4 Healing of soft tissues and bone
4.1 Skin and subcutaneous tissue

4.1.1 General aspects of initial tissue response to injury

The normal response to tissue injury is a timely and orderly healing process resulting in restoration of anatomical and functional integrity [1]. Wound healing, however, is not a simple, linear process but rather a complex interaction of dynamic processes involving cell-to-cell and cell-to-matrix activities mediated by humoral messengers (Fig 4.1-1a) [2, 3]. Knowledge of the normal physiological process of tissue healing and repair helps to appreciate pathophysiological responses. Wound healing is characterized by three classic phases that, however, do not follow sequentially, but rather partially overlap in time (Fig 4.1-1b). The three phases are:

- **inflammatory or substrate phase** (hemostasis and inflammation)
- **proliferative or fibroblastic phase** (cellular migration and proliferation, protein synthesis)
- **remodeling and maturation phase** (wound contraction).

The goal of these well-orchestrated biological processes is the repair of the injured skin and subcutaneous tissue with fibroblast-mediated scar tissue. Various categories of wound healing have been described. However, a distinction must be made between primary and secondary healing. Primary wound healing or healing by first intention (Fig 4.1-2a–c) occurs within hours after closing of a surgical incision where wound edges are directly approximated without significant tissue loss (this generally signifies full-thickness) (chapter 10.1). Wound closure is performed with sutures, staples, or adhesive. A surgical incision only destroys a limited number of cellular constituents and scarring is minimal. In contrast, secondary wound healing or healing by secondary intention (Fig 4.1-3a–c) is characterized by the formation of granulation tissue, which contracts and finally reepithelializes (chapter 10.1). In such cases the wound may be superficial, intermediate, or full thickness. The different phases of wound healing are more distinct than in primary wound healing. Furthermore, granulation tissue only develops because there is a need for final wound closure. This may result in pronounced contraction of wounds.

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**Fig 4.1-1a–b** Overlapping phases of wound healing.

- **a** Complex cell-to-cell and cell-to-matrix interactions mediated by humoral messengers.
- **b** The five distinct processes.
Fig 4.1-2a–c Three overlapping phases of primary wound healing. Epidermis (E) and dermis (D).

a Inflammatory phase (first hours): Vascular dilation (1), thrombocytes (2), activation and release of fibrin (3), transmigration of leukocytes (4) and erythrocytes (5) into the wound.

b Proliferative phase (days): Ingrowth of newly formed microvessels (6) originating from buds and sprouts. High density of macrophages (7) and fibroblasts (8) within the wound.

c Remodeling and maturation phase (weeks): Avascular collagenous fibers (9) replace woundmatrix. Presence of histiocytes (10) and giant cells (11) near sutures or staples (foreign bodies). The epidermal layer has been reestablished.

Fig 4.1-3a–c The three overlapping phases of secondary wound healing. Epidermis (E) and dermis (D).

a Inflammatory phase (several days): The wound defect is filled with granulation tissue (1) originating from inflammatory cells.

b Proliferative phase (weeks): Fibroblasts differentiate into myofibroblasts (2), resulting in wound contraction (arrows).
4.1 Skin and subcutaneous tissue

4.1.2 Phases of wound healing

Inflammatory or substrate phase
Trauma to living tissue creates a vascular injury and bleeding, which in turn triggers the cellular and molecular responses to initiate hemostasis. The healing process cannot start before hemostasis has been accomplished. Any disturbance at this stage will lead to an impairment of wound healing. Key players in hemostasis are vasoconstriction, platelet aggregation, and fibrin deposition resulting in clot formation, which is primarily composed of embedded blood cells, aggregated platelets and a fibrin mesh. Vasoactive amines are responsible for vasoconstriction, which starts as soon as the epidermis and dermis are penetrated. This process also triggers the secretion of prostaglandins, such as thromboxane. Platelet aggregation is stimulated by tissue factors released by damaged cells. Platelets adhere to the vascular endothelium and to each other in a process involving fibrinogen and von Willebrand factor. Fibrin deposition in the clot seals the wound, preventing further fluid and electrolyte loss, and limiting the risk of contamination from outside. Fibrin is also the endogenous mesh material within the provisional wound matrix into which fibroblasts and other cells migrate as the healing process continues.

Inflammation was first described by John Hunter in 1794 as erythema, edema, heat, and pain (rubor, tumor, calor, and dolor). One of its main functions is to attract inflammatory cells to the injured area in order to repair the damaged tissue. Increased vascular permeability allows leukocytes and macrophages to migrate into the extravascular space starting phagocytosis, destroying bacteria, and eliminating debris in order to allow the repair processes to take over.

More explicitly, vasoconstriction is followed within 10–15 minutes after injury by vasodilation. Simultaneously, the endothelial cells lining the capillaries adjacent to the wound form intercellular gaps allowing leakage of plasma and cells into the extravascular space. The inflammatory phase is initiated and regulated by the release of numerous cytokines: α-granules liberate platelet-derived growth factor (PDGF), platelet factor IV, and transforming growth factor β (TGF-β), while vasoactive amines such as histamine and serotonin are released from dense bodies found in platelets. Platelet-derived growth factor acts as a chemotactic agent for fibroblasts and, along with transforming growth factor β, is a potent modulator of fibroblastic mitosis, leading to prolific collagen fibril construction in later phases. Fibrinogen is converted to fibrin and the framework for completion of the coagulation process is formed. Fibrin provides the structural support for the cellular constituents of inflammation. This process starts immediately after the insult and may continue for a few days.

Within the first 6–8 hours, the next phase of proliferation sets in, with polymorphonuclear leukocytes (PMN) engorging the wound. Transforming growth factor β facilitates migration of polymorphonuclear leukocytes from surrounding blood vessels into the extracellular space. The highest concentration of polymorphonuclear leukocytes is reached 24–48 hours after tissue injury. The start of their activity correlates with the termination of the inflammatory phase. An imbalance of bacteria against polymorphonuclear leukocytes may lead to an acute infection, which becomes clinically visible after ~72 hours.
Proliferative or fibroblastic phase

Even before the inflammatory phase has come to an end, ie, 2–3 days after injury, fibroblasts begin to enter the wound, marking the onset of the proliferative phase that will last up to 14 days [2]. The process of angiogenesis starts concurrently with fibroblast proliferation when endothelial cells migrate to the area of the wound in order to supply the tissue with oxygen and other nutrients. The tissue in which angiogenesis has set in typically looks red due to the presence of numerous newly developed microvessels. Key factors in the angiogenic process include high lactate levels, acidic pH, and, in particular, decreased oxygen tension.[8]. Angiogenesis is initiated by endothelial buds or sprouts deriving from preexisting, intact capillaries at the wound periphery and possibly from the wound ground [9]. These buds or sprouts grow by cellular migration and proliferation and may eventually come into contact with a bud or a sprout stemming from another nearby capillary. They interconnect and generate a new functional capillary network, ie, offering passage for cellular components such as erythrocytes and leukocytes. The two most important cytokines that contribute to angiogenesis are fibroblast growth factor 2 (FGF-2) and vascular endothelial growth factor (VEGF).

The resulting granulation tissue, which is typical for secondary wound healing, functions as rudimentary tissue. It first appears in the wound as early as the inflammatory phase, 2–5 days postinjury, and continues to grow until the wound bed is covered. Beside fibroblasts, inflammatory cells, endothelial cells, and myofibroblasts, granulation tissue consists of a new, provisional extracellular matrix as well as newly formed, patent blood vessels. Granulation tissue approximately contains 30% type III collagen.

Finally, reepithelialization of the wound is crucial for the reestablishment of the barrier function of the skin. Incisional skin injuries, with a minimal epithelial gap are typically reepithelialized within 24–48 hours. During the first 24 hours after injury, basal cells appear at the wound edge and begin to migrate across the denuded wound surface. If the initial injury does not destroy epithelial appendages such as hair follicles, sebaceous and sweat glands, these structures also contribute migratory epithelial cells to the healing process. The migration of epithelial cells continues until there is an overlap with other epithelial cells migrating from different directions. When two epithelial cells meet, “contact inhibition” stops their movement [10].

Remodeling and maturation phase

The quality and quantity of matrix deposited during this phase of healing significantly influences the strength of a scar [11]. Collagen constitutes more than 50% of the protein in scar tissue, and its production is essential to the healing process. Fibroblasts are responsible for the synthesis of collagen and other regenerative proteins during the repair process. Collagen synthesis is stimulated by transforming growth factor β, platelet-derived growth factors, and epidermal growth factors [12, 13]. Collagen synthesis also depends on the wound and the characteristic constitution of the patient’s body including age, tension and pressure (chapter 4.4). Collagen synthesis continues at a maximum rate for 2–4 weeks and subsequently begins to slow down. Disturbed healing resulting in chronic wounds often is the result of aberrations in collagen deposition, for example, as observed in diabetic patients or smokers (chapter 4.4). Conversely, hypertrophic scar or keloid formations result from excessive collagen synthesis.

Initially the wound matrix is primarily composed of fibrin and fibronectin, which are gradually replaced by collagen and other proteins such as proteoglycans, the key components of a mature matrix. Additional proteins such as thrombospondin I and secreted protein acidic rich in cysteine (SPARC), which support cellular recruitment and stimulate wound remodeling, are also produced and found in the mature wound matrix [14]. The concentration of collagen subtypes varies among tissues. Type I collagen predominates and makes up 80–90% of the collagen seen in intact dermis. The remaining 10–20% consist of type III collagen.

Remodeling of the scar begins to dominate the wound-healing activities ~ 3 weeks after injury and can continue for up to 2 years. The rate of collagen synthesis reaches a peak by the third week, then starts to decrease and levels off at a balance with the rate of collagen breakdown. The downregulation of collagen synthesis is mediated by γ-interferon [15], tumor necrosis factor α (TNF-α) [16] and the collagen matrix itself [17]. Contraction of the wound is an ongoing process resulting in part from the proliferation of the specialized fibroblasts termed myofibroblasts, which resemble contractile, smooth muscle cells. Wound contraction occurs to a greater extent with secondary healing than with primary healing and greatly depends on the rate of fibroblasts differentiating into myofibroblasts (Fig 4.1-3b). Maximal tensile strength of the wound is achieved by the twelfth week. The ultimate resultant scar only has 80% of the tensile strength of the original skin, which has been replaced [18, 19].
4.2 Muscle and tendon

4.2.1 Healing of muscle

The forces involved in producing a fracture almost always cause some degree of injury to the surrounding soft-tissue envelope. This injury can range from very minimal to a severe lesion with cavitation and loss of entire motor units (chapter 3).

The repair process is characterized by three phases, which run concurrently, respectively overlap in time (chapter 4.1). Immediately after injury, the damaged muscle enters the inflammatory phase. Proteases begin to degrade the necrotic portions of the muscle. As the surrounding vascular system has also been damaged, inflammatory cells invade the zone of injury from the lacerated vessels. These cells include macrophages, polymorphonuclear leukocytes and lymphocytes that release chemotactic factors and continue to enhance the inflammatory response (Fig 4.2-1). Interestingly, the local area affected by the injury is topographically contained by contraction bands that limit the repair process to the injured area. This intensifies the inflammatory effect within the zone of injury and protects normal tissue from the inflammatory cascade (chapter 10.3.3) [20, 21].

The proliferative phase starts at the earliest 7–10 days after the insult. The cytokine stimulus from the inflammatory cells triggers satellite cells that are dormant in the basal lamina. These muscle progenitor cells are activated and join the damaged muscle cells to promote healing and reconstitution of the muscle unit. This process of regeneration is at its climax ~2 weeks following the injury (Fig 4.2-2) and concludes ~2 weeks later [20, 21].

The formation of scar tissue within the damaged muscle is the hallmark of the final phase of remodeling and maturation (Fig 4.2-3). Granulation tissue is formed very early in the repair process under the influence of fibronectin and fibrin released from the hematoma. Fibroblasts migrate to the injured area and predominantly secrete fibronectin that subsequently increases the strength and elasticity of the repair tissue. As the proliferative phase draws to an end, the fibroblasts begin to produce type I collagen. Transforming growth factor β (TGF-β) and other growth factors stimulate this response, and collagen type I strengthens the fibrotic scar. The remodeling of the muscle is complete once the fibrotic scar has matured. However, the muscle never returns to its preinjury state as it will always be bridged by scar tissue [20, 21].

Healing of muscle is improved by a brief period of immobilization after injury. This helps to minimize contraction of the muscle edges as well as to decrease the size of the hematoma, which subsequently results in a smaller fibrotic scar [22].

Fig 4.2-1 Blunt injury in a rat muscle at 1 week. Note the myofibril necrosis (white arrows) and the perivascular inflammation (black arrow).

Fig 4.2-2 Contusion in a rat muscle at 2 weeks. Note the invasion of polymorphonuclear leukocytes (arrows) and early fibroblast ingrowth with widespread inflammation throughout the zone of injury.
4 Healing of soft tissues and bone

Extensive muscle loss will obviously hamper the function of a particular muscle unit. If there are other muscles remaining, the injured muscle unit may still be able to contribute to the overall function. However, the joint affected by the muscle loss may subsequently suffer from an imbalance of forces since formerly antagonistic muscle groups are now relatively unopposed.

4.2.2 Healing of tendon

Despite the fact that tendons basically are nonvascularized structures, they follow a similar healing pattern to that of traumatized skin or muscle, ie, vascularized tissue. The following process describes the healing mechanism of tendons covered by paratenon. After an injury to a tendon, the inflammatory phase begins with the migration of inflammatory cells into the area. Tenocytes are activated, developing into tenoblasts under the influence of fibronectin. Fibronectin also attracts fibroblasts to the damaged edges of the tendon. The paratenon and surrounding connective tissues combined constitute the source of the initial cellular response. Macrophages help to prepare the torn tendon edges for the repair process [20].

The next phase is the proliferative phase. During this phase, there is an increase in fluid content and of proteoglycan, hyalurionate, chondroitin sulfate and dermatan sulfate in the zone of injury. The gap in the injured tendon is filled by scar tissue comprised of collagen and fibroblasts. In this phase, collagen formation actually can be found as early as 3 days after injury. The initial collagen fibrils are rather disorganized but they become more longitudinally oriented within 4 weeks postinjury [1].

During the remodeling and maturation phase, the scar begins to mature. As the healing process proceeds, there is a decrease in cellular activity in the zone of injury, with an increase in the state of organization of the matrix and a conversion from type III collagen to type I collagen. Tendon remodeling is complete once type I collagen and proteins have formed the definitive scar in the tendon, and cellular activity has again returned to its preinjury level [20].

There are some differences in the way paratenon-covered tendons and sheathed tendons heal. The origin of the reparative cells is still unclear in sheathed tendons, while both an intrinsic and an extrinsic healing mechanism have been postulated. The formation of granulation tissue is postulated as the hallmark of the extrinsic response. The tendon sheath contributes the cells that form the granulation tissue while tenocytes are not involved in the healing process. The intrinsic mechanism is a newer theory, which assigns the source of healing cells to the epitenon and the actual tendon itself. Both mechanisms are likely to contribute to tendon healing with the extrinsic mechanism dominating the process early on and the intrinsic mechanism taking over in the later stages [23].

Smooth gliding of tendons within the tendon sheath is essential for effective function. If the tendon heals with exuberant tissue formation, resulting in a tendon that is too thick or bound to the sheath, the muscle-tendon unit will be ineffective in its performance. Tendon healing requires initial immobilization, followed by early protected motion in order to avoid adhesions. Healing tendons must be protected from excessive force that will endanger their repair. Adhesions may cause pain and swelling as well as loss of active joint motion due to decreased tendon excursion. About 20 weeks after tendon injury, the tendon histologically appears very similar to normal tendon, but in terms of biochemical and biomechanical characteristics the repaired tendon remains inferior to an uninjured one. Although the tendon may not return to its preinjury state, the final outcome is usually functionally acceptable [20, 23].

Tendon healing differs from muscle healing in several ways. The role of type III collagen in the initial stages of tendon repair and the eventual conversion from type III collagen to type I collagen is unique to tendon healing. Both tissues heal with a fibrotic scar, but, in contrast to muscle, tendons cannot tolerate thick scaring if a functional end result is to be achieved [20].
Phases of normal bone healing

After a fracture or osteotomy an immediate reduction of the blood flow within the bone of up to 50% can be observed [24]. This is the result of physiological vasoconstriction or disruption of periosteal and medullary vessels [25]. With the onset of bone healing—as an inflammatory reaction—hypopermia of intra- and extraosseous vessels sets in, with a peak at ~2 weeks, which slowly levels off again. Parallel to these vascular phenomena, bone healing itself begins with inflammation, followed by the phases: formation of soft callus, formation of hard callus, and remodeling. While each of the four phases has its own characteristics, they gradually merge, showing clear periods of overlapping as in skin and subcutaneous tissue (chapter 4.1).

The inflammatory phase is initiated by the forces causing the fracture as such and formation of hematoma and lasts from 1–7 days until a fibrous network has been formed (Fig 4.3-1). The effect of the hematoma is augmented by a localized increase in permeability of the adjacent blood vessels, while cytokines and inflammatory mediators are released. The hematoma is invaded by polymorphonuclear leukocytes, macrophages, and mesenchymal stem cells followed by the development of new capillaries infiltrating the injured area and forming a network of fibrin, reticular and collagen fibrils. Subsequently the hematoma is replaced by granulation tissue. At the same time osteoclasts start to erode the necrotic cortical bone ends [21, 26, 27].

Formation of soft callus is part of the next phase, which corresponds to the proliferative phase of wound healing. It consists of intramembranous ossification, which starts at same distance from the fracture gap to form a cuff of immature, woven bone, while within the gap fibrous and cartilage tissue is invaded by new vessels as the callus slowly calcifies (Fig 4.3-2). This process starts in the periphery and moves towards the center, lasting for 2–3 weeks. Clinically, the pain subsides at this point as the callus becomes “sticky” and axial stability increases.

In the vicinity of the fracture gap, mesenchymal precursor cells proliferate and migrate through the callus, differentiating into fibroblasts and chondrocytes. Thereby the third

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**Fig 4.3-1** Inflammatory phase of bone healing: hematoma and inflammation. Note the presence of acute inflammatory cells: fibroblasts, polymorphonuclear leukocytes (PMNs), macrophages, and mesenchymal stem cells (MSCs).

1 Periosteum.
2 Necrosis.
3 Endosteum.

**Fig 4.3-2** Repair phase in secondary bone healing. Note ingrowth of new blood vessels from periosteal vessels and the formation of a cartilage anlage, similar to endochondral ossification.

1 Cartilage anlage.
2 Capillary ingrowth.
3 Osteoblasts.
phase is initiated, which amongst others includes endochondral ossification. This process eventually converts the soft into hard, calcified callus.

The fracture callus continues to grow stiffer with time as the fracture progresses toward healing, as the width of the callus typically is wider than native cortical bone and the bending strength of bone correlates to the diameter cubed. This process lasts for about 3–4 months. Therefore, even though bone in the hard callus stage is woven bone, it is strong. In a canine model, torsional stiffness increases until the eighth week and then levels off [28]. If a fracture is exposed to increased strain for a prolonged period of time, the production of fibrous tissue and cartilage in the fracture gap will continue and, in the absence of calcification, a delay of bridging of the soft callus may result rather than bone healing, and the fracture can even result in a nonunion [21, 26, 27].

The remodeling phase is the final and longest period, lasting for up to 2 years until the bone has been completely restructured and has regained its original strength and form (Fig 4.3-3). The initial restoration that occurs during the remodeling phase is often disorganized; the order of the new bone is subsequently refined. Osteoclasts resorb the woven bone, and osteoblasts convert the immature bone into mature lamellar bone [24–26].

![Fig 4.3-3 Remodeling phase of secondary fracture healing. Note that woven bone has been replaced by lamellar bone within the cortex.
1 Lamellar bone.
2 Osteoblasts.](image)

The repair cells that modulate fracture healing originate from a variety of sources (Fig 4.3-4). Osteoclasts arise from either monoclastic bone marrow cells or circulating monocytes, while osteoblasts derive from undifferentiated mesenchymal cells that are in close proximity to the bone (periosteum, endosteum, etc) or the bone marrow. Osteoblasts eventually transform into osteocytes, and they are integrated within the new bone as the surrounding osteoblasts continue to synthesize osteoid. The fracture hematoma that develops due to trauma to the bone and soft tissues provides an accumulation point for fibroblasts and inflammatory cells [24–26].

### 4.3.2 Primary versus secondary bone healing

Primary bone healing, which should better be called direct bone healing, occurs if the fracture is rigidly fixed by interfragmentary compression (plate and screws), resulting in absolute mechanical stability. Under this condition, which is defined by the absence of micromotion at the fracture site under physiological loading, direct healing will take place with new osteons growing directly across the fracture line, interdigitating within the opposing cortices. There is no or only minimal periosteal or endosteal callus formation (Fig 4.3-5a–b). So-called gap healing occurs in areas where a small gap (150–200 μm) still exists between the bone ends, and which is filled with lamellar bone. Thereafter osteons will be able to grow across it into the opposite fragment: Haversian remodeling occurs as the cortical bone is transformed. The induction of blood vessels and progenitor cells is influenced by the local oxygen tension. Areas with a higher oxygenation and decreased fracture strain tend to encourage the proliferation of osteoprogenitor cells that form lamellar bone. This requires fracture fixation that is sufficiently rigid in order to produce an environment of low fracture strain [21, 26, 27].

Secondary bone healing is also known as indirect or intramembranous ossification. This type of bone healing occurs if the cartilaginous callus is substituted into bone by the process of endochondral ossification (Fig 4.3-2). Fixation providing relative stability (intramedullary nailing, bridge plating and external fixation) results in fracture areas with an intermediate or rather high level of strain and lower oxygenation, which usually heals by secondary fracture healing similar to the “normal”, biological healing pattern by callus formation as already described above [21, 26, 27].
4.3 Bone

**Fig 4.3-4** Origin of bone cells.

**Fig 4.3-5a-b** Haversian remodeling.
- **a** Photomicrograph of bone after healing by direct (primary) bone healing.
- **b** Remodeling of cortical bone by cutting cones. Osteoclasts dissolve old or necrotic bone, creating a cutting cone, which is then filled in by osteoblasts.
4.4 Factors that affect healing

Author: Jian Farhadi

4.4.1 Overview

If undisturbed, wound healing generally progresses in a predictable sequence as described previously (chapter 4.1). There are, however, a number of factors which can affect the orchestrated wound healing process, and impairment can occur on different levels. These factors include gender, age, systemic diseases, immune response, iatrogenic factors, drugs, nutritional state, smoking, local and mechanical factors, which may affect any phase of the healing process (Table 4.4–1). A clear understanding of these mechanisms of disturbed wound healing is necessary when treating acute or chronic wounds.

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<th>Systemic factors</th>
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<td>Local factors</td>
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4.4.2 Systemic factors

Introduction

Many common causes such as the patient’s predisposition to atherosclerosis, vasculitis, renal failure causing uremia, impaired liver function resulting in hypoproteinemia, vitamin deficiencies, hormonal imbalance, neuropathy associated with disturbed sensation, and diabetes mellitus may often be treated, respectively taken into consideration prior to a surgical procedure. The treatment of fresh wounds, of course, differs from that of chronic wounds (eg, in diabetic patients) in two respects:

1. Early decision on correct wound treatment, depending on wound extent and the exposure of vital structures (chapter 6).
2. Wound care as such, ie, irrigation and debridement to reduce further damage to the surrounding tissue (chapter 7.1, 7.2). Failure to do so can lead to more extensive loss of tissue as closure of the wound becomes a major challenge.

In chronic wounds it is more important to control the causes of disturbed healing than the treatment of the wound itself.

Gender

Androgenic and estrogenic steroids can affect normal healing of acute wounds. Testosterone and its metabolite 5α-dihydrotestosterone have been implicated in the inhibition of wound healing and repair [29, 30]. Factors such as the transforming-growth-factor-β-activated transcription factor Smad3 are said to act as inhibitors of androgens [29], whereas the proinflammatory and pleiotropic cytokine macrophage migration inhibitory factor (MIF) is responsible for delaying repair in ovariectomized female mice [30]. Interestingly, the male gender seems to be associated with decreased tissue necrosis and improved wound-healing capacity resulting from an increased tolerance to ischemic stress as compared to the female gender undergoing the same ischemic injury [31].

Age

Evidence for age-related effects on wound healing has mainly been derived from empirical observations without adjustment for confounding factors other than age. Age-related changes in the structure and function of the skin do occur. But some of these changes most probably result from chronic solar radiation and its consequences on the skin rather than aging as such. The tensile strength of wounds, the accumulation of wound-healing factors, and the rate of wound closure have all been examined in relation to chronological aging [32]. However, the clinical impact of such changes in acute wound healing appears to be small. Poor healing in chronic wounds, however, is more often related to comorbidities rather than age alone. Since the majority of these chronic wounds occur in the elderly, this has contributed to the conclusion that aging itself may influence
healing. To date, the influence of aging as such has only been established in regard to a decreased survival of tissue, reduced formation of new collagen fibrils, and an impaired healing potential in senescent subjects, which is associated with an increased susceptibility to microvascular perfusion failure [33].

**Drugs**

A number of drugs are known to impair wound healing, but may be overlooked due to the patient’s comorbidities [34]. Next to anticoagulants, immunosuppressive agents, ie, cytostatic drugs, steroids and nonsteroidal antiinflammatory agents are the most important drugs. Often, the medication cannot be discontinued, eg, in case of cytostatic drugs or some anticoagulants. The effects of coumarin derivatives and steroids can be reversed by the administration of vitamin K, respectively vitamin A. Yet, the effect of steroids on the tensile strength of wounds is dose and time dependent [35]. Low doses of steroids administered for short periods of time will not interfere with wound healing, nor will it impair tissue morphology, ie, lead to muscular and dermal atrophy or bleeding. With long-term administration of steroids, however, wound healing will be impaired for up to 1 year after cessation of drug intake.

As a general rule, minor surgical procedures at the skin level do not need any discontinuation of aspirin or any other nonsteroidal antiinflammatory agents [36]. In order to decide upon the operability of a patient, administration of coumarin derivatives need monitoring of the international normalized ratio (INR), [37]. If large dissections are performed as, for example, for a flap (eg, latissimus dorsi flap, gracilis muscle flap, etc.), abundant postoperative oozing is to be expected, possibly resulting in an increased risk of hematoma and seroma formation and hence impaired wound healing. These patients might benefit from discontinuation of any drug interfering with coagulation.

**Nutritional state**

Delayed wound healing is inevitable in a patient with a deficient nutritional state. Regardless of the nature of the wound, a careful initial assessment of the nutritional state is important as it may have a major impact for the further treatment plan. This includes:

- a history including questions about weight loss, appetite, vomiting, diarrhea, eating habits, and current medication.
- a physical exam including search for muscle wasting, subcutaneous fat loss, or edema associated with hypoalbuminemia.
- a basic laboratory work-up including protein and albumin levels. Amino acids, in particular arginine and methionine, play a central role in wound healing through the production of collagen [38]. Amino-acid depletion can be caused by loss (nephrotic syndrome), consumption (trauma, burns, sepsis, chronic wounds), underproduction (liver disease), or inadequate intake (malnutrition). The consequences of protein depletion for wound healing comprise decreases in angiogenesis and fibroblast proliferation, which results in decreased synthesis, accumulation and remodeling of collagen [39].
- micronutrients such as vitamins and minerals that are critically important in wound healing and immune function. Many trace metals, including zinc, magnesium, copper, iron, and calcium are cofactors in collagen production, and deficiencies impair collagen synthesis [38].

**Smoking**

Cigarette smoking has long been known to have a detrimental effect on wound healing. Although the association between cigarette smoking and delayed wound healing is accepted in clinical practice, there are no controlled clinical studies to prove this relationship. Most studies are based on animal models that examined the individual components of cigarette smoke and tobacco, including nicotine, carbon monoxide, and hydrogen cyanide. Nicotine has significant vasoconstrictive properties that can last for up to 50 minutes after smoking [40]. Nicotine has also been shown to enhance platelet adhesion, whereby increasing the risk of thrombus formation in small vessels, challenging microcirculation. Finally, nicotine has been associated with an inhibitory effect on the proliferation of red blood cells, macrophages, and fibroblasts, which reduces the production of collagen and impairs wound healing [41, 42].

Active smokers have increased levels of carbon monoxide in their serum that will reduce tissue oxygenation due to carbon monoxide competing with oxygen in hemoglobin transportation. The result is a decreased delivery of oxygen to the tissues. Similarly high levels of hydrogen cyanide, a common by-product in tobacco smoke, are seen in smoking individuals. The enzyme system selectively inhibits the oxidative metabolism in oxygen transport on the cellular level, thus interfering with cellular respiration. Commonly, patients are asked to completely stop smoking 2–3 weeks before a planned surgical procedure. However, presently the evidence shows that only a 4-week abstinence from smoking significantly reduces smoking-associated complications to a level of nonsmokers [43, 44].
4.4.3 Local factors

Mechanism of injury
In every trauma, with or without association of the skeleton, the soft-tissue cover is involved. A small penetration of the skin may hide a complex injury of the skeletal system, and an extended degloving injury can be missed, if there are no apparent skin lesions or fractures (chapter 3). The history and assessment of the mechanism of injury is therefore paramount in the treatment of a fracture and the evaluation must include a careful examination of the soft-tissue envelope (chapter 5.1). A variety of classifications for the soft tissues and bones have been developed in order to establish a grading and severity score of the injury (chapter 5.2).

Wound conditions
Local factors that can influence wound healing include hematoma, seroma, infection, and necrotic tissue. The latter two are enhanced by foreign bodies such as sutures, staples, and implant material, while preexisting scars or postoperative radiation may disturb the local vascularity. Considerable hematoma and seroma will increase tension on the skin and impair microcirculation and oxygenation of the tissue, which is detrimental to wound healing. Although hypoxia is the strongest stimulus for angiogenesis, the wound will not proceed through the later phases of wound healing [45].

Foreign body can either act as a physical obstacle to wound healing or as a host for bacteria. Too tight surgeon’s knots, too much tension on the wound edges, or too many stitches can impair wound healing due to local ischemia, inflammation or infection. Foreign bodies prolong the inflammatory phase of wound healing (chapter 4.1) and delay contraction, respectively epithelialization of a wound. Additional incisions placed in parallel or using an acute angle to the preexisting scars may jeopardize microcirculation and lead to local skin necrosis. Necrotic tissue also inhibits healing and must be excised in order to allow a wound to heal [46].

Radiation has both acute and chronic effects on the skin. Acute effects include erythema, dry desquamation at moderate dose levels, and moist desquamation at higher dose levels. Chronic effects include increased or decreased pigmentation, thickening and fibrosis of the skin and subcutaneous tissues, telangiectasias, and alterations in sebaceous and sweat-gland function.

References and further reading