Surgical Wound Healing in the Oral Cavity: a Review

Abstract: Wound healing is a fundamental survival mechanism, largely taken for granted. It consists of four intricately tuned phases: haemostasis, inflammation, proliferation and remodelling. Successful wound healing only occurs if each phase occurs in the correct sequence and timeframe. Moreover, the oral cavity serves as a unique and remarkable setting whereby wound healing takes place in a saliva-filled environment containing millions of micro-organisms. Many local and systemic factors can impair oral wound healing. This article provides an overview of the wound healing process, with a discussion of these respective local and systemic factors, along with the potential cellular and/or molecular mechanisms involved.

CPD/Clinical Relevance: On a daily basis, dentists perform procedures such as exodontia and implant placement that rely on adequate wound healing. An improved understanding of the local and systemic factors that can impair oral wound healing can help clinicians to control these factors more accurately, resulting in improved patient outcomes.

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Wound healing is an intricately tuned sequence of overlapping processes, serving to protect the body. This physiological process must adhere to a strict sequence, timeline and operate at an ideal intensity for a given duration. Multiple factors can interfere with one or more of the phases of wound healing, thereby resulting in impaired bone and soft tissue healing. Moreover, the oral cavity serves as a unique and remarkable setting whereby wound healing takes place in a saliva-filled environment containing a plethora of micro-organisms.

Process of wound healing

Oral surgery usually involves both bone and soft tissues. The modes of recovery of these respective tissues differ.

Soft tissue healing

The dynamic process of wound healing constitutes four accurately programmed stages, each with specific biophysiological functions (Table 1). Upon wound infliction, haemostasis is initiated via a combination of vascular constriction and generation of a fibrin clot. This clot, along with the surrounding tissues, releases biochemical modulators such as growth factors and pro-inflammatory cytokines. Cytokines potentiate an inflammatory response charged with eliminating debris, micro-organisms and necrotic tissue. The cells involved in this phase are described in Table 2.

This is then followed by the proliferative phase involving formation of granulation tissue, re-epithelialization and angiogenesis. The final phase of remodelling involves contraction of the wound, which is mediated by myofibroblasts and collagen remodelling so that the final healed tissue mimics the architecture of normal tissue as closely as possible.
Finally, there is vascular maturation and regression. 3

Table 3 summarizes cellular and physiological events across the healing process.

Bone healing
Bony healing occurs via one of two ways: firstly, by primary intention with the absence of callus formation and, if there is a rich blood supply and a fracture defect, is less than 1 mm. If these criteria are not met, healing occurs via an indirect secondary intention approach with callus formation. This is the predominant mode of healing in oral surgery. 8 Indirect bone healing is summarized in Table 4.

To put this in context, exodontia follows this exact healing process, with the additional bone healing phase. 10 Within minutes of surgery, the alveoli are closed due to thrombosis. Twenty-four hours post-operatively, re-epithelialization is initiated. Over seven days, the thrombus is substituted with granulation tissue. Ten weeks post-exodontia, the site is full of bone. The bony remodelling process can last up to six months after extraction and the resorptive process can lead to loss of alveolar depth and width. 8

The healing involved in placement of dental implants is unique (Figure 1).

Any obstacles, aberrancies or disruptions to this sophisticated and precisely tuned process can result in a delay in wound healing or, worse still, a chronic wound that fails to heal.

Factors affecting healing
Internal or external influences can interfere with programmed physiological processes and, in turn, impair the healing process. External influences are known as local factors and directly alter the condition of the surgical site. Internal factors are known as systemic factors and tend to be medical conditions of the patient that affect their inherent ability to heal. Local and systemic factors that can influence healing are listed in Table 5 and are further discussed below.

Local factors affecting healing
Oxygenation
Oxygen is paramount for the production of adenosine triphosphate. 11 This is the source of cellular energy and is vital for the energy hungry process of wound healing. Furthermore, ideal levels of oxygen and energy help prevent infection, allow wound contraction, stimulate angiogenesis and promote re-epithelialization and subsequent collagen synthesis. 12 It is clear that suboptimal levels of oxygenation lead to impaired wound healing.

In terms of clinical relevance,
review demonstrated some evidence of HBOT preventing osteoradionecrosis post extraction in an area that underwent irradiation. However, these results must be approached with caution as this review concluded that the studies appraised were of moderate quality due to small sample sizes, limited information on methods and an element of bias. 13

Finally, the literature shows that the importance of oxygen has predominantly been researched through animal and in vitro investigations. 14 The results must be interpreted with caution due to the difficulties in mimicking the unique oral environment in a laboratory – how can the moist, flora-rich habitat of the mouth be replicated in vitro?

**Infection**
Dental surgery generates an opening for oral microbes or corpus alienum to contaminate deeper soft and bony tissues. As described earlier, inflammation forms an integral part of wound healing. Extravasation of neutrophils towards the wound is responsible for removal of microorganisms, thus preventing contamination from turning to colonization and into infection. 3

Clinically, exodontia results in bacteraemia due to millions of microorganisms present within the oral cavity. 15 One can conclude that, if the flora is reduced prior to surgery, there is reduced risk of colonization. This can be achieved by giving antimicrobial mouthwashes prophylactically. A systematic review and meta-analysis by Arteagoitia et al concluded that there was 12% reduction in bacteraemia cases with prophylactic chlorhexidine mouthwash prior to extraction. 16 This is classed as level one on the hierarchy of evidence and is therefore useful to integrate into clinical practice. Furthermore, the included studies were assessed using a toolkit to ascertain bias, ensuring inclusion of only higher quality studies.

**Inflammation**
Persist until microbes have cleared the wound. 3 Thus, ineffective decontamination of the wound will cause prolonged inflammation. This results in a chronic unhealed wound, allowing continuous invasion of bacteria. A vicious circle ensues because the wound

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**Table 5.** Factors that can affect wound healing (modified from Politis, Schoenaers, Jacobs and Agbaje, 2016).

<table>
<thead>
<tr>
<th>Local Factors</th>
<th>Systemic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation</td>
<td>Increasing age</td>
</tr>
<tr>
<td>Infection</td>
<td>Physiological stress</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>Diseases such as diabetes, Cushing's syndrome, jaundice</td>
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<tr>
<td>Venous insufficiency</td>
<td>Obesity</td>
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<td></td>
<td>Malnutrition</td>
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<td></td>
<td>Medications such as chemotherapeutic agents and glucocorticoid steroids</td>
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<td></td>
<td>Alcohol abuse</td>
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<td></td>
<td>Tobacco smoking</td>
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<tr>
<td></td>
<td>Immunocompromise: such as in cancer, HIV and those undergoing radiotherapy</td>
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</tbody>
</table>

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it is important to identify patients at risk of prolonged hypoxic wounds following surgery, including patients of advancing age, as well as systemic conditions, such as diabetes, which can result in poor vascular flow and consequently reduced tissue oxygenation. 3 Research has been published on the use of hyperbaric oxygen therapy (HBOT) to restore tissue oxygen levels optimally. In particular, a Cochrane
cannot close due to chronic inflammation, and the inflammation is mediated by the continuous ingress of bacteria. Furthermore, colonizing bacteria organize into a biofilm impenetrable by systemic antibiotics. Such conditions are a challenge to manage, such as chronic osteomyelitis of the jaw.

### Age

It is widely acknowledged that older patients have a temporal delay in healing compared to younger counterparts. In fact, a study found delays in re-epithelialization, less effective angiogenesis, reduced collagen production and remodelling and resultant weaker wounds in older mice compared to younger ones. Again, the results of animal studies must be acknowledged with considered caution as there may be inherent differences in wound healing between mice and humans. Nonetheless, these results were mirrored by those of a systematic review that concluded that each of the four phases of wound healing are negatively affected, resulting in a delay in T-cell infiltration, changes in chemokine release, and reduced phagocytic activity of macrophages. In terms of clinical relevance, clinicians should treat older patients with a degree of caution due to their impaired healing capacity. One such scenario is when implants should be left longer prior to loading in geriatrics due to longer osseointegration periods. A study in mice showed that trabecular bone formed more rapidly around implants in a younger cohort compared to the older cohort, indicating that new bone is formed at a slower rate with increasing age.

### Diabetes

Impaired wound healing is well documented in diabetics. This is multifactorial: firstly, there is accumulation of toxic sorbitol in the tissues; secondly, diffusion of oxygen and nutrients to the

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**Table 6. Factors associated with the surgical procedure that can impair wound healing.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Flap design</td>
<td>A. An ill-designed flap can prevent wound healing, become necrotic or even result in failure of a graft. Consequently, prior to surgery, clinicians should have a clear plan regarding their flap design. This should follow well known principles, such as having a wider base than apex. This helps to maintain the blood supply. Failure to do so results in poor perfusion, hypoxia and subsequent poor wound healing. B. The wound incisions should be on sound bone to ensure that there is a scaffold for healing. C. Ensuring that there is no excess tension on the wound edge as this can result in strangulation and subsequent flap necrosis.</td>
</tr>
<tr>
<td>Local anaesthesia</td>
<td>A. In vitro and animal studies have demonstrated that wound healing can be inhibited by local anaesthesia, particularly the inflammatory and proliferative tiers of wound repair. In addition, adrenaline found in local anaesthetic emphasizes this effect. Again, this research should be acknowledged with caution since limited human studies have failed to show any significant clinical effects. Clinically, to err on the side of caution, large amounts of local anaesthesia should not be injected at the gingival incision site.</td>
</tr>
<tr>
<td>Suture selection</td>
<td>A. Primary wound closure following dental surgery is achieved by closing a flap with sutures. A multitude of sutures are available, differing in their origin and durability. These various sutures cause differing levels of tissue inflammation and in turn wound healing. Javed et al published a systematic review which concluded that silk should not be a material of choice owing to its greater bacterial adherence, thereby posing a threat to rapid wound healing. Conversely, nylon and polyglyconate sutures are shown to be the least reactive.</td>
</tr>
<tr>
<td>Post-operative bleeding</td>
<td>A. Failure to stabilize a blood clot after surgery impairs formation of granulation tissue and impairs healing. It is therefore imperative to identify patients who are at risk of heavy post-operative bleeding because of bleeding disorders or those on anticoagulant or anti-platelet therapy through a detailed medical history. Furthermore, local haemostatic measures should be employed post-operatively, such as oxidized cellulose, bone wax, tranexamic acid and sutures.</td>
</tr>
<tr>
<td>Thermal trauma</td>
<td>A. Extensive electrocautery of bone or drilling without a cooling irrigant can cause necrosis or sequestration of bone. Surgeons should therefore minimize thermal trauma of bone and soft tissue.</td>
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**Factors associated with the surgical procedure**

Factors associated with the surgical procedure, along with the skill of the operator, are shown to affect the success of healing directly. These are described in Table 6.

**Systemic factors affecting wound healing**

**Age**

It is widely acknowledged that older patients have a temporal delay in healing compared to younger counterparts. In fact, a study found delays in re-epithelialization, less effective angiogenesis, reduced collagen production and remodelling and resultant weaker wounds in older mice compared to younger ones. Again, the results of current literature show clear correlation between psychological stress and diminished wound healing. Highly stressed adolescents taking examinations and carers of Alzheimer’s patients exhibited slow healing wounds. The mechanism behind this is complex but is postulated as follows: glucocorticoid production is precipitated by stress which in turn down-regulates production of the cytokines IL-6 and TNF-α. The result is a delayed inflammatory phase. Figure 2 illustrates the domino-effect stress has on wound healing. A comprehensive social history is essential, as patients’ occupation and social behaviours give an indication of their stress level; in turn, surgery can be approached with an appropriate plan to manage any concerns over wound healing.

**Diabetes**

Impaired wound healing is well documented in diabetics. This is multifactorial: firstly, there is accumulation of toxic sorbitol in the tissues; secondly, diffusion of oxygen and nutrients to the
wound tissues is hampered through the deposition of pericapillary albumin; and, finally, there is altered collagen production. Diabetics also have a degree of macrophage dysfunction which prolongs the inflammatory phase. Figure 3 illustrates the effect of diabetes on wound healing.

Clinically, impaired wound healing in diabetics have long reaching ramifications. Disturbances in collagen synthesis and maturation lead to the healed tissues being more friable. This makes it more difficult to handle for clinicians, for example if they were to raise a flap for implant placement after a healing period post extraction.

Radiotherapy
Oncology patients treated with a radiotherapy dose exceeding 50 Gy are more likely to encounter post extraction difficulties with wound healing. Furthermore, mandibular molars pose a greater risk of osteoradionecrosis following exodontia. Irradiation is thought to bring about chronic vascular injury, affecting the supply of oxygen and nutrients to the wound post-operatively. A retrospective study by Jacobsen et al reported that implant survival in non-irradiated grafted fibula bone was 86% compared to 38% in irradiated bone. This is a substantial difference. The positive of this study was the eight-year follow-up period which is a reasonable marker for survival. However, the sample size was 33 patients, meaning that the results can be skewed by outlier results, giving a distorted result.

Other documented problems following surgery in irradiated sites include the formation of fistulas and fenestrations, fibrosis and necrosis. Surgery post irradiation can be detrimental to wound healing. Therefore, patients due for radiotherapy should have all necessary dental procure/surgery prior to cancer treatment.

Chemotherapy
Chemotherapeutic drugs inhibit cellular activity, replication and angiogenesis. They are used to treat neoplasms, but also inadvertently impair the pathways of wound repair. For example, they delay T-cell infiltration to a wound site, reduce collagen synthesis, inhibit fibroblast proliferation and weaken the immune system. Additionally, they cause neutropenia and thrombocytopaenia, meaning wounds are at risk of infection and prolonged bleeding. Almost all anti-resorptive medications have been shown to cause medication-related osteonecrosis of the jaw (MRONJ).

Undoubtedly, accurate anamnesis and drug history is of utmost importance in oncology patients. Risk of MRONJ should be carefully assessed as patients at risk of MRONJ may be contraindicated to implants. As with radiotherapy, patients should achieve good dental health prior to commencing treatment.

Alcohol
The evidence base shows that alcohol impairs wound healing and increases susceptibility to infection. Furthermore, the effect of alcohol on wound healing is clinically applicable as a lot of maxillofacial trauma incidents are alcohol related. A recent systematic review looked at alcohol exposure. Acute exposures inhibit cytokine activity, thereby impeding the inflammatory phase of wound healing.

Figure 2. Stress and wound healing (modified from Guo and DiPietro, 2010).

Figure 3. Diabetes and wound healing (modified from Guo and DiPietro, 2010).
Furthermore, there is reduced phagocytic macrophage activity and neutrophil employment resulting in high rates of wound infection. Chronic exposure is thought to play a greater role in inhibiting angiogenesis, thereby causing wound hypoxia. Chronic alcoholics suffer from impaired liver function, affecting production of clotting factors imperative in achieving haemostasis. Again, a detailed history may reveal patients who abuse alcohol. Surgeons may request a clotting screen and pre-empt excessive haemorrhage.

Smoking
Wound healing following extractions and after placement of dental implants has been shown to be impaired in smokers. Nicotine causes tissue ischaemia through its vasoconstrictive activity. Furthermore, it stimulates the sympathetic nervous system to release adrenaline, potentiating vasoconstriction and causing wound hypoxia. Smoking targets the proliferative phase, resulting in reduced fibroblast activity, decreased wound contraction, and subsequent changes in collagen deposition. This culminates in the wound having a low tensile strength.

Smoking is clinically relevant as it increases the risk of alveolar osteitis following exodontia. Furthermore, implants placed in smokers are at greater risk of failure due to greater marginal bone loss and post-operative infections than their non-smoking counterparts. A recent systematic review and meta-analysis looked at 19836 implants placed in smokers with a failure rate of 6.35% compared to 60464 implants placed in non-smokers with a failure rate of 3.18%. Not only is this classed as level 1 evidence on the hierarchy of evidence base, but the large sample size ensured a high-powered study.

Obesity
Obese individuals commonly suffer from wound problems. This is attributed to reduced vascularity of adipose tissue, greater wound tension, greater pressure on the wound and higher risks of seroma and haematoma formation. Furthermore, skin folds are a nidus for micro-organisms, causing wound contamination.

Nutrition
Malnourished individuals lacking dietary food groups and vitamins are deprived of vital components required for healing. Clearly, nutritional requirements for wound healing are far reaching and, as such, a varied diet ensures that the body receives all components vital for repair and regeneration.

Non-healing, intra-oral wounds can have wide-ranging clinical manifestations which are summarized in Table 8. These can be debilitating for the patient and a challenge for the clinician to manage. Early diagnosis of a disturbance

### Table 7. The components of a varied diet required for adequate wound healing.

<table>
<thead>
<tr>
<th>Type</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates</td>
<td>Glucose is the main energy source for ATP synthesis. Reduced ATP production because of impaired carbohydrate intake negatively impacts on angiogenesis and new tissue deposition.</td>
</tr>
<tr>
<td>Protein</td>
<td>Reduced protein intake negatively affects capillary formation; fibroblast differentiation and collagen synthesis. There is also greater risk of infection due to an impaired immune system.</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Arginine is vital in wound healing as it supports angiogenesis, new collagen formation and wound contraction. The most prolific amino acid in plasma is glutamine, a foundation of metabolic energy for cells vital to the healing process such as fibroblasts and macrophages.</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Omega-3 fatty acids have been found to promote cytokine production and angiogenesis. Thus, omega-3 supplements are recommended for those with chronic inflammatory diseases.</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Vital for collagen synthesis and fibroblast formation. Also, lack of vitamin C can result in a reduced immune reaction and greater vulnerability to wound infection.</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Vitamin A has an anti-oxidant role and is involved in cellular proliferation.</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>This anti-oxidant is thought to reduce excess scars in the wound healing process.</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium acts as an enzymatic co-factor during collagen formation.</td>
</tr>
<tr>
<td>Iron</td>
<td>Iron is vital for the chemical process of hydroxylation of the amino acids proline and lysine. Iron deficit can result in collagen malformation.</td>
</tr>
</tbody>
</table>

### Table 8. How non-healing wounds may present.

- Premature loss of a blood clot presenting as alveolar osteitis
- Wound and flap necrosis
- Pus exudate
- Fibrosis
- Trismus
- Prolonged pain and chronic inflammation

Furthermore, there is reduced phagocytic macrophage activity and neutrophil employment resulting in high rates of wound infection. Chronic exposure is thought to play a greater role in inhibiting angiogenesis, thereby causing wound hypoxia. Chronic alcoholics suffer from impaired liver function, affecting production of clotting factors imperative in achieving haemostasis. Again, a detailed history may reveal patients who abuse alcohol. Surgeons may request a clotting screen and pre-empt excessive haemorrhage.
in wound healing is key to achieving best clinical outcomes.

**Conclusion**

Wound healing is a finely tuned and complex physiological process that relies on many cell types. Multiple factors can affect one or more of this sequential process. Furthermore, the mouth poses a unique environment for wound healing due to the presence of warm oral fluid and a habitat for large numbers of micro-organisms. Due diligence, anamnesis, comprehensive examination and skilled execution of the surgical procedure is essential in minimizing 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.

Informed Consent: Informed consent was obtained from all individual participants included in the article.

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