Chapter 2

Burn Etiology and Pathogenesis

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Additional information is available at the end of the chapter

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Abstract

As a trauma type, "Burn" is one of the high-frequency accidents in the world. It is mostly caused by electricity, hot water, and chemical agents. A trauma can have acute effects on burns, skin, and other organ systems. These complications might be seen as myocardial infarction, thromboemboli, respiratory, and renal failure. In case of acute burns, the skin surface is severely destroyed. During this period, infection may develop on damaged skin. Therefore, in the treatment of burn wounds, protecting the damaged skin and multidisciplinary approaches are needed for preventing scar formation while healing process.

Keywords: burn etiology and pathophysiology, burn types, burn degrees, burn scar etiopathogenesis

1. Introduction

Burn is defined as destruction found in the epidermal tissue, dermal tissue, or deeper tissues, due to contact with thermal, chemical, or electrical agents. According to the World Health Organization, thermal burns account for an estimated 6.6 million injuries and 300,000 deaths each year worldwide [1]. Burn pathophysiology can be broken into local and systemic response. When excessive heat is transferred to the skin, it radiates outward from the point of initial contact and forms a local response with three zones in all directions. The systemic response following a burn can be massive. In a large burn, two clinically significant processes occur. The release of systemic inflammatory mediators and cytokines result in increased capillary permeability and wide scale extravasation of fluid and proteins from the intravascular to the extravascular space.

During wound healing, proinflammatory factors, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-alpha) are released. This promote chronic inflammation and

various inflammatory cells are formed in the affected tissue. Angiogenesis starts into the damaged tissue. Tumor necrosis factor-alpha, prostaglandin E2 also play a role in the formation of inflammatory response in wound healing. Any damage to the formation of this response can result in scarring after the burn. The primary cytokine responsible for scar formation is transforming growth factor-beta (TGF-β) secretion which is released from the other inflammatory cells and myofibroblasts. Hypertrophic scar does not develop when the reticular layer is not affected in burning. As a result, inflammatory cells, fibroblasts, newly formed blood vessels, and collagen deposits develop hypertrophic scar tissue in the reticular layer [2, 3].

2. Description

The skin, which is the largest organ of the body, constitutes 16% of the total body weight. It is 6–10 kg and 1.5–2 m^2 in length in adult man. The skin is a protective covering for the organism and also acts as a sensory organ. It regulates body temperature and blood pressure by means of dermal vascular component. It synthesizes vitamin D3 with the effect of ultraviolet. Stratum corneum creates a barrier to prevent fluid and electrolyte loss and regulates transepidermal fluid passage. It provides homeostasis of the body against trauma that can be caused by various physical and chemical factors originating from the external environment [4]. Physical and chemical agents cause various damages to be formed directly, with thermal, mechanical, and radial factors, or as a result of the reactions they create [4].

Dermatitis developed due to high temperature trauma is defined as burn. Burn is an acute tissue injury caused by exposure to materials, solid or liquid, hot or showing effects of hot [5]. In skin and/or subcutaneous tissues, all of the acute damage caused by exposure to heat, cold, electricity, radiation, or chemical agents is burn. Although the developed damage is in the skin and subcutaneous tissues, it is a very comprehensive trauma that affects the entire organism due to the conditions, such as the depth of the burn, the surface area, the causative agent, and the infection and metabolic circumstances that may occur in the follow-up process, that determines the prognosis with the pathophysiology it caused [5, 6]. The skin loses its functions when it is burned. Burns can spread from outer layers of skin to deeper tissues [5].

The form of occurrence and duration of exposure to the active agent (flame, liquid, gas, chemical agents, etc.) is important in planning the treatment. A more detailed evaluation of the patient should be examined about general examination findings accompanying the burn. Whether there is evidence of dry cough, hoarseness, and breathing difficulties suggesting inhalation injury should be questioned in burns that develop due to flames. The anamnesis of the burn plays an important role, especially since antidote treatment may be needed aimed to the agent in chemical burns.

3. History

The first written documents about burns were found 2400 years ago during the times of Hippocrates. In 1607, Hildanus had graded the burns. In 1799, Earle found that applying ice

water to the burned area could prevent pain. During World War I, burns related to the use of sulfur-containing chemicals were observed and advanced treatment facilities were established for the treatment of burns after World War II [7].

4. Epidemiology

Although the awareness level of the individuals is increasing nowadays and preventive technologies are developed, the burn is still one of the important causes of mortality and high morbidity. It is known that more than 6 million people are exposed to burns every year in the world, and that the mortality rate due to burns is 6–7%. About 75% of the deaths are due to CO inhalation and at the scene primarily [8]. Another cause of mortality is sepsis. As the total body surface area affected by burn increases, the mortality rate also increases [8]. Burns are most commonly seen in the upper and lower extremities [8, 9]. Burn traumas often result from an accident or neglect. About 80% of the burns arise from individual errors and 70% occur at home [4]. Burn epidemiology varies with age. Child age group and elderly population are more at risk. Studies show that more than half of the cases are in the child age group. About 19% are under the age of 5 and 12% are over 60 years old [1]. While boiled water and flame burns are seen most commonly, they are followed by electrical and chemical burns. While hot water burns are seen in approximately 70% of the pediatric age group, burns due to flame at home or office are seen in adults [10]. In a study conducted in Tokyo, 82% of cases were due to hot water and 11% of cases were due to flames in children under 16 years of age [11]. In the study of Aytaç et al. causes of burns were found as 68.8% hot water, 1.5% flame, 3.8% hot material contact injuries, and 1.1% chemical burns, respectively [9].

5. Etiology

At least 44°C of heat is required for the skin to be burned. Besides, the duration of the heat is also important; transepidermal necrosis occurring with 70°C of heat in a second, occurs in 45 minutes with 47°C of heat [4].

Burns can be grouped according to thermal, chemical, electricity, and radiation [12]. The causative of burns should be known since a different treatment protocol is applied in each case. Thermal burns that occur with direct effects of flames with high levels of heat, contact with hot objects, hot liquids, or hot vapors are commonly seen. The duration of the contact and the degree of the temperature determine the degree of cell damage [1]. Chemical burns due to acid or alkali salts and solutions may cause burns due to corrosive effects of these substances. Other than these, burns can also develop due to electrical current, radiation, ultraviolet, and laser rays [4]. Serious burns due to flames of weapons, explosives, and combustibles can occur during warfare [12].

5.1. Thermal burns

It develops in two different ways as hot water and flame burns. Thermal burns are skin injuries caused by excessive heat, typically from contact with hot surfaces, hot liquids, steam,

or flame. Thermal damage to skin results in cellular death as a function of temperature and length of contact time. Thermal burns are the most common type of burn injuries, making up about 86% of the burned patients requiring burn center admission. About 70% of the burns in children develop due to hot water. It is most often caused by hot drinks or hot bath water. These burns are usually first-degree or superficial second-degree burns [13, 14]. Flame burns account for 50% of adult burns [14]. Inhalation burn may also develop together with it. It usually appears as a second or third-degree burn.

5.2. Chemical burns

It is the cause of burns caused by cleaning materials that are used in daily life at home or by work accidents. While 3–6% of all burns constitute chemical burns, they constitute 14–30% of burn-related mortalities [15]. Generally, it is developed due to contact with strong acid or alkaline substances. Unlike thermal burns, there is longer contact with the agent. Inhalation or ingestion of the chemical material may result in systemic symptoms and injuries in the mouth, esophagus, and stomach where it contacts. Bleach, cement, plaster, and hydrofluoric acid used in glassware artwork, phenol, and petroleum-derived organic compounds, phosphorus used in the construction of various warfare materials are the most common reasons of chemical burn incidents [12].

Acid burns tend to limit themselves. Hydrofluoric acid is one of the most frequently used acids for construction of electrical circuits and for scraping paintings on glass and that causes burn most [16]. Hydrofluoric acid passes quickly through the skin and continues to damage tissue until it reaches a tissue rich in calcium, such as bone. Even small hydrofluoric acid burns may develop hypocalcemia, which is sufficient for cardiac effects to occur. More than 10% hydrofluoric acid may be fatal. The gels containing calcium gluconate can be administered topically, or IV calcium gluconate can be given in severe cases [16].

Bleach, oven cleaners, fertilizer, cement, plaster, and lime contact result in basic burns. Bases penetrate deep into the tissue, combine with cutaneous lipids to form soap, and continue to dissolve the skin until neutralized. Pain in the base burns occurs late, which delays first aid. Base burns are more dangerous than acid burns [16].

Phenol and petroleum-derived compounds are organic compounds. They break down proteins by direct reactions or production of heat [14].

Compounds containing sodium, phosphorus, lithium, and chlorine are inorganic compounds. They cause skin damage by direct bonding and salt formation [14].

Some modern bombs contain white phosphorus. When this element comes into contact with air, it burns and the oil-soluble phosphorus fragments are scattered across the wound and spread through the subcutaneous fat tissue. As long as phosphorus is in contact with oxygen, it continues to burn, and therefore phosphorus burns are deep and painful, may extend to the bone. Local treatment is more urgent than conventional burns. Phosphorus burns must be prevented from contacting with air; it should be isolated by wrapping the wound with wet dressings or by immersing the affected areas in water. It should not be allowed to remain dry at any times. Phosphorus can cause hypocalcemia and hyperphosphatemia. There may

be many unwanted effects of absorbed phosphorus, delirium, psychosis, convulsions, coma; hepatomegaly, jaundice; proteinuria, acute tubular necrosis; thrombocytopenia, hypoprothrombinemia, ventricular arrhythmia, and myocarditis may develop [4, 14].

Other than these, burns due to coal tar can also develop, especially in the treatment of psoriasis. Tar is an industrial material used in road cladding and roof isolation [17]. It is obtained by dry distillation from organic substances, has a liquid oil consistency and is a water-insoluble substance. The boiling point reaches up to 232°C. This may cause severe burns. In the literature, it has been shown that the majority of hot tar burns often occur in the workplace in male workers with accidents [18]. Continuation of the skin contact with tar causes the heat transfer to continue and leads the burn to progress. Therefore, the tar should be removed from the body in a short time. In the literature, successful cases have been reported in which unsterilized sunflower oil, olive oil, as well as lanolin and surfactant-containing creams and other antibiotic creams were used [19]. Again, in the tar adhered skin zone, the ice cubes were left for 10–20 minutes, and the tar was frozen and separated in the form of a crust.

Chemical burns due to mercury-containing substances can cause blistering (bullae). Blisters must be excised because mercury is found in the bullae liquid.

5.3. Electrical burns

Electric burns, which are most common in men between 20 and 40 years of age, constitute 20% of burn-related mortalities [15]. It occurs by electric current or lightning strike. Low-voltage electrical burns are considered to be less than 1000 volts and high-voltage electrical burns are considered to be more than 1000 volts; electrical burns between 250 and 1000 volts should be followed up just like high-voltage electrical burns since these patients may develop unconsciousness, compartment syndrome, and myoglobinuria/hemoglobinuria [15].

In low-voltage accidents, burns are limited on the skin, however, go down into deeper tissues. In high-voltage accidents, there are traces just like stapler pierce, ulceration, and scarring. In the lightning strike, necrotic areas start from where the current entered and progress along the line [4]. As a result of direct contact with the electricity, systemic complications such as cardiac arrhythmia, necrotic areas in the soft tissues and bones may develop as well as thermal damage as the current passes through the whole body.

5.4. Radiation burns

It is caused by the uptake of radioactive material. The local radiation burns caused by high radiation doses (8–10 Gy) are similar to thermal burns except for several days to weeks of delayed latency. Taking high doses causes sudden cell death. The most sensitive tissues to radiation are lymphocytes and hematopoietic cells. The degree of radiation damage depends on the dose [20]. Erythema on the skin is the earliest finding. After weeks of exposure to high-dose radiation, necrosis and ulceration of the skin may develop.

Although it is not dependent on excessive heat or flame, sunburns and frostbites should be considered in the integrity of the burn etiology.

5.5. Sunburns

It develops due to uncontrolled and prolonged exposure to sun or light sources containing UVB. Sunburn is the contact dermatitis due to ultraviolet B rays (295–315 nm), which is the most erythematous wavelength. The formation of sunburn requires more ultraviolet light than the minimal erythematous dose (MED) [10]. While 20 minutes is enough to get a minimal erythematous dose (MED) in a clear summer day, 1 full day sunbathing is needed to reach 20 times the MED dose. People reaching this dose have sunburns with individual differences. The skin reaction starts at 4–6 hours and ends at 72 hours [4].

5.6. Cold burn (frostbite)

It is developed with cooling of the body. The skin is frozen at −2 to −10°C and irreversible changes occur under −22°C. Cold burn is different from thermal burns; trauma occurs at the cellular level and extracellular fluid directly, at the organ functions indirectly [21]. Electrolyte concentration increases with development of ice crystals in the intracellular and extracellular fluid, enzyme systems do not work and tissue destruction begins [4]. Vasoconstriction endothelial damage and thromboembolism increases ischemia and failure [21]. Prostoglandins are primarily responsible cytokines. In the first-degree frostbite, firstly, reflex erythema starts against cold, then vasoconstruction and paleness are seen. In the second-degree frostbite, erythema, edema, and subepidermal bullae, in the third-degree frostbite, blue-black color changes and hardening are observed [4]. It is usually seen at the outer regions such as ear, nose, and fingers [10]. Ischemia developed in the tissue and is spread to the body.

Besides these burn types, other rare burn traumas have been reported. There are also types of burns that are common in eastern societies and are associated with low socio-cultural level. As an alternative to modern medicine, particularly those commonly used in muscle joint disorders, include herbal applications and cupping therapy [22].

6. Physiopathology

6.1. Local and systemic changes in the formation of burn scars

When burns occur, cell proteins in the skin denature and coagulate and thrombosis develops in the vessels. Vascular permeability increases and denatured cell particles increase intercellular osmotic pressure. Vasoactive amines such as histamine, kinin, prostaglandin, and serotonin are released from the burn developing tissue. Platelet and leukocyte adhesion to endothelium occurs. The complement system is activated cytotoxic T cells increase, and the tissue develops into an open site for infection [23].

Heat injuries occur in two stages. First, coagulative type necrosis develops in the epidermis and tissues. Afterwards, late type injury occurs due to cell lysis as a result of progression of dermal ischemia (within 24–48 hours). The depth of necrosis is determined by degree of temperature it is exposed to and the time of duration [24].

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Burn injury causes both local and systemic changes. Vasodilatation and vascular permeability are also increased in the skin and subcutaneous tissues due to local reaction. As a systemic response, all internal organ systems are affected **(Figure 1).** In severe burns, cytokines and other inflammatory mediators are released in excess both in the burn area and in the unburned areas. These mediators cause vasoconstriction and vasodilatation, increase in capillary permeability, and development of edema both in the burn site and in remote organs. Pathological changes occur in metabolic, cardiovascular, renal, gastrointestinal, and coagulation systems. With burn shock, blood volume and cardiac output are decreased, renal blood flow and glomerular filtration rate decrease, gastrointestinal mucosal atrophy develops and intestinal permeability increases. Catabolism is accelerated and often results in widespread microthrombosis [14, 25].

When the burn occurs, three damage zones are described as local changes in the skin. These regions were first described by Jackson in 1947 [13]. It consists of coagulation (necrosis) zone, stasis (ischemia) zone and the outermost hyperthermia (inflammation) zone (**Figure 2**). The innermost region is the area closest to the heat source and the one with the greatest damage. Coagulation of structural proteins that develop in this region results in irreversible tissue injury. The area outside this region is called the stasis (ischemic) zone. In this area, tissue perfusion has reduced but is a layer of living tissue. Cells in this area can be saved if treatment is done to increase tissue perfusion. Otherwise, progressive ischemia and necrosis develop within 24–48 hours [13]. The third and outermost zone is hyperemia (inflammation) zone. Tissue perfusion is increased in this region and is characterized by vasodilation due to the

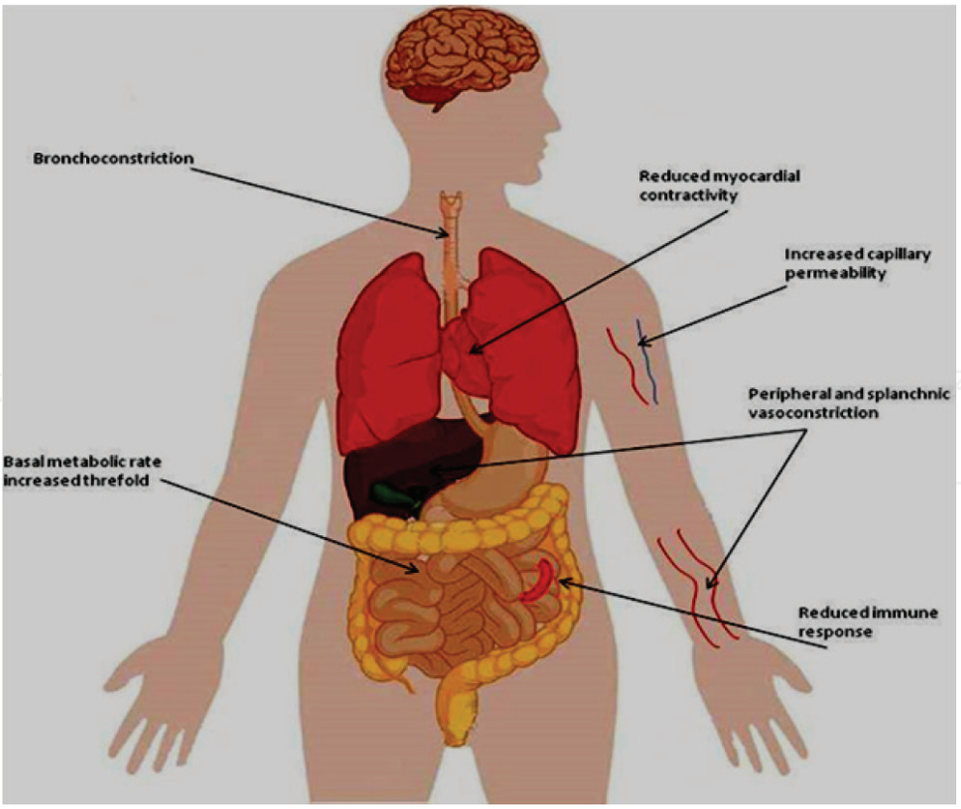

Figure 1. Systemic changes that occur after a burn injury.

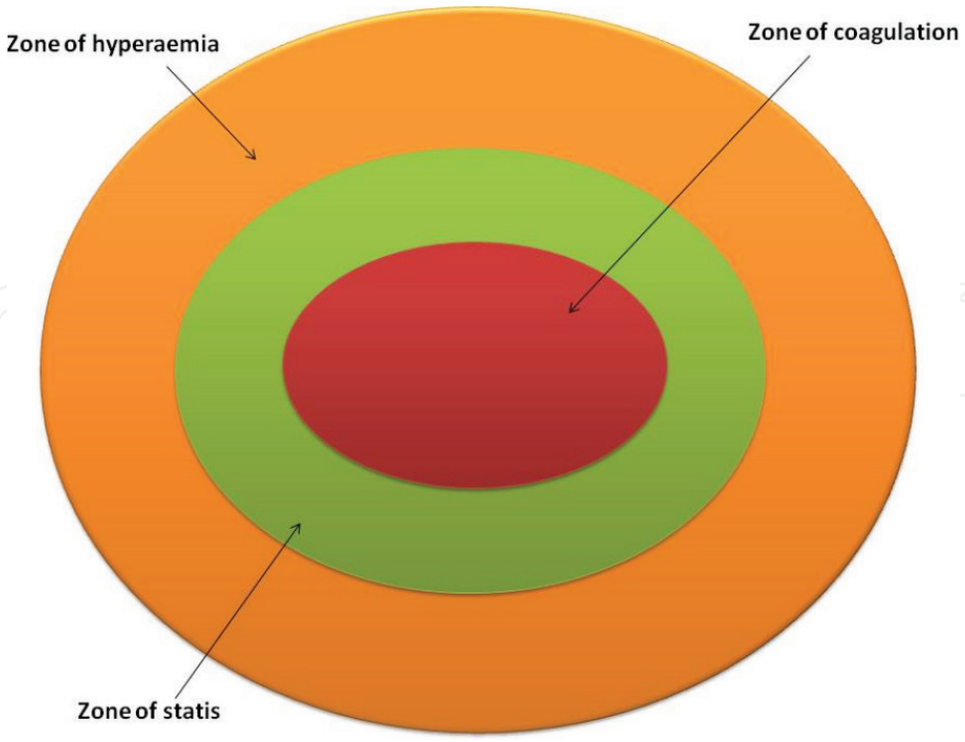

Figure 2. Jackson's burns zones.

inflammation surrounding the burn. The tissues in this area will heal within 7–10 days unless there is an intervening infection. It is important that treatment is initiated within 24 hours due to necrosis progression in burns where the stasis zone is progressive to dermal ischemia [26].

6.2. Burn shock ve pathogenesis

If the burn area exceeds 30% of the total body surface area, cytokines released from the burn area and other inflammatory mediators reach levels that will produce a systemic response [13]. An inflammatory reaction also occurs as a result of a minor thermal injury lasting for 20–60 seconds and at a temperature of 51–60°C. Burn shock period can be examined in three periods:

Early period (exudative period): It covers the first 36–72 hours after trauma. Vasodilatation is the first response to trauma in the burn area. Systemic inflammatory mediators (histamine, TNF-α, IL-1, IL-6, GM-CSF, interferon-γ, and prostaglandins) are excessively released from both the burn site and from other tissues. Capillary permeability increases, due to inadequate tissue perfusion, intracellular sodium increases, and edema develops in the cells [27]. Burn shock developed after burns is hypovolemic shock and is directly proportional to the extent and severity of burns. In adults 20%, in children younger than 12 years of age 10%, of burn area leads to a higher risk for hypovolemic shock development [4, 24]. Hypovolemia resulting from circulatory fluid loss due to edema, occurs within the first 2 days utmost. Hemodynamic insufficiency develops due to decreased blood volume. As circulation in the brain, kidneys, liver, muscles, and gastrointestinal system deteriorates, oxygenation is reduced. Ischemia

develops in the tissues as a result of hypovolemia and slowing down of blood flow. Damage to cells that develops in hypoxia leads to dysfunction in organs [13, 24]. Clinical signs of hypovolemic shock are observed as follows:

- Pale, moist, cool skin.
- Hyperthermia have coldness at extremities.
- Tachycardia and hypotension.
- Fast and shallow breathing.
- Decrease in urine volume.

Intermediate period (intoxication period): Includes 2–4 weeks after burn. During this period, the formation of edema stops and polyuria develops. While edema is regressing, the denatured proteins released from the cells pass through the circulation to form the intoxication case. At the end of the first week after burn, the hemodynamic situation is completely reversed and there is an abnormally high cardiac output accompanied by vasodilatation in the burn patient. On the 10th day after the burn, the cardiac output is increased by 2.5 times of normal [28].

Late (infectious) period: Acute and chronic infections may occur during this period. The cellular and humoral immune response is suppressed in direct proportion to the size of the burn. Lymphopenia develops chemotaxis, phagocytosis, and migration of neutrophils are reduced. IL-2 level decreases in burns that hold large surface area. IL-1, IL-6, and IL-8 levels decrease in the first week after burn [23]. Increased catabolism and capillary leakage result in reduced circulating IgG, IgA, and IgM. The decrease in IgG, especially after burn injuries, is closely related to septic complications [13, 29]. With respect to the grade of the burn, T cell activation is impaired, creating a predisposing condition for viral and fungal infections [24].

6.3. Evaluation of burn severity

The determination of the severity of a burn depends on the depth of the burn and the width of the area. It is necessary to wait 24–48 hours to determine the exact burn grade, as the depth of the burn may increase due to edema and infection [4, 10].

The depth of the burn varies according to the type of the causative agent, the degree of temperature, and the thickness and vascularity of the affected skin area. Burn depth is examined in three groups **(Figure 3)**.

- First-degree burn is a superficial burn and there is only damage in epidermis. There is a painful erythema and edema in the burned skin. Pain relieves after 12–24 hours, first-degree burn heals with desquamation 1 week later; does not leave any cicatrix. Sunburns are considered as first-degree burns. Cold application to erythematous and edematous area also reduces pain. Topical analgesic creams can be applied as symptomatic treatment [28].
- Second-degree burn occurs in two forms: superficial and deep. The epidermis and the dermis layer down to the sebaceous glands are affected in the superficial type [4]. Edema

and subepidermal bullae formation are observed on the skin. Hair roots are intact and not affected by burns. In the deep type, burn goes down as far as to reticular dermis. The skin is pale and thickened. Some areas have erythema, if the bullae are opened, the surface appears moist due to plasma leak. If the skin surface remains dry during this period, the pain will increase, so wet dressing should be done. A superficial type of second-degree burn heals within 2–4 weeks without cicatrix. Hypo-hyperpigmentation may develop. In the deep type, healing is slow, may exceed to 4 weeks, and healing results in cicatrix. There may be loss of function in skin and hair. Fluid resuscitation may be needed for second-degree burns that hold more than 20% of the total body surface area [28, 30].

- Whole skin (epidermis, dermis, and hypodermis) is affected in third-degree burns. More severe burns can affect muscles, tendons, and bones. The skin surface is dry and free from erythema. This tissue, which has lost its vitality and is hard, is defined as eschar. A few days later, when the eschar layer is removed, deep granulation tissue is observed. This tissue absolutely heals with cicatrix. Large scars do not close up and skin grafting may be necessary [31].

Accurate calculation of the burn surface area, as well as burn depth, is very important for the initiation of emergency treatment and fluid replacement. When the surface area of the burn is determined, what percentage of the whole body surface area is burned is calculated. The body surface area of a normal adult is about 1.72 m^2 [4, 10]. "Rule of Nines" of Wallace is used to determine the area of the burned surface **(Figure 4)**. With this approach, the burned area is calculated approximately in a short time.

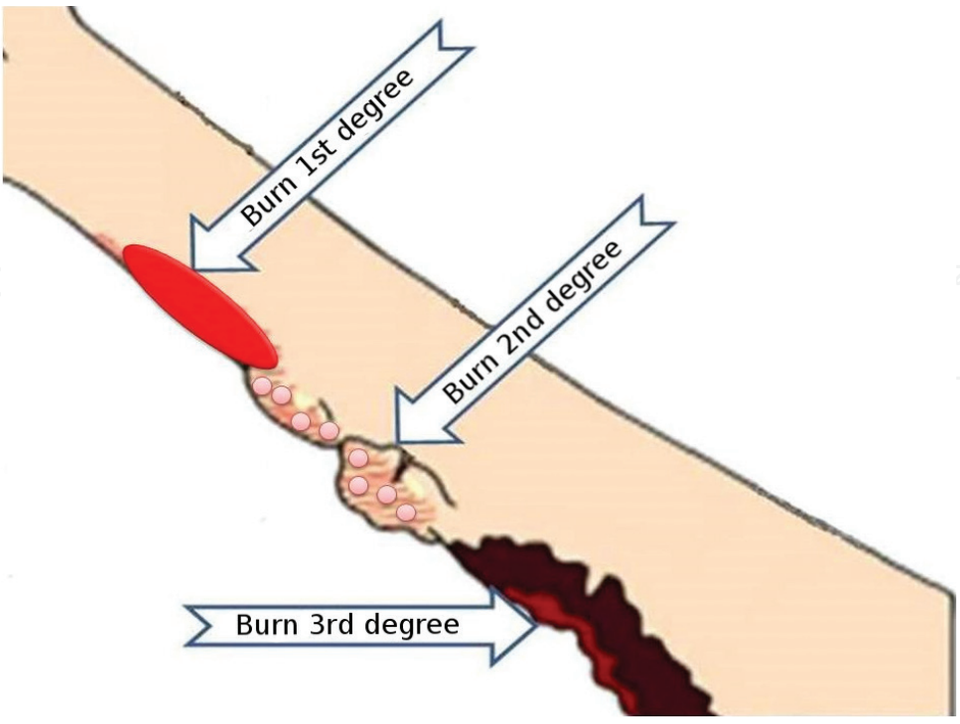

Figure 3. Burn types.

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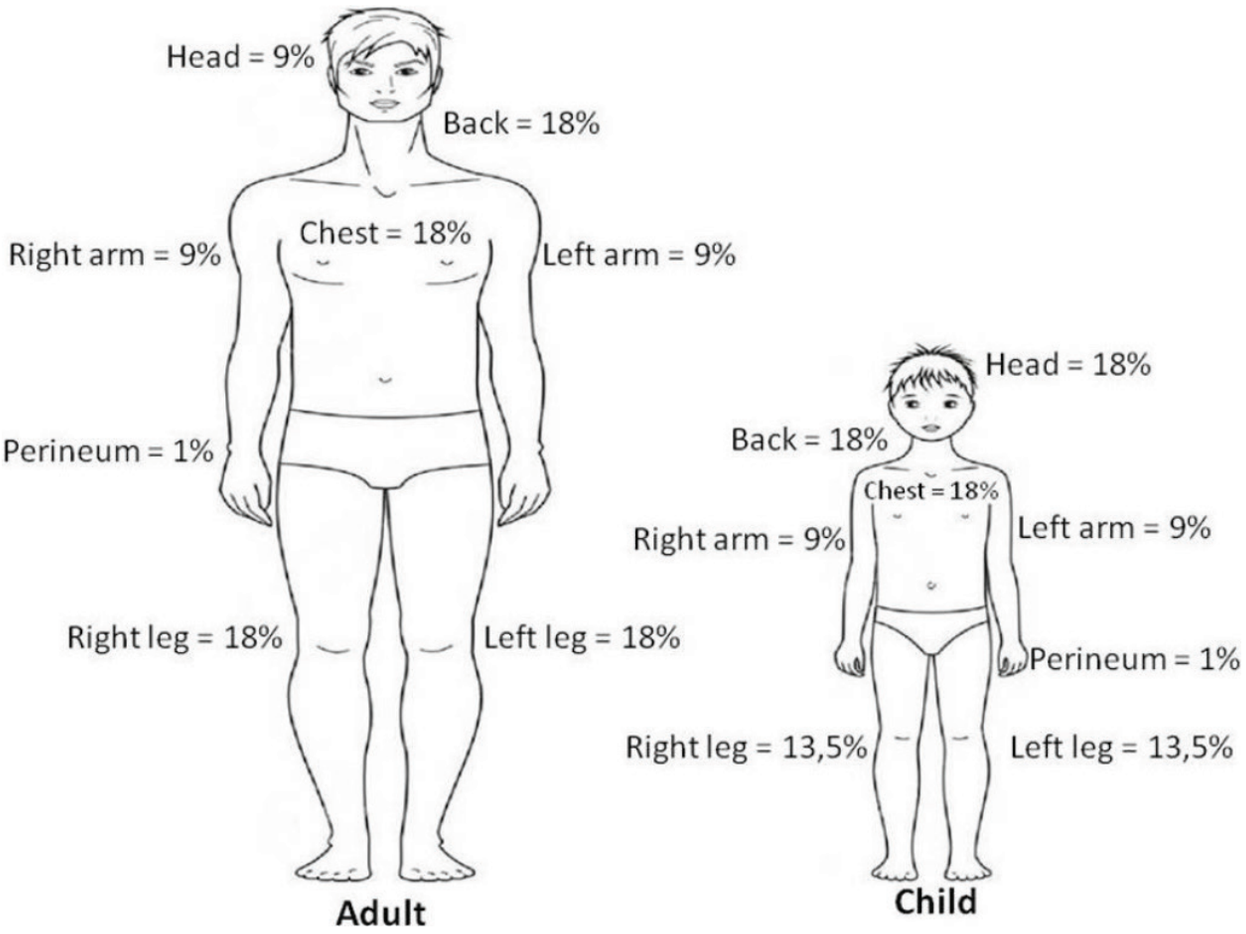
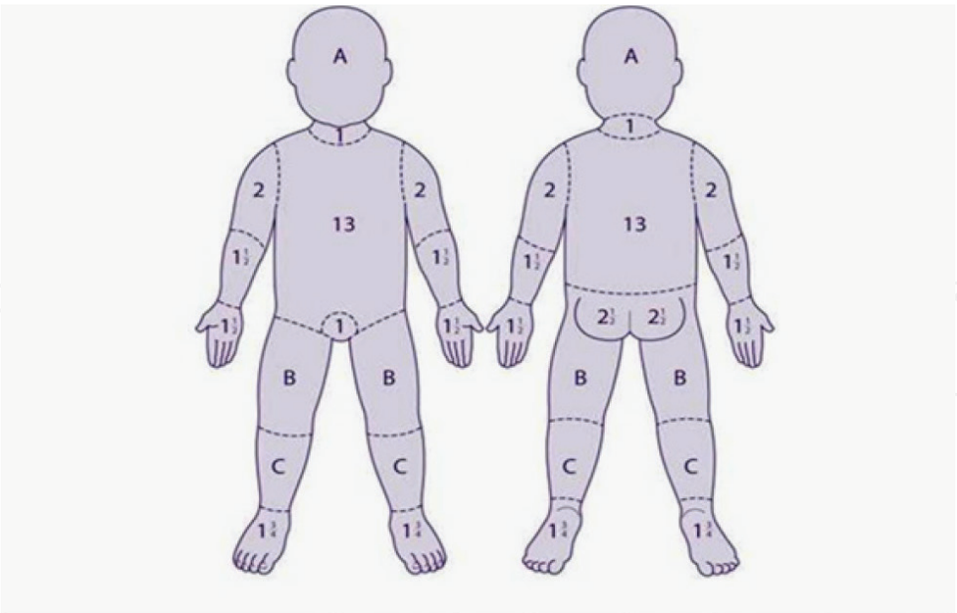


Figure 4. Wallas rule of nines.

According to the Rule of Nines, head is 9%, each upper limb is 9%, each lower limb is 18%, anterior trunk except head and extremities is 18%, posterior trunk is 18%, and perineal region is 1% of total body surface area. The palm area of a patient, including the fingers, constitutes 0.8% of the total body surface area. The palmar surface area is generally used to estimate small or large burns [32]. In children, the head and neck region has a larger portion of the entire body surface. The lower limbs form smaller body surface area. Because of this, Rule of Nines can not be applied to children under 14 years old. Therefore "Lund and Browder Chart" has been developed (**Figure 5**).

Burns with area smaller than 5% are considered as simple burns. About 1–15% burn in adults (1–7% in children) is "mild burn", above 15% deep burn in adults (7% in children) is "severe burn" and 40% superficial burn in adults (20% in children) is "intermediate burn", above 30% deep burn in adults (20% in children) "severe burn" involving the face and upper respiratory tract and severe electrical burns. There is a high risk of developing hypovolemic shock in second- and third-degree burns with 10% area in children and elderly, and with 15% area in other age groups [32].

Pigmented skin may be difficult to evaluate, in such cases it may be necessary to remove all loose epidermal layers to calculate the extent of burn [48].



Area	Age 0	1	5	10	15	Adult
A= ½ of head	9½	8½	6½	5½	4½	3½
B=½ of one thigh	2¾	3¼	4	4½	4½	4¾
C= ½ of one lower leg	2½	2½	2¾	3	3¼	3½

Figure 5. Lund and browder chart.

7. Burn scars

It is estimated that more than 6 million people per year have burn wounds. Despite improvements in treatment and survival rates, scar formation rates are high and such scars cause severe functional impairment, psychological morbidity, and costly long-term treatments [33].

Scars that develop are often late complications of the burn, usually seen after an inadequate and inappropriate treatment for burn wounds as well as immediately after the treatment. Post-burn cicatrix can be divided into three main groups: hypertrophic, atrophic scars, and contractures [34]. In a study conducted in Italy, in cases 23 days after reepithelialization and meanly 15 months after; hypertrophic scars in 77%, contracture in 44%, hypertrophic contracture scars in 5%, hypertrophic induction in 28% were observed to be developed [33]. Especially hypertrophic scars that develop after thermal injuries may be together with contracture, which can also lead to loss of function in joints [34, 35].

Burn wound healing occurs in three phases. These are the inflammation, proliferation, and remodeling phases. Prolongation and expansion of the inflammatory phase is the most important factor in scar formation [36]. Scar formation is affected by the depth of the burn, the duration of the healing, the development of infection, the age of the patient, genetic factors, circulatory disturbances, or the development of diseases that suppress the immune system [37].

In particular, hypertrophic scars or keloids do not develop in burns that do not reach reticular dermis. During wound healing, several factors increase or prolong the inflammation in the reticular dermis. In a study conducted, the most frequent factors in scar development were found to be flame-induced burns, followed by hot water and less frequently as chemical and electrical burns [34]. The development of infection or folliculitis in the wound bed, mechanical trauma, large and deep burns, and improper treatment in the first period increase the risk of scar development [38]. The rate of hypertrophic scar development in burns recovered under 10 days is 4%, while the risk of scar development in burn wounds healing in 21 days or longer is up to 70% [39]. One of the most important factors in pathological wound healing is mechanical stretching of the skin [45, 46, 48]. Anterior chest wall, arms, and shoulders are the most common areas for hypertrophic scars. Another risk factor for scar development is that the person is adolescent or pregnant. Vasodilator effects of hormones such as estrogen and androgens increase scar development. Children and adolescents with pigmentation injury skin type were more likely to develop scarring [40, 41]. In a study by Arima and colleagues, hypertension was found to be another risk factor for the development of scarring [42]. Among burn cases with systemic inflammation, the patients who undergo reconstructive surgery have been shown to develop scarring within 1 year [38]. Predisposing factors for scar development include A blood group, hyperimmunoglobulin E syndrome (high allergy risk), Afro-American, and Asian ethnicity [43]. Wound healing is a natural process that reinstates deep integrity of the skin as quickly as possible. Wound healing can lead to an excessive process that is causing pathological scar formation or to a dynamic process that does not heal or turns into a chronic wound. Singer and Clark argue that hypertrophic scar formation is caused by an abnormal wound healing [35]. Unlike keloids, the hypertrophic wound remains at its limits and these marks can regress over time [44].

7.1. Pathophysiology

TGF-β is the most important cytokine involved in wound healing. TGF-β plays a role in fibroblast proliferation, collagen synthesis, and storage and reshaping of the new extracellular matrix (ECM) by stimulating inflammation and angiogenesis [45]. It has been demonstrated by several groups that fibroblasts derived from hypertrophic scarring have a phenotype that varies from normal scars or fibroblasts produced from undamaged dermis [2]. Wang et al. have shown that hypertrophic fibroblasts and hypertrophic scar tissue produce more mRNA and protein for TGF-β1 compared to normal skin-derived normal skin or fibroblasts, suggesting that TGF-β1 may play a role in hypertrophic scar formation [3]. Type 1 and type 2 collagen synthesis is increased by smooth muscle expression with proliferation in myofibroblasts, which leads to fibrosis.

In hypertrophic scars, it has been shown that type III collagen fibers which are parallel to the epidermal surface predominate. Scar tissue consists mainly of differentiated fibroblast nodules including myofibroblasts, collagen filaments, and other extracellular matrix proteins [2]. Immediately after injury, platelet degranulation and activation of the complement and coagulation stages occur. For hemostasis, fibrin clots form and become a framework for wound repair [2]. Together with platelet degranulation, a number of potent cytokines such as epidermal growth factor (EGF), insulin growth factor (IGF-I), platelet-derived growth factor (PDGF), and transforming growth factor (TGF-β1) are released. Fibroblasts synthesize the reparative tissue skeleton, called the extracellular matrix (ECM). This granulation tissue

consists of procollagen, elastin, proteoglycans, and hyaluronic acid. Decorin, a proteoglycan, is found extensively in the dermal extracellular matrix. Decorin regulates collagen fibril, fiber, and fiber bundle organization, and has been shown to reduce approximately 75% in hypertrophic scars [3]. Decorin can bind to TGF-β and neutralize it, thus minimizing the stimulatory effects of this cytokine on collagen, fibronectin, and glycosaminoglycan production. The conversion of a wound clot to granulation tissue requires a precise balance between ECM protein accumulation and disintegration, and when this procedure is impaired, scarring abnormalities occur [46].

As mediators of the TGF-β pathway, SMADs are the intracellular protein family that regulates the signaling of the TGF-β type I receptor in response of the cell to a specific TGF-β. R-SMAD3 and 4 were identified as predominant mediators of autocrine stimulation with TGF-β in hypertrophic wound-derived fibroblasts [46].

Other than these, keratinocytes are thought to play an important role in scar formation by producing signals that stimulate fibroblasts in the dermis or by producing more ECM [47, 48]. It has been shown that the mast cells that mediate the secretion of soluble mediators such as histamine, heparin, and cytokines promote fibroblast proliferation [47].

In particular, IL-1β, PDGF, EGF, and TNF-α play an important role in the expression of matrix metalloprotein in fibroblasts and are responsible for scar formation [49, 50]. Apoptosis has also been shown to play a critical role in the transition to scar formation following tissue damage [47, 50].

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