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Review Article

Hydrolyzed Versus Native Collagen in Management of Acute Surgical Wounds: A Literature Review

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Abstract

Surgical wound management aims to protect and heal a patient's wound quickly and without complications. In the healing process, collagen is a component of normal wound healing in which native collagen is broken into collagen fragments. Hydrolyzed collagen, for which the breakdown process is started, provides a "head start" to wound healing. However, the published literature has scattered articles addressing benefits of hydrolyzed collagen in the healing process of acute surgical wounds. To consider research on hydrolyzed collagen in acute surgical wound management, we reviewed literature from 2018 to 2023 in PubMed to find research that addresses hydrolyzed collagen in acute wound management. The literature search uncovered 15 articles that address the numerous benefits of hydrolyzed collagen in acute surgical wound management. In the management of acute surgical wounds, hydrolyzed collagen provides benefits that help with a timely inflammatory response and resolution, epithelialization, wound appearance, and tensile strength. Based on existing data, we encourage surgeons to utilize hydrolyzed collagen powder as an effective tool in acute surgical wound management and suggest that additional research, particularly large focused studies, would benefit patient care.

Keywords: Acute surgical wound management; Collagen powder; Type 1 hydrolyzed collagen

Introduction

Acute surgical wound management focuses on four major goals: (1) hemostasis, (2) healing support, (3) prevention of complications such as infection and pain (often associated with inflammatory process), and (4) wounds healing without complications (e.g., seroma, hematoma, or scarring abnormality) [1-3]. For the first three goals, the surgeon ensures hemostasis and provides the appropriate technique for tissue approximation. [4] In considering effective surgical wound repair, researchers (e.g., [5,6,7]) have investigated products to support wound healing and to reduce complications during the post-surgical recovery process. Surgeons are particularly concerned about surgical wound closure to prevent infection and additional tissue damage and abnormalities. [8] For primary intention, the surgeon ensures that the edges of the incision fit neatly together to be easily closed and to ensure that the healing process leaves as little impact as possible on the site of the wound.

Research demonstrates that type 1 collagen, which is used in a variety of sectors (including nutraceuticals, skin care, and the food industry [9]), can directly and positively influence management of acute surgical wounds. During wound healing, proteases break down native collagen peptide bonds, which, if not regulated by inhibitors, may prolong the healing process. Creating a balance between proteases and inhibitors can control inflammation and assist in the healing of surgical wounds [8].

Collagen for Wound Management

Native collagen properties differ from those of hydrolyzed collagen, including their solubility, molecular weight, viscosity, and isoelectric point. [10] Selecting a collagen product for effective surgical wound management requires that the surgeon understands differences in collagen biomechanical properties, including the functions during synthesis and differences in its native, fibrillar conformation or as soluble fragments. Native collagen functions as structural support for healing cells, [5] and collagen-derived fragments participate in various cellular functions including cell shape and differentiation, migration, and synthesis of several proteins. [11,12] However, when native collagen is used in acute surgical wound management, many of its characteristics may not be applicable.

A 2023 retrospective study by Nowrouzi and Awad of 5,335 surgical cases investigated activated [type 1 hydrolyzed] collagen peptides applied in surgical wounds of 1,489 of the patients (not in wounds of 3,846 patients, who served as the control group). [12] The study found that activated collagen was safely used to promote healing of incisions (acute wounds) and that patients experienced a 59% reduction in SSI [12]. Native collagen functions as structure with limited solubility and requires innate protease activity over time for the collagen-derived fragments to become available. [13] Native collagen is an amphoteric macromolecule that possesses an isoelectric point (pI) value between 7 and 8 [14] and a molecular weight of 285–300 kDa [15]; the pI value and molecular size affects the solubility of the protein molecule at a given pH. The pH of the skin is 4.5–6.5. [16] Proteins display the least solubility in solutions that are at or above the pH that corresponds to their pI, often resulting in protein aggregation. Due to its low solubility, native collagen products form a paste-like texture on hydration, and it continues to require further degradation by proteases into polypeptide fragments to release chemotactic properties [17].

In contrast to native collagen, type 1 hydrolyzed collagen fragments allow for a soluble product. [12,18] This solubility supports tissue approximation and provides the benefits of hemostatic, chemotactic, and adhesive properties in surgical wound management, as the collagen is already broken down into collagen-derived amino-acid fragments. Type 1 hydrolyzed collagen fragments (collagen hydrolysate) have been broken down to collagen peptides (small protein chains) that are used to support surgical wound care. “Unlike natural [native] collagen, HC [type 1 hydrolyzed collagen] is a bioactive compound with lower molecular weight than gelatin, making it better from a biological and pharmacological standpoint, due to its easy digestion, absorption, and distribution in the human body through the bloodstream” [19].

Because of its simplified structure, type 1 hydrolyzed collagen demonstrates bioabsorbability. [20] Hydrolyzed collagen powder for surgical wounds is utilized to bypass the time for native collagen to be degraded into fragments by natural enzymatic breakdown. Furthermore, type 1 hydrolyzed collagen supports ECM production and acts as a signaling molecule, recruiting inflammatory cells, fibroblasts, and keratinocytes. [21] Type 1 hydrolyzed collagen products are often focused on supporting this signaling in the goal of timely surgical wound healing.

Benefits of Hydrolyzed Collagen

Type 1 hydrolyzed collagen fragments or peptides have a low molecular weight (3–6 KDa) and pI value (3.68–5.7) and thus are more soluble than their native version. [10] Therefore, because the body is not required to break down the collagen—a process that typically takes 3–5 days—hydrolyzed collagen is easily distributed in the human body and thus is more quickly and easily used by the body for wound management. Hydrolyzed collagen is thought to replace native collagen biosynthesis by bypassing normal enzymatic breakdown, which takes 2–5 days in a healthy individual. [22] The process of breaking down native collagen may also be inhibited or impaired by comorbidities such as iron deficiency [8] and vascular disease, [23] extending the time that the body needs to process native collagen. Therefore, hydrolyzed collagen can serve the patient by providing an already processed collagen from its native state into hydrolyzed collagen fragments or peptides to support wound healing, particularly in acute surgical wounds.

Specific hydrolyzed-collagen solubility and functional activity (antioxidant capacity, antimicrobial activity, and bioavailability) are related to the type and degree of hydrolysis as well as other specific processing-related factors [10] and are, therefore, proprietary processes. The smaller size of amino acid fragments or of peptides overall have novel biological activities not exhibited directly by the native collagen molecule, with activities including angiogenic, antimicrobial, mitogenic, and chemotactic properties. [24] The spectrum of amino acids resulting from the hydrolysis of collagen differs from that of other proteins [25]; type 1 hydrolyzed collagen has a high content of glycine and proline with a key differentiator of hydroxyproline and hydroxylysine, [26] and these amino acids allow for differentiation between native collagen and other protein hydrolysates.

SStudies in the past 10 years have identified benefits of type 1 hydrolyzed collagen powder and its effect on acute surgical wounds; these benefits include decreased surgical-site infection (SSI), fewer surgical complications, lower rates of post-operative wound complications, accelerated histologic wound maturation, and faster inflammation and wound resolution. One study reported a significant (59%) overall reduction in SSIs. To calculate SSI rates, the investigators analysed a real-world registry, evaluating records

of 5,335 patients undergoing elective surgery. [27] In analysing patient records, the investigators case-matched hydrolyzed collagen (CellerateRX® Surgical Powder, Sanara MedTech, Fort Worth, TX, USA) 1:3 to non-hydrolyzed collagen patients [27].

A retrospective case series analysed patients who had undergone spinal surgery and whose physicians treated their surgical incisions (covering the entire wound) with type-1 hydrolyzed collagen powder prior to the application of dressing. [28] Of the 54 patients who met the study requirements, no patients (0.0%) experienced SSIs or surgical-site dehiscence (per CDC definition). [28] Approximately one-third of patients were considered "high risk," demonstrating comorbidities including diabetes mellitus, obesity, history of smoking, or history of prior spinal surgery, all which may affect the patient's ability to heal or may incite post-operative wound complications. [28] The study had limitations—no control group, one surgical practice completing all procedures, and a small population; however, the study is relevant because of the consistent treatment and the absence of complications in surgical wounds that were treated with type 1 hydrolyzed collagen [28].

Two separate studies, one considering 154 patients [29] and another evaluating 102 patients, [30] evaluated patients who were treated with type 1 hydrolyzed collagen (CellerateRX®, Sanara MedTech, Fort Worth, TX) after spinal surgery and neurosurgery. Dickerman et al. reported that all patients who were treated post-operatively with a mixture of hydrolyzed collagen and vancomycin experienced no dehiscence or infection. [30] Hotchkiss reported that hydrolyzed collagen powder used during primary total joint arthroplasty surgery benefited patients; only three patients (1.9%) experienced minor wound complications, which resolved after oral antibiotics and local wound care; this complication rate was lower than literature control rates. [29] Both studies concluded that type 1 hydrolyzed collagen powder is an effective agent for surgical wound site management following spinal surgeries. [29,30] In a prospective, randomized controlled study of platelet-rich plasma and hydrolyzed collagen (CellerateRX® Surgical Powder, Sanara MedTech, Fort Worth, TX, USA), Evans and Evans reported early wound improvements (at 2 weeks) in patients in two treatment groups (platelet-rich plasma and hydrolyzed collagen powder versus standard of care), but those improvements were not evident at 6 weeks. [31] They did, however, report that the complication rate in postoperative wounds was significantly lower for high-risk patients treated with either platelet-rich plasma or hydrolyzed collagen over standard of care. [31] Additionally, Evans and Evans reported that patients experienced significantly less total blood loss during the first 48 hours after surgery in the treatment groups [31].

Another study—a systematic review of literature presented at a conference for the American Society of Plastic Surgery—reported multiple benefits from hydrolyzed collagen powder in post-operative care of surgical sites. [32] Considering abdominoplasty (28) and breast reduction (16) studies, the investigators reported that the procedures could be performed without drains or quilting/progressive tension sutures if surgical sites were treated with hydrolyzed collagen (CellerateRX® Surgical Powder, Sanara MedTech, Fort Worth, TX, USA), with additional benefits including shorter operative time and lower seroma rates. [32] The report also reported higher patient satisfaction [32].

A recent retrospective study of 5,335 surgical cases [11] investigated activated collagen peptides applied in surgical wounds of 1,489 of the patients (not of 3,846 patients in the control group). The study found that activated collagen was safely used to promote healing of incisions (acute wounds) and that patients experienced a 59% reduction in SSI [11].

"Defining and understanding the difference between collagen products, collagen hydrolyzates, and ultrahydrolyzed collagen can be difficult, confusing, and remains unclear in the literature." [33] One literature review identified these benefits of type 1 hydrolyzed collagen [34] (compared to native collagen, as compared in Table 1):

- highly soluble,
- immediately available for delivery in the body,
- easily absorbed and distributed for wound management,
- simplified emulsification and stabilization,
- antioxidant and antimicrobial properties, and
- able to stimulate cell proliferation and migration [34].

Because of these qualities, type 1 hydrolyzed collagen does not rely on the patient's body to break the collagen down into usable form. Researchers acknowledge that type 1 hydrolyzed collagen has benefits that native collagen does not provide for surgical wound management.

Native Collagen	Hydrolyzed Collagen
Is structured as tightly wound triple helix [26]	Is fragmented into amino acid peptides [17]
Relies on the patient's body to naturally hydrolyze into soluble peptides [7]	Is already broken down into soluble fragments or peptides [12,18]
Has high viscosity and may "clump" or become paste-like on contact with wound exudate [17]	Has low viscosity, which allows formation of soluble gel on contact with wound exudate [34]
Presents larger (>300 kDa), which delays time to breakdown into amino acid peptides [14]	Presents smaller (3–6 kDa), which simplifies the body's work to incorporate [10,34]
Supports tissue as a scaffolding or sacrificial substrate [5]	Supports adhesion, chemotaxis, and cellular proliferation [34]

Table 1: Characteristics of Native and Hydrolyzed Collagen for Surgical Wound Management.

These benefits have been shown in other literature. For example, Kumar et al. recently reported that hydrolyzed collagen powder "boosted phagocytosis and efferocytosis of wound-site macrophages," increased "inducible reactive oxygen species," and encouraged complete closure of excisional wounds within 21 days (compared to still-open control wounds). [6] Other benefits seen in wounds treated with hydrolyzed collagen powder included increased vascularization, decreased wound inflammation, and stronger repaired skin at closure. [6]

To identify research that reports these and other benefits and to establish best surgical practices, we conducted a systematic literature review, using the terms "hydrolyzed collagen wound" and "hydrolysed collagen wound." Our findings are presented in the "Findings" section of this manuscript.

Materials and Methods

To evaluate the recent available research and benefits of hydrolyzed collagen, we conducted a review of the existing literature. Prior to a search of the literature, we began with an internal industry report that provided 18 sources that reported research of hydrolyzed collagen in wound management; these 18 sources are included in those sources that were addressed in the "Introduction" of this manuscript.

To gather additional related literature using keywords from the industry report, we searched PubMed to find all articles published from 2018 to 2023 that reported research related to hydrolyzed collagen and wound care. No other inclusion criteria were applied to the search. The search in PubMed provided limited results: 34 results for "hydrolyzed collagen wound" and 24 results for "hydrolysed collagen wound." We then limited studies for consideration, integrating inclusion criteria to review publications that were published in English (so the investigators could read the articles) and that addressed type 1 hydrolyzed collagen for wound care or wound-care-related characteristics. Our final review includes 15 studies.

Results

In the past 6 years (2018–2023), 15 studies investigate the characteristics of hydrolyzed collagen and—no matter the source (e.g., marine, algae, snail, animal)—hydrolyzed collagen consistently improved the healing process of skin, indicating a potential for benefiting post-operative patients in healing surgical wounds. (The 15 studies are listed in Table 2 with notes about the type of study, the collagen product tested in the study, and a brief summary of benefits/outcomes.)

Study and Method	Collagen Product	Benefits/Outcomes
Benito-Martínez et al., 2022 [35] Acute wound study in murine model (rat)	Catrix® bovine cartilage collagen powder (Lescarden Inc., New York, USA); hydrolyzed bovine dermal collagen powder (Viscofan, S.A., Tajonar, Navarra, Spain)	• slightly increased epithelialization • fewer inflammatory cells • greatest wound closure
Berechet et al., 2020 [36] laboratory study on cellular models	concentrated collagen hydrolysate with thyme or oregano essential oils	• absent cytotoxicity • new nanofiber mats promising for wound dressing and tissue engineering

Chang, 2023 [37] wound study in murine model (rat)	hydrolyzed collagen and polyester dressing	• decreased time to hemostasis • retained non-adhesion properties (typical of polyester dressings) • improved granulation • reduced wound shrinkage
Chotphruethipong, Binlateh, et al., 2021 [38] laboratory study of various hydrolysis processes	hydrolyzed collagen from defatted Asian sea bass skin	• higher peptide count • additional beneficial (healing) characteristics (Hydrolyzed collagen is suitable for skin nourishment and wound healing.)
García-Hernández et al., 2022 [39] laboratory study on biomembranes	PVA-based electrospun wound dressings added with hydrolyzed collagen with Hypericum perforatum ethanolic extract	• dressing-adequate porosity and pore size, strong barrier • specific anti-inflammatory and antimicrobial activity
Ibrahim, Thangavelu, & Khalifa, 2022 [40] laboratory study on murine (mouse) model	wound dressing material of collagen hydrolysates	• increased epithelialization • improved recovery and wound healing
Ilie et al., 2022 [41] laboratory study of hydrolysis process	hydrolyzed (epsin-soluble) collagen from silver carp skin	• optimal conditions for hydrolyzing collagen • increased migration in wounds • properties that indicate improved wound healing
Kumar et al., 2020 [42] laboratory study on cellular models	bovine hydrolyzed collagen	• nanofiber mats of collagen hydrolysate (with polycaprolactone and ferulic acid) • excellent proliferation and migration • potential candidate for tissue engineering
Kumar et al., 2023 [6] wound study in murine model (rat)	specific hydrolyzed collagen powder	• increased defense • higher reactive oxygen species • decreased inflammation, faster healing • improved breaking strength of repaired dermis
Póvoa et al., 2020 [43] wound study in animal model	nitric-oxide-releasing hydrolyzed collagen sponge	• improved infiltration of defense mechanisms to wounded tissue • new blood vessels • accelerated healing process
Pozzolini et al., 2021 [44] laboratory study on cellular models (on UV radiation injury and wounds)	marine-sourced collagen hydrolysates derived from sponges	• biomaterials for tissue engineering and regeneration • increased antioxidation • increased proliferation
Prelipcean et al., 2022 [45] laboratory study on cellular models	hydrolyzed Rapana venosa collagen	• higher repair rate • higher closure area • higher cell migration
Râpă et al., 2021 [46] wound study in murine model (mouse)	collagen hydrolosate powder (from bovine tendons and rabbit skins) with essential oils (lemon balm and dill)	• efficient antimicrobial activity • efficient against all but *E. coli* • biocompatible and suitable for wound healing

Table 2: Results of Literature Review through PubMed, 2018 to 2023.

Discussion

The properties of hydrolyzed collagen differ from those of native collagen, and choosing the best materials for surgical wound management of a patient promotes optimal healing. High-risk patients often have pathologic impairments in collagen, including conditions such as diabetes, malnutrition, and obesity. The goal of surgical wound treatment, which involves acute wound management, includes the timely achievement of mechanically sound wound closure without complication and with a cosmetically acceptable scar.

The studies that we identified reported a variety of benefits; the most frequently reported benefits include

- decreased inflammation/inflammatory cells; [35,39]
- accelerated wound healing process; [37,43,45]
- higher peptide count; [38]
- improved wound closure, [35,40,41,45] reduced wound shrinkage, [37] and stronger healed skin; [7]
- increased epithelialization, [35,40] migration, [41,42,45] and proliferation [42,44] in wounds;
- increased defense [43] and antimicrobial activity [39,46] (except against *E. coli* [46]); and
- new blood vessels (angiogenesis) [43].

Most of the studies were conducted in laboratory models or on patients with post-surgical wounds, which are categorized as acute wounds. The literature review was limited to PubMed as the database, and the search was limited to 6 years (2018 to 2023) to consider the most recent and relevant research.

Conclusion

Type 1 hydrolyzed collagen is demonstrated to be a strong adaptation of collagen for acute wound healing and, per calls in the field, have addressed complications and have improved therapeutic outcomes by simplifying the process and the interactions of hydrolyzed collagen in wounds. In acute surgical wound management, surgeons seek to encourage wounds to heal faster and more fully with less impact after healing on the wound site.

Type 1 hydrolyzed collagen benefits the patient with characteristics including improved healing, improved defense, and improved wound site tensile strength. These characteristics may also be a significant factor in reducing surgical site wound recurrence.

Disclosure

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