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Review Article

What Factors Can Have an Impact on the Wound Healing Process from An Oral Surgery Perspective? A Review

Faisal Alzahrani, BDS, MSc[1]*, Faris Alabeedi, BDS, PgDip, MMedSc, MSc[2], Salvatore Luca La Terra, DDS, MSc, PgCert, PgDip[3] and Akram Alshirah, DDS, MSc, PhD[4]

[1] Oral surgeon, Oral Surgery Department, College of Medicine and Dentistry, Ulster University. Birmingham B4 6BN, United Kingdom. Faisal.m.z.2011@gmail.com, Alzahrani-F1@ulster.ac.uk

[2] Oral pathologist, Department of Maxillofacial Surgery and Diagnostic Sciences, Faculty of Dentistry, Najran University, 55461. p.o.box 1988., Saudi Arabia. fmalabeedi@nu.edu.sa.

[3] Periodontist, Periodontology Department, College of Medicine and Dentistry, Ulster University. Birmingham B4 6BN, United Kingdom (UK). Visiting Professor International University of Gorazde, Bosnia-Herzegovina (BIH). Private Practice in Rome 00100 and Ragusa 97100, Italy (ITA). DDS, MSc, PgCert, PgDip. laterra3@virgilio.it

[4] Periodontist, Periodontology Department, College of Medicine and Dentistry, Ulster University. Birmingham B4 6BN, United Kingdom. Alshirahakram@gmail.com

***Corresponding Author**: Faisal Alzahrani, Oral surgeon, Oral Surgery Department, College of Medicine and Dentistry, Ulster University. Birmingham B4 6BN, United Kingdom. Faisal.m.z.2011@gmail.com, Alzahrani-F1@ulster.ac.uk*

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Abstract

Wound healing is a complex and dynamic process that involves a series of intricately regulated phases, each contributing to the restoration of tissue integrity. This comprehensive review dives into the fundamental aspects of wound healing, exploring the physiological mechanisms, phases, and influencing factors. The review begins with describing the significance of wound healing and navigates through sequential phases, such as hemostasis and inflammation, proliferation, remodelling, wound classification and closure techniques, thus providing insights into the diverse strategies employed in clinical settings. Much focus lies to bone healing, addressing both primary and secondary healing mechanisms, as well as the bone healing in extraction sockets. A significant segment of the review explores the factors affecting wound healing, which are categorized into local, surgical, and systemic factors encompassing ageing, diabetes mellitus, hormonal changes, immunocompromised conditions, medications, smoking, alcohol consumption, obesity, and nutrition deficiency. A synthesis of the reviewed content highlights the interplay of these factors in the 'wound healing' process. Understanding these elements is imperative for clinicians and researchers alike to develop effective therapeutic interventions tailored to individual patient needs. This review serves as a valuable resource for those seeking a comprehensive understanding of the intricate dynamics of wound healing in the human body.

***Keywords:** Wound healing, Inflammation, Proliferation, Remodelling, Local and systemic factors.*

1. Introduction

The human body has a complex yet undeniable and overlooked wound healing mechanism that is crucial for survival and overall well-being. Available data on wound healing is limited, especially on interrupted wound healing, and currently, there is a lack of universally recognized or standardized classification for wound healing in the oral region. Some intellectuals classify three while others maintain four wound healing processes, which adds to the confusion. Wound healing comprises a series of intricate biological processes with numerous chemical signals for repair and recovery. All tissues follow a nearly identical pattern to facilitate healing with minimum scars.

One key distinction between wound healing and regeneration is while all tissues are capable of regeneration, repaired tissues do not always have the same functionality or morphology as lost tissues[1]. This review will examine the various elements that can impact the healing process of bones and soft tissues, especially following a surgical procedure involving both tissues in the oral cavity.

2. Wound Healing

The process of wound healing is a complex and dynamic process that involves the regeneration and restoration of damaged cellular structures and tissue layers. The classification of wound healing can be broadly categorized into three main groups: primary healing, delayed primary healing, and secondary intention healing. Nevertheless, the process of wound healing in adults can be classified into three or four distinct phases. Certain authors define it as three distinct phases: the inflammatory phase, the proliferation phase, and the remodelling phase, whereas the alternative categorization comprises four stages: hemostasis, inflammatory, proliferation, and remodelling phases. This paper will focus on the latter, which categorizes the wound healing process into four phases. Current available refers these stages by using different terms, such as remodelling or maturation, as well as proliferation or granulation. As our comprehension of the wound healing process advances, it is conceivable that additional stages and sub-phases may be identified and recognized[2] . Figure 1 below summarizes the four phases of wound healing:

Hemostasis
Timeline: Immediate post-injury.
Key Elements:
- Vasoconstriction to stop bleeding.
- Platelet activation in primary and secondary hemostasis.

Insights:
- The intricacies of the aggregation phase and secondary hemostasis are critical components of the coagulation process.

Inflammatory
Timeline: Commences with tissue injury, lasts 3-5 days
Key Elements:
- Initial involvement of polymorphonuclear leukocytes.
- Transition to a prevalence of monocytes and macrophages.

Insights:
- The inflammatory phase seamlessly begins during the hemostasis phase, showcasing their interconnected initiation.

Proliferation
Timeline: Day 4 to Day 14 post-surgery
Key Elements:
- Formation of provisional fibrin strands
- Dynamic participation of fibroblasts
- Creation of granulation tissue
- Re-establishment of epithelial layer
- Synthesis of collagen

Insights:
- Fibrin strands offer a provisional matrix facilitating cellular migration.
- Fibroblasts play a central role in the synthesis of collagen, contributing to the structural integrity of the healing tissue.
- Granulation tissue provides a scaffold for new blood vessels and facilitates tissue regeneration.
- Collagen, a primary structural protein, imparts tensile strength to the healing tissue.

Remodelling
Timeline: Begins around week three and can extend up to twelve months.
Key Elements:
- Collagen remodelling
- Maturation

Insights:
- Collagen matrix undergoes a meticulous process of remodelling, enhancing tissue strength and durability.
- Maturation involves the culmination of healing processes, contributing to the tissue's resilience.

Additional Details:
- This phase plays a crucial role in providing improved resistance and tensile forces to the healed wound.

Figure 1. *Four phases of wound healing.*

A better understanding of wound healing involves studying the healing index developed by Landry, Turnbull, and Howley in 1988. This tool has proven to be beneficial in assisting clinicians to evaluate the progression of wound healing and analyze it from a clinical point of view[3]. The Healing index is presented in Table 1 below:

Table 1. Healing index by Landry, Turnbull and Howley will help the clinician to determine the healing process of the wound and to know how to evaluate the wound. *Adopted from* [68]

Healing index	Tissue color	Bleeding on palpation	Granulation tissue	Incision margin	Suppuration
Very Poor: two or more signs are present	≥ 50% of red gingiva	yes	yes	not epithelialized, with loss of epithelium by the end incision margin	yes
Poor	≥50% of red gingiva	yes	yes	not epithelialized, with exposed connective tissue	no
Good	25 -50% of red gingiva	no	no	no exposed connective tissue	no
Very good	< 25% of red gingiva	no	no	no exposed connective tissue	no
Excellent	all pink tissues	no	no	no exposed connective tissue	no

3. Healing Phases Explained

The intricate process of wound healing unfolds through three interconnected, yet distinctly delineated biological phases: hemostasis/inflammation, proliferation, and remodelling[4]. Together, these stages culminate the intricate tapestry of the wound-healing cascade, and any disruption within these phases has the potential to impede the body's capacity for effective wound healing[5].

3.1 Hemostasis and Inflammation

Immediately the body sustains a wound, hemostasis begins. This process affects the integrity of the skin in many ways[6]. Blood vessels constrict, triggering platelet activation upon contact with exposed collagen. This cascade leads to further platelet activation and aggregation, alongside the activation of the coagulation cascade, resulting in the deposition of a provisional fibrin matrix within the wound[7] . The release of cytokines, including transforming growth factor-β (TGF-β) and platelet-derived growth factor during platelet activation, propels the chemotaxis of neutrophils and macrophages, marking the initiation of the inflammatory phase[8,9]. Neutrophils emerge as the initial responders, while macrophages, pivotal to this phase and overall wound healing, contribute to phagocytosis and produce additional cytokines and growth factors [10,11]. Dysregulated wound macrophage function has been associated with impaired wound healing, particularly in diabetic wounds, where blood glucose is higher than normal levels[12].

3.2 Proliferation

Within 2 to 3 days of the initial injury, enough fibroblasts migrate to the wound, heralding the commencement of the proliferative phase, which can extend up to 3 weeks in a healing cutaneous wound. Fibroblasts play a pivotal role by generating disorganized collagen, predominantly comprising immature type III collagen, into the provisional matrix[13]. These fibroblasts may transform into myofibroblasts under the influence of various cytokines, culminating in heightened collagen production and eventual wound contraction[14,15]. Numerous signaling pathways, including angiotensin II and TGF-β, through both canonical and non-canonical pathways, intricately modulate the wound healing process during this phase [16,17]

3.3 Remodelling

In the remodelling phase of wound healing, granulation tissues undergo replacement and form permanent scars. Net collagen production remains active for 4 to 5 weeks, succeeded by the substitution of type III reticular collagen with type I fibrillar collagen over the ensuing year[18]. Zinc-dependent endopeptidases, specifically matrix metalloproteinases secreted by epidermal cells, assume a central role in the intricacies of tissue remodelling[19,20]. Each of these phases—hemostasis/inflammation, proliferation, remodelling—stand as a vital cornerstone to the success of the wound healing process[5,21].

4. Methods

A comprehensive literature exploration regarding wound healing in the oral region was conducted on PubMed, NCBI, Google Scholar, and Clinicaltrials.gov. The keywords used related to the topic of this narrative review included wound healing, inflammation, proliferation, remodelling, local and systemic factors. Selected articles described the wound healing process and classification, with special attention paid to those that focused on the oral region, which is the main aim of this review. The selected sources that inspired the different subtopics in this review were books, and peer-reviewed journals, with the latter involving meta-analyses, systematic reviews, retrospective analyses, and literature reviews. The articles chosen were to be quality and reputable sources to maintain the integrity, reliability, and validity of the review. Studies that also looked at chronic conditions like diabetes and the wound healing process were also included. The authors actively contributed towards the review's execution. Faisal Alzahrani was involved in the review's conceptualization, methodology, preparing, drafting, and writing the original text, and the editing and reviewing process. Faris Alabeedi was in charge of supervision, data curation, preparing and drafting the original text, and edited and reviewed the document. Akram Alshirah reviewed and edited the paper. Salvatore Luca La Terra was responsible for proofreading, reviewing, and editing the paper to eliminate redundancy and ensure coherence, structure, and quality.

5. Wound Classification

The Surgical Wound Classification (SWC) was initially introduced in 1964 and has since become a standard component in the documentation of surgical procedures[22,23]. This practice, which has undergone continuous improvement over several decades, serves as a defining factor in maintaining the sterility of the surgical environment. SWC's significance lies in the observed association between wound contamination and the subsequent risk of developing postoperative Surgical Site Infections (SSIs)[22,24–30].

The categorization of wounds is typically delegated to either the surgical team or the operating nursing staff. Notably, research has indicated that SWC is frequently documented inaccurately [22,31]. Centers for Disease Control's (CDC) Wound classification can be delineated into classes according to Cruse's classification, also known as the "CDC Wound Classification System," as showing in Table 2.

While wound healing has a fundamental focus in all surgical practice, there is a notable lack of attention given to the topic of disrupted wound healing in the existing literature for oral region. Additionally, there is a notable absence of an established classification system to delineate the various wound healing processes or phases, specifically within the oral cavity[1].

Table 2. Centers for disease control (CDC) guidelines for surgical wound classification Adopted from[22,28].

Class I: Clean	Uninfected operative wounds made under ideal conditions No inflammation No entry into respiratory, alimentary, genital, or uninfected urinary tracts No lapse in sterile technique Primary wound closure Closed drainage
Class II: Clean contaminated	Entrance into mucosalized tissue under controlled conditions (respiratory, alimentary, genital, or urinary tract) No unusual contamination by foreign body No evidence of infection or major break in sterile technique

Class III: Contaminated	Open or fresh accidental wounds Operations with major breaks in sterile technique Gross spillage from the gastrointestinal tract Any acute, non-purulent inflammation
Class IV: Dirty/ infected	Old traumatic wounds with retained devitalized tissue. Existing clinical infection or purulence Environmental debris Perforated viscera

6. Wound Closure Techniques

Wound closure methods consist primary, secondary, and tertiary closures. Primary closure is typically indicated for incisional wounds characterized by minimal tissue damage, as it serves to minimize the incidence of postoperative complications and yields a favourable cosmetic outcome. Conversely, traumatic wounds, characterized by lacerations and tissue loss, necessitate comprehensive evaluation, potentially leading to a need for delayed primary closure, secondary closure, or healing via secondary intention. The choice of an appropriate closure technique hinges upon an assessment of the level of contamination. Postoperative wound infection rates, categorized according to Centers for Disease Control (CDC), reveal infection rates of 1.4% for clean procedures, 6.3% for clean-contaminated procedures, 13.3% for contaminated procedures, and 39.9% for dirty procedures, resulting in an overall infection rate of 4.4% when preoperative antibiotics are not administered. Furthermore, it is imperative to consider the time elapsed between the traumatic injury and the decision to close the wound. In instances where a traumatic wound occurred more than six hours prior, the principle advises against immediate closure. However, exceptions apply, permitting safe closure beyond this timeframe for wounds classified as clean and those affecting the facial region[32].

7. Bone Healing

The same processes that occur during normal soft tissue wound healing, such as hemostasis, inflammation, granulation, and remodelling, take place during the repair of affected bones. In addition, osteoblasts and osteoclasts are also engaged in the reconstruction and remodelling of damaged ossified tissues[33].

Bone healing can also be described using the terms “primary intention” and “secondary intention.” In cases where a bone is fractured and the fragments of the bone are separated by a distance greater than 1 millimeter, the healing process occurs through secondary intention. During the fibroblastic stage of healing, a significant deposition of collagen is necessary to bridge the gap in the bone. In cases where a bone is incompletely shattered, a fracture occurs where the fractured ends of the bone do not separate from each other (greenstick fracture), or when surgery successfully establishes a closed and rigid stabilization of the fractured bone ends pieces, primary intention healing occurs (anatomic reduction of fracture) [33]. The sequence of indirect bone healing[34] is outlined as follows:

1. Formation of a hematoma at the injury site.
2. Initiation of an inflammatory response.
3. Periosteal and endosteal synthesis, contribute to the stabilization of the fragment.
4. Endochondral and membranous osteogenesis.
5. Development of osteons and Haversian canals.

7.1 Primary Bone Healing

Primary healing, also referred to as direct healing, necessitates a precise anatomical realignment that remains stable, and devoid of any gaps. This form of healing solely involves the restructuring of lamellar bone, the Haversian canals, and the blood vessels, without the development of callus. The duration of this process may vary from several months to a few years depending on individuals[35].

Worth noting is that the restoration of mechanical and physical continuity necessitates the establishment of a seamless connection between bone segments located on opposing sides of the cortical structure. Notably, the formation of cutting cones at the extremities of osteons in proximity to the fracture site is a key aspect of this intricate process. These cutting cones navigate the fracture border, giving rise to longitudinal cavities through the enzymatic actions of osteoclasts. Subsequently, these cavities are replenished with bone matrix through the osteoblast-mediated deposition, terminating in the generation of bony union and the restoration of Haversian systems. As a result, the process plays an indispensable role in facilitating the overall bone healing process. Indeed, this process leads to the generation of bony union and the restoration of Haversian systems, allowing for the re-establishment of blood supply[36]. Ultimately, osteons undergo maturation and transform into lamellar bone, thus achieving the healing of the fracture site without the formation of a callus or an inflammatory response[37].

7.2 Secondary Bone Healing

Secondary bone healing, representing a more common mode of bone regeneration and distinct from primary healing typically achieved by open reduction and internal fixation under compression, encompasses both intramembranous and endochondral ossification processes, progressing through four primary stages:

The initial stage begins with the acute inflammatory response, commencing with the formation of a hematoma. This hematoma undergoes coagulation, forming a transient scaffold serving as a template for callus formation [38]. Simultaneously, acute inflammatory markers, such as tumor necrosis factor-alpha (TNF-α), IL-1, and IL-6, are mobilized, attracting macrophages, monocytes, and lymphocytes, which subsequently aid in the removal of necrotic tissue and release cytokines. The process also includes vascular endothelial growth factor (VEGF), which promotes angiogenesis and healing. This inflammatory stage typically has a duration of approximately 5 days[39]. The second stage is characterized by the formation of a fibrocartilaginous network. In this phase, mesenchymal stem cells are recruited and then undergo differentiation into fibroblasts, osteoblasts, and chondroblasts[40]. This differentiation initiates chondrogenesis, marked by the deposition of a collagen-rich fibrocartilaginous network spanning the fracture site, commonly referred to as the "soft callus." Alongside, a layer of woven bone is deposited this stage typically starts around post-fracture and stands for approximately 5 days[41]. The third stage involves the formation of the bony callus, wherein the cartilaginous callus (soft callus) undergoes endochondral ossification to transform into the hard callus. This transformation occurs through the actions of chondroblasts, osteoblasts, and osteoclasts, involving the resorption of the cartilaginous callus and the deposition of woven bone subperiosteally [41]. In this stage, often occurring over a period of up to 4 weeks post-injury, the substantial overlap with the preceding stage is of notable significance, enclosing the mesenchymal cell recruitment and hard callus formation. The fourth and final stage, known as bone remodelling, entails the reconfiguration of the bony callus by osteoclasts and osteoblasts to develop compact bone centrally and lamellar bone peripherally. This transformation ultimately gives the newly formed bone with the requisite rigidity and biomechanical stability characteristic of normal bone. Notably, this stage may extend over years depending on the individual[42].

An understanding of the distinct stages of bone healing and their respective timelines enhances our comprehension of treatment protocols and the necessary duration of immobilization[39].

7.3 Bone Healing in the Extraction Sockets

Initially, it should be noted that the alveolar ridge experience collapses shortly after surgical procedures as a result of thrombosis. The subsequent step involves the initiation of re-epithelialization, which commences within a twenty-four-hour timeframe after the surgical procedure. Additionally, the thrombus undergoes replacement by granulation tissue within a span of seven days. Furthermore, it is expected that the site will undergo complete osseous healing within an average of ten weeks following the extraction of the tooth. Ultimately, the resorptive mechanism has the potential to result in a reduction in the overall volume of the alveolar ridge, while the bone remodelling process may persist for a duration of up to six months following to the extraction procedure[34]. Figure 2 illustrates the healing sequence of normal healing in the alveolar ridge post-extraction:

Immediately Following Tooth Extraction:

- Shortly after tooth extraction, the socket is filled with blood, and clot formation occurs through both the extrinsic and intrinsic pathways. Maturation of the clot initiates within 1 to 2 days, marked by blood vessel dilatation within the remnants of the periodontal ligament. Leukocytes migrate towards the center of the clot, while the top layer of the clot is covered by a dense fibrin layer [45–47].

During the First Week After Extraction:

- The formed clot serves as a scaffold for the migration of additional cells during the healing process. Within the remnants of the periodontal ligament, epithelial and fibroblast cells originate from connective tissue cells. Meanwhile, endothelial cells migrate towards the center of the alveolar bone crest following tooth extraction, and osteoclasts move toward the boundary of the alveolar bone process [45–47].

In the Second Week:

- Internal growth of blood vessels continues, reaching the center of the clot. The remnants of the periodontal ligament become indistinct, and resorption becomes more pronounced along the alveolar ridge due to the action of osteoclasts [45–47].

By the Third Week:

- The organizing clots evolve into mature granulation tissue, with poorly calcified tissue present around the cavity wall. Osteoclasts contribute to the polished and rounded appearance of the alveolar bone at the socket crest [45–47].

By the Fourth Week:

- Internal remodelling may persist for several more weeks, and radiographic evidence of bone formation does not become apparent until the 6th week [45–47].

Figure 2. *Heling Sequence of Normal Healing in the Alveolar Ridge Post-Extraction*[43–45]

8. Factors affecting Wound Healing

From a clinical standpoint, it is vital to have a thorough understanding of the local and general factors that are associated with disturbances in the normal wound healing processes [1]. Table 3 summaries the local and systemic factors effecting the wound healing.

Table 3. Factors affecting wound healing, local factors, surgical producers, and systemic factors. Adopted and modified from [33,46–51].

Local factors	Surgical procedures	Systemic factors
Local Infection	Flap design	Chronic disease, such as diabetes, keloids, fibrosis, hereditary healing disorders, jaundice, uremia
Foreign body	Thermal damage	Age
Necrotic	Sharp bone edges	Hormonal change
Ischemia	Local anaesthesia	Immunocompromised conditions: cancer, radiation therapy.
Hypoxia / Oxygen Tension	Sutures	Medication, such as glucocorticoid steroids, non-steroidal anti-inflammatory drugs, chemotherapy
	Postoperative bleeding	Smoking and Alcohol consummation
		Obesity and Nutrition deficiency

8.1 Local Factors

Wound healing can be interrupted by numerous local factors, such as infection, necrotic tissue, ischemia, foreign material, hypoxia, and bleeding. It is worth mentioning that the oral cavity is a remarkable environment in which wound healing occurs in warm oral fluid that contains millions of microorganisms[48].

Local infection is considered the main element in local factors affecting wound healing. In order to reduce the risks, some surgeons implement the surgical session by using antimicrobial mouthwash before and after the oral surgery procedure. As such, ineffective disinfection of the wound will result in long-standing irritations, which, consequently, lead to an unhealed wound, and susceptibility enables the bacteria to invade it on a constant basis[34]. Moreover, a comprehensive review and meta-analysis by Arteagoitia et al [52] on the use of a preventive chlorhexidine mouthwash before tooth extraction resulted in a 12% decrease in bacteremia cases. Additionally, systemic antibiotics become ineffective against colonizing bacteria since they form a biofilm impermeable by antibiotics[53].

On the other hand, foreign materials bacteria can multiply and produce an infection that results in the destruction of host tissue through the release of bacterial proteins due to the nonbacterial material acting as a safe habitat for bacteria, thus promoting infection. Hence, these chronic inflammatory reactions can reduce fibroplasia (caused by antigenic foreign material)[33]. The possible foreign materials which may be encountered within the extraction socket are cotton fibers, suture materials, gauze pieces, and sponge particles[54].

In addition, a systematic review by Javed et al[55] concluded that silk sutures should not be used due to an increased risk of bacterial adhesion, which might impair wound healing. Thus, nylon and polyglyconate represent the suture of choice and the least reactive[34]. Moreover, necrotic tissue typically contains blood that has accumulated in a wound (hematoma), where it provides a great source of nutrients for bacteria that will result in a prolonged inflammatory stage [33].

On that note, the reduced blood supply to a wound slows wound healing in a variety of ways. Insufficient blood supply (ischemia) can result in additional tissue necrosis and disturb the transport of antibodies, white blood cells, and antibiotics to the wound site, which might subsequently elevate the risk of infection [33]. Finally, it is essential to recognize individuals at high risk of prolonged hypoxic wounds following surgery, particularly those who are in advanced age and those who have systemic chronic diseases, such as diabetes, that can result in a decreased vascular flow and, as a consequence, oxygenation[35].

8.2 Surgical Procedures

It is mandatory to closely follow proper surgical principles to obtain a wound healing with adequate re-epithelization and minimal tissue scaring, thereby restoring function. Having said that, there is no wound healing either in the skin, oral mucosa, or muscles that can heal without scarring. A further surgical consideration is to ensure that wound incisions are performed on the sound bone to provide a healing scaffold. In addition to minimize thermal damage, the application of insufficient irrigation or extensive electrocautery may produce necrosis or sequestration. Furthermore, excessive suture stress on the wound edges might cause strangulation and eventual flap necrosis. Another surgical consideration is stabilizing the blood clot after surgery, which promotes granulation tissue production and healing[33,48].

Finally, a comprehensive medical history should be conducted to identify those individuals at risk of significant postoperative bleeding (bleeding disorders, anticoagulants, or antiplatelet medication). In order to counter these local factors, it is notable that the use of oxidation cellulose, bone wax, tranexamic acid, and insuring the suture act as a local hemostatic. With respect to Local Anesthesia (LA), unlike the conventional biomedical research paradigm, there is no well-defined clinical symptom of impaired wound healing linked to LA infiltration. On the contrary, the adrenaline included in local anesthetics enhances this impact. However, these findings should be viewed with-caution because only limited investigations have been performed to demonstrate any substantial therapeutic effects[34,56].

8.3 Systemic Factors

8.3.1 Ageing

In a research paper by Karamanos et al, [57] the-authors argue that when patients are assessed for surgical intervention, their age should not be a determining factor, whereas Guo et al [53] show that in a healthy older person, ageing holds a temporal delay in wound healing but not a quality impairment. Therefore, the basic biology of chronic wounds combined with the impact of age-related changes on wound healing are not fully recognized, and most research has used in vitro and animal models. Thus, the identified changes do not translate well to human healing conditions[58].

8.3.2 Diabetes Mellitus

According to a review paper by Shah et al,[34] Diabetes Mellitus has a higher risk of impaired wound healing due to hypoxia, fibroblast and epidermal cell dysfunction, poor angiogenesis and neovascularisation, metalloproteases, reduced host immunological response, and neuropathy[53]. Additionally, patients with diabetes develop vascular problems, such as sclerosis of the arteries and veins that become obstructed, resulting in decreased blood flow[59]. Diabetics also have some macrophage malfunction, which causes the inflammatory phase to last longer. This makes it more challenging for surgeons to manage when they need to elevate a flap for implant insertion during a healing period following extraction [34].

8.3.3 Hormonal Changes

Reduced wound healing is connected to changes in sex hormone levels. For example, aged males heal acute wounds slower than old females[53]. On the contrary, a study found that women heal mucosal wounds slower than men by hypothesizing that sex hormones influence wound healing rates by modulating effects on inflammation[60].

8.3.4 Immunocompromised Conditions and Medications

Wound healing and cancer have always been linked. The inflammation and wound healing pathways are not only shown to boost cancer stem cell populations but also, tumor cells invade surrounding tissues, inducing angiogenesis and metastasis. Moreover, the cytokines, developmental pathways, and growth factors involved in normal wound healing are activated[61,62].

Likewise, patients who receive more than 50Gy of radiation for oral cancer are more prone to wound healing complications after tooth extraction. A systematic review by Lajolo et al [63] observed that osteoradionecrosis (ORN) occurs especially in the mandibular molar region, thus increasing the risk of ORN of the jaws in these patients. [63,64]. Despite that, surgery after irradiation may exhibit slow wound healing. Therefore, before radiotherapy, patients should have all dental treatments performed[34].

On the other hand, many drugs that interfere with clotting or platelet's function, inflammatory reactions, and cell proliferation have an impact on the wound healing process. Examples of pharmaceuticals that have a significant effect on healing include glucocorticoids, non-steroidal anti-inflammatory drugs, and chemotherapeutic agents [53]. Furthermore, most chemotherapeutics could prevent wound healing by blocking cellular metabolism, cell division, and angiogenesis.

These drugs reduce wound fibroplasia and neovascularization, inhibiting deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), or protein synthesis[61]. In addition, in the same systematic review mentioned earlier by Lajolo et al [65], the author argues that interpretations found in the literature do not address the possibility that patients may develop medication-related osteonecrosis of the jaw (MRONJ), which can be used to treat a variety of tumors and should not be ruled out but at least considered in the differential diagnosis.

8.3.5 Smoking and Alcohol Consummation

By all means, smoking has adverse effects on wound healing. For example, an increase in infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and a decrease in tensile strength of wounds has been reported in smokers post-operatively[53]. Recent studies suggested that abstaining from smoking for four weeks prior to surgery improves the inflammatory phase, but it interrupts the proliferative phase. However, vitamin C and E supplementation may help to mitigate the damage caused by smoking, especially in the areas of collagen formation[46]. Another systemic review by Mills et al[66] mentioned that smoking cessation has been associated with reductions in postoperative complications. On the other hand, alcohol can reduce the host resistance and ethanol intoxication at the time of tissue injury increases the infection risks[67].

Chronic alcoholics have compromised liver function, which affects the synthesis of clotting factors necessary for maintaining hemostasis. A thorough medical history may once again uncover people who are alcoholics. Surgeons may order a clotting test before the surgical procedure to prevent, anticipate, and manage excessive bleeding during or after the surgery[34].

8.3.6 Obesity and Nutrition Deficiency

Obese individuals frequently encounter wound issues due to decreased adipose tissue vascularity, increased wound tension, pressure on the wound, and high seroma and hematoma risk[53]. In daily practice, certain patients with mouth cancer, ethanol misuse, and depressed elderly patients who are socially isolated, suffer from undernutrition. For example, protein and vitamin deficiency could also affect wound healing process[48].

9. Conclusion

The unique characteristics of the oral cavity distinguish it from other anatomical regions within the human body. However, it is imperative to acknowledge the lack of literature related to the healing process of oral wounds. Therefore, it becomes essential to thoroughly consider the various factors, both specific to the site of the wound and those affecting the body as a whole, which can influence the healing process. In order to effectively manage impaired wound healing, it is of utmost importance to adhere to the most up-to-date research findings and guidelines, ensuring that decisions and interventions are based on evidence-based practises. The process of wound healing is characterised by a series of intricate phases, including hemostasis, inflammation, debridement, repair (proliferation), and remodelling. These phases are subject to the influence of a range of internal and external factors. Having a comprehensive understanding of the typical wound-healing process and the fundamental mechanisms behind impaired or delayed healing is of vital importance in developing effective strategies for wound management. In addition, the unique features of the oral cavity's environment give rise to particular difficulties, which in turn require a comprehensive approach when conducting dental examinations and interventions. In this context, it is necessary for dentists and healthcare professionals to carefully evaluate the local, systemic, and surgical factors that have an influence on the process of wound healing.

Author Contributions

Faisal Alzahrani: Conceptualization, Methodology, Writing- Original draft preparation, Writing- Reviewing and Editing.

Faris Alabeedi: Supervision, Data curation, Writing- Original draft preparation, Writing- Reviewing and Editing.

Salvatore Luca La Terra: Proofreading, Writing- Reviewing and Editing.

Akram Alshirah: Writing- Reviewing and Editing.

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The authors declare that there is no conflict of interest.

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