# INTRODUCTION

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Patients frequently seek cosmetic improvement for existing scars. While no scar can be completely erased, dermatologic surgeons can employ a variety of approaches to achieve more esthetically pleasing scars. Classification of a scar abnormality guides the choice of treatment technique. Lasers and injectables are useful tools; however, for certain scar abnormalities, scalpel-based surgery remains the mainstay.[1]

## Anatomy and histology of the skin contents

The skin is considered the largest organ of the body and has many different functions. The skin functions in thermoregulation, protection, metabolic functions and sensation. The skin is divided into two main regions, the epidermis, and the dermis, each providing a distinct role in the overall function of the skin. The dermis is attached to an underlying hypodermis, also called subcutaneous connective tissue, which stores adipose tissue and is recognized as the superficial fascia of gross anatomy.[2]

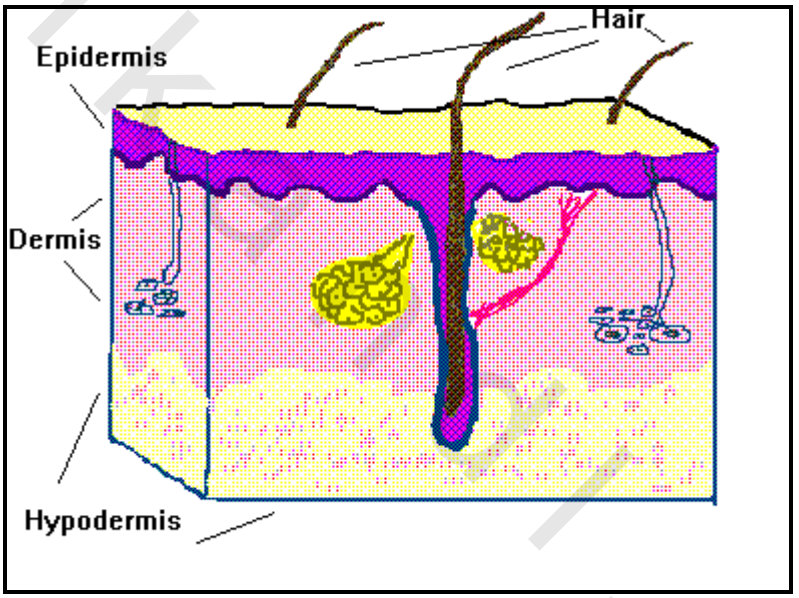


**Figure (1):** Anatomy and Histology of the Skin Contents.[2]

The epidermis is the most superficial layer of the skin and provides the first barrier of protection from the invasion of foreign substances into the body. The principal cell of the epidermis is called a keratinocyte. The epidermis is subdivided into five layers or strata, the stratum germinativum (**SG**), the stratum spinosum (**SS**), the stratum granulosum (**SGR**), the stratum lucidum(not seen in this photomicrograph) and the stratum corneum (**SC**) in which a keratinocyte gradually migates to the surface and is sloughed off in a process called desquamation.[2]

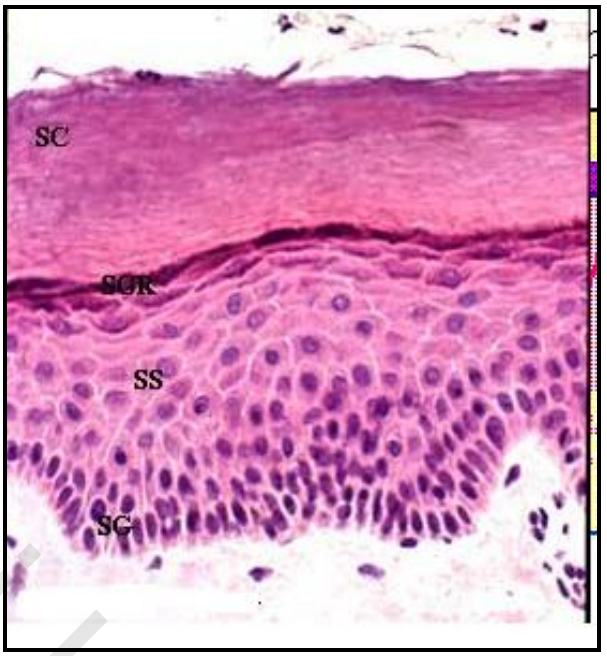


**Figure (2):** Anatomy and Histology of the Skin Contents.[2]

The stratum germinatum(SG) provides the germinal cells necessary for the regeneration of the layers of the epidermis. These germinal cells are separated from the dermis by a thin layer of basement membrane. After a mitotic division a newly formed cell will undergo a progressive maturation called keratinization as its migrates to the surface.[2]

The cells that divide in the statum germinativum soon begin to accumulate many desmosomes on their outer surface which provide the characteristic prickles of the stratum spinosum (**SS**), which is often called the prickle-cell layer.[2]

The progressive maturation of a keratinocyte is characterized by the accumulation of keratin, called keratinization. The cells of the stratum granulosum (**SGR**) accumlate dense basophilic keratohyalin granules. These granules contain lipids, which along with the desmosomal connections, help to form a waterproof barrier that functions to prevent fluid loss from the body.[2]

Epidermis varies in thickness throughout the body depending mainly on frictional forces and is thickest on the palms of the hands and soles of the feet. The stratum lucidum is normally only well seen in thick epidermis and represents a transition from the stratum granulosum to the stratum corneum.[2]

As a cell accumulates keratinohyalin granules, it is thought that rupture of lysosomal membranes release lysosomal enzymes that eventually cause cell death. The dead and dying cells filled with mature keratin form the stratum corneum (**SC**). The deeper cells of the stratum corneum retain their desmosomal junctions, but as they are pushed to the surface by newly forming cells of the stratum germinativum (**SG**), the dead cells gradually break apart and are lost, a process called desquamation.[2]

The dermis (**D**) assumes the important functions of thermoregulation and supports the vascular network to supply the avascular epidermis with nutrients. The dermis is typically subdivided into two zones, a papillary dermis and a reticular layer. The dermis contains mostly fibroblasts which are responsible for secreting collagen, elastin and ground substance that give the support and elasticity of the skin. Also present are immune cells that are involved in defense against foreign invaders passing through the epidermis.[2]

The papillary dermis (**PD**) contains vascular networks that have two important functions. The first being to support the avascular epidermis with vital nutrients and secondly to provide a network for thermoregulation. The vasculature is organized so that by increasing or decreasing blood flow, heat can either be conserved or dissipated. The vasculature interdigitates in areas called dermal papillae (**DP**). The papillary dermis also contains the free sensory nerve endings and structures called Meissners corpuscles in highly sensitive areas.[2]

The reticular layer of the dermis (**RD**) consists of dense irregular connective tissue, which differs from the papillary layer (**PD**), which is made up of mainly loose connective tissue. The reticular layer of the dermis is important in giving the skin it overall strength and elasticity, as well as housing other important epithelial derived structures such as glands and hair follicles.[2]

A wound by true definition is a breakdown in the protective function of the skin; the loss of continuity of epithelium, with or without loss of underlying connective tissue (i.e. muscle, bone, nerves)[3] following injury to the skin or underlying tissues/ organs caused by surgery, a blow, a cut, chemicals, heat/ cold, friction/ shear force, pressure or as a result of disease, such as leg ulcers or carcinomas.[4]

Wounds heal by primary intention or secondary intention depending upon whether the wound may be closed with sutures or left to repair, whereby damaged tissue is restored by the formation of connective tissue and re-growth of epithelium.[5]

Wound healing is a complex and dynamic process of replacing devitalized and missing cellular structures and tissue layers. The human adult wound healing process can be divided into 3 or 4 distinct phases. Earlier authors referred to 3 phases: inflammatory, fibroblastic, and maturation,[6] which had been denoted in earlier versions as inflammatory, proliferative, and remodeling and this is maintained by some authors.[7] In the 4-phases concept, there are the hemostasis phase, the inflammatory phase, the proliferative phase, and the remodeling phase. In the 3-phases approach, the hemostasis phase is contained within the inflammatory phase.

Not only do authors vary the number of phases, but authors also denote differences in the phase descriptors used as: hemostasis phase, inflammatory phase, proliferative phase, and remodeling phase[8] or hemostasis phase, inflammatory phase, proliferative phase, and maturation phase.[9] Therefore, certain phases have more than one name, such as remodeling or maturation and proliferation or granulation.[10]

**Table (1): Normal Wound-healing Process.**[11]

| Phase | Cellular and Bio-physiologic Events |
|---|---|
| **Hemostasis** | 1. Vascular constriction<br>2. Platelet aggregation, degranulation, and fibrin formation (thrombus) |
| **Inflammation** | 1. Neutrophil infiltration<br>2. Monocyte infiltration and differentiation to macrophage<br>3. Lymphocyte infiltration |
| **Proliferation** | 1. Re-epithelialization<br>2. Angiogenesis<br>3. Collagen synthesis<br>4. ECM formation |
| **Remodeling** | 1. Collagen remodeling<br>2. Vascular maturation and regression |

# Phases of wound healing

The first phase of **hemostasis** begins immediately after wounding, with vascular constriction and fibrin clot formation. The clot and surrounding wound tissue release pro-inflammatory cytokines and growth factors such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF). Once bleeding is controlled, inflammatory cells migrate into the wound (chemotaxis) and promote **the inflammatory** phase, which is characterized by the sequential infiltration of neutrophils, macrophages, and lymphocytes [12-14] A critical function of neutrophils is the clearance of invading microbes and cellular debris in the wound area, although these cells also produce substances such as proteases and reactive oxygen species (ROS), which cause some additional bystander damage.

Macrophages play multiple roles in wound healing. In the early wound, macrophages release cytokines that promote the inflammatory response by recruiting and activating additional leukocytes. Macrophages are also responsible for inducing and clearing apoptotic cells (including neutrophils), thus paving the way for the resolution of inflammation. As macrophages clear these apoptotic cells, they undergo a phenotypic transition to a reparative state that stimulates keratinocytes, fibroblasts, and angiogenesis to promote tissue regeneration.[15,16] In this way, macrophages promote the transition to the proliferative phase of healing.

T-lymphocytes migrate into wounds following the inflammatory cells and macrophages, and peak during the late-proliferative/early-remodeling phase. The role of T-lymphocytes is not completely understood and is a current area of intensive investigation. Several studies suggest that delayed T-cell infiltration along with decreased T-cell concentration in the wound site is associated with impaired wound healing, while others have reported that CD 4+ cells (T-helper cells) have a positive role in wound healing and CD8+ cells (T-suppressor-cytotoxic cells) play an inhibitory role in wound healing.[17-18] Interestingly, recent studies in mice deficient in both T- and B-cells have shown that scar formation is diminished in the absence of lymphocytes.[19]

In addition, skin gamma-delta T-cells regulate many aspects of wound healing, including maintaining tissue integrity, defending against pathogens, and regulating inflammation. These cells are also called dendritic epidermal T-cells (DETC), due to their unique dendritic morphology. DETC are activated by stressed, damaged, or transformed keratinocytes and produce fibroblast growth factor 7 (FGF-7), keratinocyte growth factors, and insulin-like growth factor-1, to support keratinocyte proliferation and cell survival. DETC also generate chemokines and cytokines that contribute to the initiation and regulation of the inflammatory response during wound healing. While cross-talk between skin gamma-delta T-cells and keratinocytes contributes to the maintenance of normal skin and wound healing, mice lacking or defective in skin gamma-delta T-cells show a delay in wound closure and a decrease in the proliferation of keratinocytes at the wound site.[20,21]

**The proliferative** phase generally follows and overlaps with the inflammatory phase, and is characterized by epithelial proliferation and migration over the provisional matrix within the wound (re-epithelialization). In the reparative dermis, fibroblasts and endothelial cells are the most prominent cell types present and support capillary growth, collagen formation, and the formation of granulation tissue at the site of injury. Within the wound bed, fibroblasts produce collagen as well as glycosaminoglycans and proteoglycans, which are major components of the extracellular matrix (ECM). Following robust proliferation and ECM synthesis, wound healing enters the final **remodeling** phase, which can last for years. In this phase, regression of many of the newly formed capillaries occurs, so that vascular density of the wound returns to normal. One critical feature of the remodeling phase is ECM remodeling to an architecture that approaches that of the normal tissue. The wound also undergoes physical contraction throughout the entire wound-healing process, which is believed to be mediated by contractile fibroblasts (myofibroblasts) that appear in the wound.[13-14]

The role of stem cells (SC) in cutaneous wound healing and tissue regeneration is a topic of increasing research attention, with a focus on the role of adult stem cells such as epidermal stem cells and bone-marrow (BM)-derived cells (BMDCs). Epidermal stem cells reside in the bulge area of hair follicles and in the basal layer of the epidermis and give rise to the keratinocytes that migrate and re-epithelialize wounds. Normal skin is also a target organ for BMDCs. Two main stem cell populations are present in the bone marrow: hematopoietic SC (HSC) and mesenchymal SC (MSC). BM-MSCs are able to differentiate into a variety of cell types, including adipocytes, osteoblasts, chondrocytes, fibroblasts, and keratinocytes.[22,23] Endothelial progenitor cells (EPCs) derived from the HSC lineage are key cells that contribute to neovascularization. Both BM-MSCs and EPCs are involved in the cutaneous wound-healing process. Wound-induced hypoxia triggers the mobilization of bone marrow EPCs to the circulation, playing a significant role in the process of neovascularization.[23-25]

Several different cell types are involved in the wound-healing process, and, as described above, the cellular activities of any particular cell type may also vary during different stages of repair. The complexity and coordination of the healing process are major hurdles to therapeutic approaches, since any therapeutic must effectively be sequenced to the appropriate stage.

# Factors affecting wound healing

Multiple factors can lead to impaired wound healing. In general terms, the factors that influence repair can be categorized into local and systemic. Local factors are those that directly influence the characteristics of the wound itself, while systemic factors are the overall health or disease state of the individual that affect his or her ability to heal.[26] Many of these factors are related, and the systemic factors act through the local effects affecting wound healing.

**Table (2): Factors Affecting Wound Healing.**

| Local Factors | Systemic Factors |
|---|---|
| • Oxygenation<br>• Infection<br>• Foreign body<br>• Venous sufficiency | • Age and gender<br>• Sex hormones<br>• Stress<br>• Ischemia<br>• Diseases: diabetes, keloids, fibrosis, hereditary healing disorders, jaundice, uremia<br>• Obesity<br>• Medications: glucocorticoid steroids, non-steroidal anti-inflammatory drugs, chemotherapy<br>• Alcoholism and smoking<br>• Immunocompromised conditions: cancer, radiation therapy, AIDS<br>• Nutrition |

# Local factors that influence healing

## Oxygenation

Oxygen is important for cell metabolism, especially energy production by means of ATP, and is critical for nearly all wound-healing processes. It prevents wounds from infection, induces angiogenesis, increases keratinocyte differentiation, migration, and re-epithelialization, enhances fibroblast proliferation and collagen synthesis, and promotes wound contraction [26,27] In addition, the level of superoxide production (a key factor for oxidative killing pathogens) by polymorphonuclear leukocytes is critically dependent on oxygen levels.

Due to vascular disruption and high oxygen consumption by metabolically active cells, the microenvironment of the early wound is depleted of oxygen and is quite hypoxic. Several systemic conditions, including advancing age and diabetes, can create impaired vascular flow, thus setting the stage for poor tissue oxygenation. In the context of healing, this overlay of poor perfusion creates a hypoxic wound. Chronic wounds are notably hypoxic; tissue oxygen tensions have been measured transcutaneously in chronic wounds from 5 to 20 mm Hg, in contrast to control tissue values of 30 to 50 mm Hg.[28]

In wounds where oxygenation is not restored, healing is impaired. Temporary hypoxia after injury triggers wound healing, but prolonged or chronic hypoxia delays wound healing.[26,27] In acute wounds, hypoxia serves as a signal that stimulates many aspects of the wound-healing process. Hypoxia can induce cytokine and growth factor production from macrophages, keratinocytes, and fibroblasts. Cytokines that are produced in response to hypoxia include PDGF, TGF-β, VEGF, tumor necrosis factor-α (TNF-α), and endothelin-1, and are crucial promoters of cell proliferation, migration and chemotaxis, and angiogenesis in wound healing.[27]

In normally healing wounds, ROS such as hydrogen peroxide ($H_2O_2$) and superoxide ($O^2$) are thought to act as cellular messengers to stimulate key processes associated with wound healing, including cell motility, cytokine action (including PDGF signal transduction), and angiogenesis. Both hypoxia and hyperoxia increase ROS production, but an increased level of ROS transcends the beneficial effect and causes additional tissue damage.[27]

In summary, the proper oxygen level is crucial for optimum wound healing. Hypoxia stimulates wound healing such as the release of growth factors and angiogenesis, while oxygen is needed to sustain the healing process.[26] One therapeutic option that can sometimes overcome the influence of tissue hypoxia is hyperbaric oxygen therapy.[27] While HBOT can be an effective treatment for hypoxic wounds, its availability is limited.

## Infections

Once skin is injured, micro-organisms that are normally sequestered at the skin surface obtain access to the underlying tissues. The state of infection and replication status of the micro-organisms determine whether the wound is classified as having contamination, colonization, local infection/critical colonization, and/or spreading invasive infection. Contamination is the presence of non-replicating organisms on a wound, while colonization is defined as the presence of replicating micro-organisms on the wound without tissue damage. Local infection/critical colonization is an intermediate stage, with micro-organism replication and the beginning of local tissue responses. Invasive infection is defined as the presence of replicating organisms within a wound with subsequent host injury.[29]

Inflammation is a normal part of the wound-healing process, and is important to the removal of contaminating micro-organisms. In the absence of effective decontamination, however, inflammation may be prolonged, since microbial clearance is incomplete. Both bacteria and endotoxins can lead to the prolonged elevation of pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF-α and elongate the inflammatory phase. If this continues, the wound may enter a chronic state and fail to heal. This prolonged inflammation also leads to an increased level of matrix metalloproteases (MMPs), a family of proteases that can degrade the ECM. In tandem with the increased protease content, a decreased level of the naturally occurring protease inhibitors occurs. This shift in protease balance can cause growth factors that appears in chronic wounds to be rapidly degraded.[29,30] Similar to other infective processes, the bacteria in infected wounds occur in the form of biofilms, which are complex communities of aggregated bacteria embedded in a self-secreted extracellular polysaccharide matrix.[29] Mature biofilms develop protected microenvironments and are more resistant to conventional antibiotic treatment. *Staphylococcus aureus* (*S.aureus*), *Pseudomonas aeruginosa* (*P.aeruginosa*), and β-hemolytic*streptococci* are common bacteria in infected and clinically non-infected wounds.[29,31]

*P. aeruginosa* and *Staphylococcus* appear to play an important role in bacterial infection in wounds. Many chronic ulcers probably do not heal because of the presence of biofilms containing *P. aeruginosa*, thus shielding the bacteria from the phagocytic activity of invading polymorphonuclear neutrophils (PMNs). This mechanism may explain the failure of antibiotics as a remedy for chronic wounds.[32]

# Systemic factors that influence healing

## Age

The elderly population (people over 60 years of age) is growing faster than any other age group (World Health Organization [WHO, www.who.int/topics/ageing]), and increased age is a major risk factor for impaired wound healing. Many clinical and animal studies at the cellular and molecular level have examined age-related changes and delays in wound healing. It is commonly recognized that, in healthy older adults, the effect of aging causes a temporal delay in wound healing, but not an actual impairment in terms of the quality of healing.[14-33] Delayed wound healing in the aged is associated with an altered inflammatory response, such as delayed T-cell infiltration into the wound area with alterations in chemokine production and reduced macrophage phagocytic capacity.[17] Delayed re-epithelialization, collagen synthesis, and angiogenesis have also been observed in aged mice as compared with young mice.[17] Overall, there are global differences in wound healing between young and aged individuals. A review of the age-related changes in healing capacity demonstrates that every phase of healing undergoes characteristic age-related changes, including enhanced platelet aggregation, increased secretion of inflammatory mediators, delayed infiltration of macrophages and lymphocytes, impaired macrophage function, decreased secretion of growth factors, delayed re-epithelialization, delayed angiogenesis and collagen deposition, reduced collagen turnover and remodeling, and decreased wound strength.[14]

Several treatments to reduce the age-related impairment of healing have been studied. Interestingly, exercise has been reported to improve cutaneous wound healing in older adults as well as aged mice, and the improvement is associated with decreased levels of pro-inflammatory cytokines in the wound tissue. The improved healing response may be due to an exercise-induced anti-inflammatory response in the wound.[33,34]

## Sex hormones in aged individuals

Sex hormones play a role in age-related wound-healing deficits. Compared with aged females, aged males have been shown to have delayed healing of acute wounds. A partial explanation for this is that the female estrogens (estrone and 17β-estradiol), male androgens (testosterone and 5α-dihydrotestosterone, DHT), and their steroid precursor dehydroepiandrosterone (DHEA) appear to have significant effects on the wound-healing process.[35] It was recently found that the differences in gene expression between elderly male and young human wounds are almost exclusively estrogen-regulated.[36] Estrogen affects wound healing by regulating a variety of genes associated with regeneration, matrix production, protease inhibition, epidermal function, and the genes primarily associated with inflammation.[36] Studies indicate that estrogen can improve the age-related impairment in healing in both men and women, while androgens regulate cutaneous wound healing negatively.[35]

## Stress

Stress has a great impact on human health and social behavior. Many diseases-such as cardiovascular disease, cancer, compromised wound healing, and diabetes-are associated with stress. Numerous studies have confirmed that stress-induced disruption of neuroendocrine immune equilibrium is consequential to health.[37,38] The pathophysiology of stress results in the deregulation of the immune system, mediated primarily through the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal medullary axes or sympathetic nervous system.[39,40]

Studies in both humans and animals have demonstrated that psychological stress causes a substantial delay in wound healing. Caregivers of persons with Alzheimer's and students undergoing academic stress during examinations demonstrated delayed wound healing.[41] The hypothalamic-pituitary-adrenal and the sympathetic-adrenal medullary axes regulate the release of pituitary and adrenal hormones. These hormones include the adrenocorticotrophic hormones, cortisol and prolactin, and catecholamines (epinephrine and norepinephrine). Stress up-regulates glucocorticoids (GCs) and reduces the levels of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α at the wound site. Stress also reduces the expression of IL-1α and IL-8 at wound sites-both chemoattractants that are necessary for the initial inflammatory phase of wound healing.[39,40] Furthermore, GCs influence immune cells by suppressing differentiation and proliferation, regulating gene transcription, and reducing expression of cell adhesion molecules that are involved in immune cell trafficking.[42] The GC cortisol functions as an anti-inflammatory agent and modulates the Th1-mediated immune responses that are essential for the initial phase of healing. Thus, psychological stress impairs normal cell-mediated immunity at the wound site, causing a significant delay in the healing process.[39]

Stressors can lead to negative emotional states, such as anxiety and depression, which may in turn have an impact on physiologic processes and/or behavioral patterns that influence health outcomes. In addition to the direct influences of anxiety and depression on endocrine and immune function, stressed individuals are more likely to have unhealthy habits, which include poor sleep patterns, inadequate nutrition, less exercise, and a greater propensity for abuse of alcohol, cigarettes, and other drugs. All of these factors may come into play in negatively modulating the healing response.

The effects of stress on wound healing. Stress-impaired wound healing is mediated primarily through the hypothalamic-pituitary-adrenal, sympathetic-adrenal medullary axes, and psychological-response-induced unhealthy behaviors.

## Diabetes

Diabetes affects hundreds of millions of people worldwide. Diabetic individuals exhibit a documented impairment in the healing of acute wounds. Moreover, this population is prone to develop chronic non-healing diabetic foot ulcers (DFUs), which are estimated to occur in 15% of all persons with diabetes. DFUs are a serious complication of diabetes, and precede 84% of all diabetes-related lower leg amputations.[43] The impaired healing of both DFUs and acute cutaneous wounds in persons with diabetes involves multiple complex pathophysiological mechanisms. DFUs, like venous stasis disease and pressure-related chronic non-healing wounds, are always accompanied by hypoxia.[28] A situation of prolonged hypoxia, which may be derived from both insufficient perfusion and insufficient angiogenesis, is detrimental for wound healing. Hypoxia can amplify the early

inflammatory response, thereby prolonging injury by increasing the levels of oxygen radicals.[11] Hyperglycemia can also add to the oxidative stress when the production of ROS exceeds the anti-oxidant capacity.[44] The formation of advanced glycation end-products (AGEs) under hyperglycemia and the interaction with their receptors (RAGE) are associated with impaired wound healing in diabetic mice as well.[45] High levels of metalloproteases are a feature of diabetic foot ulcers, and the MMP levels in chronic wound fluid are almost 60 times higher than those in acute wounds. This increased protease activity supports tissue destruction and inhibits normal repair processes.[46,47]

Several dysregulated cellular functions are involved in diabetic wounds, such as defective T-cell immunity, defects in leukocyte chemotaxis, phagocytosis, and bactericidal capacity, and dysfunctions of fibroblasts and epidermal cells. These defects are responsible for inadequate bacterial clearance and delayed or impaired repair in individuals with diabetes.[47,48]

As mentioned above, hypoxia contributes to the compromised healing of DFUs, and diabetic wounds exhibit inadequate angiogenesis. Several studies that have investigated the mechanisms behind the decreased restoration of vasculature in diabetic wounds have implied that EPC mobilization and homing are impaired, and that the level of VEGF, the primary pro-angiogenic factor in wounds, is decreased in the diabetic state[43,49,50] Stem-cell-based therapies aimed at inducing EPCs or BM-MSCs have shown a promising outcome in diabetic non-healing wounds, both in animals and in clinical trials[23-25] In animal studies, therapeutic restoration of VEGF has been shown to improve repair outcomes significantly.[51,52]

The neuropathy that occurs in diabetic individuals probably also contributes to impaired wound healing. Neuropeptides such as nerve growth factor, substance P, and calcitonin gene-related peptide are relevant to wound healing, because they promote cell chemotaxis, induce growth factor production, and stimulate the proliferation of cells. A decrease in neuropeptides has been associated with DFU formation. In addition, sensory nerves play a role in modulating immune defense mechanisms, with denervated skin exhibiting reduced leukocyte infiltration.[47-53]

In summary, the impaired healing that occurs in individuals with diabetes involves hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization, high levels of metalloproteases, damage from ROS and AGEs, decreased host immune resistance, and neuropathy.

## Medications

Many medications, such as those which interfere with clot formation or platelet function, or inflammatory responses and cell proliferation have the capacity to affect wound healing. Here we review only the commonly used medications that have a significant impact on healing, including glucocorticoid steroids, non-steroidal anti-inflammatory drugs, and chemotherapeutic drugs.

## Glucocorticoid steroids

Systemic glucocorticoids (GC), which are frequently used as anti-inflammatory agents, are well-known to inhibit wound repair *via* global anti-inflammatory effects and suppression of cellular wound responses, including fibroblast proliferation and collagen synthesis. Systemic steroids cause wounds to heal with incomplete granulation tissue and reduced wound contraction.[54] Glucocorticoids also inhibit production of hypoxia-inducible factor-1

(HIF-1), a key transcriptional factor in healing wounds.[55] Beyond effects on repair itself, systemic corticosteroids may increase the risk of wound infection. While systemic corticosteroids inhibit wound repair, topical application produces quite different effects. Topical low-dosage corticosteroid treatment of chronic wounds has been found to accelerate wound healing, reduce pain and exudate, and suppress hyper granulation tissue formation in 79% of cases. While these positive effects are striking, careful monitoring is necessary to avoid a potential increased risk of infection with prolonged use.[56]

## Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are widely used for the treatment of inflammation and rheumatoid arthritis and for pain management. Low-dosage aspirin, due to its anti-platelet function, is commonly used as a preventive therapeutic for cardiovascular disease, but not as an anti-inflammatory drug.[57] There are few data to suggest that short-term NSAIDs have a negative impact on healing. However, the question of whether long-term NSAIDs interfere with wound healing remains open. In animal models, systemic use of ibuprofen has demonstrated an anti-proliferative effect on wound healing, resulting in decreased numbers of fibroblasts, weakened breaking strength, reduced wound contraction, delayed epithelialization,[58-60] and impaired angiogenesis.[61] The effects of low-dose aspirin on healing are not completely clear. Clinical recommendations suggest that, to avoid anti-platelet effects, individuals should discontinue NSAIDs for a time period equal to 4 to 5 times the half-life of drugs before surgery. Thus, the majority of surgical patients do not have significant NSAID activity at the time of wound repair. The exception may be those cardiac patients who must be maintained on low-dose aspirin due to severe risk of cardiovascular events.[57] In terms of the topical application of NSAIDs on the surfaces of chronic wounds, the local use of ibuprofen-foam provides moist wound healing, reduces persistent and temporary wound pain, and benefits chronic venous leg ulcer healing.[62]

## Chemotherapeutic drugs

Most chemotherapeutic drugs are designed to inhibit cellular metabolism, rapid cell division, and angiogenesis and thus inhibit many of the pathways that are critical to appropriate wound repair. These medications inhibit DNA, RNA, or protein synthesis, resulting in decreased fibroplasia and neovascularization of wounds.[54-63] Chemotherapeutic drugs delay cell migration into the wound, decrease early wound matrix formation, lower collagen production, impair proliferation of fibroblasts, and inhibit contraction of wounds.[54] In addition, these agents weaken the immune functions of the patients, and thereby impede the inflammatory phase of healing and increase the risk of wound infection. Chemotherapy induces neutropenia, anemia, and thrombocytopenia, thus leaving wounds vulnerable to infection, causing less oxygen delivery to the wound, and also making patients vulnerable to excessive bleeding at the wound site.

Impaired wound healing due to chemotherapeutic drugs such as adriamycin is most common when the drugs are administered pre-operatively or within 3 weeks post-operatively.[64] Additionally, low post-operative albumin levels, low post-operative hemoglobin, advanced stage of disease, and electrocautery use have all been reported as risk factors for the development of wound complications.[65]

A newer generation of tumor chemotherapeutics is the angiogenesis inhibitors, such as bevacizumab, which is an antibody fragment that neutralizes VEGF. These therapies work in conjunction with traditional chemotherapeutics to limit the blood supply to tumors, reducing their ability to grow. Wound-healing complications, including an increase in wound dehiscence, have been described in patients on angiogenesis inhibitors.[66] A caveat is that most patients on angiogenesis inhibitors are also on traditional chemotherapeutics, making it difficult to sort out whether angiogenesis inhibitors alone would perturb repair.[67] Nevertheless, current recommendations include discontinuation of angiogenesis inhibitors well in advance of any surgical procedures.

## Obesity

The prevalence of obesity continues to increase among adults, children, and adolescents in the United States, with more than 30% of adults and 15% of children and adolescents classified as obese in a recent survey (Centers for Disease Control and Prevention, CDC). Obesity is well-known to increase the risk of many diseases and health conditions, which include coronary heart disease, type 2 diabetes, cancer, hypertension, dyslipidemia, stroke, sleep apnea, respiratory problems, and impaired wound healing. Obese individuals frequently face wound complications, including skin wound infection, dehiscence, hematoma and seroma formation, pressure ulcers, and venous ulcers.[68] An increased frequency of wound complications has been reported for obese individuals undergoing both bariatric and non-bariatric operations.[69-71] In particular, a higher rate of surgical site infection occurs in obese patients. Many of these complications may be a result of a relative hypoperfusion and ischemia that occurs in subcutaneous adipose tissue. This situation may be caused by a decreased delivery of antibiotics as well. In surgical wounds, the increased tension on the wound edges that is frequently seen in obese patients also contributes to wound dehiscence. Wound tension increases tissue pressure, reducing microperfusion and the availability of oxygen to the wound.[68,69]

The increase in pressure ulcers or pressure-related injuries in obese individuals is also influenced by hypovascularity, since poor perfusion makes tissue more susceptible to this type of injury. In addition, the difficulty or inability of obese individuals to reposition themselves further increases the risk of pressure-related injuries. Moreover, skin folds harbor micro-organisms that thrive in moist areas and contribute to infection and tissue breakdown. The friction caused by skin-on-skin contact invites ulceration. Together, these factors predispose obese individuals to the development of impaired wound healing.[68-70]

In addition to local conditions, systemic factors also play an important role in impaired wound healing and wound complications in obese patients. Obesity can be connected to stress, anxiety, and depression, all situations which can cause an impaired immune response.[68]

The function of adipose tissue used to be considered as primarily caloric storage. However, more recent findings have documented that adipose tissue secretes a large variety of bioactive substances that are collectively named adipokines. Both adipocytes themselves as well as macrophages inside the adipose tissue are known to produce bioactive molecules including cytokines, chemokines, and hormone-like factors such as leptin, adiponectin, and resistin. Adipokines have a profound impact on the immune and inflammatory response. The negative influence of adipokines on the systemic immune response seems likely to influence the healing process,[72-74] although direct proof for this is

lacking. Impaired peripheral blood mononuclear cell function, decreased lymphocyte proliferation, and altered peripheral cytokine levels have been reported in obesity. Importantly, though, many of the obesity-related changes in peripheral immune function are improved by weight loss. The factors related to wound impairment in obesity are summarized in.[75-77]

**Table (3): Summary of Factors Related to Wound Impairment in Obesity.**

| Local Wound Conditions | Associated Diseases and Conditions | Factors Altering Immune and Inflammatory Responses |
|---|---|---|
| 1. Decreased vascularity in adipose tissue<br>2. Skin folds harbor micro-organisms<br>3. Friction caused by skin on skin<br>4. Increased wound tension<br>5. Increased tissue pressure<br>6. Hematoma and seroma formation<br>7. Venous hypertension | 1. Hard to reposition<br>2. Coronary heart disease<br>3. Atherosclerosis<br>4. Type 2 diabetes<br>5. Cancer<br>6. Hypertension<br>7. Dyslipidemia<br>8. Stroke<br>9. Respiratory problems | 1. Adipokines: leptin, adiponectin, resistin<br>2. Cytokines: TNF-alpha, IL-1, IL-6, IL-8, IL-10<br>3. Chemokines: IL-8, MCP-1, IP-10 |

## Alcohol Consumption

Clinical evidence and animal experiments have shown that exposure to alcohol impairs wound healing and increases the incidence of infection.[78,79] The effect of alcohol on repair is quite clinically relevant, since over half of all emergency room trauma cases involve either acute or chronic alcohol exposure.[80,81] Alcohol exposure diminishes host resistance, and ethanol intoxication at the time of injury is a risk factor for increased susceptibility to infection in the wound.[82] Studies have demonstrated profound effects of alcohol on host-defense mechanisms, although the precise effects are dependent upon the pattern of alcohol exposure (*i.e.*, chronic *vs*. acute alcohol exposure, amount consumed, duration of consumption, time from alcohol exposure, and alcohol withdrawal). A recent review on alcohol-induced alterations on host defense after traumatic injury suggested that, in general, short-term acute alcohol exposure results in suppressed pro-inflammatory cytokine release in response to an inflammatory challenge. The higher rate of post-injury infection correlates with decreased neutrophil recruitment and phagocytic function in acute alcohol exposure.[83]

Beyond the increased incidence of infection, exposure to ethanol also seems to influence the proliferative phase of healing. In murine models, exposure to a single dose of alcohol that caused a blood alcohol level of 100 mg/dL (just above the legal limit in most states in the US) perturbed re-epithelialization, angiogenesis, collagen production, and wound closure.[84-87] The most significant impairment seems to be in wound angiogenesis, which is reduced by up to 61% following a single ethanol exposure. This decrease in angiogenic capacity involves both decreased expression of VEGF receptors and reduced nuclear expression of HIF-1alpha in endothelial cells.[86] The ethanol-mediated decrease in wound vascularity causes increased wound hypoxia and oxidative stress.[85]

Connective tissue restoration is also influenced by acute ethanol exposure, and results in decreased collagen production and alterations in the protease balance at the wound site.[84] In summary, acute ethanol exposure can lead to impaired wound healing by impairing the early inflammatory response, inhibiting wound closure, angiogenesis, and collagen production, and altering the protease balance at the wound site.

As mentioned previously, the host response to chronic alcohol exposure appears to be different from that of acute alcohol exposure. Analysis of clinical data indicates that chronic alcohol exposure causes impaired wound healing and enhanced host susceptibility to infections, but the detailed mechanisms that explain this effect need more investigation.

## Smoking

It is well-known that smoking increases the risk of heart and vascular disease, stroke, chronic lung disease, and many kinds of cancers. Similarly, the negative effects of smoking on wound-healing outcomes have been known for a long time.[88-90] Post-operatively, patients who smoke show a delay in wound healing and an increase in a variety of complications such as infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and a decrease in the tensile strength of wounds.[91,90] In the realm of oral surgery, impaired healing in smokers has been noticed both in routine oral surgery and in the placement of dental implants.[92,93] Cosmetic outcomes also appear to be worse in smokers, and plastic and reconstructive surgeons are often reluctant to perform cosmetic surgeries on individuals who refuse to quit smoking.[88] Approximately over 4000 substances in tobacco smoke have been identified, and some have been shown to have a negative impact on healing.[90] Most studies have focused on the effects of nicotine, carbon monoxide, and hydrogen cyanide from smoke. Nicotine probably interferes with oxygen supply by inducing tissue ischemia, since nicotine can cause decreased tissue blood flow *via* vasoconstrictive effects.[90-94]

Nicotine stimulates sympathetic nervous activity, resulting in the release of epinephrine, which causes peripheral vasoconstriction and decreased tissue blood perfusion. Nicotine also increases blood viscosity caused by decreasing fibrinolytic activity and augmentation of platelet adhesiveness. In addition to the effects of nicotine, carbon monoxide in cigarette smoke also causes tissue hypoxia. Carbon monoxide aggressively binds to hemoglobin with an affinity 200 times greater than that of oxygen, resulting in a decreased fraction of oxygenated hemoglobin in the bloodstream. Hydrogen cyanide, another well-studied component of cigarette smoke, impairs cellular oxygen metabolism, leading to compromised oxygen consumption in the tissues. Beyond these direct tissue effects, smoking increases the individual's risk for atherosclerosis and chronic obstructive pulmonary disease, two conditions that might also lower tissue oxygen tension.[88-90]

Several cell types and processes that are important to healing have been shown to be adversely affected by tobacco smoke. In the inflammatory phase, smoking causes impaired white blood cell migration, resulting in lower numbers of monocytes and macrophages in the wound site, and reduces neutrophil bactericidal activity. Lymphocyte function, cytotoxicity of natural killer cells, and production of IL-1 are all depressed, and macrophage-sensing of Gram-negative bacteria is inhibited.[90-95] These effects result in poor wound healing and an increased risk of opportunistic wound infection.

During the proliferative phase of wound healing, exposure to smoke yields decreased fibroblast migration and proliferation, reduced wound contraction, hindered epithelial regeneration, decreased extracellular matrix production, and upset in the balance of proteases.[90]

Pharmacologically, the influence of smoking on wound healing is complicated, and neither nicotine alone nor any other single component can explain all of the effects of smoking on wounds. What is certain is that smoking cessation leads to improved repair and reduces wound infection.[94-96] For surgery patients who find it difficult to forego smoking, the use of a transdermal patch during the pre-operative period might be beneficial. A study has shown that the use of a transdermal nicotine patch as a nicotine replacement for smoking cessation therapy can increase type I collagen synthesis in wounds.[94] Despite the overall negative effects of smoking, some recent studies have suggested that low doses of nicotine enhance angiogenesis and actually improve healing.[97,98]

## Nutrition

For more than 100 years, nutrition has been recognized as a very important factor that affects wound healing. Most obvious is that malnutrition or specific nutrient deficiencies can have a profound impact on wound healing after trauma and surgery. Patients with chronic or non-healing wounds and experiencing nutrition deficiency often require special nutrients. Energy, carbohydrate, protein, fat, vitamin, and mineral metabolism all can affect the healing process.[99]

## Carbohydrates, protein, and amino acids

Together with fats, carbohydrates are the primary source of energy in the wound-healing process. Glucose is the major source of fuel used to create the cellular ATP that provides energy for angiogenesis and deposition of the new tissues.[100] The use of glucose as a source for ATP synthesis is essential in preventing the depletion of other amino acid and protein substrates.[99]

Protein is one of the most important nutrient factors affecting wound healing. A deficiency of protein can impair capillary formation, fibroblast proliferation, proteoglycan synthesis, collagen synthesis, and wound remodeling. A deficiency of protein also affects the immune system, with resultant decreased leukocyte phagocytosis and increased susceptibility to infection.[101] Collagen is the major protein component of connective tissue and is composed primarily of glycine, proline, and hydroxyproline. Collagen synthesis requires hydroxylation of lysine and proline, and co-factors such as ferrous iron and vitamin C. Impaired wound healing results from deficiencies in any of these co-factors.[13]

Arginine is a semi-essential amino acid that is required during periods of maximal growth, severe stress, and injury. Arginine has many effects in the body, including modulation of immune function, wound healing, hormone secretion, vascular tone, and endothelial function. Arginine is also a precursor to proline, and, as such, sufficient arginine levels are needed to support collagen deposition, angiogenesis, and wound contraction.[13-100] Arginine improves immune function, and stimulates wound healing in healthy and ill individuals.[102] Under psychological stress situations, the metabolic demand of arginine increases, and its supplementation has been shown to be an effective adjuvant therapy in wound healing.[13]

Glutamine is the most abundant amino acid in plasma and is a major source of metabolic energy for rapidly proliferating cells such as fibroblasts, lymphocytes, epithelial cells, and macrophages.[13-99] The serum concentration of glutamine is reduced after major surgery, trauma, and sepsis, and supplementation of this amino acid improves nitrogen balance and diminishes immunosuppression.[13] Glutamine has a crucial role in stimulating

the inflammatory immune response occurring early in wound healing.[99] Oral glutamine supplementation has been shown to improve wound breaking strength and to increase levels of mature collagen.[103]

## Fatty acids

Lipids are used as nutritional support for surgical or critically ill patients to help meet energy demands and provide essential building blocks for wound healing and tissue repair. Polyunsaturated fatty acids (PUFAs), which cannot be synthesized *de novo* by mammals, consist mainly of two families, n-6 (omega-6, found in soybean oil) and n-3 (omega-3, found in fish oil). Fish oil has been widely touted for the health benefits of omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The effects of omega-3 fatty acids on wound healing are not conclusive. They have been reported to affect pro-inflammatory cytokine production, cell metabolism, gene expression, and angiogenesis in wound sites.[104,105] The true benefit of omega-3 fatty acids may be in their ability to improve the systemic immune function of the host, thus reducing infectious complications and improving survival.[99]

## Vitamins, micronutrients, and trace elements

Vitamins C (L-ascorbic acid), A (retinol), and E (tocopherol) show potent anti-oxidant and anti-inflammatory effects. Vitamin C has many roles in wound healing, and a deficiency in this vitamin has multiple effects on tissue repair. Vitamin C deficiencies result in impaired healing, and have been linked to decreased collagen synthesis and fibroblast proliferation, decreased angiogenesis, and increased capillary fragility. Also, vitamin C deficiency leads to an impaired immune response and increased susceptibility to wound infection.[13,99] Similarly, vitamin A deficiency leads to impaired wound healing. The biological properties of vitamin A include anti-oxidant activity, increased fibroblast proliferation, modulation of cellular differentiation and proliferation, increased collagen and hyaluronate synthesis, and decreased MMP-mediated extracellular matrix degradation.[106]

Vitamin E, an anti-oxidant, maintains and stabilizes cellular membrane integrity by providing protection against destruction by oxidation. Vitamin E also has anti-inflammatory properties and has been suggested to have a role in decreasing excess scar formation in chronic wounds. Animal experiments have indicated that vitamin E supplementation is beneficial to wound healing,[99,106] and topical vitamin E has been widely promoted as an anti-scarring agent. However, clinical studies have not yet proved a role for topical vitamin E treatment in improving healing outcomes.[107]

Several micronutrients have been shown to be important for optimal repair. Magnesium functions as a co-factor for many enzymes involved in protein and collagen synthesis, while copper is a required co-factor for cytochrome oxidase, for cytosolic anti-oxidant superoxide dismutase, and for the optimal cross-linking of collagen. Zinc is a co-factor for both RNA and DNA polymerase, and a zinc deficiency causes a significant impairment in wound healing. Iron is required for the hydroxylation of proline and lysine, and, as a result, severe iron deficiency can result in impaired collagen production.[13,99,100]

As indicated above, the nutritional needs of the wound are complex, suggesting that composite nutrition support would benefit both acute and chronic wound healing. A recent clinical research study examined the effects of a high-energy, protein-enriched supplement

containing arginine, vitamin C, vitamin E, and zinc on chronic pressure ulcers and indicated that this high-energy and nutrition-enriched supplement improved overall healing of the pressure ulcer.[108] In summary, proteins, carbohydrates, arginine, glutamine, polyunsaturated fatty acids, vitamin A, vitamin C, vitamin E, magnesium, copper, zinc, and iron play a significant role in wound healing, and their deficiencies affect wound healing. Additional studies will be needed to fully understand how nutrition affects the healing response.

## Scars and their types

Scar formation is a necessary process for the healing of tissue after insult. However, abnormal or disturbed collagen production can cause poor restoration of the cutaneous surface and textural irregularities. A cosmetically acceptable scar is often level with the surrounding skin, a good color match, soft, and narrow. Favorable lines of closure are usually within or parallel to relaxed skin tension lines (RSTLs): lines due to dynamic action of the underlying musculature.[109] Preoperative planning and prevention are critical to achieving scar cosmesis.[110]

Abnormal scars usually fall into four etiologic categories: traumatic, poorly designed, poorly healed, and disease-related.

**Table (4): The different etiologies of poor scars.[111]**

| Category | Examples of causes |
|---|---|
| Traumatic or irregular wound creation | • Burn<br>• Laceration |
| Poorly designed | • Not parallel or within RSTs<br>• Lack of respect of facial landmarks<br>• Distortion of free margin e.g., lip or eyelid<br>• Long linear design<br>• Depressed scar from lack of evertional closure |
| Prior poor healing | • Infection<br>• Excess tension<br>• Necrosis or slough |
| Disease-related | • Acne<br>• Varicella<br>• keloidal |

**A keloid** is an abnormal proliferation of scar tissue that forms at the site of cutaneous injury (eg, on the site of a surgical incision or trauma); it does not regress and grows beyond the original margins of the scar. Keloids should not be confused with hypertrophic scars, which are raised scars that do not grow beyond the boundaries of the original wound and may reduce over time.[111] (Figure 3)

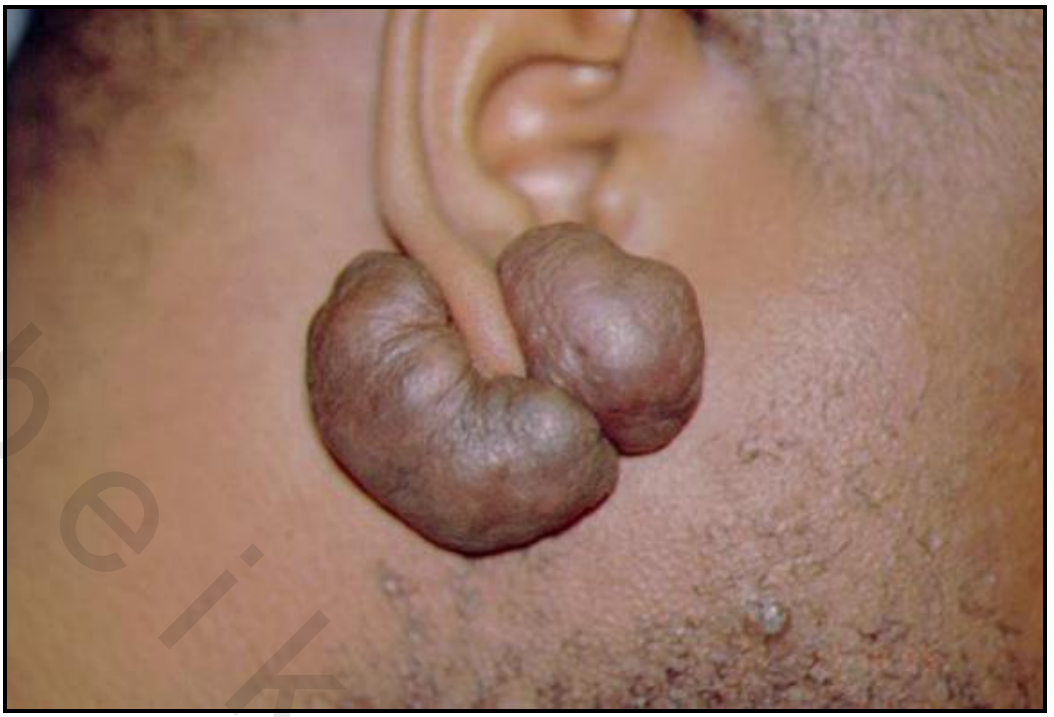

**Figure (3):** Ear lobe keloid scar from piercing.

Keloids are benign dermal fibroproliferative tumors with no malignant potential. The first description of abnormal scar formation in the form of keloids was recorded in the Smith papyrus regarding surgical techniques in Egypt around 1700 BC.[112] The term *keloid*, meaning "crab claw," was first coined by Alibert, in an attempt to illustrate the way the lesions expand laterally from the original scar into normal tissue.[113]

Keloids are found only in humans and occur in 5-15% of wounds. They tend to affect both sexes equally, although a higher incidence exists of women presenting with keloids, possibly secondary to the cosmetic implications associated with the disfigurement. The frequency of keloid occurrence in persons with highly pigmented skin is 15 times higher than in persons with less pigmented skin.[114] The average age at onset is 10-30 years. Persons at the extremes of age rarely develop keloids.

Studies have consistently demonstrated that persons of certain races are more susceptible to keloid scar formation. Individuals with darker pigmentation, black persons, and Asian persons are more likely to develop keloids.[114] In a random sampling of black individuals, as many as 16% have reported developing keloid scars, with an incidence rate of 4.5-16% in the black and Hispanic populations. White persons and albinos are least affected. Alhady's 1969 study found that Chinese individuals were more likely to develop keloids than Indian or Malaysian individuals.[114]

Some evidence supports a relationship between genetic predisposition and an individual's propensity to form keloid scars. Genetic associations for the development of abnormal scars have been found for HLA-B14, HLA-B21, HLA-BW16, HLA-BW35, HLA-DR5, HLA-DQW3, and blood group A.

Regions of the human genome highly correlated with keloid formation in 2 pedigrees with familial keloids have been recently identified. The regions identified were in 2 separate, unrelated locations on the human genome, underscoring the complex and multivariable pathogenesis of this disease.[115]

Keloids have a normal epidermal layer; abundant vasculature; increased mesenchymal density, as manifested by a thickened dermis; and increased inflammatory-cell infiltrate when compared with normal scar tissue. The reticular layer of the dermis consists mainly of collagen and fibroblasts, and injury to this layer is thought to contribute to formation of keloids. Collagen bundles in the dermis of normal skin appear relaxed and in an unordered arrangement; collagen bundles are thicker and more abundant in keloids, yielding acellular, nodelike structures in the deep dermal region. The most consistent histologic distinguishing characteristic of keloids is the presence of large, broad, closely arranged collagen fibers composed of numerous fibrils. In addition to collagen, proteoglycans are another major extracellular matrix (ECM) component deposited in excess amounts in keloid scars.

There are four histologic features that are consistently found in keloid specimens that are deemed pathognomonic for their diagnosis.[116] They are: 1) the presence of keloidal hyalinized collagen, 2) a tonguelike advancing edge underneath normal-appearing epidermis and papillary dermis, 3) horizontal cellular fibrous bands in the upper reticular dermis, and 4) prominent fascialike fibrous bands.[116]

In contrast, **hypertrophic scars** are characterized by erythematous, pruritic, raised fibrous lesions that typically do not expand beyond the boundaries of the initial injury and may undergo partial spontaneous resolution. Hypertrophic scars are common after thermal injuries and other injuries that involve the deep dermis.[117]

Unlike keloids, the hypertrophic scar reaches a certain size and subsequently stabilizes or regresses. Similar to keloids, hypertrophic scars are associated with adverse wound healing factors.[118]

No racial or familial preponderance occurs with hypertrophic scarring, unlike keloid formation. Scanning electron microscopy reveals flattened collagen bundles that are parallel in orientation. Similar to keloids, a higher percentage of type III collagen is present in these scars than in normal wounds. Hypertrophic scars are more likely to occur in the same anatomic locations as keloids (eg, mandibular border), presumably because of elevated tension in these areas.[118] (Figure 4).

**Widened scars** are wounds that separate during the healing process, usually in response to tension perpendicular to the wound edge.[120]

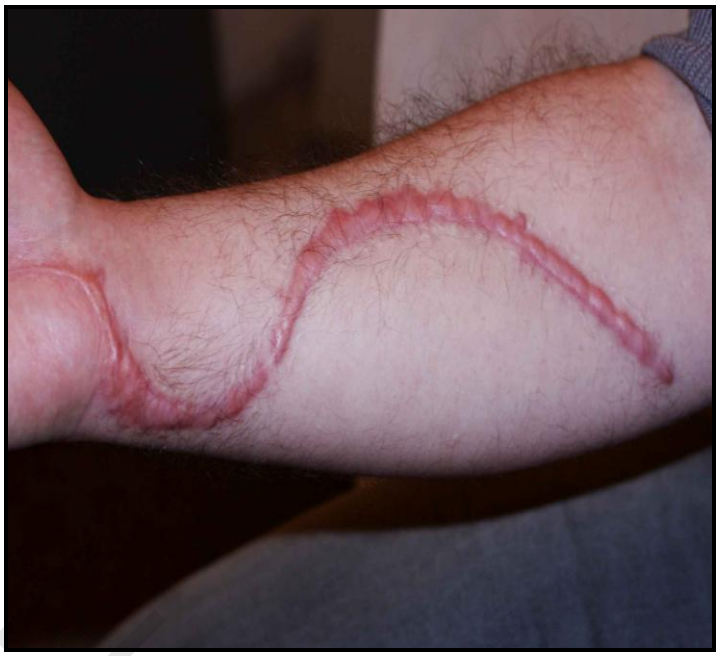

**Figure (4):** Hypertrophic scar in the volar aspect of forearm.

## Pathophysiology of scars

Hypertrophic scars and keloids can be described as variations of typical wound healing. In a typical wound, anabolic and catabolic processes achieve equilibrium approximately 6-8 weeks after the original injury. At this stage, the strength of the wound is approximately 30-40% that of healthy skin. As the scar matures, the tensile strength of the scar improves as a result of progressive cross-linking of collagen fibers. At this point, the scar is usually hyperemic and it may be thickened, but it tends to subside gradually over months until a flat, white, pliable, possibly stretched, mature scar has developed. When an imbalance occurs between the anabolic and catabolic phases of the healing process, more collagen is produced than is degraded, and the scar grows in all directions. The scar is elevated above the skin and remains hyperemic. Excessive fibrous tissue is classified as either a keloid or a hypertrophic scar.[117]

Kischer and Brody declared the collagen nodule is the identifying structural unit of hypertrophic scars and keloids.[119] The nodule, which is absent from mature scars, contains a high density of fibroblasts and unidirectional collagen fibrils in a highly organized and distinct orientation. In addition, keloids and hypertrophic scars differ from healthy skin by a rich vasculature, high mesenchymal cell density, and thickened epidermal cell layer. Attempts to clinically differentiate keloids from hypertrophic scars have proved to be difficult in the early phases of formation. Clinical differences become more apparent as lesions mature. The most consistent histologic difference is the presence of broad, dull, pink bundles of collagen (hyalinized bundles of collagen) in keloids, which are not present in hypertrophic scars.[119]

Widened scar formation is thought to result from wound edge separation with tension perpendicular to the healing skin wound. A state of tension exists naturally in skin; wounded skin gapes and becomes elliptical rather than round. Although Dupuytren first noted this property of skin, Langer received most of the credit.[121] Langer studied the direction of these ellipses by stabbing a round-tipped awl into hundreds of cadavers. When a wound is closed opposite to the lines of tension, the chance of widened scar formation is increased.

## Clinical presentation of scars

Keloids and hypertrophic scars do not usually cause symptoms, but they may be tender, painful, or pruritic or they may cause a burning sensation. In addition to symptomatic relief, cosmetic concern is the primary reason patients seek medical intervention.[117]

Keloids manifest as exaggerated growths of scar tissue, usually in areas of previous trauma. Keloids extend past the areas of trauma, projecting above the level of the surrounding skin, but they rarely extend into underlying subcutaneous tissue.[117]

Hypertrophic scars remain limited to the traumatized area and regress spontaneously within 12-24 months, although regression may not necessarily be complete.[117]

## Clinical findings in lesions

**Keloids** range in consistency from soft and doughy to rubbery and hard. Studies have demonstrated how to differentiate and classify keloids according to how they feel. Early lesions are often erythematous. Lesions become brownish red and then pale as they age. Lesions are usually devoid of hair follicles and other functioning adnexal glands.[117]

Once lesions occur, the clinical course varies. Most lesions continue to grow for weeks to months and others grow for years. Growth is usually slow, but keloids occasionally enlarge rapidly, tripling in size within months. Once they stop growing, keloids do not usually cause symptoms and remain stable or involute slightly.[117]

Keloids on the ears, neck, and abdomen tend to be pedunculated. Keloids on the central chest and extremities are usually raised with a flat surface, and the base is often wider than the top.[117]

Most keloids are round, oval, or oblong with regular margins; however, some have clawlike configurations with irregular borders. Keloids overlying a joint can contract and restrict movement.[117]

Most patients present with 1 or 2 keloids; however, a few patients, especially patients with spontaneous keloids, have multiple lesions, as do patients who develop keloids as a consequence of acne or chickenpox.[117]

Keloids may be distinguished from **hypertrophic scars** by their clawlike projections, which are absent in the hypertrophic scar.[117]

Different from hypertrophic and keloid scars, **widened scars** are flat and sometimes depressed. With adequate wound maturation, these wounds fade to the pigment of the surrounding uninjured skin. Widened scars are not usually red or pruritic.[120]

## Frequency of lesion sites

In white persons, keloids tend to be present, in decreasing order of frequency, on the face (with cheek and earlobes predominating), upper extremities, chest, presternal area, neck, back, lower extremities, breasts, and abdomen.[117]

In black persons, the descending order of frequency tends to be earlobes, face, neck, lower extremities, breasts, chest, back, and abdomen.[117]

In Asian persons, the descending order of frequency is earlobes, upper extremities, neck, breasts, and chest.[117]

The exact mechanisms of keloid and hypertrophic scar pathogenesis continue to be an enigma for physicians and researchers alike, and no specific gene or set of genes has been identified; however, the increased prevalence of keloids paralleling increased cutaneous pigmentation suggests a genetic basis or, at least, a genetic linkage. Trauma to the skin, both physical (eg, earlobe piercing, surgery) and pathological (eg, acne, chickenpox), is the primary cause identified for the development of keloids. The presence of foreign material, infection, hematoma, or increased skin tension can also lead to keloid or hypertrophic scar formation in susceptible individuals.[117]

Diagnosis is usually based on clinical findings. Biopsy may confirm the diagnosis in equivocal cases.[117]

# Histopathology of keloid and hypertrophic scar

Distinguishing between the two types of scars on histopathological basis is sometimes difficult as the 'keloid collagen', the hallmark of keloid, is not always present. Plus the α-smooth muscle actins, a differentiating marker of hypertrophic scar is variably expressed in both forms of scars. The morphological features and the expression of α-smooth muscle actins in myofibroblasts in the two conditions have been investigated. These results demonstrate that keloids are characterized by the presence of collagen fibers, which are abnormally large, dense, broad, glassy, eosinophilic, focally fragmented complexes, arranged haphazardly and packed together by "keloid collagen". In contrast hypertrophic scars exhibit collagen, which is discretely nodular, fibrillar with fairly regular thickness of fibers with its long axis parallel to the epidermis. It was confirmed that such nodular structures are always present in hypertrophic scar and rarely in keloid. The collagen fibers are cigar-shaped and run parallel to the surface of the skin. They are located in the middle or deeper layer of the scar, and are oriented along the tension lines of the scar. The absence of such nodules is characteristic of keloid scars. Furthermore, keloid scars occasionally show myofibroblasts expressing α-smooth muscle actins, while hypertrophic scars are negative for α-smooth muscle actins.[122]

Histopathological differences between keloid and hypertrophic scar have been reported using hematoxylin and eosin stain. Among these differences, keloid scar is characterized by the presence of thick, hyalinized collagen bundles or 'keloid collagen' with mucinous ground substance and relatively few fibroblasts. Conversely, little or no keloidal collagen is found in hypertrophic scar. A histopathological characteristic of hypertrophic scar is the presence of nodules containing a high density Keloid and Hypertrophic Scars of cells and collagen.[122]

# Treatment of keloid and hypertrophic scar

## Medical care

No single therapeutic modality is best for all keloids. The location, size, and depth of the lesion; the age of the patient; and the past response to treatment determine the type of therapy used.[117]

Prevention is key, but therapeutic treatment of hypertrophic scars and keloids includes occlusive dressings, compression therapy, intralesional corticosteroid injections, cryosurgery, excision, radiation therapy, laser therapy, interferon (IFN) therapy, 5-fluorouracil (5-FU), doxorubicin, bleomycin, verapamil, retinoic acid, imiquimod 5% cream, tamoxifen, tacrolimus, botulinum toxin, and over-the-counter treatments (eg, onion extract; combination of hydrocortisone, silicon, and vitamin E).[117]

Other promising therapies include antiangiogenic factors, including vascular endothelial growth factor (VEGF) inhibitors (eg, bevacizumab), phototherapy (photodynamic therapy [PDT], UVA-1 therapy, narrowband UVB therapy), transforming growth factor (TGF)–beta3, tumor necrosis factor (TNF)-alpha inhibitors (etanercept), and recombinant human interleukin (rhIL-10), which are directed at decreasing collagen synthesis.[117]

## Prevention

Prevention is the first rule in keloid therapy. Performing nonessential cosmetic surgery should be avoided in patients known to form keloids; however, the risk is lower among patients who have only earlobe lesions. All surgical wounds should be closed with minimal tension. Incisions should not cross joint spaces. Midchest incisions should be avoided, and incisions should follow skin creases whenever possible.[117]

## Standard treatments

These include occlusive dressings, compression therapy, and intralesional corticosteroid injections.

## Occlusive dressings

Occlusive dressings include silicone gel sheets and dressings, nonsilicone occlusive sheets, and Cordran tape. These measures have been used with varied success. Antikeloidal effects appear to result from a combination of occlusion and hydration, rather than from an effect of the silicone.[117]

Previous studies have shown that in patients treated with silicone occlusive sheeting with pressure worn 24 h/d for up to 12 months, 34% showed excellent improvement, 37.5% showed moderate improvement, and 28% demonstrated no or slight improvement.[117]

Of patients treated with semipermeable, semiocclusive, nonsilicone-based dressings for 8 weeks, 60% experienced flattening of keloids, 71% had reduced pain, 78% had reduced tenderness, 80% had reduced pruritus, 87.5% had reduced erythema, and 90% were satisfied with the treatment.[117]

Cordran tape is a clear surgical tape that contains flurandrenolide, a steroid that is uniformly distributed on each square centimeter of the tape, and it has been shown to soften and flatten keloids over time.[117]

## Compression therapy

Compression therapy involves pressure, which has long been known to have thinning effects on skin. Reduction in the cohesiveness of collagen fibers in pressure-treated hypertrophic scars has been demonstrated by electron microscopy.[117]

Cellular mechanoreceptors may have an important role of compression therapy. Mechanoreceptors induce apoptosis and are involved in the integrity of the extracellular matrix. An increase in extracellular matrix rigidity produced by compression garments leads to a higher level of mechanoreceptor activity and therefore more cellular apoptosis. Migration, proliferation, and differentiation of cells has been shown to be affected by rigidity; therefore, the rigidity caused by compression may also inhibit the differentiation and proliferation of scar fibroblasts in vivo.[123,124]

Compression treatments include button compression, pressure earrings, elastic adhesive bandages, compression wraps, spandex or elastane (Lycra) bandages, and support bandages. In one study, button compression (2 buttons sandwiching the earlobe applied after keloid excision) prevented recurrence during 8 months to 4 years of follow-up observation.[123]

Other pressure devices include pressure earrings and pressure-gradient garments made of lightweight porous Dacron, spandex (also known as elastane), bobbinet fabric (usually worn 12-24 h/d), and zinc oxide adhesive plaster. Overall, 60% of patients treated with these devices showed 75-100% improvement.[123,124]

## Corticosteroids

Corticosteroids, specifically intralesional corticosteroid injections, have been the mainstay of treatment. Corticosteroids reduce excessive scarring by reducing collagen synthesis, altering glucosaminoglycan synthesis, and reducing production of inflammatory mediators and fibroblast proliferation during wound healing. The most commonly used corticosteroid is triamcinolone acetonide (TAC) in concentrations of 10-40 mg/mL administered intralesionally with a 25- to 27-gauge needle at 4- to 6-week intervals.[125]

Intralesional steroid therapy as a single modality and as an adjunct to excision has been shown to be efficacious in various studies. Response rates varied from 50-100%, with recurrence rates of 9-50% in completely resolved scars. When combined with excision, postoperative intralesional TAC injections yielded a recurrence rate of 0-100%, with most studies citing a rate of less than 50%. Complications of repeated corticosteroid injections include atrophy, telangiectasia formation, and pigmentary alteration.[125]

In a recent report, a new standardized corticosteroid therapy protocol has been shown to reduce the recurrence of keloids and hypertrophic scars after excision. Intralesional TAC injection was performed after removal of the sutures and then once every 2 weeks (total of 5 treatments). In addition, patients were instructed to apply corticosteroid ointment twice daily for 6 months to the wounds after suture removal. Only 3 (14.3%) of 21 keloids and 1 (16.7%) of 6 hypertrophic scars recurred.[125]

A recent study by Aradi et al studied 21 earlobe keloids that were treated using keloidectomy with core fillet flap and given intraoperative intralesional steroid injections. This study showed an efficacy of 87.6%. Immediate recurrence was 9.5%, with an average of 29.9 months of follow up and with few complications encountered. Subjectively, 82.3% of patients were satisfied.[126]

Published data show molecular-based evidence of the clinical benefits of adding 5-fluorouracil to a steroid injection for improved scar regression and reduced recurrence of keloids. 5-Fluorouracil–induced cell-cycle arrest and apoptosis may be associated with p53 activation and p21 up-regulation. 5-Fluorouracil significantly affects the treatment when combined with triamcinolone, leading to more significant cell proliferation inhibition, apoptosis, Col-1 suppression, and MMP-2 induction.[127]

## Current and new treatments

Current treatments for keloids and hypertrophic scars include intralesional IFN; 5-FU; doxorubicin; bleomycin; verapamil; retinoic acid; imiquimod 5% cream; tacrolimus; tamoxifen; botulinum toxin; TGF-beta3; rhIL-10; VEGF inhibitors; etanercept; mannose-6-phosphate inhibitors (M6P); onion extract; the combination of hydrocortisone, silicon, and vitamin E; PDT; intense pulsed light (IPL); UVA-1; and narrowband UVB.[117]

IFN therapy, including IFN alfa, IFN beta, and IFN gamma, has been demonstrated in in vitro studies to reduce keloidal fibroblast production of collagen types I, III, and VI mRNA.[117]

IFN alfa and IFN beta also reduce fibroblast production of glycosaminoglycans (GAGs), which form the scaffolding for the deposition of dermal collagen. IFN gamma enhances GAG production.[117]

IFN alfa, IFN beta, and IFN gamma have been shown to increase collagenase activity. Studies have shown that IFN gamma modulates a p53 apoptotic pathway by inducing apoptosis-related genes. p53 is a protein synthesized following DNA damage. Once damage is repaired, p53 is degraded. Mutations of this protein are believed to predispose cells to hyperproliferation, possibly resulting in keloid formation. In addition, p53 is a potent suppressor of interleukin (IL)–6, a cytokine implicated in hyperproliferative and fibrotic conditions.[117]

IFN injected into the suture line of keloid excision sites may be prophylactic for reducing recurrences. Berman and Flores reported statistically significant fewer keloid recurrences in a study of 124 keloid lesions after postoperative IFN alfa-2b injection treatment (5 million U, 1 million U injected per cm of scar) into keloid excision sites (18%) versus excision alone (51.1%) and TAC treatment (58.4%).[128]

Tredget et al showed a significant increase in the rate of scar improvement compared with the control period of time ($P = .004$) after injecting 9 patients with hypertrophic scars with 1 X $10^6$ units of human recombinant IFN alfa-2b subcutaneously, daily for 7 days, and then 2 X $10^6$ units administered 3 times per week for 24 weeks in total.[1] Scar assessment ($P < .05$) and scar volume ($P < .05$) also improved after 3 months of treatment. No recurrences were reported after stopping IFN therapy.[117]

Conejo-Mir et al reported that 66% of keloids (n = 20) did not recur after 3 years of follow-up after treating 30 keloids with ultrapulse carbon dioxide laser ablation followed by sublesional and perilesional injections of 3 million IU of IFN alfa-2b 3 times per week.[129]

In a 2008 prospective study, Lee et al reported decreases in depth (81.6%, $P = .005$) and volume (86.6%, $P = .002$) treating 20 keloids with a combination of intralesional TAC and IFN alfa-2b compared with only a nonsignificant improvement ($P = .281$ and $P = .245$, respectively) obtained in 20 keloids treated with TAC alone.[130]

Notably, however, several studies have failed to demonstrate the efficacy of IFN alfa-2b for the treatment of keloids and hypertrophic scars, including a case series of 5 patients treated by Wong et al,[131] a case series by al-Khawajah of 22 patients with keloids using lower doses of IFN alfa-2b than in prior studies,[132] and a prospective randomized clinical trial by Davison et al in which 50 patients with keloids received intraoperative intradermal injections of IFN alfa-2b at 10 million U/mL or TAC at 40 mg/mL, both receiving an extra injection 1 week later.[133]

Hypertrophic scar intralesional injections of human recombinant IFN gamma at 200 mcg (6 X $10^6$ U) per injection for 4 weeks have been reported by Pittet et al to be effective for relieving the symptoms in 6 of 7 patients and decreases in redness, swelling, firmness, and lesion area in 7 of 7 patients.[134] At week 16, the reappearance of symptoms was minimal in only 2 of 7 patients and a small increase in the lesion area occurred in 4 of 7 patients, although these lesions remained smaller than the original area.[134]

# Surgical Care

## Cryotherapy

Cryosurgical media (eg, liquid nitrogen) affects the microvasculature and causes cell damage via intracellular crystals, leading to tissue anoxia. Generally, 1, 2, or 3 freeze-thaw cycles lasting 10-30 seconds each are used for the desired effect. Treatment may need to be repeated every 20-30 days. Cryotherapy can cause pain and permanent depigmentation in selected patients. As a single modality, cryosurgery led to total resolution with no recurrences in 51-74% of patients after 30 months of follow-up observation.[117]

Newer methods of application of liquid nitrogen include the insertion of a lumbar puncture needle through the long axis of the keloid, from one side to the other, passing the liquid nitrogen with an intravenous drip set for 2 freeze-thaw cycles of 20-30 seconds each for 5-10 sessions. Flattening was achieved in 75% of the patients.[135] A single treatment with an intralesional cryoprobe was used to treat 10 earlobe keloids in 10 white patients, obtaining a statistically significant reduction in the scar volume of 67.4% after 18 months of follow up compared with baseline measurements. Zero recurrences were reported. Other scar parameters also improved.[136]

## Excision

Basic soft tissue handling techniques should be applied at primary wound repair sites. Carefully plan the closure with minimal tension, paralleling the relaxed skin tension lines. Use buried sutures, when necessary, for a layered closure and to reduce tension. Whenever feasible, apply pressure dressings and garments during the immediate postoperative period to wounds in patients in whom hypertrophic scars and keloid formation occur.[117]

Decreased recurrence rates have been reported with excision in combination with other postoperative modalities, such as radiotherapy, injected IFN, or corticosteroid therapy. Excisional surgery alone has been shown to yield a 45-100% recurrence rate and should very rarely be used as a solitary modality, although excision in combination with adjunct measures can be curative. Most studies in which excisional surgery was combined with injected steroids reported a recurrence rate of less than 50%. Surgery followed by adjunctive radiotherapy has obtained recurrence rates of 0–8.6%.[137-139]

Other studies showed the effects of topically applied imiquimod 5% cream (Aldara) on the postexcision recurrence rates of 13 keloids excised surgically from 12 patients. Starting the night of surgery, imiquimod 5% cream was applied for 8 weeks. Patients were examined at weeks 4, 8, 16, and 24 for local erythema, edema, erosions, pigment alteration, and/or recurrence of the keloid. Of the 11 keloids evaluated at 24 weeks, none (0%) recurred. The rate of hyperpigmentation was 63.6%. Two cases of mild irritation and superficial erosion cleared with temporary discontinuation of imiquimod. Both patients completed the 8 weeks of topical therapy and the final 24-week assessment. At 24 weeks, the recurrence rate of excised keloids treated with postoperative imiquimod 5% cream was lower than recurrence rates previously reported in the literature.[140]

# Laser therapy

## Ablative lasers

### *Carbon dioxide, argon laser, and Nd:YAG laser (1064 nm)*

Ablation of keloids and hypertrophic scars using a carbon dioxide laser (10,600 nm) can cut and cauterize the lesion, creating a dry surgical environment with relatively minimal tissue trauma. When used as a single modality, the carbon dioxide laser was associated with recurrence rates of 39-92%, and when the carbon dioxide laser was combined with postoperative injected steroids, it was associated with recurrence rates of 25-74%.[117]

A Korean study included 30 patients with hypertrophic scars treated with a combination of 3 different therapeutic modalities: 10600-nm ablative carbon dioxide laser (AFL), copper bromide laser (CBL), and intralesional TAC. At the end of the study, CBL achieved better outcomes for vascularity and pigmentation. AFL and AFL plus TAC were especially effective with regard to thickness and pliability. AFL produced epidermal resurfacing due to collagen remodeling. CBL plus TAC did not aggravate vascularity and pigmentation, suggesting that CBL may compensate for the erythema resulting from TAC. In conclusion, the combination of CBL, AFL, and intralesional TAC may provide a new treatment option for hypertrophic scars.[141]

Er: YAG laser showed a decrease of 51.3% in redness, 50% in elevation, and 48.9% in hardness of keloids in one study after treating 21 keloids. The recurrence rate was not reported.[142]

Similar to the carbon dioxide laser, the argon 488-nm laser can induce collagen shrinkage via generation of excessive localized heat. The argon laser has demonstrated recurrence rates of 45-93%.[142]

## Nonablative lasers

### *Pulsed-dye laser (585 nm)*

The 585-nm PDL provides photothermolysis, resulting in microvascular thrombosis. Beginning in the 1980s, authors noted that scars became less erythematous, more pliable, and less hypertrophic after treatment with the 585-nm PDL. The findings were later confirmed using objective measurements of erythema by reflectance spectrometry readings, scar height, and pliability measurements. Because of its efficacy, safety, and relatively low cost, the PDL remains the laser treatment of choice for hypertrophic scars. Multiple publications have continued to confirm the role of the 585-nm PDL for the treatment of keloids and hypertrophic scars.[117]

In a randomized clinical trial, Manuskiatti et al treated 10 keloidal or hypertrophic median sternotomy scars with a 585-nm flashlamp-pumped PDL at fluences of 3, 5, and 7 J/cm$^2$, and one segment was left untreated as a control. They showed consistently better results in the treatment groups over the control. A trend was obtained towards lower fluences having more rapid onset of benefits and enhanced resolution of erythema, induration, and elevation of the scar. Multiple treatment sessions achieved greater clinical improvement.[117]

Alster treated 44 bilateral, symmetric hypertrophic breast-reduction scars with a 585-nm PDL at 4.5-5.5 J/cm$^2$ alone or in combination with intralesional TAC at 10-20 mg/mL injected immediately after the PDL irradiation. All scars showed clinical improvement. The average pliability scores decreased by 50% after 2 sessions in both groups. The concomitant use of TAC reduced symptom scores by 70% compared with PDL alone (50%).[143]

In a prospective, randomized clinical trial, Nouri et al treated 11 patients with 12 postoperative scars with 585-nm PDL at 3.5 J/cm$^2$ versus no treatment. The average overall improvement scores after one treatment was superior to the control ($P$ = .0002). Vascularity improved 54% in treated halves, compared with 8% in controls. ($P$ = .002). A total of 38% of halves returned to normal vascularity, compared with 0% in controls. Pliability improved 64% versus 1%, respectively ($P$ = .002). A total of 62% of halves returned to normal pliability compared with 0% in control halves. The cosmetic appearance score was significantly better for the treated halves than for the untreated controls (7.3 vs 5.2; $P$ = .016).[144]

In contrast, Wittenberg et al found in a prospective, single-blinded, randomized, controlled study an overall reduction in blood flow ($P$ = .001), volume ($P$ = .02), and pruritus ($P$ = .005) over time after a follow-up period of 4 months after treatment discontinuation, but no differences were noted among treatment and control groups treating hypertrophic scars with a 585-nm flashlamp-pumped PDL at 6.5-8 J/cm$^2$ or silicone gel sheeting, or no treatment.[145]

## *Pulsed-dye laser (595 nm)*

Two studies have demonstrated that the 585-nm PDL has more effectively cleared port-wine stains than the 595-nm PDL at the same settings. Murine studies determined that the beneficial effect of lasers inhibiting the scar tissue growth decreased as the wavelength of the laser was increased from 585 to 600 nm. Further studies are necessary to obtain similar conclusions in human tissue. However, longer wavelength (eg, 595 nm) is an alternative vascular-specific laser for dark-skinned patients, with higher amounts of epidermal melanin, which absorbs more readily the 585-nm wavelength, causing nonspecific damage to pigmented epidermis. Currently, 595-nm PDL systems incorporate in the handpiece a cryogen-spray cooling device, which permits safe and effective treatment of hypertrophic scars by raising the threshold for epidermal damage, avoiding the resultant epidermal necrosis when the skin surface temperatures exceeds 70°C immediately after PDL exposure.[117]

In a prospective randomized clinical trial, Conologue et al treated 16 patients with postoperative scars immediately after suture removal with a 595-nm cryogen-cooled PDL at 8 J/cm$^2$ and showed significant improvement (60%) versus the untreated control (-3%) in the average sum of all clinical parameters measured. Improvement was noted in vascularity (69%) versus the control (0%) ($P$ = .53) and in pliability (67%) compared with the control (-8%) ($P$ = .337).[146]

In order to compare the 0.45-millisecond (short) pulse width with the 40-millisecond (long) pulse width, Manuskiatti et al treated 19 patients with keloidal and hypertrophic sternotomy scars in a prospective randomized clinical trial, with a 595-nm PDL at 7 J/cm$^2$ and a cryogen spray cooling device. The short pulse width demonstrated greater overall improvement ($P$ = .046) and scar pliability. Both pulse widths significantly reduced scar height compared with baseline; however, no differences were found between the groups. No effects were noted on scar erythema with either treatment. Both treatments were safe and effective in dark-skinned individuals.[147]

Bellew et al randomly treated 15 hypertrophic scars with a 595-nm long-pulsed PDL at 7 J/cm$^2$ with a concomitant skin-surface cooling device or with an IPL system with a 570-nm cut-off filter and a fluence of 40-45 J/cm$^2$ and a triple pulse, reporting a mean improvement in the long-pulsed PDL group of 80% compared with 65% in the IPL group. However, no statistical difference was noted between the 2 groups. Both systems are equally effective in improving the appearance of hypertrophic surgical scars. IPL minimizes the risk of purpura.[148]

In contrast, however, Alam et al found no beneficial effect on clinical scar appearance at 6 weeks post treatment versus untreated control, after treating 20 patients with postoperative scars in a prospective, randomized, controlled trial using a 595-nm PDL at 7 J/cm$^2$ and a 30-millisecond dynamic cooling spray.[149]

# Light therapies

## Photodynamic therapy

Chiu et al studied the in vitro effect of 5-aminolevulinic acid (ALA) and 635-nm diode laser irradiation on keratinocyte-fibroblast co-culture (Raft model), determining that 5 J/cm$^2$ reduces tissue contraction and collagen synthesis and preserves fibroblast viability.[150]

### *Ultraviolet A-1*

UVA-1 (340-400 nm) has been reported as an effective treatment for morphea and systemic sclerosis through induction of collagenase I (matrix metalloproteinase I) produced by fibroblasts. Asawanonda et al reported clinical improvement in one keloid in addition to the histological reappearance of normal-looking collagen and elastic fibers, while others have not reported as good clinical results.[151]

Animal models have shown a significant decrease in dermal thickness and collagen content in scars irradiated postsurgically with UVA-1 at 110 J/cm$^2$. UVA-1 exposure to hypertropic scars in rabbits after epithelialization may lead to softening of the scar, thinning of the skin, and a decrease in collagen content. However, immediate irradiation with UVA-1 after wounding could not prevent the development of hypertrophic scarring in rabbits.[152]

### *Narrowband UVB*

Narrowband UVB in the wavelength range of 310-315 nm (peak at 312 nm) has demonstrated for more than 20 years to be less potent than broadband UVB for erythema induction, hyperplasia, edema, sunburn cell formation, and Langerhans cell depletion from the skin. Studies on human skin fibroblasts by Choi et al have demonstrated that narrowband UVB reduces type I collagen synthesis by down-regulating TGF-beta1 expression at both the mRNA and protein levels and promoting the release of MMP-1.[153] Oiso et al reported flattening of a hypertrophic scar after treating a patient with vitiligo and a Koebner phenomenon with low-dose narrowband UVB (ie, 300 mJ/cm$^2$) once a week for 4 months.[154]

### *Broadband UVB*

Broadband UVB (290-320 nm) at high doses (up to 320 mJ/cm$^2$) has also been theorized to improve fibrosing skin conditions, including keloids, hypertrophic scars, scleroderma, acne keloidalis nuchae, old burn scars, and granuloma annulare, among other related conditions with altered dermal matrix, safely through collagenase-mediated removal of excess dermal collagen via activation of MMP-1 pathways in patients with increased skin pigmentation.[155]

High keloid incidence is found among individuals with high melanin content in their skin. Since melanin serves as a UVB light absorber, lack of UVB light penetration may play a role in keloid etiology. Wirohadidjojo et al evaluated the effect that UVB irradiation to monolayer keloid fibroblasts has on cell proliferation, collagen deposition, and TGF-beta1 production. Keloid fibroblasts were cultures and exposed to various dosages of UVB irradiation. Collagen depositions and TGF-beta1 production were measured. UVB 100 and

150 mJ/cm$^2$ were able to suppress keloid fibroblast viabilities and collagen accumulation significantly ($P$ < .01). Significant suppression of TGF-beta1 production required UVB irradiation of 150 mJ/cm$^2$ ($P$ < .01). UVB irradiation with a minimal dosage of 150 mJ/cm$^2$ is possible therapy for keloid prevention and treatment.[156]

## Intense pulsed light

Bellew et al obtained equal effectiveness improving the appearance of hypertrophic surgical scars with IPL compared with 595-nm long-pulsed PDL.[148] IPL minimized the risk of developing postlaser purpura, frequently seen in patients treated with long-pulsed PDL.[148]

## Treatment of widened scar

Widened scars are treated differently than hypertrophied scars. Widened scars can be flat or even depressed. Therefore, the administration of intralesional steroids is not recommended; these agents could worsen the depression. Widened scars are best treated with the Millard 2-flap technique over a deepithelialized scar. This technique provides soft tissue fill under the approximated wound edges. Furthermore, if the widened scar recurs, the risk for another recurrence can be minimized by reorienting the wound tension along the lines of relaxed skin tension. Other techniques described in the treatment of widened scars to correct the indentation include insertion of dermal-fat grafts or the injection of fat grafts or other tissue substitutes (hyaluronic acid or calcium hydroxyapatite recombinants). However, these materials are known to resorb with time.[120]

## 5-Fluorouracil

5-FU, a pyrimidine analogue with antimetabolite activity, inhibits fibroblastic proliferation in tissue culture and is believed to reduce postoperative scarring by decreasing fibroblast proliferation. Its efficacy and safety have been reported when used as a monotherapy or when used in combination with other drugs (eg TAC) for the treatment of other fibrosing conditions, including infantile digital fibromatosis, knuckle pads, rheumatoid nodules, and adverse foreign body reaction and sarcoidal granulomatous complications after soft tissue filler injection. Some data suggest that 5-FU is effective in the treatment of hypertrophic scars and is somewhat effective in small keloids. Several studies have shown the effectiveness of 5-FU.[117]

## Medical uses

Fluorouracil has been given systemically for anal, breast, colorectal, oesophageal, stomach, pancreatic and skin cancers (especially head and neck cancers).[4] It has also been given topically for actinic keratosesand Bowen's disease.[157]

## Adverse effects

Adverse effects by frequency include:[157]

## During systemic use

Common (> 1% frequency):

- Nausea.
- Vomiting.
- Diarrhea (see below for details).

- Mucositis.
- Headache.
- Myelosuppression (see below for details).
- Alopecia (hair loss).
- Photosensitivity.
- Hand-foot syndrome.
- Maculopapular eruption.
- Itch.
- Cardiotoxicity (see below for details).
- Persistent hiccups.
- Mood disorders (irritability, anxiety, depression).

Uncommon (0.1–1% frequency):

- Oesophagitis
- GI ulceration and bleeding.
- Proctitis.
- Nail disorders.
- Vein pigmentation.
- Confusion.
- Cerebellar syndrome.
- Encephalopathy.
- Visual changes.
- Photophobia.
- Lacrimation (the expulsion of tears without any emotional or physiologic reason).

Rare (< 0.1% frequency):

- Anaphylaxis.
- Allergic reactions.
- Fever without signs of infection.

Diarrhea is severe and may be dose-limiting and is exacerbated by co-treatment with calcium folinate. Neutropenia tends to peak about 9–14 days after beginning treatment. Thrombocytopenia tends to peak about 7–17 days after the beginning of treatment and tends to recover about 10 days after its peak. Cardiotoxicity is a fairly common side effect, but usually this cardiotoxicity is just angina or symptoms associated with coronary artery spasm, but in about 0.55% of those receiving the drug will develop life-threatening cardiotoxicity. Life-threatening cardiotoxicity includes: arrhythmias, ventricular tachycardia and cardiac arrest, secondary to transmural ischaemia.[157]

## During topical use

Common (> 1% frequency):

- Local pain
- Itchiness
- Burning
- Stinging
- Crusting
- Weeping
- Dermatitis

- Photosensitivity

Uncommon (0.1–1% frequency):

- Hyper- or hypopigmentation.
- Scarring.

## Contraindications

It is contraindicated in patients that are severely debilitated or in patients with myelosuppression due to either radiotherapy or chemotherapy. It is likewise contraindicated in pregnant or breastfeeding women.[157]

## Interactions

Its use should be avoided in patients receiving drugs known to modulate dihydropyrimidine dehydrogenase (such as the antiviral drug sorivudine). It may also increase the INR and prothrombin times in patients on warfarin.[157]

## Mechanism of action

5-FU acts in several ways, but principally as a thymidylate synthase (TS) inhibitor. Interrupting the action of this enzyme blocks synthesis of the pyrimidine thymidine, which is a nucleoside required for DNA replication. Thymidylate synthase methylates deoxyuridine monophosphate (dUMP) to form thymidine monophosphate (TMP). Administration of 5-FU causes a scarcity in dTMP, so rapidly dividing cancerous cells undergo cell death via thymineless death Calcium folinate provides an exogenous source of reduced folinates and hence stabilises the 5-FU-TS complex, hence enhancing 5-FU's cytotoxicity.[157]

5-FU in combination with other therapies significantly increases the efficacy over single modalities.[117]