REVIEW ARTICLE

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Tissue Engineered Skin: A New Solution for Plastic Surgeons to Treat Skin Burns

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Abstract: Tissue engineering is a rapidly growing field in medicine. Its applications are used in various fields in order to create fully functional tissues such as cartilage, heart valves, bladder, and the skin. As skin burns continue to leave a severe implication on one's health, the use of tissue engineered skin grafts serves to be a unique solution in order to restore damaged skin. Compared to autografts or allografts, tissue engineered skin is a better solution in order to replace damaged skin due to its ability to accelerate wound-healing processes with the help of various biomaterials. Once the tissue engineered skin graft is created, reconstructive plastic surgeons come into play in order to safely implant the skin graft. They follow a complex surgical procedure in order to effectively implant the skin graft in the safest way possible without any complications. Once implanted, reconstructive plastic surgeons also have to choose the best wound closure technique in order to achieve the best cosmetic result. As tissue engineering is a rapidly growing field, more research studies should be conducted to focus on how it can be applied to regenerative medicine in order to solve problems such as tissue degeneration, treating traumatic injuries, and the organ shortage crisis.

1. Introduction

Millions of people across the world are affected by skin burns. They are capable of destroying one's physical, emotional, and psychological health. To further explain, approximately 6 million people end up reporting a skin burn to a medical professional each year, and in those 6 million people about 300,000 result in deaths from fire-related burn injuries.[1] Skin burns are capable of leaving serious implications on one's skin and overall well-being. Most doctors decide to treat severely damaged skin using autografts or allografts. Autografts are pieces of healthy skin taken from one part of a patient's body and implanted onto the damaged area. Allografts on the other hand are pieces of healthy skin taken from another individual and implanted onto the patient. Both of these methods are extremely popular and have been in use for years, but they do have various disadvantages. To further explain, using autografts requires the creation of an additional surgical site which the patient must recover from in order to get a healthy piece of skin. On the other hand, skin tissue from healthy individuals may not always be available in order to transplant an allograft. This is where tissue engineering comes into play. Tissue engineering involves the use of biomaterials to create tissue under laboratory conditions. Tissue engineered skin consists of natural polymers, synthetic polymers, and scaffolds in order to maintain the function of the tissue. One important point to note is that the tissue engineered skin graft needs to be biocompatible in the biological environment that it's going to be in. For example, a tissue that is compatible in subcutaneous tissue might not be so in a nerve. Reconstructive plastic surgeons are doctors that can help restore the function and appearance of skin after a major skin burn. These surgeons follow a strict procedure and use a variety of surgical techniques in order to safely implant the skin graft without any complications. Tissue engineered skin grafts serve to be a better solution for plastic surgeons compared to autografts or allografts when replacing damaged skin caused by burns.

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2. Characteristics of skin burns, and the body's response to fighting them

Skin burns are defined as damage to the skin or other organic tissue caused by thermal trauma. They can either be minor or life-threatening medical problems that require immediate medical attention. Many factors can cause burns, such as overexposure to heat, high temperature solids and liquids, chemicals, electricity, and radiation such as sunburn and radioactivity. In addition to that, respiratory damage due to smoke inhalation is also considered a type of burn. The skin has three layers, the epidermis, dermis, and the subcutaneous tissue (hypodermis). Skin burns are characterized by how deep each layer of the skin is affected.

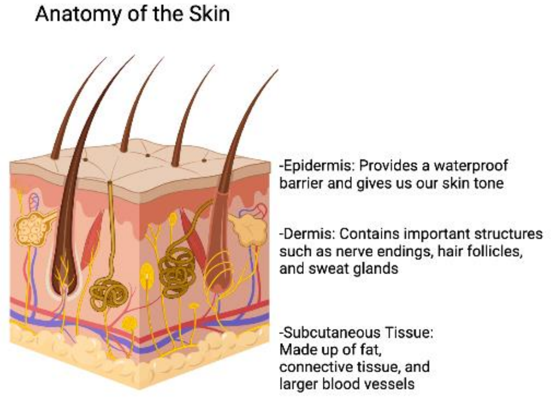

Figure 1. The Anatomy of the Skin. This image shows the different layers of the skin and their respective functions. The deeper the burn, the more severe it gets as various structures of the skin gets damaged leading to varioys symptoms.

2.1 The Different Degrees of Burns

Epidermal burns, also known as first-degree burns, are restricted to the epidermis. First-degree burns are not that critical and do not require immediate medical attention. These burns cause redness, swelling, and pain that goes away after 48-72 hours. They are known to heal rapidly and spontaneously with no visible scarring[2]. Second-degree burns, also known as partial-thickness burns, involve damage to the dermis. These burns often heal with scarring. The amount of scarring is determined by the severity of the burn. There are two types of second-degree burns, superficial partial-thickness burns and deep partial-thickness burns. The characteristics of superficial partial-thickness burns include damage to the papillary or the superficial upper layer of the dermis. Several blisters form around the area of the burn and the patient experiences lots of pain. These burns take anywhere between 14 to 21 days to heal. On the other hand, deep partial-thickness burns damage the lower layer of the dermis. Due to the depth of these burns, they take anywhere between 21-35 days to heal. Several blisters that are filled with fluid form, and the skin becomes severely painful and red[2]. Third-degree burns, also known as full-thickness burns, damage all three layers of the skin. The color of the skin turns red, bronze, or brown[2]. Since they destroy the nerves in the skin, third degree burns are less painful than second degree burns. If third degree burns manage to extend beneath the skin causing damage to fat, muscle, or bone tissues they are called full-thickness and/or fourth-degree burns. A first-degree skin burn heals quickly as the body replaces the burned skin cells of the epidermis with new cells. However, deep second and third-degree burns require skin grafts in order to restore the patient's skin.

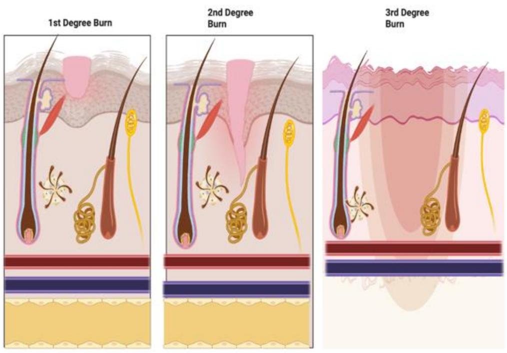

Figure 2. The Depth of Each Burn. This figure illustrates the depth of how each burn penetrates the different layers of the skin. First degree burns only damage the surface of the epidermis. A second degree burn is even more severe as it causes blistering and discoloration. Third degree burns penetrate all layers of the skin causing swelling and dry skin. These burns require immediate medical attention.

2.2 The Zones of a burn

The three main zones of a burn are the zone of coagulation, zone of stasis, and the zone of hyperaemia. The zone of coagulation is the point of maximum damage. Coagulation is defined as the process by which blood changes from a liquid to a gel, forming a blood clot. In the zone of coagulation there is irreparable tissue loss due to the coagulation of essential proteins. The zone of stasis is adjacent to the zone of coagulation and there is decreased tissue perfusion, which is the delivery of oxygen and nutritional supply through blood flow[3]. Burn resuscitation focuses on increasing blood flow to this area and minimizing the size of it. In addition to that, in this zone the tissue has the capability to be saved and repaired. The zone of hyperaemia has increased tissue perfusion due to vasodilation induced by mediators[4]. The tissue in this zone has good chances of recovery unless there is severe sepsis or prolonged hypoperfusion.

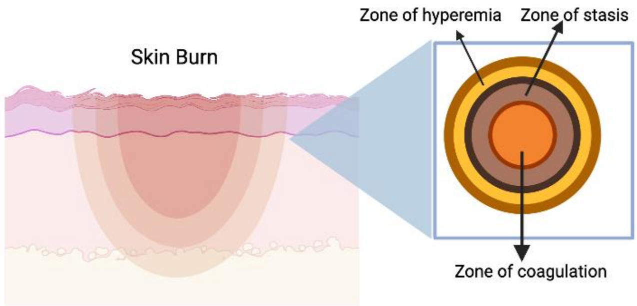

Figure 3. The zones of a burn. The figure above shows where each zone is in a skin burn. The zone of coagulation is always at the center of the burn. The zone of stasis surrounds the zone of coagulation and the zone of hyperemia surrounds the zone of stasis.

It's important to note that the three zones of a burn are three dimensional. The loss of tissue in the zone of stasis can lead to wound deepening and widening. In addition to that, the body goes through various systemic changes after a burn injury[5]. To further explain, At the site of the burn, the release of cytokines and other inflammatory mediators come into play in order to decrease the effects of the burn. Due to the increase in inflammatory mediators, bronchoconstriction occurs in the lungs. When it comes to cardiovascular changes, capillary permeability is increased and myocardial contractility is decreased. Along with these changes, fluid loss from the burn results in systemic hypotension and end organ hypoperfusion[5]. A patient will be required to get a skin graft implantation if the cells needed to repair the skin have been lost or damaged. Skin grafts can help reduce infection and scarring, have the ability to reduce the amount of fluid loss, and decrease the duration of hospitalization.

3. Tissue engineered skin serving as a replacement to traditional methods

One of the primary functions of the skin is to protect us from foreign substances. When the skin gets damaged due to a burn or a wound, keratinocytes play a vital role in skin repair. They execute the re-epithelialization process, in which keratinocytes migrate, proliferate, and differentiate to restore the epithelium[6]. However, the majority of the keratinocytes die off when there is a burn or a wound that extends deep through the skin, damaging several layers. When this happens, a skin graft is necessary to repair the damaged area. Deep dermal wounds and burns heal slowly and poorly when there are little to no keratinocytes. In this scenario, an autograft will be suitable to replace the damaged skin. An autograft is when a patient's own skin tissue is borrowed from one part of the body (such as the inner thighs or buttocks) and implanted at the wound site. Autografts that include a full epidermis and a partial dermis are known as split-thickness grafts. On the other hand, an allograft is a skin graft that is donated from another person and is used on the patient[6]. These approaches are still used today in many medical settings, but they do have many disadvantages such as pain, infection at the donor or the recipient site, and a high risk of graft rejection. In addition to that, split-thickness grafts are prone to increased graft contraction and hypertrophic scarring. Donor sites may be limited for those who decide to go with split-thickness grafts, especially if they have extensive burns[7]. Tissue-engineered skin grafts solve these problems since they have the ability to accelerate wound-healing processes by releasing cytokines and growth factors at the wound site. Furthermore, tissue engineered skin acts as a bioactive wound dressing, and promotes the functioning of the wound. It takes as long as three weeks to produce an autologous epidermal graft using autologous keratinocytes and the patient's skin biopsy. In contrast, the use of biomaterials in tissue engineered skin reduces the time needed for production of a skin graft tremendously.

3.1 The components & characteristics of Tissue Enginnered Skin

A skin graft should have five major characteristics. It should be sterile (free from bacteria), act as a barrier, have low inflammatory response, provide no local or systemic toxicity, and allow water vapor transmission. Furthermore, tissue engineered skin grafts should conform to the wound surfaces when implanted and facilitate angiogenesis[6]. The graft should be able to carry out all the necessary skin functions such as thermoregulation, preventing loss of moisture, protecting the body from UV radiation, etc. Tissue engineered skin serves to be effective in closing full-thickness burns that are greater than 50% of the total burn surface area due to both their epidermal and dermal components. There are three types of tissue engineered skin: (a) cultured epidermal cells with no dermal components; (b) with only dermal components; or (c) a bilayer containing both dermal and epidermal components[6]. All tissue engineered skin consists of scaffolds. Scaffolds serve an important role of restoring, maintaining, and improving the function of the tissue. They are made up of naturally occurring degradable, or non-degradable polymeric materials.

3.1 Biomaterials in Tissue Engineered Skin

Biomaterials also play a major role in the creation of skin grafts. There are two types of biomaterials, natural polymers and synthetic polymers. Natural polymers include collagen, gelatin, chitosan, fibrin, and hyaluronic acid (HA). These naturally occurring polymers can restore the functionality of the extracellular matrix (ECM) and provide the best healing process for severe wounds. They are able to do this since they have certain characteristics such as low antigenicity, good biodegradability, and low toxicity. Type I collagen is an essential protein that is part of the dermis. It is known to improve skin elasticity, hydration, and overall quality of the skin by minimizing wrinkles. Chitosan is another important natural polymer in tissue engineered skin, as it is obtained when chitin is deacetylated. The structure of chitosan is very similar to glycosaminoglycans (GAGs), and it is responsible for accelerating the growth of keratinocytes and supporting fibroblasts. Hyaluronic acid (HA) is a linear polysaccharide that is used in the ECM since it contains β-1,4-linked D-glucuronic acid and β-1,3-linked *N*-acetyl-D-glucosamine disaccharide units[6]. Various scientists and researchers have developed skin grafts using natural polymers. For example, Matsumine et al. applied a fibroblast growth factor-impregnated collagen-gelatin sponge in order to treat patients with full-thickness skin defects. By doing so, the patient's wound was able to close off quickly without any complications. Along with natural polymers, synthetic polymers are also used in order to create tissue engineered skin. Some synthetic polymers include polyethyleneglycol (PEG), polylactic-co-glycolic acid (PLGA), polylactide (PLA), and polyurethane (PU),[8]. These synthetic polymers have to be combined with natural polymers in order to produce materials that are biocompatible to the skin. To further explain this process, scientists such as Sobhanian et al. implemented the electrospinning technique to produce a collagen-grafted poly(vinyl alcohol)/gelatin/alginate skin substitute. By doing so, they were able to increase its biocompatibility and wound healing properties[9]. To add on, Haldar et al. produced a trilayer acellular dermo-epidermal PCL/gelatin scaffold that had the same characteristics and properties of the actual layers of the skin. Once tissue engineered skin is made, next comes the responsibility of the plastic surgeon in order to safely implant the skin graft without any complications in order to achieve the best cosmetic result.

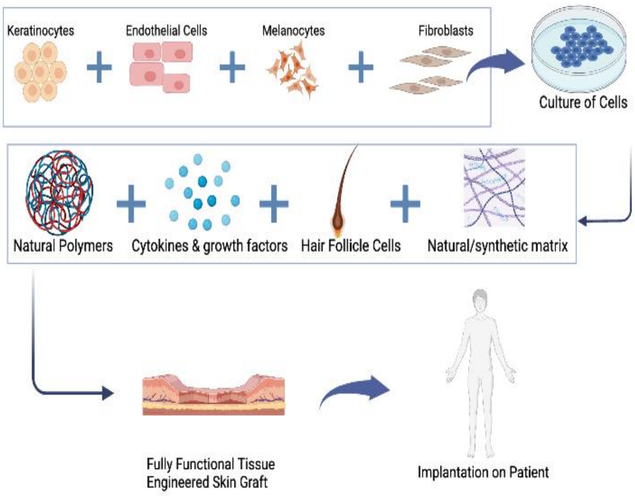

Figure 4. Process of creating tissue engineered skin. This figure outlines the specific components that go into the making of tissue engineered skin. Each of these components are crucial in order to create biocompatible skin that can carry out necessary functions just like normal skin. Figure created and copyrighted by Rishabh Katla using biorender.com

4. How plastic surgeons use tissue engineered skin to replace damaged skin

Plastic surgery is the branch of medicine that deals with the restoration and reconstruction of the human body[10]. The word plastic is derived from the word "*plastikos*" which means "to mold." Plastic surgeons operate on soft tissue, which includes skin, muscle, and fat. Plastic surgery is divided into two areas, cosmetic plastic surgery and reconstructive plastic surgery. Cosmetic plastic surgery focuses on enhancing the appearance of the patient. Some cosmetic procedures include breast augmentation, rhinoplasty, and liposuction. On the other hand, reconstructive plastic surgery focuses on correcting facial and body abnormalities caused by birth defects, injury, and disease.

4.1 How tissue-engineered skin serves to be a solution for plastic surgeons compared to other solutions

It is essential for tissue-engineered skin to have a bilayer structure composed of insoluble dermal extracellular matrix components followed by cultured epidermal cells. The extracellular matrix contains fibroblast embedded collagen gel scattered among glycosaminoglycan and hyaluronic acid. These important components make up the bulk of synthetic skin, which for plastic surgeons, serve to be an effective solution to cover up open wounds. The common solution for plastic surgeons when it comes to covering up such wounds caused by burns are topical antibiotic dressings and porcine skin. Nonetheless, the use of a xenograft (a graft from the donor of a different species from the recipient) has been limited due to intense foreign body reaction, eventual rejection, and an increased risk of graft infection. Fortunately, tissue-engineered skin proves itself to be a unique solution for plastic surgeons as it shows a significant reduction in the partial-thickness burn healing rate and hospitalization in a clinical trial.

4.2 Procedure used to implant tissue engineered skin

Implanting the tissue engineered skin onto patients is a long and complicated process for plastic surgeons. Many steps can be modified or improved based on the type of skin substitute used or the type of patient, whether it be a pediatric or a geriatric patient. The first step before the surgery takes place is to identify any causes that may prevent the tissue engineered skin from attaching to the burn site. These may include poor blood supply to the burn site, exposed burn or nerve, and insufficient soft tissue coverage with exposed tendon[11]. After this, the surgeon should remove all non-viable tissues using biological, hydro-surgical, and/or chemical techniques. In addition to that, it's also important to thoroughly clean the wound where the tissue engineered skin is going to be placed. By doing so, no bacteria or harmful pathogen can grow causing a disease or infection. Once the tissue engineered skin is prepared, it should be contoured or carved to the size of the wound. To begin the surgery, the patient should be placed on the operating room table in a supine position[11]. After that, the surgeon should place the tissue engineered skin parallel to the wound in order to prevent any complications in the future. Once done so, plastic surgeons should choose the simplest closure technique in order to produce the best cosmetic result. They may choose to use either sutures, surgical staples, or adhesive strips to secure the skin. When using sutures, the surgeon will suture the artificial skin with the help of sutures such as chromic gut, nylon, or basting sutures. When using a basting suture it's important to allow some time for homeostasis by bleeding to take place caused by the suture placement. After this step, a bolster dressing is placed over the tissue engineered skin to ensure contact with the recipient bed and to connect with the surrounding blood supply[12]. Once the surgery is complete, the patient can remove the dressing after one week. After two weeks, non-absorbable sutures can be removed if they were used.

Conclusion and Outlook

It can be seen from this paper that skin burns can have a detrimental impact on one's health and emotional well-being. Deep 2nd and 3rd degree burns have the capability to damage various structures of the skin, such as the blood vessels, nerves, hair follicles, lymphatic vessels, etc. This damage can lead to huge amounts of pain, discomfort, and hairloss of the skin. As these burns continue to affect thousands of people across the world, it's important to note that tissue engineered skin serves to be a better option compared to traditional methods such as autografts or allografts. Tissue engineered skin is an efficient and safe solution in order to replace damaged skin. Compared to skin grafts such as allografts, autografts, or xenografts, tissue engineered skin rapidly accelerates the wound-healing processes due the various biomaterials it is composed of, and it offers a complete regeneration of human skin. In addition to that, reconstructive plastic surgeons prefer implanting tissue engineered skin than xenografts since tissue engineered skin greatly reduces hospitalization and the healing time after a burn. Furthermore, reconstructive plastic surgeons follow a step by step process to implant the tissue engineered skin in an effective way in order to fully replace the damaged skin. As tissue engineering is a rapidly growing field, it has a great potential to revolutionize regenerative and personalized medicine. From functional organs to personalized medical treatments, it is a field that has the capability to make a powerful impact on every patient.

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Keywords: Tissue Engineering• Plastic Surgery• Skin Burns • Skin Substitutes

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