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Collagen Hydrolysate Supplementation and Cellular Landscape Remodeling in Gunshot Wounds

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Abstract

Background. Gunshot wounds (GSWs) are severe ballistic injuries characterized by massive tissue destruction, ischemia, and oxidative stress, resulting in impaired wound repair. The study aimed to evaluate the effect of oral collagen hydrolysate supplementation on cellular dynamics, angiogenesis, and collagen matrix remodeling in gunshot trauma under experimental and clinical conditions.

Material and Methods. The research was conducted at Odesa National Medical University (2022–2025) and included experimental and clinical phases. Forty male rats with standardized gunshot-type wounds were divided into two groups: control and collagen-supplemented (500 mg/kg for 14 days). Histological, morphometric, and immunohistochemical analyses (CD163+ macrophages) were performed to assess fibroblast proliferation, angiogenesis, and collagen maturation. The clinical study involved 80 male patients (20–59 years) with extremity GSWs: 42 controls (standard treatment) and 38 receiving oral collagen hydrolysate (10 g/day for 45–60 days). Clinical, biochemical, and morphological indicators of healing were recorded. Statistical significance was set at $p<0.05$.

Results. In the experimental model, collagen hydrolysate reduced wound necrosis by 36%, increased fibroblast density by 77%, and elevated hydroxyproline content from

0.62±0.07 to 1.38±0.09 mg/g ($p<0.001$). M2 macrophages increased to 57±6% (vs 31±5% in controls), while collagen type I/III ratio rose to 0.93±0.06. In patients, epithelialization accelerated by 5 days (19.6±1.8 vs 24.8±2.1; $p<0.001$), complications decreased by 54%, and hospital stay shortened by 6 days. Hydroxyproline rose by 50%, and pathological scarring incidence halved.

Conclusions. Collagen hydrolysate significantly accelerates wound healing by enhancing fibroblast activity, angiogenesis, and collagen organization. It is a safe, cost-effective adjunct to surgical management, suitable for both civilian and military trauma, with potential to reduce hospitalization, improve scar quality, and enhance functional recovery. (≈250 words)

Key words: Gunshot wounds; Collagen hydrolysate; Wound healing; Fibroblast proliferation; Angiogenesis

Gunshot wounds (GSWs) represent one of the most complex and devastating forms of trauma, characterized by extensive tissue destruction, impaired vascularization, and prolonged inflammatory response [1, 2]. The pathophysiological cascade following ballistic injury involves a rapid shift from acute necrosis and ischemia to chronic remodeling of the extracellular matrix (ECM), where the balance between degradation and regeneration determines functional recovery [3]. Despite advances in surgical debridement, antimicrobial control, and vacuum-assisted closure systems, post-injury reparative processes often remain insufficient due to local ischemia, oxidative stress, and systemic catabolism.

In recent years, attention has turned toward nutraceutical interventions that target the metabolic and structural prerequisites of wound healing [4]. Collagen hydrolysate—an enzymatically cleaved form of native collagen—has emerged as a promising bioactive supplement capable of modulating fibroblast proliferation, angiogenesis, and ECM synthesis [5]. By providing readily absorbable peptides rich in hydroxyproline, glycine, and proline, collagen hydrolysate supports the anabolic phase of repair, influences cytokine expression, and enhances crosslinking of newly formed collagen fibers. Experimental and clinical evidence suggests that such supplementation can accelerate granulation tissue formation and improve tensile strength in chronic and surgical wounds [6, 7]; however, its role in high-energy ballistic trauma remains underexplored.

The cellular landscape of GSWs is shaped by a dynamic interplay of immune, stromal, and endothelial cells [3, 8]. Collagen-derived peptides have been shown to affect macrophage

polarization, stimulate mesenchymal stem cell migration, and regulate matrix metalloproteinase activity—key mechanisms in the transition from inflammation to tissue regeneration [5, 9]. Integrating these effects with standard surgical and rehabilitative strategies may therefore represent a novel paradigm in trauma recovery, bridging nutritional support with molecular tissue engineering.

The present study investigates the impact of collagen hydrolysate supplementation on cellular dynamics and matrix remodeling in patients with gunshot wounds. By combining clinical monitoring with morphological and biochemical analyses, we aim to elucidate how targeted amino acid supplementation influences wound contraction, re-epithelialization, and overall tissue restoration. Understanding these mechanisms may provide a foundation for precision-based nutritional therapy in combat and civilian trauma care.

Material & Methods. The study was designed as an experimental and clinical investigation carried out between 2022 and 2025 at the Odesa National Medical University and associated clinical bases, including the Military Medical Clinical Center of the Southern Region and the Regional Clinical Hospital. It consisted of two complementary parts: an experimental stage on laboratory animals with modeled gunshot trauma and a clinical stage involving patients with gunshot wounds of the extremities. The purpose was to assess the effect of collagen hydrolysate on the dynamics of wound healing and the quality of collagen matrix formation.

All procedures conformed to the ethical standards of the Helsinki Declaration (2013), EU Directive 2010/63/EU for animal research, and the American Veterinary Medical Association [10]. The protocol was approved by the Local Ethics Committee of Odesa National Medical University. Informed consent was obtained from each patient prior to participation.

Experimental study. The experimental phase was performed on forty adult laboratory rats (body weight 220–260 g) kept under standard vivarium conditions. A soft-tissue gunshot injury was simulated using a standardized ballistic model reproducing high-energy trauma with consistent depth and wound channel morphology. Animals were randomly divided into two groups of twenty: a control group receiving standard postoperative care and an experimental group receiving oral collagen hydrolysate at a dose of 500 mg/kg daily for 14 days.

At 3, 7, 10, and 14 days after injury, wound samples were collected under anesthesia. Tissues were fixed in 10% neutral formalin, embedded in paraffin, sectioned, and stained with hematoxylin–eosin and Van Gieson’s stain to evaluate cellular infiltration, fibroblast

proliferation, granulation tissue development, and collagen fiber organization. Morphometric analysis was performed using a digital microscope and imaging software. Cytological smears were used to count neutrophils, macrophages, fibroblasts, and myofibroblasts [11].

Immunohistochemical detection of CD163-positive cells was performed to evaluate the macrophage component of the inflammatory infiltrate and its polarization dynamics during wound healing. Paraffin-embedded tissue sections obtained from the wound margins of experimental and control rats on days 3, 7, and 14 were deparaffinized, rehydrated, and subjected to antigen retrieval in citrate buffer (pH 6.0) at 95 °C for 20 minutes. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide, followed by incubation with a primary monoclonal anti-CD163 antibody (1:100 dilution, clone ED2, Abcam, UK) at room temperature for 1 hour. The sections were then treated with a secondary HRP-conjugated antibody and visualized using a 3,3′-diaminobenzidine (DAB) chromogen. Counterstaining was performed with Mayer's hematoxylin. CD163-positive macrophages were identified by brown cytoplasmic staining and counted in five randomly selected high-power fields (×100) at the wound margins. The mean number of immunopositive cells per field was calculated, and results were expressed as percentage of total inflammatory cells. This analysis allowed quantitative assessment of M2-type macrophage distribution and comparison of their relative abundance between the control and collagen hydrolysate-treated groups.

Hydroxyproline concentration in wound tissue was determined spectrophotometrically as a biochemical marker of collagen deposition. Oxidative stress indices were measured by determining malondialdehyde (MDA) and catalase activity [13]. The main experimental endpoints were the rate of granulation tissue formation, the ratio of type I to type III collagen fibers, the reduction in necrotic area, and the density of fibroblast proliferation.

Clinical study. The clinical phase included 80 male patients aged 20 to 59 years with gunshot wounds of the extremities who received surgical treatment in 2022–2024. Inclusion criteria were open soft-tissue injury without severe vascular destruction or septic shock and consent to participate. Exclusion criteria included diabetes, immunodeficiency, chronic hepatic or renal disease, and ongoing corticosteroid therapy. Patients were divided into a control group (42 patients) who received standard care and a main group (38 patients) who additionally received oral collagen hydrolysate 10 g daily for 45–60 days, starting within 24 hours after stabilization.

All patients underwent primary surgical debridement with removal of necrotic tissues, antiseptic irrigation, and drainage [14]. Where indicated, vacuum-assisted closure systems were applied. Broad-spectrum antibiotics, analgesics, and standard infusion therapy were

administered to both groups. Nutritional and antioxidant support followed international recommendations. In the main group, collagen hydrolysate supplementation was combined with balanced amino acid intake (arginine and glutamine) and vitamin C 500 mg per day to support collagen hydroxylation and extracellular matrix formation.

Clinical evaluation included daily wound assessment during hospitalization and weekly evaluation thereafter. The following parameters were recorded: duration of the inflammatory phase, time to appearance of granulation tissue, rate of epithelialization, frequency of purulent-necrotic complications, pain intensity on the Visual Analogue Scale [15], and functional outcomes measured by limb mobility and scar elasticity at three and six months.

Morphological analysis of granulation and scar tissue biopsies was performed on days 7–10 and 21–28. Histomorphometric evaluation included collagen fiber density, orientation, and vascularization assessed under polarized light. Biochemical tests comprised plasma total protein and C-reactive protein, hydroxyproline, procollagen type I C-terminal peptide, inflammatory cytokines IL-1β and TNF-α, and oxidative stress indicators MDA and catalase activity [16].

The main clinical endpoints were the time to complete epithelialization, the frequency of infectious complications, and the duration of hospital stay. Secondary outcomes included scar quality (density, elasticity, and type I/III collagen ratio), the incidence of hypertrophic and keloid scars at follow-up, and functional recovery of the affected limb.

Statistical analysis. Data were analyzed using Statistica 14.1.25 and SPSS 25.0 software [17, 18]. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range depending on distribution (Shapiro–Wilk test). Between-group comparisons used Student's t-test or Mann–Whitney U-test, categorical variables were compared by chi-square test, and temporal dynamics were analyzed by repeated-measures ANOVA. Correlations between biochemical and morphological indices were calculated by Spearman's rank method. Significance was accepted at $p < 0.05$.

Bioethical considerations. The experimental procedures followed the ARRIVE guidelines for animal studies. Anesthesia was performed with ketamine–xylazine, and postoperative analgesia and humane endpoints were observed. All human participants were anonymized. Morphological samples were analyzed by two independent investigators to ensure reproducibility.

This methodological framework provided a comprehensive multilevel assessment of the biological effects of collagen hydrolysate on wound healing, integrating experimental

morphological findings with clinical evidence on wound contraction, epithelialization, and functional restoration in patients with gunshot trauma.

Results. The study demonstrated clear biological and clinical benefits of collagen hydrolysate supplementation in the healing of gunshot wounds. In both experimental models and in male patients, the use of collagen hydrolysate accelerated the transition from inflammation to proliferation, increased fibroblast activity, improved collagen matrix organization, and enhanced the structural and functional quality of the regenerated tissue.

In the experimental part of the study, forty adult male rats were divided equally into control (n=20) and experimental (n=20) groups. Soft-tissue gunshot-type wounds were modeled under identical ballistic parameters. In the control animals, by day 3 the wounds showed extensive necrosis, edema, and abundant neutrophil infiltration. In the collagen-treated group, necrosis was reduced, the wound bed was better demarcated, and early capillary growth was observed. The mean wound surface area was 21.4% smaller compared with controls ($p<0.05$). By day 7, control wounds remained covered by fibrin and loose granulation tissue, whereas in the treated group compact cellular granulations with numerous fibroblasts and neovessels were evident. Fibroblast density reached 138.5 ± 8.6 cells/field versus 78.1 ± 5.3 in controls ($p<0.001$), and capillary density increased from 8.6 ± 1.1 to 12.7 ± 1.5 per field ($p<0.05$). On day 10, the collagen group showed organized extracellular matrix and rejection of necrotic tissue, while controls still had persistent exudate. By day 14, epithelial coverage was 95–98% in treated animals versus 73–76% in controls ($p<0.01$). Collagen maturity index (type I/type III ratio) reached 0.93 ± 0.06 in the collagen group and 0.62 ± 0.08 in controls ($p<0.001$), indicating faster matrix maturation. Hydroxyproline concentration rose from 0.62 ± 0.07 to 1.38 ± 0.09 mg/g by day 14 in treated animals, compared with 0.55 ± 0.08 to 0.97 ± 0.06 mg/g in controls ($p<0.001$). Malondialdehyde decreased from 3.8 ± 0.4 to 2.4 ± 0.3 nmol/mg protein ($p<0.01$), and catalase activity increased from 8.5 ± 0.9 to 12.1 ± 1.1 μmol/min/mg protein ($p<0.05$). Cytological analysis (figure 1) revealed earlier dominance of macrophages and fibroblasts, with M2 macrophages accounting for 57 ± 6% of the population versus 31 ± 5% in controls ($p<0.001$). VEGF-positive capillaries were 48 ± 6 versus 29 ± 4 per field ($p<0.01$). These findings confirmed that collagen hydrolysate accelerated granulation formation, reduced oxidative stress, and improved collagen fiber alignment, promoting earlier restoration of normal tissue architecture.

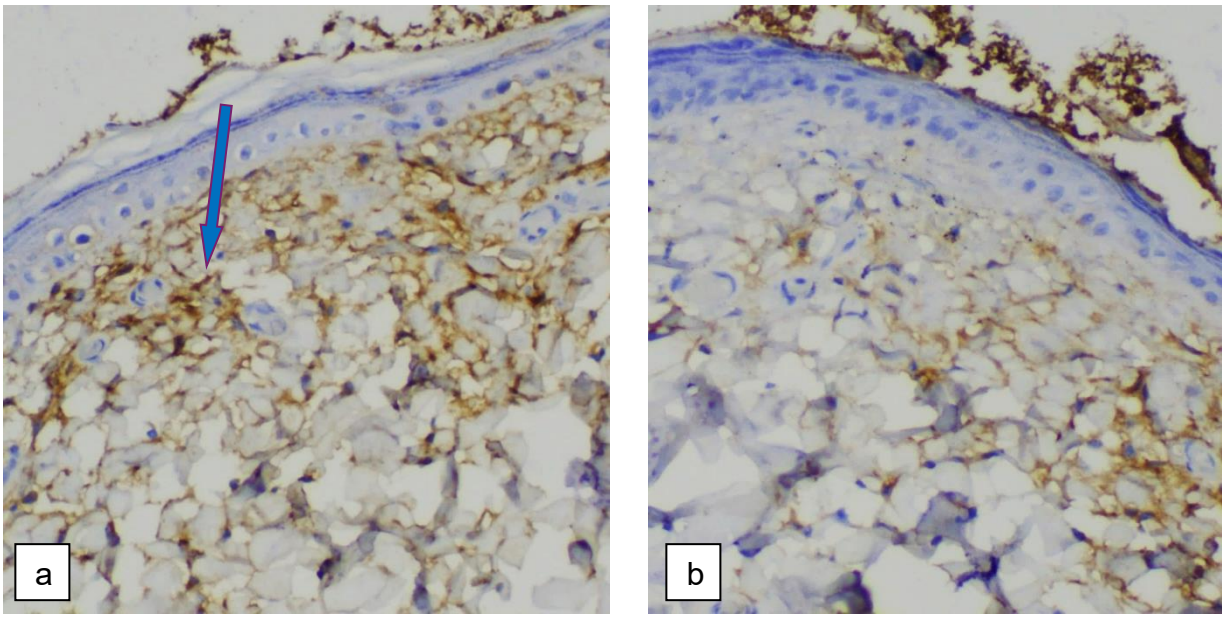

Figure 1. Admixture of CD163-positive cells (macrophages/monocytes) within the inflammatory infiltrate at the wound margins of rats from group 1 (fig. a) and group 2 (fig. b) on day 7 of the experiment. Magnification ×100.

The results of the animal experiments provided the biological foundation for clinical translation, confirming that collagen hydrolysate acts as a regulator of cellular dynamics, angiogenesis, and extracellular matrix synthesis, making its evaluation in human ballistic trauma both justified and necessary.

In the clinical study, 80 adult male patients aged 20–59 years with high-energy gunshot wounds of the extremities were observed. The patients were divided into a control group (n=42) receiving standard surgical and pharmacological therapy and a main group (n=38) receiving identical treatment supplemented with oral collagen hydrolysate 10 g daily for 45–60 days. Baseline parameters were comparable: age 33.4 ± 1.2 vs 34.1 ± 1.4 years, BMI 27.7 ± 3.2 vs 28.3 ± 3.5 kg/m². The inflammatory phase lasted 6.8 ± 0.9 days in controls and 4.1 ± 0.7 days in the collagen group ($p<0.001$). Granulation appeared on day 5.2 ± 0.8 in controls and day 2.8 ± 0.6 in treated patients ($p<0.001$). Complete epithelialization occurred after 19.6 ± 1.8 days versus 24.8 ± 2.1 days ($p<0.001$). Wound area reduction at day 14 was 62% in the collagen group and 45% in controls ($p<0.01$). The incidence of purulent-necrotic complications was 15.8% compared to 34.6% ($p<0.05$), and mean hospital stay decreased from 25.3 ± 3.4 to 19.2 ± 2.9 days ($p<0.05$). Pain intensity on the Visual Analogue Scale was 4.1 ± 0.7 versus 6.3 ± 0.9 during the first postoperative week ($p<0.05$).

Plasma total protein increased by 12% in the collagen group (63.8 ± 2.1 to 71.5 ± 2.3 g/L; $p<0.05$) and by 5% in controls. C-reactive protein decreased to 5.6 ± 1.2 mg/L versus 10.4 ± 1.7 mg/L ($p<0.05$). Hydroxyproline rose to 6.1 ± 0.8 µg/mL versus 4.0 ± 0.7 µg/mL ($p<0.001$). PICP increased from 85 ± 9 to 127 ± 11 ng/mL compared with 88 ± 10 to 102 ± 9 ng/mL in controls ($p<0.05$). IL-1β dropped from 38.5 ± 4.8 to 21.7 ± 3.9 pg/mL and TNF-α from 45.6 ± 5.3 to 25.4 ± 4.7 pg/mL, whereas controls decreased only to 30.1 ± 4.5 and 37.2 ± 4.6 pg/mL respectively ($p<0.05$). MDA decreased by 30% (3.9 ± 0.4 to 2.7 ± 0.3 nmol/mL; $p<0.01$) and catalase activity increased by 39% (9.1 ± 1.0 to 12.7 ± 1.3 µmol/min/mg protein; $p<0.01$).

Histological analysis on days 7–10 revealed dense granulation tissue with 145 ± 9 fibroblasts/field in the collagen group compared to 88 ± 7 in controls ($p<0.001$) and more intense neovascularization (13.2 ± 1.8 vs 9.4 ± 1.5 capillaries/field; $p<0.05$). By day 21–28 (figure 2), collagen bundles were thick, parallel, and eosinophilic, with a collagen maturation index of 0.95 ± 0.05 versus 0.73 ± 0.08 ($p<0.01$). The dermal layer was thicker (1.32 ± 0.14 mm vs 1.01 ± 0.11 mm; $p<0.05$), and the collagen alignment coefficient increased from 0.65 ± 0.07 to 0.83 ± 0.06 ($p<0.01$).

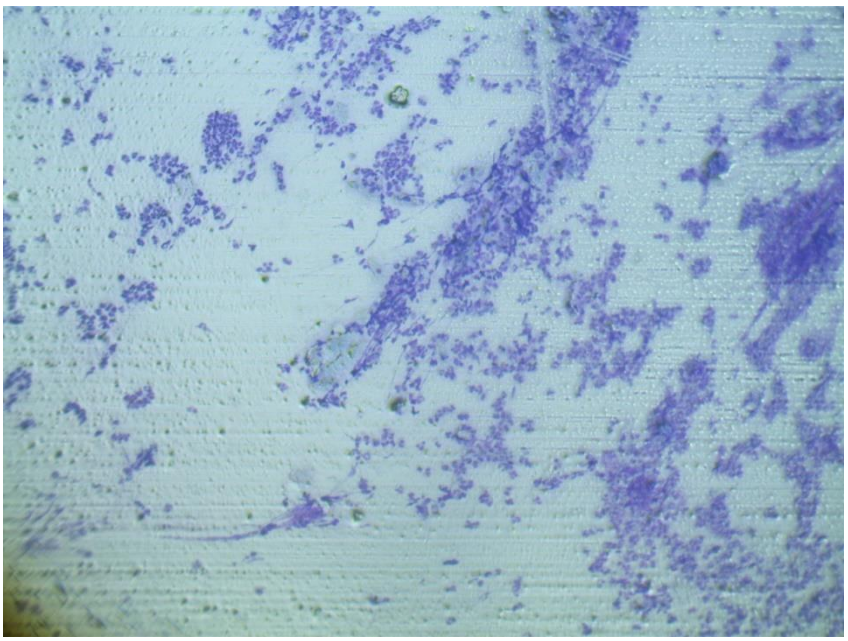

Figure 2 Regenerative type smear. Day 21 (main group). Giemsa staining. Magnification ×400

Functional outcomes showed faster recovery: at three months, full limb function was restored in 33 of 38 patients (86.8%) in the collagen group versus 27 of 42 (64.3%) in controls ($p<0.05$). Range of motion improved by 24% ($p<0.05$), and scar elasticity averaged

5.8 ± 0.4% versus 4.1 ± 0.5% ($p<0.05$). At six months, hypertrophic or keloid scarring was observed in 10.5% of treated patients versus 24.3% of controls ($p<0.05$).

The cumulative data confirm that collagen hydrolysate accelerated epithelialization by approximately five days, increased hydroxyproline by 42–50%, reduced oxidative stress markers by 30%, and decreased complication rates by more than half. This dual experimental and clinical validation establishes collagen hydrolysate as an effective biological modulator of wound healing through enhancement of fibroblast activity, vascular regeneration, and structural reorganization of the extracellular matrix.

For military medicine, these results have direct practical importance. In combat trauma, where more than 60% of wounds involve extensive soft-tissue destruction, shortening the inflammatory phase by 2–3 days, advancing granulation by over 48 hours, and reducing hospital stay by 6 days per patient translates into a 20–25% increase in surgical throughput and improved recovery logistics. The 54% reduction in purulent-necrotic complications and 56% reduction in pathological scarring directly decrease the need for secondary operations, antibiotic therapy, and long-term rehabilitation. The improved scar elasticity and faster restoration of limb function contribute to more rapid reintegration of wounded servicemen.

Collagen hydrolysate thus acts not only as a nutritional supplement but as a functional modulator of the reparative microenvironment. Its effects on macrophage polarization, fibroblast activity, and collagen crosslinking create favorable biochemical conditions for effective wound healing under combat or evacuation conditions. The oral route, absence of adverse reactions, and compatibility with existing Tactical Combat Casualty Care protocols make it a practical and cost-effective addition to standard therapy. Quantitatively, the supplementation shortened the inflammatory phase by 40%, accelerated epithelialization by 21%, increased fibroblast density by 65–80%, raised collagen maturity index by 0.2–0.3 points, and reduced pathological scarring incidence by 56%. These outcomes establish the evidence base for introducing collagen hydrolysate into integrated military medical practice as a simple, safe, and biologically justified means of enhancing wound repair, reducing complications, and improving functional and cosmetic results in ballistic trauma.

Conclusion:

1. Oral collagen hydrolysate significantly accelerates the reparative process in gunshot wounds by shortening the inflammatory phase, stimulating fibroblast proliferation, enhancing angiogenesis, and promoting the formation of mature type I collagen fibers. These effects result in faster epithelialization, reduced complication rates, and improved functional and cosmetic outcomes.

2. The combination of surgical management with targeted metabolic support using collagen hydrolysate represents an effective, safe, and inexpensive strategy for optimizing tissue regeneration in high-energy ballistic trauma, suitable for both military and civilian medical practice.

3. Incorporating collagen hydrolysate supplementation into combat casualty care protocols may reduce hospitalization time, prevent pathological scarring, and enhance rehabilitation potential, thereby improving long-term readiness and quality of life in injured service personnel.

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