oltmanns et al, said VEGF is elevated by hypoxia in vitro, but in vivo data on VEGF regulation in chronic hypoxic diseases is still a contradiction.[22] VEGF expression of mRNA is triggered rapidly and reversibly by exposure to low oxygen (pO2) stress, as well as ischemia caused by arterial occlusion.

The increased levels of VEGF mRNA are suspected that VEGF may promote spontaneous revascularization after ischemia.[20] The Flt-1 receptor is elevated by hypoxia and binds VEGF with high affinity, whereas Flk-1 / KDR is not increased by hypoxia and affinity bonds with lower VEGF.[21] Oltmanns et al, reported that systemic acute hypoxia in healthy young men decreased plasma VEGF levels compared to normoxia, whereas Flt-1 concentrations remained unchanged during hypoxia.[22]

Systemic VEGF levels have been reported in a variety of pathological conditions such as tumor growth, coronary artery disease and chronic hypoxic diseases.[23,24] This observation is thought to be possibly related to oxygen regulation. But in respiratory diseases with chronic hypoxic manifestations, the VEGF regulation is still in conflict. In respiratory diseases such as idiopathic pulmonary fibrosis, sarcoidosis, emphysema, VEGF levels are decreased compared with healthy controls, whereas in smokers and chronic obstructive pulmonary disease (COPD) is being elevated[25-27]

However, all such data can be confused by the presence of comorbids that affect the VEGF such as hypertension, insulin resistence, drugs such as statins.[28-30] Research in altitude areas in healthy people, the results can not be concluded, because there are reported the effects of hypoxia, VEGF levels in the blood increased, unchanged or even decreased.[31-33]

Cytokines

Some cytokines or growth factors may increase the expression of VEGF mRNA and / or trigger excretion of the VEGF protein. Exposure to keratinocytes or keratinocyte growth factor, epidermal growth factor (EGF), TGF-β, TGF-α, IL-1β, IL-1α, IL-6, PGE2, IGF-I trigger the apparent release of VEGF mRNA.[21] Proinflammatory cytokines stimulate the expression of VEGF mRNA with different activities. TNF-α is the most powerful activator in stimulating VEGF expression of mRNA, whereas IL-1β, TGF-β1, Interleukin-6 have lower activity.[34]

Differentiation and transformation

Cell differentiation plays an important role in the regulation of VEGF gene expression. VEGF mRNA increases during a change from 3T3 preadipocyte to adipocytes or during miogenic differentiation of C2C12 cells. In contrast the expression of the VEGF gene will be decreased or suppressed during the differentiation of pheochromocytoma cells into nonmalignant neuron-like cells.[20]

VEGF expression on diabetic foot ulcers

In diabetic foot ulcers, levels of growth factors such as VEGF, Fibroblast Growth Factor (FGF)-2 are low, since diabetic fibroblasts are unable to increase the production of VEGF and FGF-2 at normal levels in response to hypoxic conditions. Abnormal VEGF levels and activities, as well as the hypoxic state, lead to impaired ulcer healing, as most ulcers are located in the extremities of ischemia. In the absence of an appropriate angiogenesis response, the next phase of cell proliferation and matrix deposition are slow.[35] In all chronic ulcers showing tissue hypoxia, if this hypoxia continues to increase, there will be wound healing failure. Local oxygen pressure in the corneal ulcers is about half that of normal, resulting in replication of fibroblasts, collagen deposition, angiogenesis, vasculogenesis and leukocytes. Normal wound healing through several stages requires infection control and contamination, inflammatory repair, regeneration of connective tissue matrix, angiogenesis/vasculogenesis, wound constriction and reepitelialisation. Chronic ulcers failed to follow that stage.[36]

The presence of vascular changes as a chronic complication of DM, paradoxes occur, that is, increased angiogenesis in proliferative retinopathy or atherosclerosis plaque and decreased angiogenesis in coronary artery disease or diabetic foot ulcers with clinical manifestations of lack of collateral growth in the heart and failure in diabetic foot ulcer healing. There is a hypothesis that explains this paradox angiogenesis, that the response of growth factor (VEGF) is impaired in DM. This molecular disorder lies within the signal transduction system either flowing down the receptor (signal transduction defect) or at the receptor level.[37] Chou, has reported no difference in VEGF regulation in diabetic tissue.[29] Simons, proposes to reassess the paradigm of angiogenesis, arteriogenesis in DM as seen in the following Figure 2.[14]

The role of VEGF in angiogenesis and vasculogenesis in the healing of diabetic ulcers

Low levels of oxygen and nutrients, limiting functionality and viability of tissues. A natural response to the state of tissue ischemia is to increase angiogenic growth factor

along with the procurement and mobilization of cellular elements in the circulation to facilitate the growth of new blood vessels (neovascularization). Neovascularization is the result of several processes: vasculogenesis, angiogenesis and arteriogenesis. Angiogenesis is a new capillary sprouting of the existing capillaries.

Angiogenesis is stimulated primarily by tissue hypoxia through Hypoxia-Inducable Factor (HIF)-1 expression. HIF-1 activates transcription of several genes such as VEGF, VEGF flt-1 receptor, neuropilin-1 and angiopoietin-2 (Figure 4).[38]

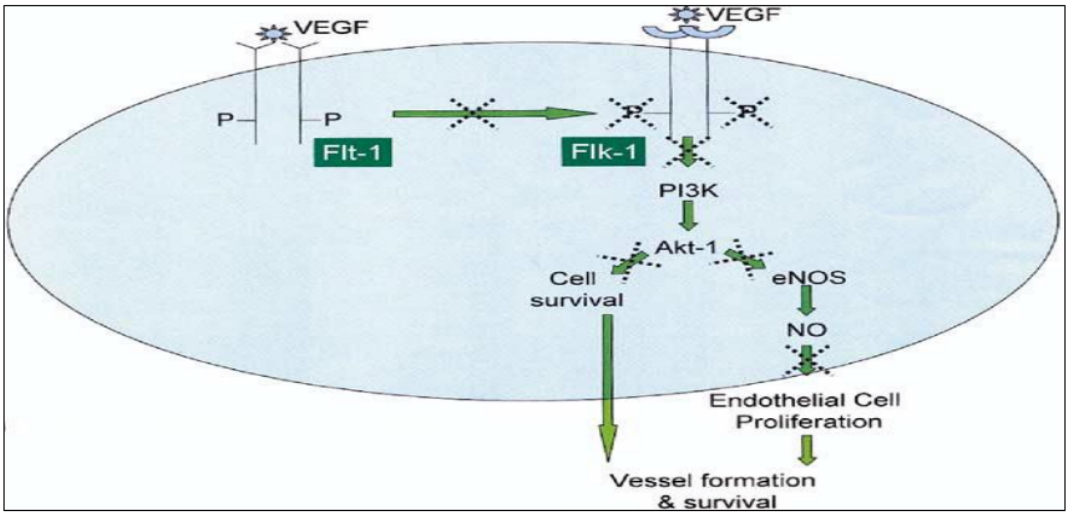

Figure 2: Signalling disturbance scheme in DM.

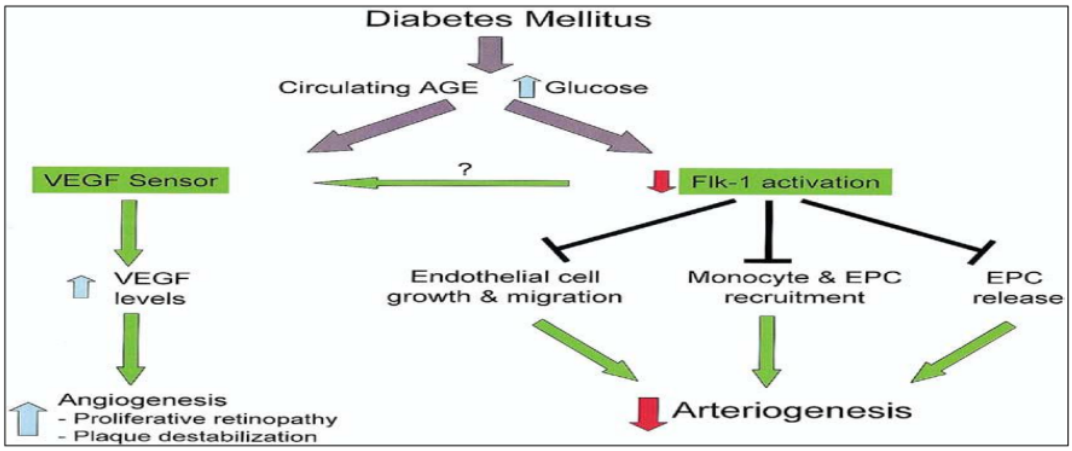

Figure 3. The sequence of angiogenesis disorders in DM.

The growth of a blood vessel from the differentiated endothelial cells in situ is called vasculogenesis, whereas the growth of new blood vessels from existing blood vessels is called angiogenesis or neovascularization. The endothelial cells present in the lining of each blood vessel must undergo proliferation, migration, and survival to form new blood vessels, or in other words the local microenvironment must convey signals to endothelial cells to multiply and avoid apoptosis. Angiogenesis is a complex, gradual process and is highly dependent on the balance between stimulating factors and inhibiting factors. Many growth factors stimulate angiogenesis. VEGF is the most specific growth factor for vascular endothelium.[39]

Neovascularization in humans has been known to occur in atherosclerotic plaques, proliferative retinopathy and malignant neoplasia. Histochemical examination of atherosclerotic plaques suggests that VEGF is expressed by smooth muscle cells and macrophages in the intima

atherosclerosis. The number of cells with VEGF positive, correlated with the number of intima veins. Excessive expression of VEGF appears in proportion to angiomatoid proliferation in experimental animals after either VEGF gene transfer or diabetes.

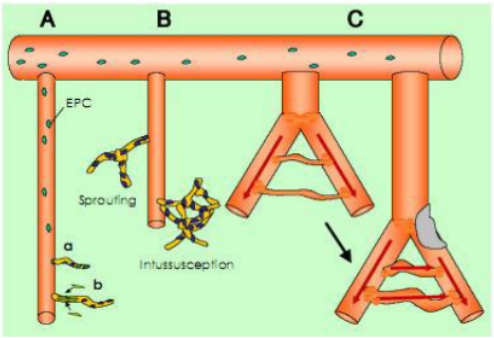

Figure 4: Mechanism of neovascularization. A. Vasculogenesis, capillary growth of progenitor endothelial cells (EPC), B. Angiogenesis, new capillary growth of existing blood vessels, C. Arteriogenesis, collateral growth with remodeling from existing collateral.

These results suggest that VEGF acts as a local and endogenous regulator of endothelial cell function, and that VEGF stimulates neovascularization under pathophysiological conditions.[40]

Galiano et al, suggested that reduced production of VEGF and angiogenesis contributed to the failure of ulcer healing in diabetic patients, thus encouraging the study of whether recombinant human VEGF165 protein topically improved wound healing in diabetic rats. The results showed a significant increase in healing rates from VEGF-treated lesions, characterized by early leaky, vascular formation followed by granulation tissue deposition, increased epithelialization, increased matrix deposition and increased cellular proliferation. Analysis of gene expression by real-time reverse transcriptase-polymerase chain reaction showed a significant increase in platelet-derived growth factor-B and fibroblast growth factor-2 associated with increased granulation tissue in the wound.

Topical administration of VEGF also has a systemic effect, with the discovery of an increase in the number of VEGFR2+/CD11b-cells in the circulation, as a reflection of an endothelial precursor. Topical VEGF administration can improve wound healing locally and systemically, whereby locally significant increases in growth factors and systemically increase angiogenesis by mobilization of bone marrow-derived cells cells for vascular formation and cells for improved wound environment where there will be accelerated wound healing.[41]

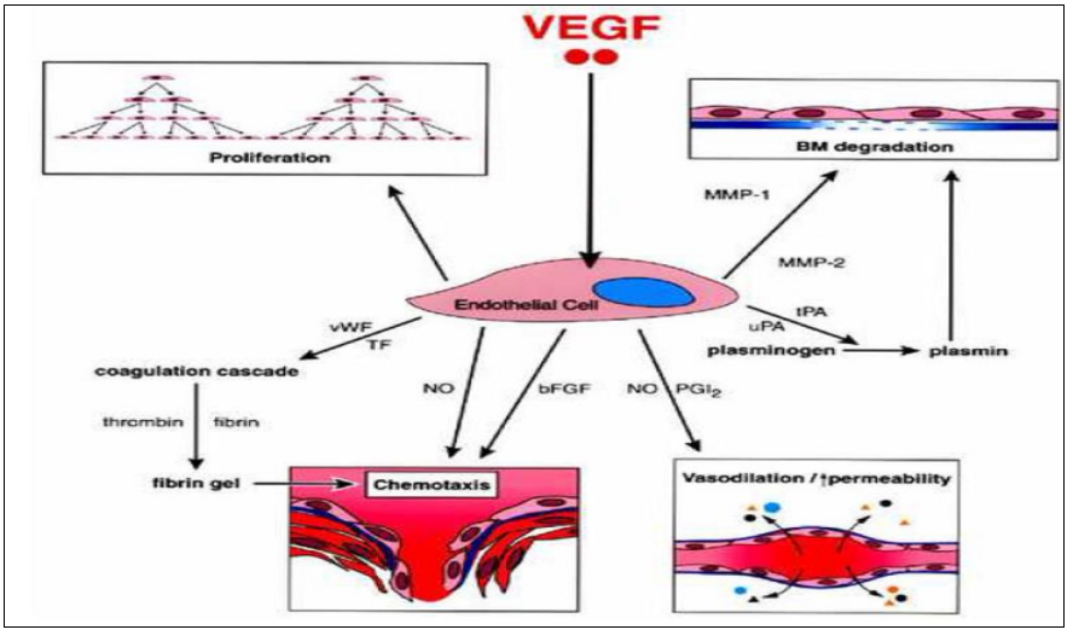

Figure 5: VEGF role diagram in wound healing. By stimulating endothelial cells, the phases of the angiogenesis cascade increase.

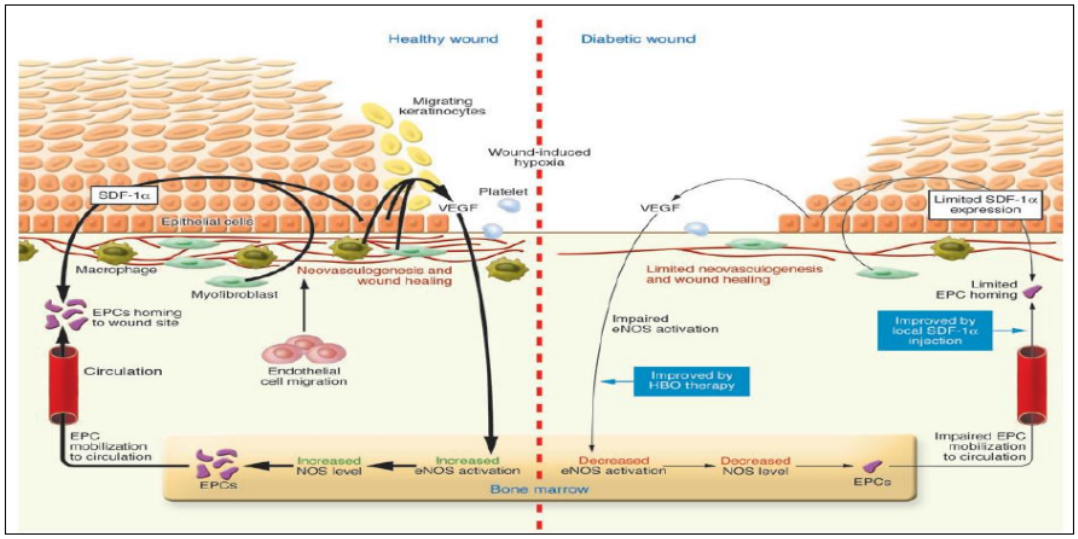

Figure 6: Wound healing mechanism in healthy people and diabetics.

Various physiological disorders lead to healing disorders in diabetic foot ulcers such as cell migratory disorders, an innervation interference and inadequate angiogenesis.[42-44] Matrix metalloproteinases (MMPs) and their inhibitors have been identified in controlling the process between the formation of capillary tubes (morphogenesis) with the cessation of capillary tubes within the collagen matrix, associated with the formation and cessation/regression of granulation tissue during wound healing. Metalloproteinase, MT1-MMP (MMP-14) membrane is required for the formation of endothelial cell tubes for sprouting in collagen matrices, but this event is inhibited by small interfering RNA (siRNA) suppression of MT1-MMP or by tissue inhibitor of metalloproteinases (TIMPs) -2, -3, -4 but not TIMP-1.[45]

VEGF stimulates wound healing through several mechanisms such as collagen deposition, angiogenesis and epithelialisation. VEGF stimulates endothelial cells, the phases of the angiogenesis cascade increase as shown in Figure 5. In clinical practice, the mitogenic, chemotactic and permeability effects of VEGF may have the potential to aid the healing of chronic wounds in patients with occlusive and diabetic artery disease, so that VEGF levels should be examined as soon as possible in diabetic foot ulcers and decubitus ulcers.[46]

Wound healing occurs as a cellular response to injury, including activation of keratinocytes, fibroblasts, endothelial cells, macrophages and platelets. Some growth factors and cytokines are released by these cells to coordinate and maintain wound healing. VEGF is an important physiological factor in wound healing in both normal and DM people but with different response quality can be seen in Figure 6.[47]

There are several clinical trials of angiogenesis therapy with VEGF proteins in patients with coronary heart disease and intrautoconal, intracoronary, intraarterial, and percutaneous peripheral peripheral arteries given varying outcomes, positive and negative.[48] In assessing the effectiveness of therapy, several parameters such as collateral enhancement, improvement of global and regional cardiac function, accelerated ulcer healing, amputation rate and exercise tolerance.[18,48-55]

CONCLUSION

The most interesting stage of the wound healing process is in the proliferation phase, as this phase determines the success of wound closure. This phase is characterized by angiogenesis or neovascularization. Angiogenesis or neovascularization is mediated by several growth factors, one of which is VEGF. Diabetic ulcer patients may present hyperglycemia and advanced glycation end-products (AGEs) accumulation that may cause disturbance to growth factors such as VEGF and its receptors, signaling pathways. The VEGF family currently consists of 7 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and PIGF. The VEGF core region is formed by a cystine bond motif with 8 invariant cystine residues in inter and intramolecular disulfide bound to the end of the central 4-stranded at each monomer with a side-by-side antiparallel orientation. The VEGF-A gene consists of 8 exons that appear on 7 amino acid isoforms 121, 145,148,165,183,189,206 and one amino acid isoform 110 as a result of proteolytic release. VEGF-B consists of 2 amino acid isoforms 167 and 186. VEGF-C and VEGF-D, are released proteolytically from each proprotein. All of these VEGF members take great care of their

homologous domains encoded by exon 1-5. VEGF stimulates angiogenesis in three dimensions: it causes encounters of microvascular endothelial cells, penetration into collagen gels, and forms capillary-like structures. VEGF has 3 receptors, namely VEGFR-1 (Flt-1/fms-like-tyrosine kinase-1), VEGFR-2 (KDR/Flk-1/fetal liver kinase-1) and VEGFR-3 (Flt-4). Regulation of VEGF gene expression malalui: (1) hypoxia; (2) cytokines and (3) differentiation and transformation. VEGF stimulates wound healing through several mechanisms such as collagen deposition, angiogenesis and epithelialisation.

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