WOUND HEALING OF PERIODONTAL AND ORAL TISSUES: PART II - PATHO-PHISIOLOGICAL CONDITIONS AND METABOLIC DISEASES. REVIEW.

Maria-Alexandra Martu[1], George-Alexandru Maftei[2]*, Ionut Luchian[1]*, Cristina Popa[3], Ana-Maria Filioreanu[3], Diana Tatarciuc[2], Giorgio Nichitean[4], Loredana-Liliana Hurjui[5], Liliana-Georgeta Foia[5]

[1]University of Medicine and Pharmacy "Grigore T. Popa", Faculty of Dental Medicine, Department of Periodontology, Iasi, Romania
[2]Phd Student, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania
[3]University of Medicine and Pharmacy "Grigore T. Popa", Faculty of Dental Medicine, Department of Oral Pathology, Iasi, Romania
[4]DMD Student, University of Medicine and Pharmacy "Grigore T. Popa", Faculty of Dental Medicine, Iasi, Romania
[5]University of Medicine and Pharmacy "Grigore T. Popa", Faculty of Medicine, Iasi, Romania

*Corresponding author*s: Maftei George-Alexandru*: E-mail: maftei.george.gm@gmail.com
Luchian Ionut*: E-mail: ionut_luchian@yahoo.com

[#]*All authors had equal contributions with the first author*

Abstract:

From a clinical perspective doctors rely on auspicious wound healing on a daily basis. Without a thorough understanding of this process success in treatment cannot be obtained. Thus it is of utmost importance that clinicians know and understand both the local, but more importantly, the systemic factors, which most of the time are not so apparent, which can affect and delay wound healing. The oral cavity hosts a plethora of tissues that serve various functions, and in this complex environment cells, bacteria, viruses, and fungi live in a subtly balanced ecosystem. It is this complexity of factors, both systemic and local, that offer the healing particularities and challenges of the oral cavity.

Keywords: *wound healing, oral tissues, periodontium, alveola, diabetes, obesity*

Introduction

In light of recent developments in the scientific literature one has to ponder upon the concept of health. Nowadays it is described not only as the lack of a disease or infirmity, but as a state of well-being, from a physical, mental and social, thus a holistic perspective. The human organism is an intricate structure comprised of multiple organs which interact through complex biological processes. The mouth is an important part in this mechanism through its multiple functions that it serves. When the oral cavity is affected and leaves the state of homeostasis, so does the rest of the body. A thorough clinical examination of the cefalic extramity can not only expose oral diseases, lesions and abnormalities but also systemic diseases and disorders, which manifest in this region, nutritional deficiencies, cancers and disorders of the immune system.

In this Part II of the issue of wound healing we will focus on systemic factors, namely the physiological conditions, but also the pathological and aggravating conditions. Furthermore, we will discuss the ascendancy of metabolic disorders such as diabetes and obesity, two of the most frequent diseases worldwide, on wound healing in the oral cavity.

Age

Old age is a major risk in the healing process, as it leads to a delay in healing but not necessarily a deterioration in its quality. Delayed healing in elderly patients is associated with an altered inflammatory response, with changes in chemokine production and a reduction in the ability to phagocytose macrophages. In addition to these changes, a delay in the processes of angiogenesis, collagen synthesis and reepithelialization was also observed [1]. Therefore, there are major differences between young and old in terms of healing. A review of healing capacity changes demonstrated that each phase of the healing process undergoes age-related changes, including increased platelet aggregation, increased secretion of inflammatory mediators, late lymphocytic infiltration, decreased growth factor secretion, and a reduced collagen turnover rate [2, 3].

Stress

Stress has a major impact on health and social behavior. Many diseases such as diabetes, cancer, cardiovascular disease and poor wound healing are associated with stress. The pathophysiological mechanism of stress causes disturbances in the immune system, mediated primarily by the hypothalamic-pituitary-adrenal complex and the adreno-medullary sympathetic axis or the sympathetic nervous system [4].

Both animal and human studies have shown that stress causes a substantial delay in wound healing. The adreno-sympathetic and adreno-pituitary-hypothalamic medullary axes regulate the release of pituitary and adrenal hormones. These hormones include adrenocorticotropic hormones, cortisol and prolactin, and catecholamines (epinephrine and norepinephrine). Stress regulates glucocorticoids and alters the levels of proinflammatory cytokines IL-1β, IL-6, TNF-α in the postextraction site. It reduces the expression of IL-1α and IL-8, both cytokines being chemoattractants needed in the inflammatory phase of healing [4]. Glucocorticoids influence immune cells by suppressing differentiation and proliferation, balancing gene transcription and reducing the expression of cell adhesion molecules that are involved in the immune cell network. Cortisol acts as an anti-inflammatory agent and modulates the Th1-mediated immune response which is essential in the initial healing phase. Therefore, stress modifies normal cell-mediated immunity in the wound, causing a significant delay in the healing process [5].

Stressors can cause negative emotional states, such as anxiety and depression, which can have an impact on physiological processes and behavioral patterns. In addition to the direct influence of depression and anxiety on the immune and endocrine systems, highly stressed subjects are more prone to unhealthy habits such as unhealthy diet, insomnia, lack of exercise and an increased predisposition to alcohol, cigarettes or other drugs. All these factors negatively modulate the healing response.

Smoking

It is well known that smoking increases the risk of heart and vascular disease, stroke, chronic lung disease and many types of cancer. Similarly, the negative effects of smoking on wound healing have long been observed in the scientific literature [6]. Postoperatively, after a tooth extraction or periodontal surgery, patients who smoke have a delay in wound healing and an increase in a variety of complications, such as infection, wound dehiscence, wound and flap necrosis, epidermolysis, and a decrease in wound tensile strength [7]. Regarding more ample oral surgery, poor healing in smokers has been observed both in routine interventions but also in other areas such as biopsies, cancer removal or in the placement of dental implants or sinus lift [8]. Aesthetic outcomes also appear to be poor in smokers, and plastic surgeons are often reluctant to perform surgery on people who refuse to quit smoking [9].

Approximately over 4,000 substances in tobacco smoke have been identified, and some have been shown to have a negative impact on healing [6]. Most studies have focused on the effects of nicotine, carbon monoxide and hydrogen cyanide in cigarette smoke. Nicotine probably interferes with oxygen supply by inducing tissue ischemia, as nicotine can cause decreased tissue blood flow through vasoconstrictor effects. Nicotine stimulates sympathetic nerve activity, leading to the release of epinephrine, which causes peripheral vasoconstriction and decreased tissue blood infusion. Nicotine also increases blood viscosity caused by decreased fibrinolytic activity and increased platelet adhesion. In addition to the effects of nicotine, carbon monoxide in cigarette smoke also causes tissue hypoxia. Carbon monoxide aggressively binds to hemoglobin with an affinity 200 times higher than that of oxygen, resulting in a decrease in the fraction of oxygenated hemoglobin in the bloodstream [10].

Hydrocyanic acid, another well-studied component of cigarette smoke, affects cellular oxygen metabolism, leading to poor oxygen distribution and usage in tissues. Beyond these direct effects on tissues, smoking increases an individual's risk of atherosclerosis and chronic obstructive pulmonary disease; two conditions that could also lower tissue oxygen tension [11].

Several cell types and processes that are important for healing have been shown to be adversely affected by tobacco smoke. In the inflammatory phase, smoking causes impaired leukocyte cell migration, resulting in fewer monocytes and macrophages in the wound, and reduces neutrophil bactericidal activity. Lymphocyte function, Nk cell cytotoxicity and IL-1 production are all diminished and the ability of macrophages to detect Gram-negative bacteria is inhibited [10]. These effects result in poor healing and an increased risk of opportunistic wound infection.

Moreover, due to impaired cell function, the periodontal tissues are some of the most affected. During the proliferative phase of wound healing, exposure to smoke decreases migration and proliferation of fibroblasts, reduces wound contraction, prevents epithelial regeneration, decreases extracellular matrix production and disrupts protease balance [9].

Pharmacologically, the influence of smoking on wound healing is complicated and neither nicotine alone nor any other

single component can explain all the effects of smoking on wound healing. What is certain is that smoking cessation leads to improved healing and reduces secondary wound infection [7]. One study showed that the use of a transdermal nicotine patch in smoking cessation therapy can increase the synthesis of type I collagen in tissues [12].

Despite the general negative effects of smoking, some studies have suggested that low doses of nicotine can promote angiogenesis and thus, effectively improve healing [13].

Alcohol consumption

Clinical evidence and animal experiments have shown that alcohol influences wound healing and raises the incidence of infections. Increased consumption decreases the body's resistance, and alcohol intoxication at the time of trauma is a risk factor for an increased susceptibility to wound infections [14].

Studies have shown major effects of alcohol on host defense mechanisms, although the precise effects are dependent on the pattern of alcohol exposure (chronic alcohol consumption vs. acute consumption, amount consumed, duration of consumption, time of exposure to alcohol and metabolisation of alcohol). A recent review of alcohol-induced changes in the host's defense mechanism after traumatic injury suggests that, in general, short-term acute alcohol exposure results in suppressed release of pro-inflammatory cytokines in response to an inflammatory challenge. The higher rate of post-interventional infection correlates with decreased neutrophil recruitment and phagocytic function in acute alcohol exposure [15].

Beyond the increased incidence of infection, exposure to ethanol also seems to influence the proliferative phase of healing. In guinea pigs, exposure to a single dose of alcohol that caused a blood alcohol level of 100 mg / dL (even above the legal limit in most countries) disrupted reepithelialization, angiogenesis, collagen production, and wound closure [16].

As mentioned earlier, the host's response to chronic alcohol exposure appears to be different from that of acute alcohol exposure. Analysis of clinical data indicates that chronic alcohol exposure causes delayed wound healing and an increased susceptibility of the host to infections, but detailed mechanisms to explain this effect need further investigation.

The most significant impairment appears to be in angiogenesis, which is reduced by up to 61% following a single ethanol exposure. This decrease in angiogenic capacity implies both a decrease in VEGF receptor expression and a reduction in HIF-1α nuclear expression in endothelial cells [17].

Decreased ethanol-mediated vascularity causes hypoxia and increased oxidative stress of the wound [16]. Connective tissue restoration is influenced by acute ethanol exposure and leads to decreased collagen production and changes in wound protease balance [18].

In conclusion, acute ethanol exposure can lead to difficult wound healing by affecting the early inflammatory response, inhibition of wound closure, angiogenesis and collagen production and alteration of the protease balance at the wound site.

Diabetes mellitus

Diabetes affects hundreds of millions of people around the world. These individuals have a well-documented

impairment in the healing of acute wounds; moreover, this population is prone to developing chronic foot ulcers that do not heal, called diabetic foot ulcers (DFU), which are estimated to occur in 15% of all people with diabetes. DFUs are a serious complication of diabetes and precede 84% of all diabetes-related lower leg amputations. Affected healing of both DFUs and acute skin wounds in people with diabetes involves multiple complex pathophysiological mechanisms. DFU, venous stasis disease and chronic incurable wounds are always accompanied by hypoxia [19].

A situation of prolonged hypoxia, which can be derived from both insufficient perfusion and insufficient angiogenesis, is detrimental to wound healing. Hypoxia can amplify the early inflammatory response, thus prolonging the healing of the lesion by increasing the level of oxygen free radicals [20]. Hyperglycemia can also join and amplify oxidative stress when the production of reactive oxygen species (ROS) exceeds the antioxidant capacity [21].

The formation of advanced glycation end products (AGEs) under conditions of hyperglycemia and interaction with their receptors (RAGE) are associated with late wound healing in diabetic mice and blockade of this signaling pathway has led to improved healing. Elevated levels of matrix metalloproteinases (MMPs) are a feature of diabetic foot ulcers, and the levels of MMPs in fluids from chronic wounds are almost 60 times higher than those of acute wounds. Increased protease activity supports tissue destruction and inhibits the normal repair processes [22].

Lower numbers of neutrophils migrating to the blood capillaries have also been reported in diabetic patients. The increased amount of AGE deposits causes a decrease in the number of infiltrated neutrophils. AGE directly inhibits the chemotactic activity of neutrophils. A previous report showed that the chemotactic ability of neutrophils was significantly lower in diabetics with a higher glucose concentration of 12mmol / L than in healthy people [23]. The chemotactic capacity of monocytes is also low [24].

Neutrophils and monocytes play a key role in innate immunity and act as a bridge between innate and adaptive immunity. Dysfunction of these cells may be crucial in suppressing host immunity in diabetic patients. Impairment of neutrophil chemotaxis can be controlled by lower blood glucose levels in diabetic patients [23].

In addition to neutrophils and monocytes, antimicrobial peptides produced by epithelial cells also act as an important part of innate immunity. Several types of antimicrobial peptides including beta-defensins, catelicidin, and psoriasine are produced by the oral epithelium. Beta-defensin expression levels are altered by insulin, glucose, or adiponectin levels [25]. Changing the concentration of glucose and insulin in the blood can decrease the function of innate immunity, inhibiting wound healing.

In the oral cavity, saliva from the surface of the oral epithelium, omong other important functions, acts as an innate immunity component through the antimicrobial effect it has through rinsing the surface of the oral epithelium [26]. In diabetics, there is a functional impairment of saliva, mainly observed in flow rate and composition, and thus it affects wound healing.

Salivary components and salivary flow in diabetes

Saliva has many functions, including digestion, buffer capacity, antimicrobial activity, the action of self-cleaning the surface of the oral mucosa while maintaining the balance of oral microbial flora. Much of the information collected through blood tests that can be detected in diabetics can also be detected in saliva, thus making it a more convenient diagnostic fluid. Serum elevated sugar and AGE levels are mirrored by high glucose and AGE levels in saliva [27].

The most important change in saliva in diabetic patients is the lower flow caused by hypofunction of the salivary gland [28]. Saliva contains many types of antimicrobial peptides and proteins, and the lower flow rate increases the incidence of bacterial infections.

Besides flow rate, the components of saliva are also modified in diabetics; in these patients it contains a lower amount of glutathione and melatonin (important antioxidant molecules) that capture free radicals when compared to healthy people. A study by Zhang et al., observed that diabetic patients have more free radicals in a wound under conditions of high blood sugar and hypoxidation than normal [29]. Higher levels of free radicals can induce more oxidative stress that causes late wound healing in diabetes.

The high concentration of MMP-8, a type of collagenase, has been detected in the saliva of diabetics, and an excessive amount of enzymes for the degradation of extracellular matrices affects wound healing [30]. Elevated levels of MMP-8 may be involved in belated wound healing. Another notable difference has been observed regarding a lower epidermal growth factor (EGF) in saliva of diabetics.

Considering the fact that EGF is produced mainly by the submandibular glands and that it fulfills multiple functions, including cell growth and differentiation in oral tissues, but also promotes re-epithelialization of the oral mucosa, a reduced level of this protective molecule can have a negative impact on healing, especially after periodontal surgery, when propitious healing is of utmost importance [31].

Growth factors in diabetes

In addition to EGF in saliva, there are many other growth factors such as insulin-like growth factor (IGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF) and nerve growth factor (NGF) produced in the injury site that promote healing [32]. Lower levels of IGF-1, TGF-β1 and NGF have been reported in both diabetic animals and humans. Low expression of these growth factors may be involved in prolonged healing of lesions. IGF-1, an isoform of IGF, stimulates endothelial cell chemotaxis and the proliferation of keratinocytes and fibroblasts, which promotes re-epithelialization and reduces wound distension [33].

Delayed expression of messenger RNA receptors of BMP-2 and IGF-1 has been observed in the healing process in diabetic mice and modulation of these mediators has been proposed as a treatment. Decreased messenger RNA expression levels have also been observed in the diabetic foot of diabetic patients [34].

TGF-β1, an isoform of TGF-β, promotes the chemotaxis of monocytes, macrophages, neutrophils, lymphocytes,

keratinocytes and fibroblasts and the production of growth factors in these cells. They accelerate vascularization, deposition of extracellular matrices and inhibit the degradation of extracellular matrices. The level of TGF-β1 production was decreased in the wound healing process in diabetic mice, also, the decrease in the level of TGF-β1 production was observed in the diabetic foot of patients [35].

PDGF, like TGF-β, promotes vascularization and deposition of extracellular matrices. PDGF production is low in chronic foot ulcers, moreover, expression levels of PDGF and its receptor were also reduced in diabetic mice. TGF-β stimulates PDGF expression, and decreased PDGF expression may be related to decreased TGF-β expression in diabetics [35].

NGF, initially discovered as a neurotrophic factor is expressed in fibroblasts, endothelial cells and keratinocytes, and is involved in the immune response and vascularization. NGF induces proliferations of keratinocytes and endothelial cells, achieves monocytic differentiation and activation of neutrophils. Also, NGF expression decreased in the skin in both diabetic patients and rats [36].

Another growth factor, keratinocyte growth factor (KGF) is reduced in skin wounds of subjects with diabetes; a group of researchers observed molecular and functional changes in keratinocytes caused by a glucose-rich environment in mice with experimentaly induced diabetes [37]. Another group of researchers noted that IL-6 stimulates the production of KGF from fibroblasts and its level of expression is altered in the wounds of diabetic patients [38].

Stress and diabetes

Diabetic patients are often under psychological stress that causes a substantial delay in wound healing. There are several possible mechanisms by which psychological stress causes a delay in wound healing. Stress results in disorders of the immune system, mediated primarily by the hypothalamic-pituitary-adrenal complex (HPA). Immune system disorders increase susceptibility to infections which leads to poor healing of lesions in diabetes [39].

Psychological stressors can cause various emotional states, such as anxiety and depression, which negatively affect endocrine and immune function. Stress causes an unhealthy attitude of some individuals, such as inadequate nutrition and a greater tendency to abuse alcohol and cigarettes. These factors can negatively modulate the wound healing process. Stress also causes hyperglycemia with increased norepinephrine and epinephrine through the sympathetic-adrenal medullary complex [40].

Some authors suggest the use of dietary supplements to counteract these negative effects and to ease the production of oxidative damage in the organism [41, 42].

In conclusion, delayed healing, especially in the oral cavity, due to the fact that it is an exceedingly populated by microorganisms environment, occurs invariably in people with diabetes and it involves complex mechanisms such as hypoxia, dysfunction of fibroblasts and epidermal cells, affected angiogenesis and neovascularization, high levels of metalloproteases, damage caused by ROS

and AGE, decreased immune resistance of the hosts but also neuropathy.

Obesity

Obesity continues to rise among adults, children and adolescents, especially in heavily industrialized countries, however it is not restricted to these areas; a recent study reporting a 39% prevalence of obesity worldwide [43].

Obesity is well known for increasing the risk of onset and evolution of many illnesses and health conditions, including coronary heart disease, type 2 diabetes, cancer high blood pressure, dyslipidemia, stroke, sleep apnea, respiratory problems and poor wound healing., Obese people frequently experience wound complications, including infection, dehiscence, hematoma, and ulcers [44,45].

A higher rate of surgical site infection occurs in obese patients. Many of these complications may be the result of relative hypoperfusion and ischemia that occurs in the subcutaneous adipose tissue. This situation can also be favored by the low absorption capacity of antibiotics. In post-surgical wounds, the tension at the edges of the wound increases in obese patients which also contribute to the dehiscence of the wound. Wound tension reduces microperfusion and oxygen availability in the wound [45].

In addition to local conditions, systemic factors also play an important role in poor wound healing and wound complications in obese patients. Obesity can be correlated with stress, anxiety and depression and all situations that can cause an affected immune response [43].

The function of adipose tissue is usually considered to be that of caloric storage. However, more recent findings have shown that adipose tissue secretes a wide variety of bioactive substances that are collectively called adipokines. Both adipocytes themselves and macrophages inside adipose tissue are known to produce bioactive molecules including cytokines, chemokines, and hormone-like factors such as leptin, adiponectin, and resistin. Adipokines have a profound impact on the immune and inflammatory response, and a negative influence of adipokines on the systemic immune response appears to influence the healing process, although there is no direct evidence of this.

Decreased function of peripheral blood mononuclear cells leads to decreased lymphocyte proliferation and altered peripheral cytokine levels [46-48].

However, it is important to note that many of the changes related to obesity in peripheral immune function are improved by weight loss [49].

Conclusion

Wound healing is a highly complex physiological process that implies collaboration between a multitude of factors, thus, these can alter one or more of this sequential process. Moreover, due to the elaborate environment and ecosystem present inside the oral cavity, these issues can be further complicated. As such, proper anamnesis, consideration and scrutiny, thorough examination and proficient implementation of the appropriate surgical procedure is imperative in reducing the risk of impaired wound healing, pain and post-operative complications.

Compliance with Ethical Standards
Conflict of Interest: The authors declare that they have no conflict of interest.

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