International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 439-448 www.ijdmsrjournal.com ISSN: 2582-6018

Healing of Wound Extraction

[1] Divyalakshmi Thirumavalavan, [2] Shanmuga rajeshwari, [3] susmitha ponnurangam, [4] DR.sandhiya.M,[5] DR.karthiga, [6] DR.sathish kumar

[1] (UG)Karpaga vinayaga institute of Dental science chengalpattu ,Tamil Nadu ,India [2] (UG)Karpaga vinayaga institute of Dental science chengalpattu ,Tamil Nadu ,India [3] (UG)Karpaga vinayaga institute of Dental science chengalpattu ,Tamil Nadu ,India [4] (PG)Department of oral maxilla facial pathology and oral microbiology ,Karpaga vinayaga institute of Dental science chengalpattu ,Tamil Nadu,India

[5] (professor) Department of oral maxilla facial pathology and oral microbiology,Karpaga vinayaga institute of Dental science chengalpattu ,Tamil Nadu ,India

[6](Head of the department) Department of oral maxilla facial pathology and oral microbiology ,Karpaga vinayaga institute of Dental science chengalpattu ,Tamil Nadu ,India

Date of Submission: 20-12-2023 Date of Acceptance: 30-12-2023

ABSTRACT

Wound healing is an important physiological process to maintain the integrity of the extracted socket after tooth extraction. Vitamin c is involved in all phases of Wound healing. Vitamin c is a powerful antibiotic that destroys the bacteria that helps with blood flow and tissue repair.Hyaluronic acid is active throughout the entire process of wound healing being involved in proliferation and tissue remodelling.Hydrogel scaffold speed up the wound contraction and healing

I. INTRODUCTION

Wound healing is an intricate physiological process consisting of a series of molecular and cellular events that facilitates regeneration of skin ,a protective barrier against an external environment (5,7). Chronic wound sites are those requiring a healing time greater than 12 weeks.these sites have increased predisposition to bacterial invasion and wound infection which can further inhibit proper wound healing .In the case of impairment wound healing the oral cavity is highly susceptible to challenge arising from trauma, related injury, prolonged, inflammation, post operative complications. In oral deformities such as cleft palate successful wound healing is difficult due to bacterial Adent environment that undergoes constant physical trauma so chronic wound are common(1,8) The integration of therapeutic nanoparticles and biomolecules into hydrogel for local wound application has been shown to enhance accelerate healing (5,9,10).

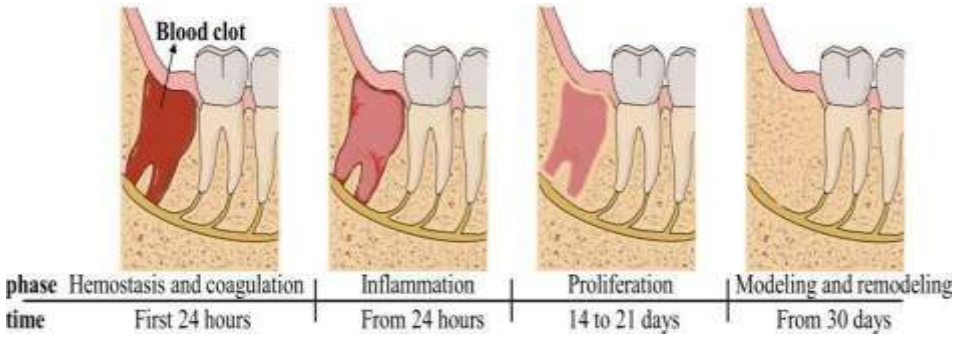
STRUCTURE AND FUNCTION OF THE ORAL MUCOSA VS THE CUTANEOUS MEMBRANES

The oral and cutaneous membrane consist of superficial epithelial layer and basement membrane .Basement membrane act as barrier against pathogens and mechanical stress. Both tissue types consist of keratinocytes that Are attached by desmosomes.(1,11)While these general similarities exist, there are critical structural and functional Differences between the oral mucosa and the cutaneous Membrane (Fig 1). The cutaneous skin is composed of Keratinized epidermal layer, dermis, and hypodermis while, the oral mucosa consists of stratified squamous epithelium (1,12,13)The palatal And gingival mucosa of the oral cavity have increased keratinised epithelium so They sustain Greater mechanical forces and Trauma from eating and chewing.(1,14)In contrast, elastic Regions of the oral mucosa that undergo less physical Stress, like the buccal tissue, are typically composed of Non keratinized epithelium with loose ECM Although, both the cutaneous epithelium and oral Mucosa display similar healing patterns, there are Marked differences in the genomics and kinetics of wound healing between the 2 sites Unlike the oral Mucosa, the cutaneous membrane contain hair follicles Which have multi-potent stem cells found within the Bulge region (Fig 1,A).(1,15)Since an injury cause homeostasis disruption by depletion of cells, stem cells within the Hair bulge activated migrate to The injury and tissue proliferation occur.(1,15,16) While the Exact contribution of hair follicles to dermal wound Healing is rapid in areas of hair-bearing regions of wounds compared to areas Lacking follicles(1,15,18,19). The cutaneous epithelium can Also utilize hair follicles and additional routes For enhanced transcutaneous permeability and can provide transappendageal absorption routes from topical Therapy (Fig 1, B).(1,20,21)The lack of appendages in the Oral cavity limits viable options critical for optimal Healing through a migratory burst of immune cells, Cytokines, and growth factors.(1,22) In contrast to cutaneous wounds, distinct genomic Expression

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 439-448 www.ijdmsrjournal.com ISSN: 2582-6018

patterns demonstrate that the oral mucosa Supports rapid healing with minimal scarring.(1,23)The Oral mucosa is intrinsically less reactive to inflammation during the healing process, with lower infiltration From macrophages, T-cells, and neutrophils.(1,24,25) Similarly compared to its counterpart, the oral epithelium Has lower expression of transforming growth factor Beta-1 (TGF-b1), a pro-fibrotic and pro-inflammatory Cytokine helps in hypertrophic Scars .(1,26) . saliva, with pH ranging from 5.5 To 7.saliva accelerates wound re-epithelialization .(1,27) Saliva also contains histatins,Antimicrobial peptides, and mucins that can aid in wound healing by assisting fibroblast proliferation and Migration, increasing keratinocyte turnover, and releasing growth factors.(1,27,28)The oral cavity is highly susceptible to bacteremia Following dental procedures like periodontal surgery And tooth extraction.(1, 29) The oral microenvironment has complex of microflora in which over few species associated with periodontitis alone .There is Millions of microorganisms contribute to human endodontic and periodontal infections.(1,30,31)A Study after root canals microorganisms Released into the bloodstream in patients. (1,32) In the case Of oral mucosal infection, bacteremia can also lead to Systemic inflammation and sepsis.28 Systemic infection Can ultimately lead to endocarditis, joint infections ,behcets syndrome, Crohn's disease, etc.(1,29,33) Therefore, many research has to made to reduce or prevent Oral infections and poor wound healing leading to infections. By understanding the differences between cutaneous and oral wounds treatment is done .

Mechanistic insight into delayed tooth extraction socket healing among diabetes patients Histologically ,there is a Four-stage healing process involving the hemostasis phase, the Inflammatory phase , the Proliferative phase and the remodeling phase, as shown below (Figure 1) (2,34,35). After extraction Osteogenic tissue proliferation and bone maturation occurs between 4 and 8 Weeks . Delayed tooth extraction socket (TES) healing occurs in patients with DM . Tooth extraction healing is slower for diabetic than the group Without diabetes (2,22).. In the study by Goss et al. There is No difference in Healing rate after tooth extraction in either T1DM or T2DM when Compared to non-diabetic patients. The Tendency for diabetic patients if it is controlled after extraction . The duration of bone healing is similar in Diabetic and normal individuals (2,36). After tooth extraction due to the presence of diabetes and delayed-wound-healing risk , there is to understand the Mechanisms involved and the treatments potentially. In recent years, the wound research field has been Broadened by an in-depth understanding of diabetes in Various aspects such as physiologically, inflammatory, immunologically, Endocrine, neurological mechanisms and microRNAs (miRNAs) Associated with the healing of extracted tooth sockets . Patient with diabetes wound healing with diabetes there is abnormal expression of all the cells and dysregulation of the expression of growth factors, Cytokines required for he normal healing process



Physiological mechanism Extraction sockets of healing is a complex process that involving

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 439-448 www.ijdmsrjournal.com ISSN: 2582-6018

remodeling of damaged soft and hard tissues. It embodies The proliferation and factor (VEGF), the Insulin-like growth factor (IGF) and the bone morphogenetic Protein (BMdifferentiation of osteocytes, as well as the Synthesis and mineralization of extracellular matrix, resulting in FIGURE

1. Healing of wound in the socket after tooth extraction in four time-related phases, Bone formation and remodeling . These activities are regulated By various cytokines(MIP 1beta TNF alpha,TNF beta), comprising the transforming growth factor B (TGFB), the vascular endothelial growthP) .. local application of growth factors in the socket may increase the recovery rate . The Deficiency of growth factors in hyperglycemia conditions Caused a low level of wound healing in animal or clinical Studies (2,37,38). In diabetic mice, wound healing is due to decreased levels of TGF B1 -3,TGFbR11 and TGFbRII .. In T2DM there is rise in salivary VEGF so palatal plate may be alleviate . In hyperglycemic Conditions VEGF is insufficient to produce new bone. Crosslinking occur in advanced glycation end products (AGEs)the bone formation is distribution occur, in spite of induction of Vascular Endothelial Growth Factor-C and VEGF Receptor-3 positivity in osteoblasts after Extraction of tooth .IGF-1 could foster the osteogenic Differentiation of stem cells apically, which is likely to Be induced by terminal kinase and p38 mitogen activated protein kinase signaling pathways . In addition, growth factors, such as IGF-1, may be associated with wound healing of the Epithelium in rats.. Noticeably, non-enzymatic glycosylation Of collagen in increase in glucose rats was found to impair the metabolism of collagen, thus producing soluble and Degradable collagen. In this case, the mechanical properties of The formed bone is weakened ,so that delay in healing And destruction of alveolar bone. Interestingly, T2DM patient gene expression was Distinguishable from control subjects. According to Liang differentially expressed genes were increased sustained in the poor diabetic control group patient in the T2DM Group, and among these genes, BMP-4, T2DM blood, is the most important gene Regulating bone marrow mesenchymal stromal cells (MSCs) Osteogenic differentiation theory basis on gene ontology annotation And forest analysis. Among the BMP family, BMP-4 has capacity of bone-formation in rat tooth sockets. BMP-4, morphogenesis of receptor protein 1, increases the osteogenic differentiation of stem cells via Activating signaling.

Recombinant BMP4/7 has an increased Capacity to induce MSC Differentiation. With increased levels of of glucose (25 mmol/l), the levels of BMP-4, sialoprotein of bone and expression of osteopontin , expression alkaline Phosphatase (ALP) were greatly reduced compared with low Glucose (5.7mmol/l) . The nature of wounds of diabetes patients that are highly resistant to healing is

Also connected to the involvement of matrix metalloproteinase (MMP). The increased Work of MMP-2 and MMP-9 in diabetic Mice wounds is similar to ulcer heal wounds and burn heal wounds, and at the same time scientist have identified MMP-8 and MMP-9 from diabetic wounds and explained That MMP-8 stop cell death and increase wound healing, while Inversely MMP-9 promotes apoptosis and prevents wounds Unhealable in mice (2,39). Wound Infection MMP-9 Activity, increase infiltration of macrophage and decrease Angiogenesis in experiments of animal and clinical activities(2,40). Selective Inhibition of MMP-9 and active Recombinant MMP-8 locally supports diabetic mice wound healing. Hyperglycemia (26 mmol/L) can affect the regulation Of cellular Na+/K+ adenosine triphosphate enzyme activity, Increased activity of protein kinase C , causes the conversion of Hormone receptors and the new blood vessels in vitro. That lower ATP Concentrations of plasma are doubled with lower blood flow in T2DM

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 439-448 www.ijdmsrjournal.com ISSN: 2582-6018

patients compared to normal healthy patients. Increased blood Glucose (>14 mmol/L) can also increase the production of AGEs and its receptor (RAGE) under metabolic Disorders and inflammatory conditions in diabetic rats . In Vitro experiments, AGE in plasma is increased to elevate MMP Inducer content outside the cell and stimulate the secretion of MMP, together with degradation of collagen and bone Strength is decreased . Large amount of aldoses of AGEs Cause endothelial cells dysfunction The matrix Of the microvascular wall present outside the cell by covalently bonding to active amino Groups, and damage capillaries and vessels by up-grading oxidative stress And inducing monocytes to produce growth Factors from platelets. Thus the walls of blood vessels are highly Permeable and inelastic, and stop the blood flow. Receptor activator of factor kappa B (RANK) and its Ligand (RANKL), as well as the deceptive receptor osteoprotegerin (OPG), are the three main proteins of the

RANKL/RANK/OPG signaling pathway .RANK and it's ligand interaction increases Osteoclast production, whereas OPG stops their binding. This pathway is famed for its roles in bone remodeling and this causes pathogenesis of T2DM . This is more common in women. For under controlled T2DM patients, an imbalance in RANKL/OPG ratio continuously may be produced in periodontium . Angiogenesis is a new vessel formation out of old cells and causes wound healing . The functional vascular supply increases proper Ossification of bone newly formed. Impaired Angiogenesis occurs in hyperglycemia that affects the rate of Wound healing, and also bone formation .hypoxia-inducible factor 1a may increase Angiogenesis and enhance new bone transcription Factor in vitro. During bone repair, its expression is increased due to decreased oxygen but its function is a mediator of Angiogenesis and ontogenesis is prevented due to high Glucose in diabetic mice . Following trauma or an ulcer, wound healing is started and four stages of change in tissue sequences, namely hemostasis, inflammation, proliferation, and remodeling, take place .

Hemostasis and inflammation will start from the first second of trauma and continue for up to 5 to7 days. The proliferation stage involves re-epithelialization, angiogenesis, formation of granulation tissue and collagen deposition. In healing of hard tissues, mineralization stage also present . This phase starts from day 4 and last up to four weeks after that soft-tissue injury. The remodeling phase of both soft and/or hard tissues will continue for about 1-2 years .(Figure 2). The wound healing of oral hard tissue and soft tissue are greatly dependent on the inflammatory response and vascular response.

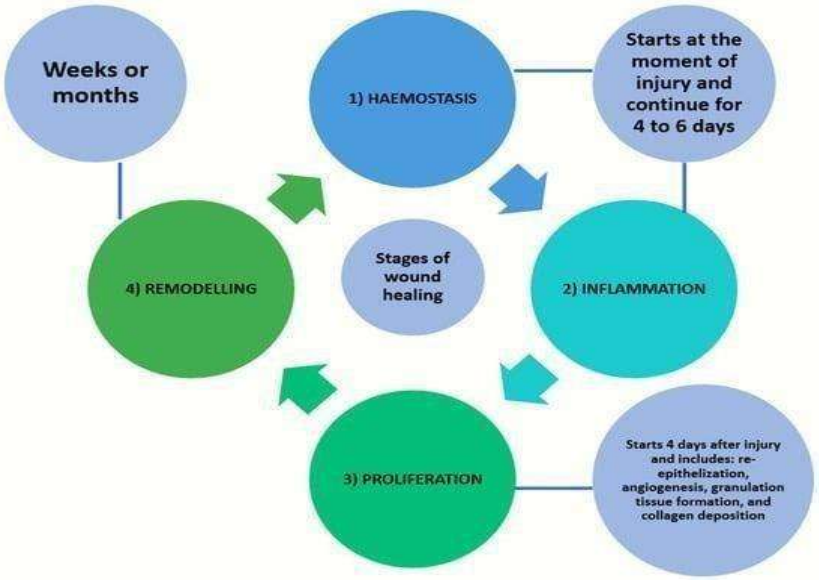


Figure 2. Four stages of tissue change in wound healing namely haemostasis, inflammation, proliferation and remodeling.

Angiogenesis in Oral Wound Healing

Angiogenesis, or neovascularization, is the hallmark process and plays a vital role in wound healing [6,41). This process includes the reestablishment of the vascular network and production of a dense, loosely arranged, capillary bed [6,42,43,44]. For optimal wound healing high capillary growth is important because

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 439-448 www.ijdmsrjournal.com ISSN: 2582-6018

it provides oxygen and micronutrients and removes metabolic waste products such as carbon dioxide and water from the healing tissues (6,41). Angiogenesis is a dynamic interaction between the vascular endothelial cells, angiogenic cytokines, and the zoo extracellular matrix and microenvironment. Fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), angiogenin, transforming growth factor (TGF-β), angiopoietin,heparanases,peroxynitrite and mast cell tryptase are the angiogenic mediators which helps in angiogenesis. Blood vessels can consist of 60% of the granulation tissue in healing oral wounds after extraction(6,43). As the extracellular matrix matures, blood vessel formation will be reduced. Diabetes patients have disturbed wound healing due to their immunologic aberrancies and angiogenesis deficiency. Angiogenesis is necessary because it brings the nutrients and oxygen to the healing wounds. Currently, the oral mucosa is better to heal with a decreased angiogenic burst composed of more mature blood vessels that provide better oxygenation 6 (6,44). Oxygen plays an important role in intraoral wound healing because it is important for energy production and protein synthesis, cellular proliferation, angiogenesis, and the restoration of tissue functions. Oxygen levels vary depending on the anatomical location in the oral cavity .In some places the oral cavity consists of good blood flow and a high tissue metabolic rate. A wound with a hypoxic environment may be prone to increasing the risk of infection . However, during the initial inflammatory process of wound healing the initial inflammatory process exhibits the acute hypoxic environment which enhances fibroblast proliferation and alters normal stromal cell function. In the Hypoxic conditions transforming growth factor is secreted by fibroblast . Oxygen homeostasis is regulated by HIF-1 and is important for cell survival and better intraoral wound-healing . In the healing process most of the process is involved by HIF-1 including cell migration, cell division, the release of growth factors, neovascularization and extracellular matrix metabolism. If oxygen level is decreased HIF is activated and it stimulates angiogenic factors such as vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), angiopoietin 2, and stromal cell-derived factor 1, which stimulate neovascularization and tissue remodeling to provide adequate oxygen supply to the tissue (Figure 3). HIF- 1 therapy is in development for wound healing therapeutically (6,45)For endothelial cell proliferation and migration MMP gene is expressed so that it induces the formation of granulation tissue on the basement membranes. MMPs also stimulate the movement of keratinocytes by degrading and degeneration of the protein in cells/matrix adhesions to stimulate re-epithelialization.MMP-2 and MMP- 9 it is the type of MMPs it play an important role in neovascularization regulation during oral wound healing through the activation of the proangiogenic mediators such as TNF beta,TNF-α, VEGF, and antiangiogenic mediator which degrade the basement membrane and extracellular matrix components (6,46). Increased expression of MMPs such as MMP-2,MMPs-9 in a chronic wound can inhibit oral wound healing by inhibiting new tissue formation.

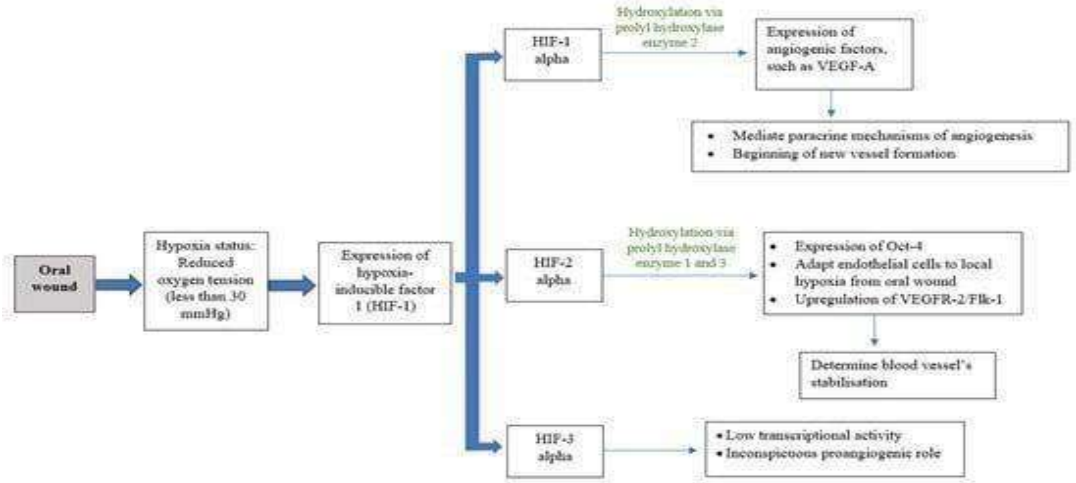


Figure 3. Schematic diagram showing correlation of oxygenation and neovascularization

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 439-448 www.ijdmsrjournal.com ISSN: 2582-6018

For chemical energy generation adenosine triphosphate is required in tissue regeneration is also involved in the adenine dinucleotide phosphate (NADPH) oxidase generation of reactive oxygen species (ROS) such as superoxide and peroxide (H 2O 2) . Normal cell homeostasis and functions is regulated by reactive oxygen species increase the cellular growth factors (vascular endothelial growth factor (VEGF) and platelet-derived growth factors (PDGF) and induce several transcription factors that brings phagocytosis and bacteriostatic H 2 O 2 in the cell defenseresponse.

ROS stimulates endothelialhydrogen cell division, neovascularization, vasculogenesis, fibroblast division and movement of the formation of collagen and the extracellular matrix, and keratinocyte proliferation and migration in tissue repair. ROS also mediates vasoconstriction and dilatation with the help of nitrous oxide (NO) following platelet exposure to the extracellular matrix. Local ROS signaling is important for the thrombus formation in the process of initial haemostasis [6,47,48,49]. As angiogenesis in wound healing is highly sensitive to autonomic nerve stimuli so adequate oxygen supply is important for the wound tissue [6,50]. Therapeutic approaches that improved oxygenation in wound tissue .So that it can be the key to success in management of wounds . Hyperbaric oxygen therapy and topical oxygen are increasing wound healing. As an overview of potential therapeutically for medical conditions has been presented, it is the objective of this review to correlate on the role of oxygen angiogenesis and healing of oral wounds. It promote angiogenesis in oral wound healing during proliferation, such as ultrasounds, lasers, increased platelet in plasma (PRP),fibrin (PRF), and various chemical agents such as hyaluronic acid, astaxanthin, and Centella (C. asiatica).

HYDROGEL AND WOUND HEALING

The Intervention of therapeutic nanoparticles (NP) and biomolecules into hydrogels for wound application to enhance and accelerate healing(5,51,52). Nowadays the alternative to incorporation of antibiotics into hydrogel instead and antimicrobial properties are used. Evidence shows application of other inclusions such as metals, growth factor-releasing nanoparticles, and enzyme-releasing nanoparticles. For effective therapeutic gels , integration of nanoparticles and synthesis of hydrogel offer wide range of possibility Chronic wounds are a very common cause in public health concern .The population of patients with obesity and advanced age, venous insufficiency, and diabetes is expected to increase along with secondary instances of chronic wounds(5,53) treatment costs for chronic wounds is correspondingly rising. If persistence of chronic wounds can lead to progression of infectious wound infiltration ,delay healing and decrease patient quality of life (5,54). Hydrogels play an important role in optimized local treatment for chronic wounds. It is non-toxic and non-irritant, biocompatible, easily applicable, and cost-effective.

Silver nanoparticles have greater efficacy in reducing bacterial growth to promote wound healing (5,55,56). Application of guar gum hydrogels with embedded silver nanoparticles as wound dressings in a rat model demonstrates antibacterial efficacy. Another study reports on the spectrum of antimicrobial activity of silver nanoparticle inclusion rapid healing with insignificant scarring after 48 h, exhibiting a stronger bactericidal selectivity against S. aureus than E. coli (92% overall bacterial reduction). A property of silver nanoparticles has enhanced wound re-epithelialization, cell proliferation, and reduced tissue inflammation.Zinc is a metal nanoparticle that exhibited antimicrobial properties when integrated into hydrogel scaffolds. Some study reports show that gold and nanoparticles have similar efficacy . It plays an important role in drug delivery, tissue engineering, cancer treatments, and imaging, each of which deserves further study.

VITAMIN C AND WOUND HEALING

Vitamin C is essential for synthesis of collagen, elastin, and cellular substances in the epithelium and prevents the formation of excess free radicals. The collagen synthesis Helps of skin firmness, disappearance of wrinkles, Vitamin C helps in healing of traumatic lesions and burns. Wound healing play a main challenges in dentistry it be painful time ,consuming process and However, at present, the sphere of research regarding medication, dental materials, their physical, Chemical and mechanical properties , their effects on dento-periodontal tissues, as well as the Methods of evaluation , has greatly expanded Wounds classified into acute and chronic. An Acute wound occurs through trauma or surgery and undergoes healing . Chronic wounds are slow healing. Wound healing involves a series of complex stages that are Influenced by the type and severity of the wound The stages of wound healing are: hemostasis, Inflammation, reepithelialization, neo-vascularisation, collagen deposition and matrix remodeling with Scar formation. In this regard a high microbial load can severely diminish acute or

chronic wound Healing, which is especially challenging in the oral cavity . When we discuss oral wounds The most common is after tooth extraction. Intraoral wound healing sustains constant physical trauma in the environment (4,57). After a tooth is extracted, the dental Alveoli (tooth sockets) are closed via blood clotting and re-epithelialization starts 24 h post-extraction. excisional wounds undergo slow wound healing after tooth extraction . The defense and regeneration mechanisms of the body are correlated with the repair process of damaged tissue (4,58,59). Vitamin C is directly involved in the process of post-extraction healing by collagen synthesis . It Can also be concluded that the human body consumes higher amounts of ascorbic acid in dental extraction . Vitamin -c increases faster healing of wounds. Studies were conducted on a population ,it is necessary to conduct a large population for accurate information. If the results will be confirmed in studies with larger samples and accelerated Post-a attractional wound healing process.

HYALURANIC ACID AND WOUND HEALING

Type 2 diabetes mellitus is a chronic metabolic disorder whose prevalence has increased globally . In chronic hyperglycemic conditions the microvascular and macrovascular complications are increased .The wound healing processes such as tissue nutrition, inflammatory response and tissue permeability microcirculatory deficiencies and impaired leukocyte functions are affected . In poorly controlled diabetes patients develop a series of complications and . Intraorally, patients with poorly controlled diabetes could be expected to suffer similar complications and be prone to oral diseases and dental problems . In poorly controlled diabetes patients have a delayed wound healing and post extraction socket changes (3,60,61). In patients with poorly controlled diabetes patients may suffer from impaired osseointegration increased risk of peri-implantitis and increased level of implant failure due to bone alteration .Hyaluronic acid (HA) is a high-molecular glycosaminoglycan (GAG)which can be found in connective tissue, synovial fluid, skin, and other body tissues such as extracellular matrix of articular cartilage . It exerts an anti-inflammatory effect during oral wound healing supports the integrity of tissues regarding osmotic pressure and tissue lubrication, and the viscosity of joint synovial fluid .It has biocompatible and biological processes related to oral tissue healing, HA most commonly used in dentistry . The studies have demonstrated the help role of HA on swelling, pain and anti-inflammatory efficiency in oral maxillofacial surgery . The role in bone repair by facilitating cell's migration, proliferation and differentiation .HA is widely used in the medical field, there is a lack of research about clinical applications of HA and its effects on patient on risks, such as decreased wound healing commonly found in person with badly controlled type 2 diabetes.The aim of this study was to investigate the e of HA on the wound healing after tooth extraction for patients with poorly controlled type 2 diabetes mellitus.0.8 hyaluronic acid placed in post-extraction socket in patients with poorly controlled diabetes may increase wound healing, especially in the first days after application. Examining the effect of HA after surgical extractions in patients with compromised wound healing would be good analyzing

II. CONCLUSION

In wound healing Microbial activity is against metal nanoparticles within hydrogel scaffolds . Vitamin – c contribute to healing of post extraction wound and also to resumption of normal microcirculation in traumatized tissue.(4).0.8% hyaluronic acid placed in post extraction socket in patient with poorly controlled diabetes may improve wound healing especially in first day after application (3).

REFERENCE

1. Toma AI, Fuller JM, Willett NJ, Goudy SL. Oral wound healing models and emerging regenerative therapies. Transl Res. 2021 Oct;236:17-34. Doi: 10.1016/j.trsl.2021.06.003. Epub 2021 Jun 20. PMID: 34161876; PMCID: PMC8380729.
2. Yang S, Li Y, Liu C, Wu Y, Wan Z, Shen D. Pathogenesis and treatment of wound healing in patientswith diabetes after tooth extraction. Front Endocrinol (Lausanne). 2022 Sep 23;13:949535. Doi: 10.3389/fendo.2022.949535. PMID: 36213270; PMCID: PMC9538860
3. Marin S, Popovic-Pejicic S, Radosevic-Caric B, Trtić N, Tatic Z, Selakovic S. Hyaluronic acid treatment outcome on the post-extraction wound healing in patients with poorly controlled type 2 diabetes: A randomized controlled split-mouth study. Med Oral Patol Oral Cir Bucal. 2020 Mar 1;25(2):e154-e160. Doi: 10.4317/medoral.23061. PMID: 32040462; PMCID: PMC7103456.

4. Klein GL. Burns: where has all the calcium (and vitamin D) gone? Adv Nutr. 2011 Nov;2(6):457-62. Doi: 10.3945/an.111.000745. Epub 2011 Nov 3. PMID: 22332088; PMCID: PMC3226383.
5. Sheikh-Oleslami S, Tao B, D'Souza J, Butt F, Suntharalingam H, Rempel L, Amiri N. A Review of Metal Nanoparticles Embedded in Hydrogel Scaffolds for Wound Healing In Vivo. Gels. 2023 July 22;9(7):591. Doi: 10.3390/gels9070591. PMID: 37504470; PMCID: PMC10379627.
6. Ngeow, Wei Cheong & Chuey Chuan, Tan & Goh, Yet Ching & Deliberador, Tatiana & Cheah, Chiawei. (2022). A Narrative Review on Means to Promote Oxygenation and Angiogenesis in Oral Wound Healing. Bioengineering. 9. 636. 10.3390/bioengineering9110636.
7. Hartmeier P.R., Pham N.B., Velankar K.Y., Issa F., Giannoukakis N., Meng W.S. Hydrogel Dressings for Chronic Wound Healing in Diabetes: Beyond Hydration. J. Pharm. Drugs. Deliv. Res. 2021;10:1000197.
8. Cho SK, et al. Development of a model to predict healing of chronic wounds within 12 weeks. Adv Wound Care (New Rochelle) 2020;9:516–24
9. Haidari H., Bright R., Strudwick X.L., Garg S., Vasilev K., Cowin A.J., Kopecki Z. Multifunctional ultrasmall AgNP hydrogel accelerates healing of S. aureus infected wounds. Acta Biomater. 2021;128:420– 434. Doi: 10.1016/j.actbio.2021.04.007.
10. El-Ezz D.A., Abdel-Rahman L.H., Al-Farhan B.S., Mostafa D.A., Ayad E.G., Basha M.T., Abdelaziz M., Abdalla E.M. Enhanced In Vivo Wound Healing Efficacy of a Novel Hydrogel Loaded with Copper (II) Schiff Base Quinoline Complex (CuSQ) Solid Lipid Nanoparticles. Pharmaceuticals. 2022;15:978. Doi: 10.3390/ph15080978. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
11. Liu J, et al. Skin and oral mucosa equivalents: construction and performance. Orthod Craniofac Res 2010;13:11–20.
12. Squier CA, Kremer MJ. Biology of oral mucosa and esophagus. J Natl Cancer Inst Monogr 2001:7Liu J, et al. Skin and oral mucosa equivalents: construction and Performance. Orthod Craniofac Res 2010;13:11–20.
13. Losquadro WD. Anatomy of the skin and the pathogenesis of nonmelanoma skin cancer. Facial Plast Surg Clin North Am 2017;25:28 3–9.
14. SquierCA, Kremer MJ, Wertz PW. Effect of ethanol on lipid metabolism and epithelial permeability barrier of skin and oral mucosa in the rat. J Oral Pathol Med 2003;32:5 95–9.mucosa in the rat. J Org for perfect skin regeneration. Science 1997;276:75–81. al Pathol Med 2003;32:595–9.
15. Ito M, Cotsarelis G. Is the hair follicle necessary for normal wound healing? J Invest Dermatol 2008;128:1059–61.
16. Ito M, et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. Nat Med 2005;11:1351–4.
17. Levy V, et al. Epidermal stem cells arise from the hair follicle after wounding. FASEB J 2007;21:1358–66.
18. Martinot V, et al. Comparative study of split thickness skin taken from the scalp and thigh inchildren. Burns 1994;20:146–50.
19. Brown JB, McDowell F. Epithelial Healing and the Transplantation of Skin. Ann Surg 1942;115:1166–81.
20. Mitragotri S. Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. J Control Release 2003;86:69–92.
21. Todo H, et al. Permeation pathway of macromolecules and nanospheres through skin. Biol Pharm Bull 2010;33:1394–9.
22. Martin P. Wound healing aiming 23 Whitby DJ, Ferguson MW. The extracellular matrix of lip wounds in fetal, neonatal and adult mice. Development 1991;112:651–68.
23. Chen L, et al. Positional differences in the wound transcriptome of skin and oral mucosa. BMC Genomics 2010;11:471.
24. Szpaderski AM, Zuckerman JD, DiPietro LA. Differential injury responses in oral mucosal and cutaneous wounds. J Dent Res 2003;82:621–6.
25. HS27. Brand , Ligtenberg AJ, Veerman EC. Saliva and wound healing. Monogr Oral Sci 2014;24:52
26. Nagy G. Role of saliva, salivary glands and epidermal growth factor (EGF) on oral wound healing. Fogorv Sz 2003;96:17–20.
27. Li X, et al. Systemic diseases caused by oral infection. Clin Microbiol Rev 2000;13:547–58.
28. Baltch AL, et al. Bacteremia in patien26 Turabelidze A, et al. Intrinsic differences between oral and skin keratinocytes. PLoS One 2014;9:e101480.ts undergoing oral

procedures. Study following parenteral antimicrobial prophylaxis as recommended by the American Heart Association, 1977. Arch Intern Med 19
29. Politis C, et al. Wound Healing Problems in the Mouth. Front Physiol 2016;7:507.
30. Debelian GJ, Olsen I, Tronstad L. Anaerobic bacteremia and Fungemia in patients undergoing endodontic therapy: an overview. Ann Periodontol 1998;3:281–7
31. Okuda K, Ebihara Y. Relationships between chronic oral infectious diseases and systemic diseases. Bull Tokyo Dent Coll 1998;39:165–74.
32. Zhou S, Li G, Zhou T, Zhang S, Xue H, Geng J, et al. The Role of Ift140 in Early Bone Healing of Tooth Extraction Sockets. Oral Dis (2021). doi: 10.1111/ odi.13833
33. de Sousa Gomes P, Daugela P, Poskevicius L, Mariano L, Fernandes MH. Molecular and Cellular Aspects of Socket Healing in the Absence and Presence of Graft Materials and Autologous Platelet Concentrates: A Focused Review. J Oral Maxillofac Res (2019) 10(3):e2. doi: 10.5037/jomr.2019.10302
34. Huang S, Dang H, Huynh W, Sambrook PJ, Goss AN. The Healing of Dental Extraction Sockets in Patients with Type 2 Diabetes on Oral Hypoglycemics: A Prospective Cohort. Aust Dent J (2013) 58(1):89–93.doi: 10.1111/adj.12029
35. Gökşen S, Balabanlı B, Coşkun-Cevher Ş.. Application of Platelet Derived Growth Factor-Bb and Diabetic Wound Healing: The Relationship with Oxidative Events. Free Radic Res (2017) 51(5):49: A Systematic Review. J Oral Maxillofac Res (2019) 10(3):e7. doi: 10.5037/jomr.2019.103078–505. doi:10.1080/10715762.2017.1327715
36. Pranskunas M, Galindo-Moreno P, Padial-Molina M. Extraction Socket Preservation Using Growth Factors and Stem Cells
37. Gooyit M, Peng Z, Wolter WR, Pi H, Ding D, Hesek D, et al. A Chemical Biological Strategy to Facilitate Diabetic Wound Healing. ACS Chem Biol (2014) 9 (1):105–10. doi: 10.1021/cb4005468
38. Chang M, Nguyen TT. Strategy for Treatment of Infected Diabetic FootUlcers. Acc Chem Res (2021) 54(5):1080–93. doi: 10.1021/acs.accounts.0c00864
39. Pulito, C.; Cristaudo, A.; La Porta, C.; Zapperi, S.; Blandino, G.; Morrone, A.; Strano, S. Oral mucositis: The hidden side of cancer therapy. J. Exp. Clin. Cancer Res. 2020, 39, 210. [Google Scholar] [CrossRef]
40. Kumar, P.; Kumar, S.; Udupa, E.G.P.; Kumar, U.; Rao, P.; Honnegowda, T.M. Role of angiogenesis and angiogenic factors in acute and chronic wound healing. Plast. Aesthetic Res. 2015, 2, 243–249. [Google Scholar] [CrossRef][Green Version]
41. Pettet, G.; Chaplain, M.; McElwain, D.L.S.; Byrne, H. On the rôle of angiogenesis in wound healing. Proc. R. Soc. B Boil. Sci. 1996, 263, 1487–1493. [Google Scholar] [CrossRef]
42. DiPietro, L.A. Angiogenesis and wound repair: When enough is enough. J. Leukoc. Biol. 2016, 100, 979– 984. [Google Scholar] [CrossRef][Green Version]
43. Hashimoto, T.; Shibasaki, F. Hypoxia-Inducible Factor as an Angiogenic Master Switch. Front. Pediatr. 2015, 3, 33. [Google Scholar] [CrossRef] [PubMed][Green Version]
44. Caley, M.P.; Martins, V.L.; O'Toole, E.A. Metalloproteinases and Wound Healing. Adv. Wound Care 2015,4, 225–234. [Google Scholar] [CrossRef] [PubMed][Green Version]
45. Dunnill, C.; Patton, T.; Brennan, J.; Barrett, J.; Dryden, M.; Cooke, J.; Leaper, D.; Georgopoulos, N.T. Reactive oxygen species (ROS) and wound healing: The functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. Int. Wound J. 2015, 14, 89–96. [Google Scholar] [CrossRef] [PubMed]
46. Zorov, D.B.; Juhaszova, M.; Sollott, S.J. Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS Release. Physiol. Rev. 2014, 94, 909–950. [Google Scholar] [CrossRef] [PubMed][Green Version]
47. Bryan, N.; Ahswin, H.; Smart, N.; Bayon, Y.; Wohlert, S.; Hunt, J. Reactive oxygen species (ROS)—A family of fate deciding molecules pivotal in constructive inflammation and wound healing. Eur. Cells Mater. 2012, 24, 249–265. [Google Scholar] [CrossRef]
48. LaVan, F.B.; Hunt, T.K. Oxygen and wound healing. Clin. Plast. Surg. 1990, 17, 463–472. [Google Scholar] [CrossRef]
49. Bright R., Strudwick X.L., Garg S.,Vasilev K., Cowin A.J., Kopecki Z.Multifunctionalultrasmall AgNP hydrogel accelerates healing of S.aureus infected

wounds. Acta Biomater. 2021; 128:420–434. doi:10.1016/j.actbio.2021.04.007. [PubMed] [CrossRef][Google Scholar]

50. El-Ezz D.A., Abdel-Rahman L.H., Al-Farhan B.S., Mostafa D.A., Ayad E.G., Basha M.T., Abdelaziz M., AbdallaE.M. Enhanced In Vivo Wound HealingEf icacy of a Novel Hydrogel Loaded with Copper (II) Schiff Base Quinoline Complex(CuSQ) Solid Lipid Nanoparticles. Pharmaceuticals. 2022;15:978.doi:10.3390/ph15080978. [PMC freearticle][PubMed][CrossRef][Google Scholar]
51. Fonder M.A., A.R.,Mamelak A.J. B., Kohli practical nonhealing wounds and wound care Dermatol.2008;58:185–206. doi:10.1016/j.jaad.2007.08.048.[PubMed][CrossRef] [Google Scholar]
52. Frykberg R.G., Banks J., Deptuła M., Karpowicz P., Wardowska A., Sass P., Sosnowski P., Mieczkowska A.,Filipowicz N., Dzierżyńska M., et al. Challenges in the Treatment of ChronicWounds. Adv. Wound Care. 2015;4:560–582. doi:10.1089/wound.2015.0635.[PMC freearticle][PubMed][CrossRef][Google Scholar]
53. Y.,Tong Q.,Tang Injectable oxidized alginate/carboxymethyl chitosan hydrogels functionalized with nanoparticles for wound repair. Carbohydr. Polym.2022;293:119733. doi: 10.1016/j.carbpol.2022.119733.[PubMed
54. IAOYING KONG, JUN FU, KAI SHAO, LILI WANG, XUEFANG LAN, JINSHENG SHI. Biomimetic Hydrogel for Rapid and Scar-free Healing of Skin Wounds inspired by the healing processof oral mucosa. Acta Biomaterialia, 2019; doi: https://doi.org/10.1016/j.actbio.2019.
55. MIN SU, XIAOLIU LIANG, XIAOXIAO XU, XINMOU WU, BIN YANG. Hepatoprotective benefits of vitamin C against perfluorooctane sulfonate-induced liver damage in mice through suppressing inflammatory reaction and ER stress. Environmental Toxicology and Pharmacology, ; Volume 65(1): 60-65.
56. HININGER, I., WATERS, R., OSMAN, M., GARREL, C., R. A. Acute pro oxidant effects of vitamin C in EDTA chelaANDERSON tion therapy and long-term antioxidant benefits of therapy. Free Radical Biology and Medicine, 2005; Volume 38, Issue 12, Pages 1565-1570.
57. Abiko Y, Selimovic D. The mechanism of protracted wound healing on oral mucosa in diabetes. Review. Bosn J Basic Med Sci. 2010:186-91.
58. Nazir MA, AlGhamdi L, AlKadi M, AlBeajan N, AlRashoudi L, AlHussan M. The burden of Diabetes, Its Oral Complications and Their Prevention and Management. Open Access Maced J Med Sci. 2018;6:1545-53.