THE MECHANISM OF PROTRACTED WOUND HEALING ON ORAL MUCOSA IN DIABETES. *REVIEW*

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Abstract

Diabetic patients increase their body's susceptibility to infection and diabetes is a risk factor for periodontal diseases and oral infection. Although many studies showed the mechanism of impaired wound healing in diabetes, there are still arguments to shed light on what kind of factors, including local and systemic factors are involved in the protracted wound healing. This review article summarizes reports on the wound healing in diabetes and discusses the mechanism of the protracted wound healing of the oral mucosa in diabetes. Delayed vascularization, reduction in blood flow, decline in innate immunity, decreases in growth factor production, and psychological stresses may be involved in the protracted wound healing of the oral mucosa in diabetics.

KEY WORDS: Diabetes, oral mucosa, wound healing

Introduction

Diabetes is found almost in every population, and the prevalence will continue to increase globally without effective prevention and control programs. Diabetic patients increase their body's susceptibility to infection and diabetes is a risk factor for periodontal diseases and oral infection. Since the diabetes often protracts wound healing leading to secondary infection, the individual surgical procedure should be cautionary undergone a change. Many studies showed the mechanism of impaired wound healing in diabetes. There are, however, still arguments to shed light on what kind of factors, including local and systemic factors are involved in the protracted wound healing. This review will discuss on the mechanism of protracted wound healing of oral mucosa in diabetes.

Factors affecting wound healing of oral mucosa
Oral mucosa is covered with stratified squamous epithelium, and the connective underneath the epithelium consists of fibroblasts, collagens and capillaries. The process of wound healing involves hemostasis, inflammation, cell proliferation and remodeling. The first phase of hemostasis begins immediately after wounding, with vascular construction and fibrin clot formation. The inflammatory phase is characterized by the sequential infiltration of neutrophil, macrophages, and lymphocytes. The proliferation phase overlaps with the inflammatory phase, and is characterized by epithelial proliferation and migration over the provisional matrix within the wound, vascularization, collagen synthesis and extracellular matrix formation. The collagen remodeling, and vascular maturation and regression occurs in the remodeling phase. Multiple local and systemic factors impair their wound healing. Supply of oxygen, infection and foreign body are the local factors. Ageing, sex, stress, failure of circulation, obesity, medications such as steroid and anti-cancer drug, alcohol, smoking, immunosuppresed state, nutrition and many types of systemic diseases can be a systemic factor for it. Diabetes, many types of fibrosis, jaundice and uremia include the systemic diseases (1).

Circulation and vascularization in diabetes
Diabetic patient contract a vascular disorder, including obstructed vascular sclerosis, leading to decrease of vascular circulation (2). The decrease of vascular circulation cause hypoxia which induces to impair wound healing. Hypoxia enhances initial inflammatory reactions and increases oxidant free radical, which delays wound healing

(3,4). Oxidant free radical is also induced by an increase in blood sugar level (5) and promote advanced glycation end-products(AGE`s) inhibiting vascularization (6). Oxidant radical induces incomplete formation and distraction of gap junctions of blood vessels (7,8,9,10). Elevated blood-sugar levels directly cause incomplete formation of gap junctions even though no oxidant stresses (11), and also promotes the production of TNF-alpha (TNF-α) involved in inhibition of hemangiogenesis (12). Many factors decrease microvascular circulation and thereby cause impaired wound healing in diabetes.

Immunoresponses in diabetes
Infections are of particular concern for diabetic patients. Local infection directly causes impaired wound healing, and the delayed wound healing increases susceptibility to infections. Diabetic patients are under state of immunosuppression, which is related to the higher susceptibility to infection. Previous reports showed the suppression of innate immunity in the diabetics (13). Decreased number of neutrophils migrated throughout from blood capillaries were reported in diabetics. Increased amount of AGE depositions causes the decreased number of infiltrated neutrophils (14). The AGE directly inhibits the chemotactic activity of neutrophils. A previous report showed that chemotactic attractant of neutrophils was significantly lower in the diabetics with more than glucose concentration of 12mmol/L than in healthy individuals (15). The chemotactic attractant of monocytes are also declined (16). Neutrophils and monocytes play a key role in innate immunity and act as a bridge between innate and adaptive immunity. The dysfunctions of those cells may be a crucial in the suppression of host immunity in diabetic patients. The dysfunction of neutrophil chemotaxis can be controlled by lower high blood-sugar levels in diabetic patients (17). In addition to neutrophils and monocytes, antimicrobial peptides produced also by epithelial cells act as an important part of innate immunity. Several types of antimicrobial peptides including beta-defensins, cathelicidin and psoriasin are produced by oral epithelium (18,19). The expression levels of beta-defensins are altered by the concentration of insulin, glucose or adiponectin (20,21). The alteration of concentration of glucose and insulin in the blood may decrease the function of innate immunity, inhibiting the wound healing. Saliva that covers the surface of oral epithelium functions as innate immunity by antimicrobial effects with rinsing the surface of oral epithelium (22). In diabetics, functional alteration of saliva such as flow rate and its component affect their wound healing (See more detain in the next section). The previous

investigations on abnormal of the adaptive immunity have mainly focused on type I diabetes (23,24). Type II diabetes and obesity increase the blood concentration of inflammatory cytokines such as IL-6 and TNF-α, which is involved in the insulin resistance (25,26). The diabetic rats injected by inactivated P. gingivalis induced more prolonged inflammation than the control (27). The inflammatory cascade response is inhibited by TNF-α in the diabetics, implying abnormal regulation of inflammatory cytokines including TNF-α in diabetes (28). Increased level of TNF-α is also induced by the high level of AGE (29). AGE`s induces production of many other types of cytokines and chemokines, suggesting that AGE is involved in the abnormal of the adaptive immunity (30). Certain concentration of AGE inhibits production of type I and III collagens (31) and often induces cell apoptosis (27). AGE may impair the wound healing owing to induction of excessive immunoresponses and negative regulations of the cell physiology.

Salivary components and flow in diabetes

Saliva has many functions including digestion, buffering capacity, antimicrobial activity, self-cleaning action of the surface of oral mucosa keeping the physiological oral flora in balance. Many of blood data that can be detected in diabetics are also detected in saliva. Increased level of sugar and AGE are followed by high level of glucose and AGE in saliva (32,33,34) . A most crucial change of saliva in diabetic patients is lower flow rate caused by hypofunction of salivary gland (35-40). Saliva contains many kinds of antimicrobial peptides and proteins (22,18,41), and the lower flow rate causes bacterial infection. The components of saliva are altered in diabetics. Saliva in diabetics contains less glutathione and melatonin that function as a scavenger for free radicals than that in health individuals (42,43,44). The diabetic patients produce more free radicals at the wound under elevated blood-sugar and hypooxidation conditions than normal (3,4). The lower level of scavengers and the higher level of free radicals may induce more oxidative stress causing the protracted wound healing in diabetes. The high concentration of MMP-8, a type of collagenase, is detected in saliva of diabetics (45,46). The excess amount of enzymes for degradation of extracellular matrices impairs wound healing (1). The high level of MMP-8 may be involved in the impaired wound healing. The diabetics have less epidermal growth factor (EGF) in saliva. EGF mainly produced by submandibular glands fulfill many functions, including cell growth and differentiation in oral tissues. EGF promotes re-epithelialization of oral mucosa

(47). The less EGF in saliva may also be involved in the protracted wound healing on oral mucosa in diabetes.

Growth factors in diabetes

In addition to EGF in saliva, many other growth factors including insulin-like growth factor (IGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF) and nerve growth factor (NGF) produced at the wound promotes the healing (48). The lower levels of IGF-1, TGF-b1 and NGF produced at the wound were reported in both diabetic animals and human. The decreased expression of these growth factors may be involved in the protracted wound healing. IGF-1, an isoform of IGF, stimulates chemotaxis of endothelial cells and proliferation of keratinocytes and fibroblasts, which promote re-epithelization and extension of wound (49,50,51). Delayed expression of IGF-1 and IGF-1 receptor mRNAs was observed in the process of the wound healing in diabetic mice (52,53,54). Decreased expression levels of those mRNAs were also observed in foot ulcer in the diabetic patients (55). TGF-b1, an isoform of TGF-b, promotes chemotaxis of monocytes, macrophages, neutrophils, lymphocytes, keratinocytes and fibroblasts, and production of growth factors from those cells. These accelerate vascularization, deposition of extracellular matrices and inhibition of degradation of extracellular matrices (56,57). The production level of TGF-b1 was decreased in the process of wound healing in diabetic rats (54). Decreased production level of TGF-b 1 was observed in foot ulcer in diabetic patients (58,59,60). PDGF, like TGF-b, promotes vascularization and deposition of extracellular matrices. PDGF production is decreased in the chronic foot ulcer (61). The expression levels of PDGF and its receptor were decreased also in diabetic rats and mice model (62,63). TGF-b stimulates the expression of PDGF (64). The decreased expression of PDGF may be linked to the decreased expression of TGF-b in diabetics. NGF originally discovered as a neurotrophic factor is expressed in fibroblasts, endothelial cells and keratinocytes (65,66,67), which is involved in immunoresponse and vascularization (68,69). NGF induces proliferations of keratinocytes and endothelial cells, monocytic differentiation and activation of neutrophils (69,70,71,72). Expression of NGF was also decreased in the skin both on diabetic patients and rats (73-77). Another growth factor, keratinocyte growth factor (KGF) is decreased in diabetic mouse (78). IL-6 stimulates KGF production from fibroblasts and the expression level of IL-6 is decreased in the wound of diabetic patients (79). As stated above, most of the growth factors that

promote wound healing are decreased. The decreased expression of these growth factors may lead to poor and delayed wound healing on the oral mucosa in diabetes.

Psychological stresses in diabetes

Diabetic patients are often under psychological stress (80,81). Psychological stress causes a substantial delay in wound healing (1). The psychological stress may be associated with protracted wound healing in diabetic patients. There are several possible mechanisms how psychological stress causes a delay in wound healing. The stress results in the deregulation of the immune system, mediated primarily through the hypothalamic-pituitary-adrenal (HPA). The deregulation of the immune system increases susceptibility to infection leading to poor wound healing in diabetes (82,83). The psychological stressors may lead to emotional states such as anxiety and depression, which adversely affects endocrine and immune function. The stress may make individuals to have unhealthy habits, including inadequate nutrition and a greater propensity for abuse of alcohol and cigarettes. These factors may negatively modulate the process of wound healing. The stress also causes hyper-

glycemia with increasing of norepinephrine and epinephrine via sympathetic-adrenal medullary (1). Stress factors may influence negatively the diabetic condition and have an even worse effect on the wound healing.

Future prospects

Multiple factors are involved in protracted wound healing on oral mucosa in diabetes. The severity and pathophysiological conditions in diabetes are of great variety among individuals. The values of blood-sugar, hemoglobin A1c (Hb1c) and 1,5-anhydroglucitol (1,5-AG) differ among diabetic patients. The pathophysiological conditions and their molecular biological mechanisms differ between types I and II diabetes. These individual differences may be crucial factors for the protected wound healing. There is not enough clinical and experimental evidence how the individual differences affect the multiple factors. Further clinical investigations need to clarify the effect of the individual differences on the multiple factors. The guideline for oral surgical procedures in diabetes should be reevaluated and then newly formulated using these clinical data.
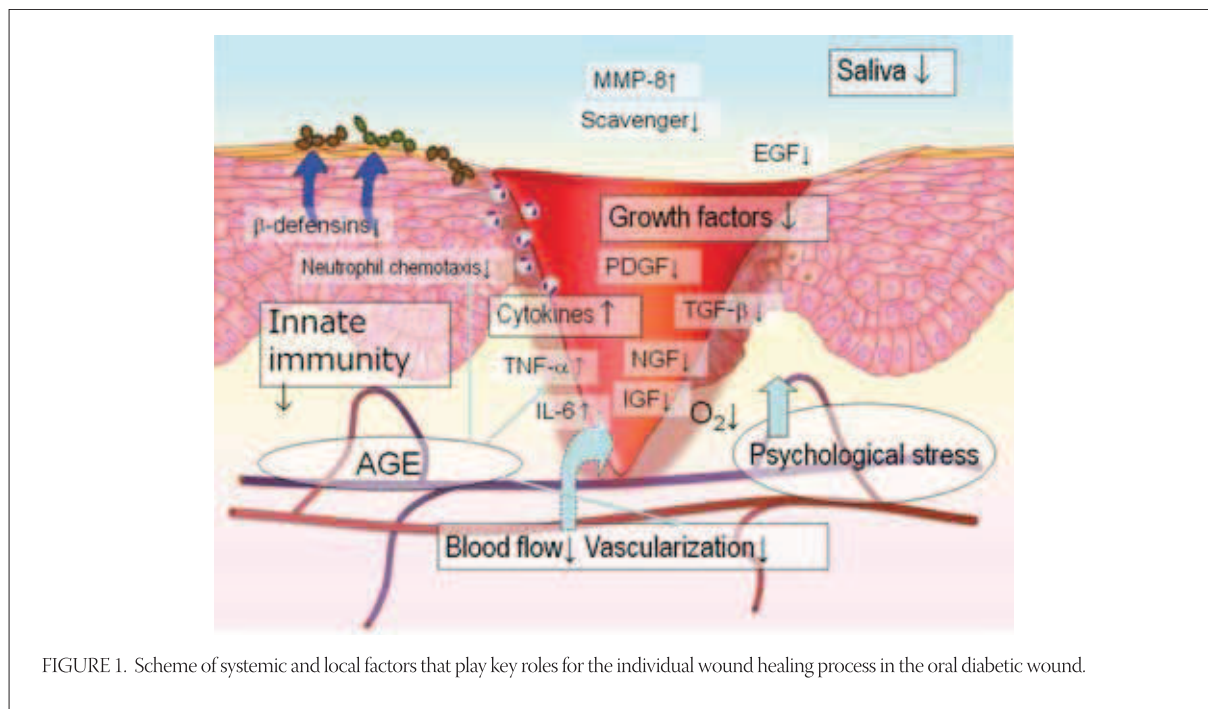

FIGURE 1. Scheme of systemic and local factors that play key roles for the individual wound healing process in the oral diabetic wound.

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