Chapter

# Calcium Alginate Polysaccharide Dressing as an Accelerated Treatment for Burn Wound Healing

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## Abstract

Patients with burn injuries suffer from pain and an inflammatory response; however, treatment methods are still not satisfactory and remain challenging. Due to the long stage of burn wound rehabilitation, which contributes to the long-term sensory problems, an effective treatment must begin at the outset of burn wound care. The functionalized wound dressing is expected to be a great treatment strategy over the commercialization wound dressing products and engineered skin substitutes nowadays. Some studies revealed the use of calcium alginate polysaccharide (CAPS) as an "active" dressing due to its calcium richness for wound healing and scar tissue formation. The outstanding outcome of CAPS dressing for severe burn injuries was indicated by natural wound healing and less scarring formation, minimum bacterial infection, cytokine enhancement regulation, and appropriate inflammatory response and pain regulation. These advantages affirmed the phytopolysaccharide dressing as the next generation of wound dressing materials with highly desirable properties.

**Keywords:** severe burn injuries, wound dressing, wound management, calcium alginate polysaccharide, inflammatory response

## 1. Introduction

Burns are the most traumatic injuries and physically harmful because of long hospitalization and rehabilitation, which lead to significant morbidity and mortality [1, 2]. The development of effective treatment associated with burn injury is a major unmet medical problem. Current burn wound treatment methods, such as eschar excision, split-thickness skin autograft, and cell-based skin constructs, are still not satisfactory and remain challenging. Not only causing painful and relative costly treatment, but those methods are also very difficult to perform in patients due to poor availability of healthy tissue [3–5].

Despite any advances in burn management, how to treat wound properly at the outset of burn injury is the important key of an effective treatment. Most patients with burn injuries suffer from long-term pain and posttraumatic situation; therefore, an appropriate burn wound handling with a good dressing initially is expected to be a great way to minimize scar formation and accelerate burn wound healing.

A good clinical dressing must be easy to handle, avoids infection and inflammation, has no toxicity, causes no allergic reactions, and permits easy and early mobilization [6, 7].

Bioactive wound dressing, or functionalized wound dressing, is expected to overcome the limitations of the current treatment in burn wound management. This dressing delivers either bioactive compounds or dressing that is constructed from a material having endogenous activity in wound healing, which contribute not only a matrix for repair but also growth factors and cytokines to enhance the healing process [8]. Various types of bioactive wound dressings are available on the market and are used clinically. However, bioactive wound dressings have advantages and disadvantages, so choosing the suitable wound dressing as needed is advised.

Alginate, commonly derived from seaweed, has been widely investigated by many researchers for possible new alternative in wound management field. Alginate, a rich natural polysaccharide, which contains glycosaminoglycan (GAG), has several major properties such as biocompatibility, gelling, and swelling that keep the wound site moist enough for proper healing and then able to reduce healing times of wounds [9, 10]. When attached with wound, an ion-exchange reaction occurs between the calcium in the alginate and the sodium in the exudate, thus producing a soluble gel that help maintain a moist wound environment and also hold bacterial infection in absorbed wound fluid at the same time. This is why alginate is recommended for the treatment of moderate to highly exuding wounds [11].

Calcium alginate polysaccharide (CAPS) has been found suitable for use in pharmaceutical drugs, as a bioactive food ingredient, and for cell encapsulation or tissue regeneration [12]. Numerous studies revealed that CAPS-containing dressing for severe burn injuries has outstanding outcomes such as rapid wound closure with less scarring formation, minimum bacterial infection, cytokine enhancement regulation, and appropriate inflammatory response and pain regulation. In addition, this material becomes substantial to be considered as optimal burn wound dressing treatment because it maintains a great moist microenvironment at the wound site. Therefore, the detail mechanisms and involvement of CAPS dressing in accelerating burn wound healing will be further discussed in this chapter.

## 2. Medical dressing for the treatment of burn injury

Generally, the treatment of burn injury depends on both depth and surface area of burn wounds, which reepithelialization is the most important stage of burn wound repair. For the severe burn injury such as deep partial-thickness or full-thickness burn, there is a need of special treatment to prevent delayed reepithelialization due to the destruction of epithelial regenerative elements in the basal layer of the epidermis and in the dermis. To date, eschar excision and split-thickness skin autograft taken from a healthy skin of the same patient are medical standard treatments for severe burn injury [3, 4]. However, the grafts are causing pain and very difficult to perform in patients due to poor availability of healthy tissue. In addition, many types of cell-based skin constructs have been developed for full-thickness burn injury, but poor survival rate of the keratinocytes in cell sheets has been a major concern in these discoveries [5].

On the other hand, for the first or superficial second-degree injury, the reepithelialization remains possible by the migration of keratinocytes from the edges of the wound, followed by their proliferation, stratification, and dedifferentiation to form an intact epithelium [3]. But still, an optimal reepithelialization

requires a supportive microenvironment to avoid infection. Bacterial infection was well known as a common cause of death after burns [13]. Commonly, antimicrobial creams and occlusive dressings are applied on the wound to avoid infection, to limit wound progression, and to improve epithelialization progression [14].

Despite any advances in burn management, how to treat wound properly at the outset of burn injury is the important key of an effective treatment. The proper burn wound handling in the beginning with the functionalized wound dressing may enhance reepithelialization progress and accelerate an intact epithelium formation with minimal scar appearance. Not only should achieve rapid healing at reasonable cost with less inconvenience to the patient, but the use of clinical dressing also must be easy to handle, avoids infection and inflammation, has no toxicity, causes no allergic reactions, and permits easy and early mobilization [6, 7].

Based on its natural action, wound dressings are normally classified as passive products, interactive products, and bioactive products [9]. Passive products consist of traditional dressings like gauze and tulle dressings which account for the largest market segment. Interactive products consist of polymeric films and forms, which are recommended for low exuding wounds due to its characteristics. Bioactive products are which deliver either bioactive compounds or dressings are constructed from a material having endogenous activity in wound healing. These materials include proteoglycans, collagen, non-collagenous protein, chitosan, or alginate. They are considered to contribute not only a matrix for repair but also growth factors and cytokines to enhance the healing process [8]. Commercially, various types of those bioactive wound dressings are currently used in the clinical setting with their advantages and disadvantages for some types of wounds. In the case of burn wound, the dressing with rich glycosaminoglycan (GAG) is expected to encourage the efficient and rapid healing process. GAG has a significant role in wound healing phases which acts as a regulator of early inflammation to modulate inflammatory cell and fibroblast cell migration, pro-inflammatory cytokine synthesis, and the phagocytosis of invading microbes [15].

Alginate, commonly derived from seaweed, is a rich natural anionic phytol polysaccharide (APS) that consists of mainly differing ratios of D-mannuronic and L-guluronic acid, which are covalently bound through 1,4-glycosidic linkages. Polysaccharides and proteins are the most common natural polymers used in the tissue engineering field for the regeneration of full-thickness wounds because of their biocompatibility, biodegradability, and similarity with ECM [16, 17]. Containing glycosaminoglycan (GAG), they play a key role in wound healing due to their ability to encourage activation of the immune system that cleans up the wound site after injury and reduces the pain simultaneously. It provides a moist environment around the wound site that leads to rapid granulation and reepithelialization. Alginate-based wound dressings have also been demonstrated for their hemostatic properties in exudation/bleeding wounds and burns [9]. Alginate can easily form gels by binding with divalent cations, especially calcium ions [18]. The gelling property of alginate helps in the dressing removal without much trauma [19].

Alginate dressings were originally presented as formed from calcium alginate fibers and have been technically fabricated with fibers woven to form a more solid and strengthen structure to obtain an applicable wound dressing. As wound dressing, treatment with calcium alginate polysaccharide (CAPS) dressings had shown great wound recovery outcome in various types of skin wounds [20–23]. They promoted healing via a direct modulatory effect on wound macrophage activation that secretes pro-inflammatory cytokines within the chronic wound bed which may initiate a delayed inflammatory phase [24]. Additionally, numerous studies revealed that CAPS-containing dressing for severe burn injuries has outstanding outcomes such as rapid wound closure with less scarring formation, minimum

bacterial infection, cytokine enhancement regulation, and appropriate inflammatory response and pain regulation. Hence, this material becomes substantial to be considered as an optimal burn wound dressing.

## 3. The problem and historical perspective of burn wound healing

The proper treatment of wound has attracted the human attention over several decades. Among the various types of wound, severe burn injuries are the most traumatic and physically harmful, which lead to significant morbidity and mortality [1, 2]. Burn injuries can lead to multifarious uncontrolled effects after the accident, and they may have a major impact to the body functions of burn-injured patients. Historically, they were accounted for an estimate of 180,000 deaths every year, which are related to burn injury worldwide, and the vast majority occurs in low- and middle-income countries [25]. Most burn victims face up a long-term hospitalization and suffer major burns covering 25% of their body surface.

The healing process of burn wound, both small burn and large severe burn injuries, occurs through several biological processes, such as hemostasis, inflammation, proliferation, and maturation. Without the right handling, a hypertrophic scar caused by fibroblastic proliferation will be formed during the healing process, which is confined to the wound site [26]. In addition to local wound repair, severe large burns also can stimulate a persistent pathophysiological stress response [27]. Most patients with burn injuries suffer pain during burn wound debridement in the clinic, which they describe as severe to excruciating despite the use of powerful opioid analgesics [28]. Based on local and systemic pathophysiologic responses, burn wound recovery is generally divided into three phases: acute phase, healing phase, and rehabilitation phase. The acute phase may be completely bypassed in smaller injuries, which specifically lasts 2–3 days [29, 30]; the healing phase may be weeks or more, whereas the rehabilitation phase most often takes at least 1 year and sometimes much longer, depending on patient participation in the treatment plan, patient age, and specification of burn [31]. These long phases of recovery often lead burn-injured patients to survive from long-term pain and encounter a posttraumatic situation.

In order to reduce the lifelong burn wound recovery phases which usually contributes to the further problems, an effective treatment must begin at the outset of burn wound care. An appropriate burn wound handling in the beginning is expected to be a great way to minimize scar formation and accelerate burn wound healing.

## 4. Application of CAPS dressing for accelerating burn injury treatment

Since burns have a heterogeneous nature, a variety of animal burn models have been developed as valuable tools to observe the pathophysiology of burns. Animal models continue to be explored to uncover the molecular and cellular aspects that characterize human burn trauma [32]. Better understanding of the burn wound healing in animal models and their relation to human wounds will significantly overcome the limited translation of research into practical treatments for burn-injured patients.

Wang et al. [33] treated a severe burn injury in swine model with calcium alginate polysaccharide (CAPS) dressing to observe wound repair and scar formation comparing to the use of carboxymethyl cellulose (CMC) as a commonly used wound dressing for many years [34, 35]. These animals were also used to assess the

secondary outcomes of the depth of scar formation at postburn, determined by the Vancouver Scar Scale (VSS) which consists of four variables: vascularity, height (thickness), pliability, and pigmentation. The total score ranges from 0 to 14, whereby a score of 0 reflects normal skin. The results showed that wounds dressed with CAPS exhibit a rapid reepithelialization and less scar formation, which appeared with a smooth wound. Based on VSS scores, there was less scar formation in the wounds dressed with CAPS, shown by significantly lower scores up to 6 weeks of observation. Scarring, or fibrosis, is known as an abnormal tissue remodeling. The management of scar formation is one of major complications encountered during the wound healing process. Without the right handling, a hypertrophic scar caused by fibroblastic proliferation will be formed during the healing process [26]. Moreover, healing by fibrosis instead of regeneration often causes lifelong disability that has a significant economic impact [36].

In line, an obvious wound closure and relative complete reepithelialization were observed to occur on wound dressed with the CAPS dressing in rat group model [37]. Their histological analysis revealed that the new dermis tissue on dressing treated wound area was composed of reorganized and stratified epithelial layer, with fully developed connective tissue, hair follicle, sebaceous glands, and aligned collagen. Another study reported that CAPS dressing treatment accelerated wound closure rate and exhibited a faster epithelialization [38]. They found that the expression of skin tissue collagen I was elevated by CAPS dressing application, and this dressing provides a moist environment and a faster collagen I-related epithelialization.

The ability of CAPS dressing reduces scar formation in burn injury is attributable to its rich contain of glycosaminoglycan (GAG), which was known to promote wound healing, lead to rapid granulation and reepithelialization, and thus yield a minimum scar formation certainly. Moreover, when attached to the wound, an ion-exchange reaction occurs between the calcium in the alginate and the sodium in the exudate, producing a soluble gel that turns to help maintain a moist wound environment [39]. CAPS dressings also have their inherent ability to augment hemostasis, as release of calcium ions leads to platelet activation [40, 41]. Additionally, calcium ions also speed up the wound healing process by modulating cell proliferation, maturation, and the creation of epidermal lipid barriers [42–44].

As another major challenge in burn injury management, bacterial infection becomes the most common cause of mortality and morbidity [13, 45, 46]. Infection is defined as the presence of high concentrations ($>10^5$ organisms/g of tissue) of bacteria in the burn wound and usually progresses to invasion of subjacent tissue within 5 days. Infection can delay wound healing process due to the development of a pronounced immune response, accompanied by sepsis or septic shock, which causes hypotension and impaired perfusion of end organs including the skin. To prevent this condition, wound dressing for burn injury treatment should create an optimal environment, which provides barrier against chronic wound infection.

Some studies have demonstrated that CAPS dressings have hemostatic [47] and some bacteriostatic [48] properties. CAPS dressing for burn wound treatment demonstrated a remarkable inhibition of bacterial growth than CMC dressing treatment, which significantly reduced the amount of bacteria at 3 weeks postburn injury [33]. This reduction was maintained until 6 weeks postburn injury. The infection control functioned by CAPS dressing might be related to its bacterial infection holding in absorbed wound fluid. As they swell, they trap wound debris and bacteria, thereby reducing overall bacterial load within the wound during dressing changes [19]. In addition, the advantages of a new technology conferring a bactericidal effect on CAPS gels for wound dressing have been explored. Poor et al. [49] developed nonthermal-plasma-treated alginate gel wound dressing, and the

results showed that this treatment has better wound decontamination and wound healing capabilities, as well as broad-spectrum antibacterial activity and negligible cytotoxicity.

CAPS dressing reduced the bacterial growth through the release of calcium, which has been recommended as an antimicrobial agent [50–55], resulting in superior bactericidal and bacteriolytic effects compared with other antimicrobial agents [52–55]. Moreover, the use of alginate derivatives such as antibacterial, antiviral, and antifungal agents has been revealed by numerous data [56, 57]. Negatively charged alginates were found to interact with the outer bacterial cellular surface, which causes disruption and leakage of intracellular substances [58, 59]. Additionally, the ability of alginate modulating the production of toxins, microbial growth, and factors crucial for microorganism's stability could be the reasons for its antibacterial efficacy characteristic. Some varieties of bacteria such as *Pseudomonas*, *Escherichia*, *Proteus*, and *Acinetobacter* have been proven to be detained by bacteriostatic activity of alginate [60, 61].

Further, the CAPS dressing treatment has also demonstrated its critical role in inflammation. Inflammation is a crucial stage to successful burn wound healing. The release of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8, interferon (INF)-γ, and tumor necrosis factor (TNF)-α, after thermal injury is one of the important systemic inflammatory responses in burn-induced skin damages [62, 63]. Pro-/anti-inflammatory cytokines act as important modulators of immune cell proliferation, differentiation, and clonal growth of lymphocyte subpopulations and also attract immune cells to the site of burn injuries [64], which are substantial in the process of burn wound recovery.

The involvement of IL-4, IL-6, TNF-α, and MCP-1 was found in the early stages of the rat's response to burn injury treated with CAPS dressing [33]. Immune cells were attracted by these cytokines to the site of injuries to initiate an immune response right away after burning. The ratio of IL-6 to TNF-α can be used to predict mortality from sepsis following burn injury [65]. IL-4 and IL-8 may serve as predictive biomarkers of mortality from sepsis and/or multiple organ failure (MOF) [66]. In addition, MCP-1, an initiator of typ. 2 T-cell generation and an indicator of bacterial infection, is essential for optimal microbial elimination [52]. The involvement of MCP-1 in Gram-positive bacterial infections has been demonstrated in the control of *Listeria monocytogenes* infections [53]. Chan et al. [67] and Thomas et al. [24] have also revealed the similar results both in vitro and in vivo. Particularly, aside from the other chemokines and cytokines, at least fivefold more of IL-1β secretion was found from CAPS gel treatment compared to agarose and collagen gel treatment [67]. IL-1β is known as a critical mediator of inflammation which has substantial roles in neutrophil mobilization, cellular adhesion to the endothelium, and white blood cell infiltration [68, 69].

Furthermore, the pain is related with the modulation of transforming growth factor (TGF-β), an important inflammatory cytokine and anti-inflammatory factor [70–72], that implicated in the pathogenesis of keloids and hypertrophic scarring. TGF-β also participates in the mechanism of pain signals including peripheral and central processing [71]. CAPS dressing for burn wound treatment demonstrated high levels of TGF-β1, TGF-β2, and TGF-β3, suggesting that it might contribute to reduced pain perception [33]. TGF-β1 is responsible for the fibrotic scarring response, whereas TGF-β2 and TGF-β3 are responsible for the scarless wound healing [70]. Another study confirmed that alginate-containing dressings can augment natural wound healing with inhibition of cytokines associated with fibrosis, resulting in decreased wound size and increasing epithelial proliferation [73].

Those data correlated very well with the use of CAPS dressing for human skin wound in the clinical setting recently. CAPS dressings were applied after perianal

abscess surgery, which was known as an acute suppurative infectious disease that occurs around the anus, anal canal, and rectum. The results showed that the expression of a variety of proliferative cytokines increases in the wound treated with CAPS dressing and helps promote wound healing [74]. The CAPS dressing treatment also was found to increase the synthesis of collagen and, on the other hand, inhibit the apoptosis of mitochondrial pathway and death receptor pathway.

Some literatures revealed that calcium ions from Ca-alginate systems [62] and oligosaccharides derived from polysaccharides (β-glucan, xyloglucan, chitin, pectin, D-mannuronic, and L-guluronic) can stimulate human cells to produce cytokines [75, 76]. Especially, enhancement of IL-1β secretion was expected due to the connection between calcium ion-induced mitochondrial damage and activation of the NLRP3 inflammasome, an important molecular platform expressed by myeloid cells in innate immune defense [77–79]. Besides, alginate-containing dressings have the potential to activate macrophages and have the ability to generate a pro-inflammatory signal which promotes granulation tissue formation [24]. However, another factor that may be important in cytokine induction not only relates to the proportions of guluronic to mannuronic acid residues but also their polymeric arrangement [80].

In summary, because of these properties, CAPS dressings are considered as a bioactive wound dressing and expected to accelerate the treatment for burn wound healing. There were few products made from CAPS related to surgery and wound management previously but, due to the small amount of these fibers used in total product with high-cost manufacture, it seems not profitable to continue the production. With the improved technology lately, CAPS has been developed into spinning fine dressing as an applicable wound dressing. Together with the increased understanding of CAPS beneficials in accelerating burn injury treatment, it is expected that CAPS dressing will give potential value for medical and business field simultaneously.

## 5. Conclusion

As the glycosaminoglycan (GAG) has influential roles in the stimulation of rapid wound healing, calcium alginate polysaccharide (CAPS), which contains a rich amount of GAG, can be regarded as a remarkable material-based wound dressing option. Since this material had technically actualized into spinning fibers woven or non-woven, it is expected that CAPS-containing wound dressing not only gives an optimal burn injury treatment alternative in medical field but also can rise up the textile industry value from the business perspective. Owing the significant benefits as an "active" dressing for burn wound recovery, such as rapid wound closure with less scarring formation, minimum bacterial infection, cytokine enhancement regulation, and appropriate inflammatory response and pain regulation, which have been demonstrated in several studies and clinical trials, therefore, the CAPS dressing holds a promising potential as the advisable preference of burn injury treatment strategies with highly desirable properties.

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## Conflict of interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



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