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A REVIEW ON WOUND AND ADVANCEMENT IN HEALING STRATEGIES

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ABSTRACT: Wound healing is a complex and dynamic physiological process that occurs by a sequence of interrelated molecular events that should work together in a proper manner and time to restore cellular function and tissue integrity. These physiological phases occur efficiently in normal healthy volunteers and/or under normal conditions. But, in some cases, these events are retarded, which results in hard-to-heal or chronic wounds. Each year the number of individuals suffering from chronic wounds is increasing. They delayed wound healing results in the infected wound, which triggers the inflammatory reaction making the situation more complicated. So, one of the main challenges for wound care society is to formulate an optimum wound care product that will reduce the healing time as well as it will provide protection from infection. Though many types of traditional wound dressings are available, but with various limitations like more wound healing time, scar formations, skin irritations. Since, a wound can be experienced by an individual anytime from birth to death; proper wound care products should exist. This review converses about different types of wounds and the advancement of wound dressings, which can improve wound healing activity and reduce complications.

INTRODUCTION: The types of wounds and the condition of the tissue play an important role in choosing an appropriate wound dressing. Day by day, wound management is becoming way more complex, along with a hike in price. The most potent dressing is the own skin of the patient because of its permeability to vapor and protects deeper tissues from mechanical injuries. The antigen property of the dressing limits its use [1]. Skin is composed of three layers that protect the internal organ from the external environment.

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Cells like fibroblasts and macrophages take part in keratin synthesis, which helps to maintain the structure of the skin and provide protection from infections [2, 3]. Modern wound care products are designed with an aim to ease the function of the wound than only to cover it.

A potent wound dressing should be permeable to oxygen, restricts dehydration, protects from infections, and also absorbs blood and fluid. It should be non-toxic, non-allergic, non-adherent as well as it should be cost-effective [4]. The selection of optimum dressings depends on several criteria like size and type of wound, the intensity of tissue damage, and the wound healing stage. Moreover, it should provide a clean healing environment by supporting body's own cleaning process [5]. Multi-layered modern wound dressings serve the demands which cannot be achieved by single material layer of conventional system. Smart wound dressing material is a novel idea which can sense various environmental situation and stimuli and can react accordingly. This intelligent type of dressing material is very helpful in the field of sports, aerospace, defense [6]. This paper will further discuss the various types of wounds and modification of different wound dressings according to the need of the wound types.

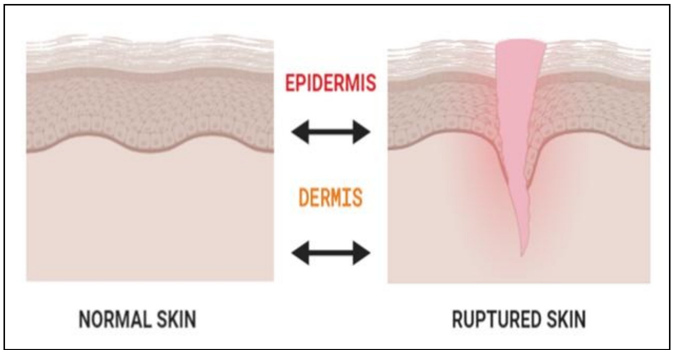

FIG. 1: CONDITION OF SKIN BEFORE AND AFTER WOUND

Wound and its Type: A wound may be defined as an interruption to the normal structure and the function of the skin cells.

The wounds that fail to get heal by standard therapy in a specific time are defined as a hard-to-heal wound [7]. **Fig. 2** categorizes the various types of wounds. Additionally, wounds can be divided as acute or chronic on the basis of the healing properties.

Acute Wounds: Acute wounds maintain less time fashion to heal, usually show no complications. The healing occurs in a predictable manner where different cells, fibroblast, platelets, and keratino-cytes help in restoring tissue integrity. These wounds can be either surgical or traumatic [8]. That would result in abrasions, avulsions, incisions, contusions, and lacerations

Chronic Wounds: Unlike acute wounds, this type of wound fails to heal in a predictable manner within a specific time and further brings several complications. The wounds which take more than 12 weeks to heal is considered as a chronic wound. Delayed healing, prolonged inflammatory phase, persistent infection, and presence of resistant microorganisms are common features of chronic wounds [9, 10].

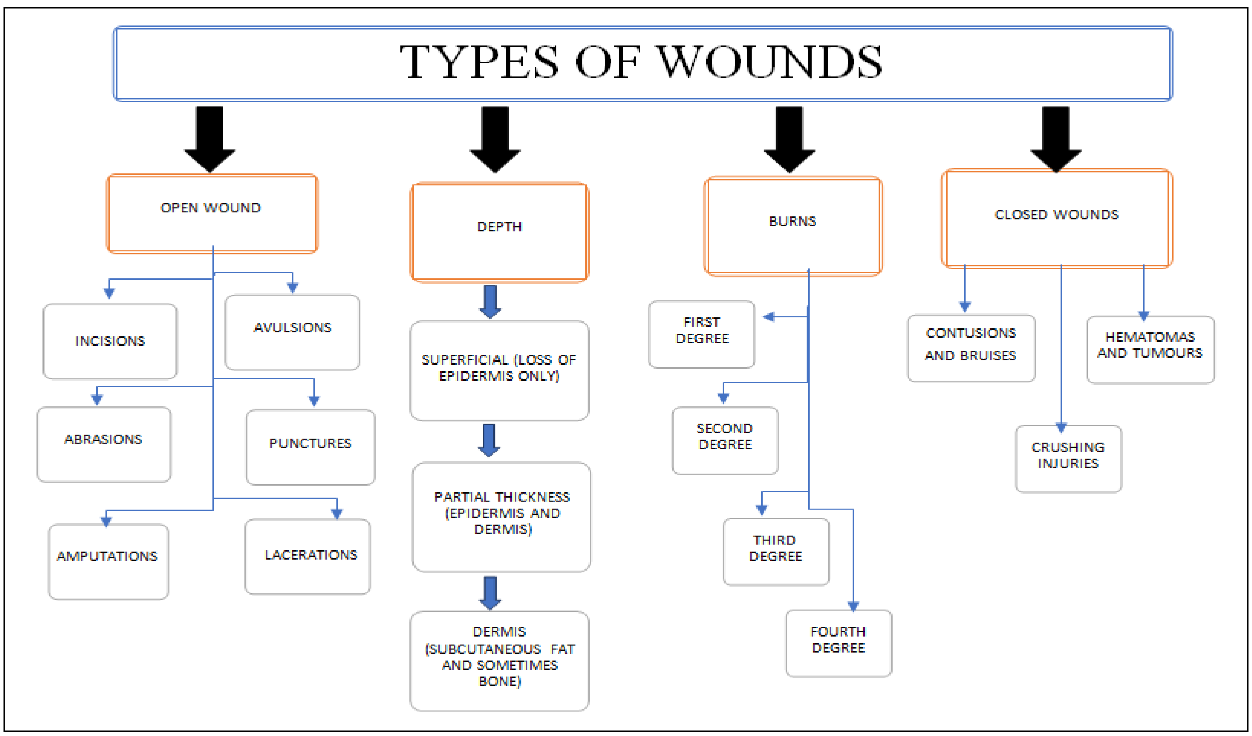

FIG. 2: DIFFERENT TYPES OF WOUNDS

Phases of Wound Healing: Wound healing is an intricate physiological process defined as a series of continuous molecular events [13]. Wound healing is categorized into four major phases: **Fig. 3**. 1. Hemostatic phase 2. Inflammatory phase 3. Proliferative phase 4. Remodeling phase. These phases are discussed below.

1. Haemostasis: Haemostatic phase occurs immediately after an injury. It is categorized by microvascular injury and blood components release in the site of the wound. The adherence of platelets initiatesthe release of cytokines, growth factors like, platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), endothelial growth factor (EGF), fibroblast growth factor (FGF), serotonin, platelet-activating factor, bradykinin, platelet factor IV, platelet-derived angiogenesis factor, prostaglandins and histamine resulting in platelet aggregation [11]. Afterward, the intrinsic and extrinsic pathways get activated and form fibrin clots.

2. Inflammatory Phase: This is the second stage with the aim to prevent infection. The inflammatory stimulus triggers cellular responses [12]. Growth factors released from platelets chemotactically pull the inflammatory cells into the infected area. Neutrophils are the first inflammatory cells to enter the wound, followed by monocytes. After activation, Neutrophils release a few lysosomal enzymes (such as neutral proteases, elastase, and collagenase), which helps to remove the scratched components of the extracellular matrix (ECM) [13]. Macrophages are essential factors for heading towards the proliferative phase

3. Proliferative Phase: The third phase starts just after the inflammatory phase diminishes and continues up to 14 days. The formation of the ECM (extracellular matrix) and angiogenesis are the identifying characteristics of this phase. Granulation tissue (composed of collagen and extracellular matrix) forms which are initiated by newly formed blood vessels.

In this phase, fibroblasts and endothelial cells replace the damaged tissue. PDGF, EGF, and FGF induce activation and proliferation of fibroblast. Macrophages convert fibroblasts to myofibroblasts, which are responsible for wound contraction and ECM production [14].

4. Maturation and Remodelling Phase: This starts once the wound is superficially closed near about 3 weeks after injury and needs a few years to complete [15]. It helps in the re-epithelialization and remodeling of the tissues which are formed freshly in the proliferative phase. Here collagen III is converted to collagen I.

The collagen fibers are arranged in a normal manner, not as uninjured tissue. So, remodeling of the fibers is needed in a proper manner. Equilibrium between collagen synthesis and degradation is maintained by remodeling of ECM.

Many enzymes, like neutrophil, released elastase, matrix metalloproteinases (MMPs), and gelatinase, collagenases are involved in this phase [16].

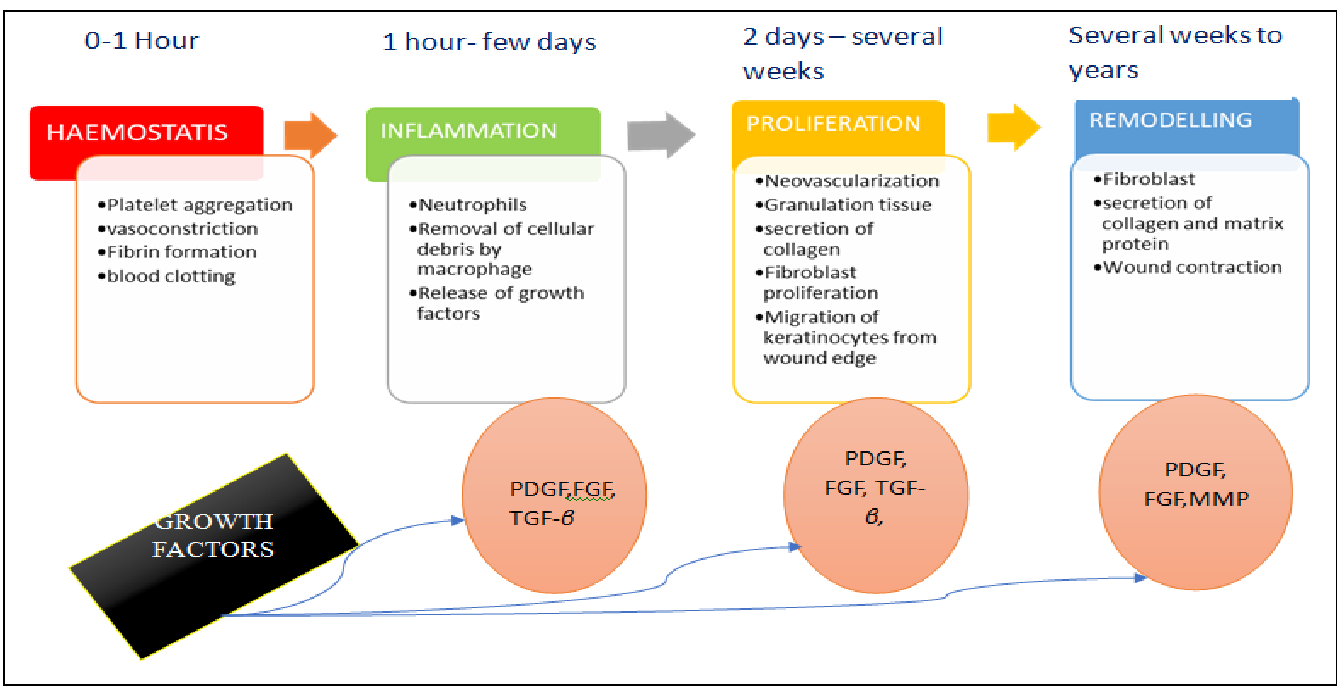

FIG. 3: PHASES OF WOUND HEALING

Factors Responsible for Delayed Healing: Following are some factors that are responsible for delayed wound healing. These factors can be divided into local and systemic.

- **Local Factors that Influence Healing:**
- **Infections:** Damaged tissues are more prone to infections. The replicating microorganism releases toxin at the wound site and thus leading to impaired healing [17].

- **Oxygen:** Oxygen increases differentiation, migration, and re-epithelisation of keratinocytes and collagen synthesis, angiogenesis, and fibroblast proliferation [18, 19]. Wound healing gets affected when oxygen is not present.

- **Systemic Factors that Influence Healing:**
- **Age:** As the age increases, there is delayed re-epithelization, high secretion of inflammatory mediators, less secretion of growth factors, and collagen deposition.

- **Sex Hormones:** Oestrogen helps in wound healing by playing a role in matrix formation, epidermal functions, and inhibition of protease. So, the wound heals more quickly in aged females than males since androgens have a negative effect on wound healing.

- **Alcohol Consumption:** Alcohol consumers are prone to infections as it weakens host resistance. Moreover, alcohol alters the proliferative phase [20].

- **Smoke:** Carbon monoxide of smoke is responsible for tissue hypoxia. Migration of WBC (white blood cell) gets affected by smoking which reduces the number of macrophage and monocyte in the wound area and weakens neutrophil bactericidal property [21].

- **Diabetes:** Diabetes is one of the vital reasons behind chronic non-healing diabetic foot ulcers (DFU). The level of metalloproteases increases and leads to neuropathy. Moreover, diabetes impairs angiogenesis and neovascularisation [22].

- **Diet:** Any particular nutrient deficiency leads to a delay in healing. Energy for angiogenesis is provided by glucose. Protein deficiency impairs wound remodeling by altering fibroblast proliferation, collagen synthesis, capillary formation. It also affects the immune system. Collagen is the main protein component. Vitamins like Vitamins C (L-ascorbic acid), A (retinol), and E (tocopherol) show good antioxidant and anti-inflammatory properties [23, 24].

Wound Healing Dressings: Traditional wound dressings like cotton gauze mainly protect the wound from contamination. But due to excessive fluid absorption, it requires frequent change, which causes pain to patient [25]. Wound dressings like plasters provide physical barriers to the wounds. Modern dressings like hydrogels are capable of providing a moist environment as they are made up of cross-linked polymers.

In addition, it provides permeability to oxygen. But it has very low strength, so it needs to hybridized with other polymers [26]. Film and foam dressings were mainly developed to control superficial and deep wounds. They can be fit according to body structure [27]. Moreover, they allow the incorporation of anti-inflammatory and anti-microbial drugs. It can also be used with other dressings like alginate dressings and hydrogels [28, 29].

Smart and Innovative Approach in Wound Prevention: The positive side of smart technologies is it provides thorough wound care evaluations. Xu *et al*. designed a model that can predict personalized time to heal by stereo photogrammetric imaging [30].

Negative Pressure Wound Technology: This technology is useful for treating acute wounds. The wound dimension and volume decrease with a less complex reconstruction of tissue [30].

It simplifies many complications, like the elimination of intra abdominal contamination, edema, and exudates. Many complex traumatic orthopedic post-operative complications have been solved by the advancement of negative-pressure wound technology. It targets non-viable tissues along with a device that provides a protected, sealed, moist healing environment that removes hematoma and edema [31].

Skin Substitutes: Autograft is a recently preferred choice, but the limitation is the availability of insufficient tissue and low patient acceptance. Allografts and xenografts provide temporary protection but prone to transfer of disease [32]. Bioengineered skin substitutes are available in large numbers and less prone to infections. Few examples of this kind of dressings are Biobrane, Transcyte, Dermagraft, Apligraft. These are mesh-like dressings composed of cells like keratinocytes, fibroblasts. And helps in quick healing of wounds [33].

Hyperbaric Oxygen: This method involves a sealed chamber with 100% oxygen, which is pressurized between 1.5 to 3 atmospheres absolute (ATA) for about 1 to 2 hours of time. This is mainly used for sea diving accidents, compartment syndrome, anaerobic infections, ischemic injuries, chronic wounds [34]. But it has various side effects like claustrophobia, neurologic oxygen toxicity, sinus irritation. Though the mechanism of action is still not clear, it increases the availability of oxygen in tissues [34]. This increased level of oxygen further promotes elongation and deposition of collagen and the killing of bacteria by the macrophage. Thus hyperbaric oxygen plays a key role in long-lasting wound healing. More studies are needed to understand the mechanism [35].

pH-Sensitive Wound Care: Normally, skin pH is acidic in nature within a range between 4.8-6.0. but this range changes from 7.15 to 8.9 in chronic wound conditions. It has been found that there is a direct correlation between the pH of the wound and time of healing; alkaline pH slower down the healing time [36]. Wound pH also affects the oxygenation; by lowering the pH by 0.6-unit, the oxygen level increases by 50%. A wound bed has the capability to evaluate the healing process. By using some surface dyes or other indicators, change of the color with the alteration of pH can be observed by naked eyes [37]. One of the examples of this is the hydrogel-based pH sensor, and another one is a potentiometric pH sensor.

Temperature Sensors Wound Care: During any inflammation and infection, the temperature increases. Low temperature is the indication of local ischemia and is harmful to wound healing [38]. There are multiple potential approaches to temperature measurement; however, the majority of sensors use a resistive change over a relevant temperature range. The material used needs a high-temperature coefficient of resistance (TCR) with sensitivity within a physiologically appropriate range.

Inkjet printers are a promising tool in sensor technology because of their various advantages, like low manufacturing cost with less waste [39]. Because of the low cost, it is also applicable for disposable use like one-time use bandages [40]. Courbet *et al.*, designed a temperature sensor by using silver nanoparticles on a paper with a passive layer of parylene. Its flexibilities make it a potent candidate for a smart bandage. But no clinical evaluation has been performed for this yet [38]. Vuorinen et al. designed another temperature sensor with inkjet-printed graphene on a bandage of polyurethane. The result showed an increase of 0.06% sensor sensitivity with Sensor sensitivity was greater than 0.06%, with TCR value negative. Recently, Sui et al. stated a novel silver-based temperature sensor [41]. They discovered that the sensitivity of the sensor was not dependent upon the used substrate material. This strategy is useful for designing customized sensors as the parameters of the conductive traces can be easily modified according to the functional needs. *In-vivo* evaluation studies of the inject printed sensors need to be done [41].

Smart Bandages to Release Drugs: Drug delivery can be both in a passive and active way. A bandage can deliver drugs in a passive way without depending on external factors. But it can be unsuitable since the wound healing process is dynamic in nature [42]. To overcome this, a smart bandage can be designed, which can modify the dosage anytime, even at a particular wound region [43]. Few regular active drug delivery includes piezoelectric pumping, iontophoretic transport, thermoresponsive system. [42]. Nabavinia *et al.*, prepared a controlled release and targeted action bandage [43]. This is flexible to wear and has a conductive core of PEGDA-ALG hydrogel and drug carriers, which can be thermally triggered. The positive side of this bandage is it can deliver the drug to any location efficiently as each fiber thread will be triggered independently. It showed a promising result in both *in-vitro* and *in-vivo* animal studies in diabetic wound healing animal model [44].

CONCLUSION: Costly treatments for chronic wounds and hospital stays for a longer period create an economic burden. Despite extreme progress in wound products, chronic wound healing still remains at an alarming stage. The field of wound care is ever-growing. New and recent researches are mainly emphasizing to develop a novel strategy to heal wounds. Advancement in different fields like tissue regeneration, biomedical engineering, micro-fluidics, stem cell biology leads to the emergence of new smart technologies.

Management of wounds by smart technology acts as a bridge between the victim and caretakers. The aim to achieve optimum healing with less cost can be achieved by the advancement of smart wound dressings, which can sense and predict the wound formation and can prevent successfully before any complications. The advancement of innovative techniques with the tint of the conventional approach has a stronghold in the future. This review mainly focussed on the advancement of the wound care field, which will be successful in providing a painless, scarless, and rapid healing of wounds.

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REFERENCES:

1. Nagubothu SR: Reconstruction of vocal fold scarring with mesenchymal stromal cell therapy 2019.
2. Wen S, Dooner M, Cheng Y, Papa E, Del Tatto M, Pereira M, Deng Y, Goldberg L, Aliotta J, Chatterjee D and Stewart C: Mesenchymal stromal cell-derived extracellular vesicles rescue radiation damage to murine marrow hematopoietic cells. Leukemia. 2016; 30(11): 2221-31.
3. Jia Y, Gan Y, He C, Chen Z and Zhou C: The mechanism of skin lipids influencing skin status. Journal of Dermatological Science 2018; 89(2): 112-9.
4. Han G and Ceilley R: Chronic wound healing: a review of current management and treatments. Advances in therapy. 2017; 34(3): 599-10.
5. Rajendran S: Advanced textiles for wound care. Woodhead Publishing. 2018.
6. Hartwell EY: inventor; Smith, Nephew PLC, assignee. Wound dressing. United States patent US 9,956,121. 2018.
7. Badia JM, Casey AL, Petrosillo N, Hudson PM, Mitchell SA and Crosby C: Impact of surgical site infection on healthcare costs and patient outcomes: a systematic review in six European countries. Journal of Hospital Infection. 2017; 96(1): 1-5.
8. Malone M, Bjarnsholt T, McBain AJ, James GA, Stoodley P, Leaper D, Tachi M, Schultz G, Swanson T, Wolcott RD: The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. Journal of wound care. 2017; 26(1): 20-5.
9. Hesketh M, Sahin KB, West ZE and Murray RZ: Macrophage phenotypes regulate scar formation and chronic wound healing. International Journal of Molecular Sciences 2017; 18(7): 1545.
10. Grubbs H and Manna B: Wound physiology. In Stat Pearls Stat Pearls. 2018.
11. Yamakawa S, Hayashida K. Advances in surgical applications of growth factors for wound healing. Burns & Trauma 2019; 7(1): s41038-019.
12. Chaudhary C and Garg T: Scaffolds: a novel carrier and potential wound healer. Critical Reviews™ in Therapeutic Drug Carrier Systems 2015; 32(4).
13. de Oliveira S, Rosowski EE and Huttenlocher A: Neutrophil migration in infection and wound repair: going forward in reverse. Nature Reviews Immunology 2016; 16(6): 378.
14. Järvinen T: Principles of wound healing–knowledge transfer to cornea. Acta Ophthalmologica. 2017; 95.
15. Cañedo-Dorantes L and Cañedo-Ayala M: Skin acute wound healing: a comprehensive review. International Journal of Inflammation 2019; 2019.
16. Rognoni E, Pisco AO, Hiratsuka T, Sipilä KH, Belmonte JM, Mobasseri SA, Philippeos C, Dilão R and Watt FM: Fibroblast state switching orchestrates dermal maturation and wound healing. Molecular Systems Biology 2018; 14(8).
17. Avishai E, Yeghiazaryan K and Golubnitschaja O: Impaired wound healing: facts and hypotheses for multi-professional considerations in predictive, preventive and personalised medicine. EPMA Journal 2017; 8(1): 23-33.
18. Kimmel HM, Grant A, Ditata J. The Presence of Oxygen in Wound Healing. Wounds: a Compendium of Clinical Research and Practice 2016; 28(8): 264-70.
19. Dunnill C, Patton T, Brennan J, Barrett J, Dryden M, Cooke J, Leaper D and Georgopoulos NT: Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. International Wound Journal. 2017; 14(1): 89-96.
20. Kany S, Janicova A and Relja B: Innate Immunity and Alcohol. Journal of Clinical Medicine 2019; 8(11): 1981.
21. Sørensen LT: Wound Healing and Infection in Surgery: The Pathophysiological Impact of Smoking, Smoking Cessation, and Nicotine Replacement Therapy A Systematic Review. Annals of Surgery 2012; 255(6): 1069-79.
22. Okonkwo UA and DiPietro LA: Diabetes and wound angiogenesis. International journal of molecular sciences. 2017; 18(7): 1419.
23. Palmieri B, Vadalà M and Laurino C: Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. Journal of Wound Care 2019; 28(10): 683-93.
24. Abdelhamied FM, Taha NM and Sakr MD: Factors affecting wound healing and needs among patients with

diabetic foot ulcer: suggested nursing guidelines. Zagazig Nursing Journal 2016; 12(1): 82-98.

25. Aljghami ME, Saboor S and Amini-Nik S: Emerging innovative wound dressings. Annals of Biomedical Engineering 2019; 47(3): 659-75.
26. Bai R, Yang Q, Tang J, Morelle XP, Vlassak J and Suo Z: Fatigue fracture of tough hydrogels. Extreme Mechanics Letters 2017; 15: 91-6.
27. Skórkowska-Telichowska K, Czemplik M, Kulma A, Szopa J: The local treatment and available dressings designed for chronic wounds. Journal of the American Academy of Dermatology 2013; 68(4): e117-26.
28. Gray TA, Rhodes S, Atkinson RA, Rothwell K, Wilson P, Dumville JC and Cullum NA: Opportunities for better value wound care: a multiservice, cross-sectional survey of complex wounds and their care in a UK community population. BMJ Open 2018; 8(3): e019440.
29. Onishi H, Machida Y, Santhini E and Vadodaria K: Novel textiles in managing burns and other chronic wounds. In Advanced Textiles for Wound Care 2019; 211-260.
30. Xu Y, Sun J, Carter RR and Bogie KM: Personalized prediction of chronic wound healing: an exponential mixed effects model using stereophotogrammetric measurement. Journal of Tissue Viability 2014; 23(2): 48-59.
31. Blott PL, Hartwell EY, Lee-Webb J, Nicolini D, Smith, Nephew PLC: Negative pressure wound therapy dressing system. United States patent application US 15/901,414. 2018.
32. Nicholas MN, Jeschke MG and Amini-Nik S: Methodologies in creating skin substitutes. Cellular and Molecular Life Sciences 2016; 73(18): 3453-72.
33. Pham C, Greenwood J, Cleland H, Woodruff P and Maddern G: Bioengineered skin substitutes for the management of burns: a systematic review. Burns 2007; 33(8): 946-57.
34. Ennis WJ, Huang ET and Gordon H: Impact of hyperbaric oxygen on more advanced wagner grades 3 and 4 diabetic foot ulcers: matching therapy to specific wound conditions. Advances in Wound Care 2018; 7(12): 397-07.
35. Lam G, Fontaine R, Ross FL and Chiu ES: Hyperbaric oxygen therapy: exploring the clinical evidence. Advances in Skin & Wound Care 2017; 30(4): 181-90.
36. Naranje N, Urewar C, Nandanwar P, Deliya V and Makkad J: Acidic environment and wound healing: a review. Wounds: a compendium of clinical research and practice. 2015; 27(1): 5-11.
37. Schreml S, Meier RJ, Weiß KT, Cattani J, Flittner D, Gehmert S, Wolfbeis OS, Landthaler M and Babilas P: A s prayable luminescent pH sensor and its use for wound imaging *in-vivo*. Experimental Dermatology 2012; 21(12): 951-3.
38. Salvo P, Dini V, Kirchhain A, Janowska A, Oranges T, Chiricozzi A, Lomonaco T, Di Francesco F and Romanelli M: Sensors and biosensors for C-reactive protein, temperature and pH, and their applications for monitoring wound healing: a review. Sensors 2017; 17(12): 2952.
39. Shamim A, Farooqui MF, inventors; King Abdullah University of Science, Technology (KAUST), assignee. Wound dressing with reusable electronics for wireless monitoring. United States patent US 10,702,153. 2020 Jul 7.
40. Vuorinen T, Niittynen J, Kankkunen T, Kraft TM and Mäntysalo M: Inkjet-printed graphene/PEDOT: PSS temperature sensors on a skin-conformable polyurethane substrate. Scientific Reports 2016; 6: 35289.
41. Sui Y, Kreider LP, Bogie KM and Zorman CA: Fabrication of a silver-based thermistor on flexible, temperature-sensitive substrates using a low-temperature inkjet printing technique. IEEE Sensors Letters 2019; 3(2): 1-4.
42. Gainza G, Villullas S, Pedraz JL, Hernandez RM and Igartua M: Advances in drug delivery systems (DDSs) to release growth factors for wound healing and skin regeneration. Nanomedicine: Nanotechnology, Biology and Medicine 2015; 11(6): 1551-73.
43. Scalamandré A and Bogie KM: Smart technologies in wound prevention and care. InInnovations and Emerging Technologies in Wound Care Academic Press 2020; 225-244.
44. Mostafalu P, Kiaee G, Giatsidis G, Khalilpour A, Nabavinia M, Dokmeci MR, Sonkusale S, Orgill DP, Tamayol A and Khademhosseini A: A textile dressing for temporal and dosage controlled drug delivery. Advanced Functional Materials 2017; 27(41): 1702399.

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