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Altitude-Induced Immunological Changes in Experimental Wound Healing

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Abstract: Wound healing is a critical global clinical issue, particularly in surgical and emergency care settings, where infections lead to significant morbidity, extended hospitalization, and increased healthcare costs. This study investigated the impact of altitude deadaptation on immune responses during wound healing in rabbits. Animals with aseptic and purulent wounds were divided into three groups: control (Bishkek), short-term (3-day), and long-term (30-day) high-altitude exposure, followed by descent to Bishkek. Leukocyte profiles and plasma levels of pro-inflammatory interleukin-1 beta (IL-1β) and anti-inflammatory interleukin-10 (IL-10) were analyzed. Short-term high-altitude exposure followed by rapid descent induced a maladaptive immune response characterized by elevated IL-1β levels, peaking at 10.1 ± 0.3 pg/ml on day 1 in aseptic wounds and 31.1 ± 2.5 pg/ml on day 3 in purulent wounds, indicating prolonged inflammation. In contrast, long-term exposure resulted in immune exhaustion, with diminished IL-1β and IL-10 responses. IL-10 levels were disrupted in the short-term exposure group, showing an initial increase followed by a decrease, suggesting inadequate anti-inflammatory effects. Leukocyte counts paralleled cytokine patterns, with initial leukopenia followed by delayed leukocytosis in the short-term exposure group. These findings demonstrate that altitude deadaptation affects immune regulation, inflammation extension, and hinders wound healing.

Keywords: Wound Healing; Hypoxia; High Altitude; Inflammation; Cytokines; Immune Response

1. Introduction

Wound healing is a critical global clinical issue owing to the widespread occurrence of infections, particularly in surgical and emergency care settings. Infections at surgical sites are a significant factor in postoperative complications, leading to higher morbidity, extended hospitalization, and increased healthcare costs. In cases of burn injuries, trauma, and chronic ulcers, infections are a leading cause of delayed recovery and negative outcomes, highlighting the strain on healthcare systems worldwide [1,2].

The intricacies of wound care have intensified due to the presence of interconnected factors. Antimicrobial-resistant microorganisms complicate infection management, rendering antibiotics less effective and necessitating advanced therapeutic strategies [2]. Additionally, wounds from severe injuries or chronic conditions, such as diabetes, show impaired healing, marked by hypoxia, inflammation, and altered cellular responses [3,4]. These issues, combined with delayed treatment during emergencies, exacerbate the challenges of wound closure. Despite medical progress, including improved surgical methods, antimicrobial treatments, advanced dressings, and tissue-engineering technologies, no single method guarantees optimal healing for all wound types [3,5,6]. Patient comorbidities, wound causes, microenvironments, and resource availability lead to varied treatment responses. Although smart dressings and bioengineered scaffolds offer promising personalized options, their use remains limited by cost, accessibility, and wound complexity [7,8].

Wound healing is hindered in high-altitude settings because of hypobaric hypoxia, reduced atmospheric pressure, cold temperatures, and increased exposure to UV radiation. These factors interfere with the processes required for immune responses and tissue repair. Hypoxia, involving reduced oxygen pressure, adversely affects oxygen-dependent stages such as inflammation, angiogenesis, fibroblast proliferation, collagen synthesis, and re-epithelialization, as oxygenation is vital for ATP production, metabolism, and redox signaling pathways that aid tissue regeneration [9]. Although temporary mild hypoxia can activate proangiogenic pathways via hypoxia-inducible factors (HIFs), persistent hypoxia at high altitudes often leads to maladaptive environments with inadequate angiogenesis and prolonged inflammation, hindering the transition to proliferative and remodeling pha- ses [9,10].

Cold temperatures at high altitudes cause peripheral vasoconstriction, limiting blood flow and nutrient delivery to injured tissues, which slows the biochemical reactions required for matrix remodeling and cell migration [11]. Increased UV radiation at elevated altitudes generates reactive oxygen species, causing oxidative stress that damages keratinocytes and dermal structures. This damage disrupts immune cell function and cytokine balance, making wounds more susceptible to infection [3,10].

Hypoxic conditions influence the immune response. Hypobaric hypoxia affects leukocyte function by disrupting chemotaxis, phagocytosis, and antimicrobial activity, which are essential defenses against wound colonization and infection. The interaction between HIF and inflammatory transcription factors, such as NF-κB, shows a complex relationship in which hypoxia can misregulate inflammatory responses, potentially leading to maladaptive inflammation that hinders healing [2,10]. Since wound infection and biofilm formation are major obstacles to recovery, particularly in immunocompromised individuals, immune dysfunction from hypoxia presents a considerable risk at high altitudes [2].

While significant research exists on human adaptation to high altitudes through genetic, hematologic, and metabolic changes influenced by HIFs and erythropoiesis, deadaptation, the physiological changes that occur when returning to normal oxygen levels remain poorly understood, particularly regarding the immune system and wound healing [10,12–14]. Although adaptation shows long-term genetic markers in groups such as Tibetans, little attention has been focused on the short-term period after descent when the body adjusts to increased oxygen.

This gap is significant in wound healing, a process dependent on oxygen and immune regulation. Wound healing requires a timed immune response that engages innate and adaptive immune cells to manage inflammation, eliminate pathogens, and regenerate tissue [15]. At high altitudes, hypoxia affects the immune function and inflammatory pathways, altering leukocyte behavior and cytokine profiles. The transition to normal oxygen levels during deadaptation causes oxidative stress from reactive oxygen species, disrupting immune mediators essential for wound resolution [10,16].

Cytokines are signaling molecules that regulate the immune system during wound healing and coordinate the inflammation required for tissue repair. Interleukin-1 beta (IL-1β) is a proinflammatory cytokine that triggers an inflammatory cascade by encouraging leukocyte recruitment, activating endothelial cells, and stimulating the re-

lease of inflammatory mediators for pathogen clearance [15,17,18]. Interleukin 10 (IL-10) is an anti-inflammatory cytokine that resolves inflammation by suppressing proinflammatory cytokines and promoting macrophage polarization towards tissue-repairing phenotypes, aiding tissue regeneration [15,19].

The balance between proinflammatory cytokines, such as IL-1β, and anti-inflammatory cytokines, such as IL-10, determines healing outcomes. Excessive IL-1β can prolong inflammation, causing tissue damage and chronic wounds, as seen in diabetic ulcers [18,20]. IL-10 helps reduce inflammatory reactions, regulate extracellular matrix deposition, and minimize scarring for regenerative healing [19]. This cytokine interaction involves macrophage adaptability, with M1-like macrophages releasing IL-1β during inflammation, whereas M2-like macrophages produce IL-10 during the repair stage [20,21].

Environmental stressors influence cytokine production, affecting the inflammatory healing stages. Hypoxia, found in ischemic wounds and high-altitude settings, affects cytokine expression by activating HIFs and interacting with NF-κB. While acute hypoxia can increase proangiogenic cytokines, chronic hypoxia leads to maladaptive inflammation with high IL-1β levels and impaired IL-10 responses, thereby disrupting normal repair [4,10]. Bacterial colonization in chronic wounds triggers proinflammatory cytokine release, hindering healing [2,11]. Environmental insults that cause oxidative stress modify cytokine networks, thereby affecting inflammatory pathways [10,22].

Rabbits are an effective model for studying wound healing because of their physiological and immunological similarities in inflammatory responses. In Kyrgyzstan, where patients frequently move between highland and lowland areas, the Tuya-Ashuu field station, located at 3,200 m, offers a natural model for high-altitude exposure. Transferring animals between this station and low-altitude facilities in Bishkek replicates the clinical path of patients receiving care in the mountains and recovering in the plains.

Although extensive research has been conducted on high-altitude adaptation, immune and healing responses during readjustment to lower altitudes remain poorly understood. This study examined changes in leukocyte profiles and cytokine expression (IL-1β and IL-10) in rabbits with aseptic and infected wounds during readjustment. These findings have practical significance for healthcare in mountainous regions, where patients move between altitudes for surgery and recovery. Adapting postoperative care to account for altitude-induced immunological changes may improve healing and reduce complications in this population.

2. Methods

Experiments and laboratory studies were conducted from February 2022 to February 2024 at the Problem Research Laboratory of Clinical and Experimental Surgery at the National Surgical Center of the Ministry of Health of the Kyrgyz Republic and at the experimental high-altitude base of the Kyrgyz State Medical Academy named after A.A. Raimzhanov near the Tuya-Ashuu pass (3,200 m), Kyrgyzstan. The study used 150 mongrel, sexually mature rabbits of both sexes, weighing 3.5–4.0 kg. All animals underwent vaccination, deworming, and a 21-day quarantine. The study design and animal care protocols were approved by the Bioethics Committee of I.K. Akhunbaev Kyrgyz State Medical Academy. Animals were housed under uniform vivarium conditions, receiving care in accordance with the "Sanitary rules for the arrangement, equipment and maintenance of experimental biological clinics (vivariums)" and the GOST standards "Keeping experimental animals in research institute nurseries" (1978). The order of the Ministry of Health of the USSR, October 10, 1983, No. 1179 "On approval of feed standards for laboratory animals in health facilities" was followed for feeding with unrestricted water access. Experiments were conducted in accordance with Good Laboratory Practice regulations, August 23, 2010, Order No. 708; guidelines for humane animal treatment according to the order of the Ministry of Health of the USSR, November 13, 1984, No. 742; and principles of the Helsinki Declaration (1964, amended 1975, 1983, 1989), considering requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental Purposes (Strasbourg, March 18, 1986).

Surgical procedures were performed under general anesthesia, following aseptic and antiseptic protocols. Ketamine was administered intravenously at 7 mg/kg of body weight to induce anesthesia. The wound process in experimental animals was divided into three groups: Group 1 – control group of 50 rabbits remained in Bishkek; Group 2 – experimental group of 50 rabbits transferred to Bishkek after a 3-day stay at the experimental high-altitude base of the Kyrgyz State Medical Academy named after A.A. Raimzhanov near to the Tuya-Ashuu pass (3,200 m), Kyrgyzstan, part of the Central Scientific Research Laboratory, for wound process modeling and observation; Group 3 – experimental group of 50 rabbits, transferred to Bishkek after a 30-day stay at the same high-altitude

base for wound process modeling. Within each series, the animals were divided into two groups: Group I, comprising 25 animals with an experimental model of aseptic inflammation, and Group 2, comprising 25 animals with an experimental model of purulent inflammation.

Once anesthetized, the animals were positioned facing down. Aseptic inflammation was induced by injecting 0.3 ml of turpentine mixed with vaseline oil under the skin between the shoulder blades. The fur in that region was trimmed, and 0.5 ml of air was injected subcutaneously. One day after turpentine administration, the rats exhibited symptoms of acute inflammation, including redness. The inflammation site was not visibly different. In the injection area, there was significant tissue swelling that was extremely painful when touched. Autopsy revealed a soft tissue burn with necrotic elements, with a limited affected area and a prominent vascular pattern.

To simulate acute purulent inflammation, a 50 mm diameter stencil made from X-ray film was used to outline a circular wound in the interscapular region using a 1% alcohol solution of brilliant green. The skin and superficial fascia were incised along the outline. The muscles were incised at the base of the wound using a scalpel. The resulting skin flap was flipped over with the wool facing the wound surface and stitched to the free skin edge and underlying tissues around the perimeter using a continuous suture with a #4 nylon thread. After 48 h, the flap was removed, revealing an infected wound with signs of inflammation. Observations were made on the 3rd, 7th, 15th, 20th, and 30th day. To evaluate the clinical picture, changes in the leukocyte formula in animals from all series were examined at these times. Blood samples (0.3 ml were collected in a vacutainer for analysis. A general clinical blood analysis, including leukocyte formula calculation, was conducted at the National Surgical Center of the Ministry of Health of the Kyrgyz Republic.

In animals across various groups, cytokine levels were measured: proinflammatory IL-1β and anti-inflammatory IL-10 at intervals of 12 hours, as well as 1, 2, 3, and 5 days after the onset of inflammation. Blood samples were collected at these time points using tubes containing a blood coagulation activator. The tubes were centrifuged at 1,000× *g* for 10–15 minutes to separate the plasma. Cytokine concentrations in the blood plasma were assessed using an enzyme immunoassay. For cytokine analysis, Austrian test kits "Rat Interleukin-1 Beta ELISA Kit" and "Rat Interleukin 10 ELISA Kit" (BenderMedSystems, Vienna, Austria) were used. To examine cytokine concentrations, well plates with fixed antibodies (polyclonal for IL-1β and monoclonal for IL-10) were used. The plates were washed with a specific solution. Samples and standard solvents were added to the wells according to the manufacturer's protocol, and the contents were incubated with a biotin-conjugated reagent for 2 hours. After washing to remove the biotin conjugate, streptavidin-HRP was added, followed by a 1-hour incubation and washing. The contents were then incubated with a substrate solution (tetramethylbenzene) for 10 minutes, producing a staining intensity indicative of plasma cytokine levels. Interleukin concentrations were measured in pg/ml, with evaluation of the wound process based on clinical data, leukocyte formula indicators using standard methods, microbiological examination, and blood plasma cytokines during wound healing.

Statistical analysis was performed using SPSS Statistics for Windows, Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Data are presented as mean ± standard deviation. Distribution normality was verified using the Kolmogorov-Smirnov test. To evaluate statistical differences, both parametric and nonparametric methods (ANOVA, Kruskal-Wallace test) were applied, with the Tukey test used as the post hoc criterion. Statistical significance was set at $p < 0.05$.

3. Results

On the first day after the induction of aseptic inflammation, a significant reduction in leukocyte count was detected in the animals' blood. At the inflammation site, there was evidence of severe soft-tissue burns and necrotic areas. The introduction of turpentine acted as a substantial stressor, requiring time for the body to respond. At the study's outset, on the third day, the leukocyte count in Group 1 during readjustment to lower altitudes after a 3-day mountain stay (Group 2) was $12.8 \pm 0.1 \times 10^9$/l ($p < 0.05$). By the day 7, this count decreased to $11.6 \pm 0.2 \times 10^9$/l, dropping to $9.6 \pm 0.2 \times 10^9$/l by the day 15, reaching $8.7 \pm 0.1 \times 10^9$/l on the day 20, and settling at $8.2 \pm 0.1 \times 10^9$/l by the day 13 ($p < 0.05$), with these figures being lower than those in the other groups ($p < 0.05$). Similar to Group 1, other groups (during readjustment after a 3-day mountain stay) exhibited a leftward shift in the leukocyte formula during the initial days.

In Group 1, 12 h after administering 0.3 ml of turpentine into the interscapular area, blood plasma IL-1β level was 1.7 ± 0.4 pg/ml. A natural decline in IL-1β was observed, with levels of 1.2 ± 0.2 pg/ml after day 1 and 0.8 ± 0.2

pg/ml after day 3 (**Table 1**). By day 4, IL-1β was undetectable in the blood plasma. In Group 2, blood plasma IL-1β was 5.9 ± 0.2 pg/ml, 12 h after turpentine-induced inflammation. Peak levels reached 10.1 ± 0.3 pg/ml after day 1, then decreased but remained high: 5.7 ± 0.2 pg/ml on day 3 and 3.2 ± 1.5 pg/ml on day 7 ($p < 0.05$) (**Table 1**). In Group 3, IL-1β levels increased in blood plasma 12 h after aseptic inflammation modeling, reaching 1.5 ± 0.3 pg/ml and 1.4 ± 0.1 pg/ml after one day. The IL-1β level dropped to 0.9 ± 0.4 pg/ml on the third day.

Table 1. IL-1β levels in rabbit blood plasma with aseptic inflammation across altitude exposure groups (%).

Day-Stay	Group 1	Group 2	Group 3
12 hours	1.7 ± 0.4	5.9 ± 0.2*	1.5 ± 0.3*
Day 1	1.2 ± 0.3	10.1 ± 0.3*	1.4 ± 0.1*
Day 3	0.8 ± 0.1	5.7 ± 0.2*	0.9 ± 0.4*

Note: Data presented as mean ± standard deviation. *$p < 0.05$.

For IL-10, its plasma concentration in Group 1 decreased to 10.3 ± 0.6 pg/ml after day 1 compared to baseline. IL-10 then gradually rose, reaching 13.1 ± 1.4 pg/ml on day 3, 15.2 ± 1.7 pg/ml on day 7, 15.6 ± 1.6 pg/ml on day 15, 15.8 ± 3.2 pg/ml on day 20, and 16.6 ± 3.1 pg/ml on day 30 (**Table 2**).

Table 2. IL-10 levels in rabbit blood plasma with aseptic inflammation during deadaptation.

Day-Stay	Group 1	Group 2	Group 3
Day 1	10.3 ± 0.6	22.1 ± 2.1	11.0 ± 1.1
Day 3	13.1 ± 1.4	20.3 ± 3.6	12.1 ± 1.2
Day 7	15.2 ± 1.7	19.6 ± 2.7	14.4 ± 2.1
Day 15	15.6 ± 1.6	18.1 ± 1.3	14.7 ± 1.1*
Day 20	15.8 ± 3.2	17.9 ± 2.7	15.0 ± 2.2*
Day 30	16.6 ± 3.1	17.6 ± 1.2	15.2 ± 1.2*

Note: Data presented as mean ± standard deviation. *$p < 0.05$.

In Group 2, after day 1, the blood plasma of the experimental animals showed increased IL-10 concentration, followed by a reduction to 22.1 ± 2.1 pg/ml. By the third and seventh days, IL-10 levels decreased to 20.3 ± 3.6 pg/ml on day 3, 19.6 ± 2.7 pg/ml on day 7, 18.1 ± 1.3 pg/ml on day 15, 17.9 ± 2.7 pg/ml on day 20, and 17.6 ± 1.2 pg/ml on day 30. In Group 3, IL-10 levels were low on days 3 and 7, measuring 12.1 ± 1.2 pg/ml and 14.4 ± 2.1 pg/ml, respectively. On day 15, it was 14.7 ± 1.1 pg/ml, on day 20 it was 15.0 ± 2.2 pg/ml, and on day 30 it was 15.2 ± 1.2 pg/ml ($p < 0.05$). In animals with acute purulent inflammation in Bishkek, IL-1β levels increased 12 h after inflammation began, peaking at 3 days (12 h, 5.6 ± 0.9 pg/ml; day 1, 11.9 ± 1.9 pg/ml; day 3, 28.9 ± 1.7 pg/ml). IL-1β then declined by day 7 to 11.3 ± 0.3 pg/ml and by day 15 to 0.7 ± 0.1 pg/ml (**Table 2**).

In Group 2 animals, 12 hours after the onset of purulent inflammation, the IL-1β concentration in blood plasma was 7.6 ± 0.7 pg/ml. The highest level was recorded on day 3, at 14.1 ± 2.1 pg/ml on day 1 and 31.1 ± 2.5 pg/ml on day 3. IL-1β levels decreased thereafter but remained high at 12.1 ± 0.7 pg/ml on day 7 ($p < 0.05$) (**Table 3**). In Group 3, IL-1β levels increased in the blood plasma after acute purulent inflammation of the soft tissues. After 12 h, the level was 4.3 ± 0.3 pg/ml, rising to 9.9 ± 0.1 pg/ml after day 1. By day 3, IL-1β levels increased to 11.3 ± 0.4 pg/ml. Subsequently, levels declined to 9.6 ± 0.2 pg/ml on day 7 and 0.6 ± 0.1 pg/ml on day 15 (**Table 3**).

Table 3. IL-1β levels in rabbit blood plasma with purulent inflammation across altitude exposure groups (%).

Day-Stay	Group 1	Group 2	Group 3
12 hours	5.6 ± 0.9	7.6 ± 0.7*	4.3 ± 0.3*
Day 1	11.9 ± 1.9	14.1 ± 2.1*	9.9 ± 0.1*
Day 3	28.9 ± 1.7	31.1 ± 2.5*	11.3 ± 0.4*
Day 7	11.3 ± 0.3	12.1 ± 0.7*	9.6 ± 0.2*
Day 15	0.7 ± 0.1	1.2 ± 0.3*	0.6 ± 0.1*

Note: Data presented as mean ± standard deviation. *$p < 0.05$.

In Group 1, within 12 hours of the onset of purulent inflammation, the IL-10 concentration decreased to 5.1 ± 1.0 pg/ml. Subsequently, IL-10 levels in blood plasma increased, reaching 17.2 ± 3.9 pg/ml on day 1 and 36.1 ± 2.1 pg/ml by day 3. Following this peak, IL-10 concentration declined, measuring 22.2 ± 3.1 pg/ml on day 7, 18.1 ± 1.7 pg/ml on day 15, 17.2 ± 2.1 pg/ml on day 20, and 17.0 ± 1.8 pg/ml on day 30 (**Table 4**).

Table 4. IL-10 levels in rabbit blood plasma with purulent inflammation during deadaptation (%).

Day-Stay	Group 1	Group 2	Group 3
12 hours	5.1 ± 1.0	25.3 ± 0.9	28.4 ± 1.5
Day 1	17.2 ± 3.9	29.3 ± 2.7	26.3 ± 1.4
Day 3	36.1 ± 2.1	43.6 ± 1.7	25.7 ± 1.2
Day 7	22.2 ± 3.1	27.1 ± 2.9	19.4 ± 1.7
Day 15	18.1 ± 1.7	20.1 ± 2.1	17.3 ± 1.7*
Day 20	17.2 ± 2.1	19.9 ± 1.9	17.2 ± 1.2*
Day 30	17.0 ± 1.8	19.6 ± 1.6	17.0 ± 0.3*

Note: Data presented as mean ± standard deviation. *$p < 0.05$.

In the blood plasma of experimental animals in Group 2, the IL-10 concentration rose to 25.3 ± 0.9 pg/ml after 12 hours. IL-10 levels were reduced to 29.3 ± 2.7 pg/ml after day 1. On days 3 and 7, IL-10 levels reached 43.6 ± 1.7 pg/ml and 27.1 ± 2.9 pg/ml, respectively. By day 15, the level was 20.1 ± 2.1 pg/ml, decreasing to 19.9 ± 1.9 pg/ml on day 20, and to 19.6 ± 1.6 pg/ml on day 30. In Group 3, on days 3 and 7, IL-10 levels were low, measuring 25.7 ± 1.2 pg/ml and 19.4 ± 1.7 pg/ml, respectively. By day 15, the level dropped to 17.3 ± 1.7 pg/ml, decreasing to 17.2 ± 1.2 pg/ml on day 20, and reaching 17.0 ± 0.3 pg/ml by day 30 ($p < 0.05$) (**Table 4**).

In cases of aseptic and purulent inflammation of soft tissues at low altitudes and during de-adaptation to high altitudes, leukogram analysis showed that, in the purulent inflammation group, after mountain stay, leukocytosis was observed on day 3, with a count of 15.5 ± 0.2 × 10^9/l (**Figure 1**). This indicator declined, registering at 14.4 ± 0.2 × 10^9/l on day 7 ($p < 0.05$), 11.6 ± 0.1 × 10^9/l on day 15 ($p < 0.05$), 10.9 ± 0.2 × 10^9/l on day 20 ($p < 0.05$), and by day 30, remained at 10.4 ± 0.3 × 10^9/l ($p < 0.05$). Alterations in cytokine levels during experimental aseptic and purulent inflammation dictate the modification and duration of cellular responses. In purulent inflammation, the cytokine secretion pattern delays all cellular phases of the inflammatory process.

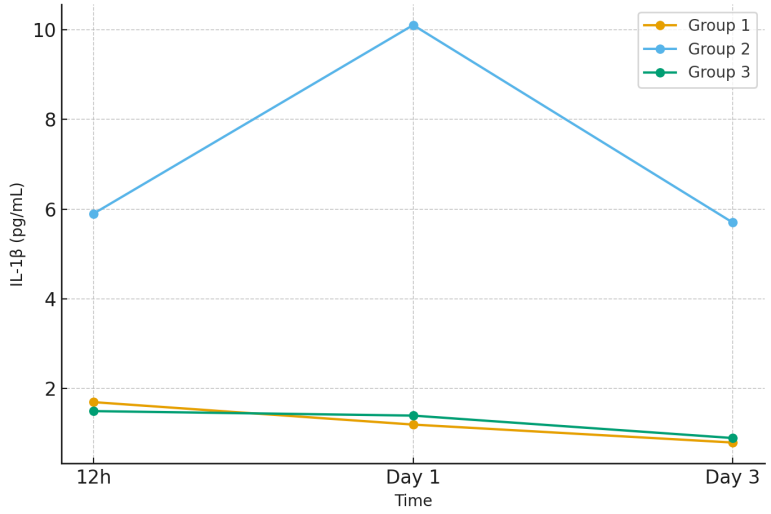

Figure 1. IL-1β dynamics in aseptic wounds during deadaptation.

Graphical analysis of IL-1β secretion showed varied responses based on the duration of exposure to high altitude. In aseptic wounds (**Figure 2**), Group 2, under short-term high-altitude conditions, showed a rapid increase in IL-1β within 24 h through day 3, indicating a maladaptive pro-inflammatory state. Conversely, Group 1 exhibited a physiological reduction in IL-1β, aligning with normal inflammation resolution, whereas Group 3, which

was exposed to extended hypoxia, displayed reduced IL-1β responses, suggesting immune exhaustion. In purulent wounds (**Figure 1**), Group 2 showed heightened IL-1β levels (~31 pg/mL on day 3), indicating prolonged inflammation, whereas Group 3 showed diminished responses, suggesting impaired pro-inflammatory activation during the deadaptation process. These findings show that short-term hypoxia followed by reoxygenation amplifies inflammation, whereas prolonged exposure diminishes cytokine activity due to exhausted adaptive mechanisms.

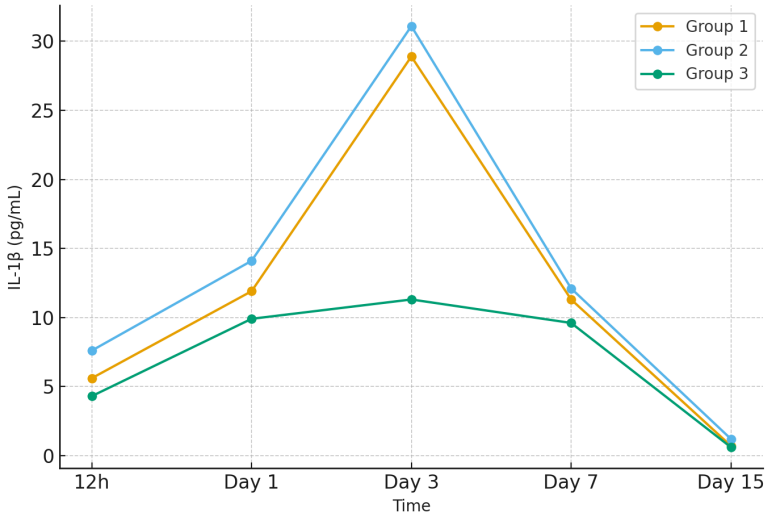

Figure 2. IL-1β dynamics in purulent wounds during deadaptation.

IL-10 secretion patterns provided insights into anti-inflammatory regulation among the groups. In aseptic wounds (**Figure 3**), Group 1 showed a gradual increase in IL-10, which aligns with effective resolution and tissue repair. Group 2 exhibited a disrupted pattern, with an initial increase followed by a decrease, suggesting inadequate anti-inflammatory activity to counter IL-1β responses. Group 3 had low IL-10 levels, indicating immune suppression and reduced repair potential following prolonged hypoxia. In purulent wounds (**Figure 4**), Group 2 showed a delayed but pronounced surge in IL-10, peaking after the increase in IL-1β, representing a poorly timed regulatory response, whereas Group 3 showed suppressed IL-10 secretion. These findings highlight that successful wound healing depends on managing IL-1β–driven inflammation and achieving a timely, sustained increase in IL-10. Disruption of this balance, whether due to maladaptive hyperinflammation or immune exhaustion, emerges as a key mechanism linking altitude deadaptation to impaired tissue repair.

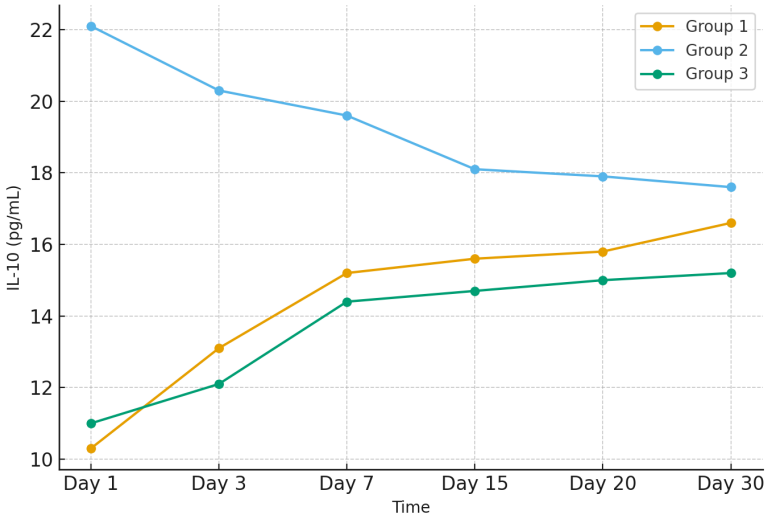

Figure 3. IL-10 dynamics in aseptic wounds during deadaptation.

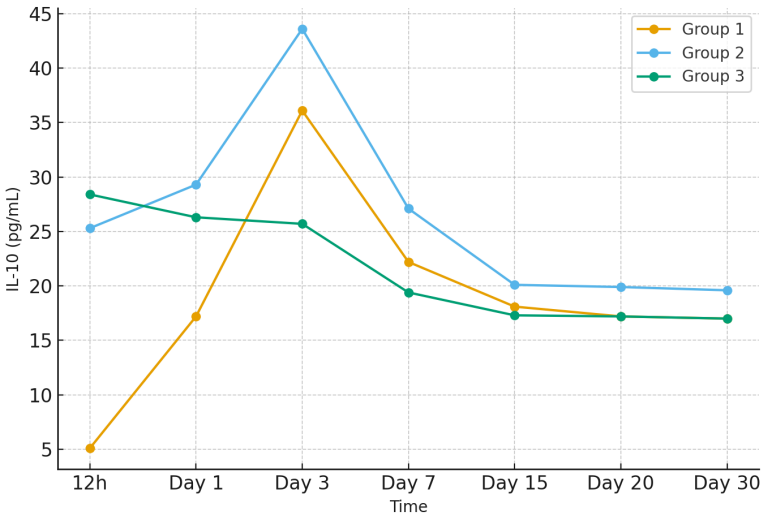

Figure 4. IL-10 dynamics in purulent wounds during deadaptation.

After extended high-altitude stays, individuals experience maladaptation with reduced secretion of IL-1β and IL-10, which is linked to the exhaustion of protective adaptive mechanisms.

In rabbits experiencing aseptic and purulent inflammation during altitude changes, notable changes in leukocyte counts and cytokine levels were observed. Within the aseptic inflammation model, leukocyte numbers decreased across all groups, with the largest reduction observed in animals that had readjusted after a brief high-altitude stay (Group 2), indicating a weakened immune response. In Group 2, IL-1β levels surged to 10.1 ± 0.3 pg/ml by day one and remained high through day seven, unlike the gradual decline observed in Groups 1 and 3, suggesting prolonged inflammation during the initial deadaptation period. IL-10 levels in Group 2 started at 22.1 ± 2.1 pg/ml and decreased over 30 days, indicating a disrupted anti-inflammatory response, while Group 1 showed a consistent increase, highlighting the differences in inflammation resolution during altitude recovery.

In the purulent inflammation model, Group 2 animals showed significantly elevated IL-1β levels, reaching 31.1 ± 2.5 pg/ml by day three. This exceeded the levels in Groups 1 and 3, indicating extended inflammation due to maladaptive immune activation during deadaptation. The IL-10 response in Group 2 showed delayed regulation, with high levels (43.6 ± 1.7 pg/ml on day 3) that decreased gradually, while Group 1 exhibited an earlier peak followed by a stable anti-inflammatory response. Group 3, with longer high-altitude exposure, had lower and delayed cytokine peaks for both IL-1β and IL-10, suggesting immune exhaustion or reduced recovery capacity. These results indicate that altitude exposure duration and inflammation type affect cytokine dynamics and immune profiles, with short-term altitude changes intensifying inflammatory responses during the healing process.

4. Discussion

This study investigated leukocyte profiles and cytokine (IL-1β and IL-10) expression in rabbits during altitude deadaptation after aseptic and purulent wounds. The study revealed that rapid descent from high altitudes, especially after brief exposure, disrupts immune regulation, extends inflammation, and hinders wound healing. These findings have important implications for the clinical care of patients descending from mountainous areas for treatment or recovery.

Wound healing is affected by hypobaric hypoxia, which triggers maladaptive immune responses. HIF-1α/β play a crucial role in cellular adaptation to low oxygen levels by orchestrating angiogenesis, fibroblast activation, and immune modulation [23]. In injured tissue, temporary hypoxia boosts proangiogenic signaling; however, ongoing hypoxic stress, such as that associated with altitude changes, disrupts homeostasis and sustains inflammation. The interaction between hypoxic signaling and inflammatory mediators is demonstrated by the finding that IL-1β and tumor necrosis factor alpha (TNF-α) can influence HIF-1 activity, even under normal oxygen conditions [24]. Moderate hypoxia increases IL-1β production in activated cells, whereas systemic hypoxia increases IL-1β, IL-6, and TNF-α levels. These elements maintain a prolonged proinflammatory environment during the early stages of

healing.

IL-1β plays a crucial role in initiating inflammatory responses by attracting neutrophils and activating endothelial cells [25]. When IL-1β levels are excessive, as seen in Groups 2 and 3, it leads to inflammatory activation up to day 7 in aseptic wounds and increases in purulent wounds, reaching approximately 31 pg/mL by day 3. This cytokine pattern mirrors that in diabetic or chronic wounds, where unchecked IL-1β causes persistent inflammation and delayed healing. The study revealed that deadaptation heightens IL-1β expression and delays its return to normal levels (**Table 3**), aligning with maladaptive immune responses to altitude stress. Elevated IL-1β can interfere with HIF-mediated angiogenesis by shifting macrophage polarization towards the M1 phenotype, thereby hindering the reparative functions of macrophages.

IL-10 plays a vital role in resolving inflammation, encouraging M2 macrophage polarization, and remodeling the extracellular matrix [26]. In control animals, IL-10 levels increased after wounding, peaking between days 3 and 7. Group 2 showed a rapid increase in IL-10 at 12 hours (~22 pg/mL), which then decreased, indicating a weakened anti-inflammatory response that was insufficient for resolution. In purulent wounds, the significant rise in IL-10 (43–44 pg/mL on day 3) in Group 2 might indicate compensatory but delayed immune regulation following IL-1β-driven inflammation. However, this delayed IL-10 peak missed the crucial period for timely inflammatory resolution, leading to prolonged tissue injury. Similarly, Group 3 showed suppressed IL-10 responses (remaining ~17 pg/mL), consistent with immune exhaustion after altitude exposure. These patterns align with those observed in chronic wounds, which show reduced IL-10 expression and persistent IL-1β dominance [27]. The balance between pro- and anti-inflammatory cytokines influences macrophage transitions, which are crucial for healing.

The graphical representation of cytokine activity (**Figures 1**–**4**) shows immune dysregulation during altitude deadaptation. In both wound scenarios, Group 2 exhibited elevated IL-1β peaks, extending inflammation, whereas Group 3 showed diminished responses, indicating immune exhaustion. These pro-inflammatory changes were linked to disrupted IL-10 regulation: Group 2 showed delayed IL-10 secretion, whereas Group 3 showed consistent suppression. The imbalance between IL-1β activity and insufficient IL-10 elevation indicates a loss of coordination between inflammation and tissue repair. These findings show that brief high-altitude exposure triggers hyperinflammation, whereas prolonged hypoxia suppresses immune responses, impairing wound healing.

In this study, changes in leukocyte count were found to parallel cytokine patterns. Group 2 rabbits showed rapid leukopenia after aseptic injury, followed by intense leukocytosis in purulent wounds, with a delayed peak compared to the controls. Initial leukopenia suggests immune suppression or redistribution of immune cells due to hypoxic changes during deadaptation. Compensatory leukocytosis develops but shows a dysregulated immune response, indicating delayed healing and excessive inflammation [28,29]. Neutrophil recruitment is crucial for wound healing but can be harmful if prolonged [30]. Hypoxia impairs leukocyte function by reducing neutrophil and monocyte chemotaxis and phagocytic activity, leading to suppression, followed by dysregulated hyperactivation [31]. In Group 2, brief high-altitude exposure followed by rapid descent induced a maladaptive immune response with excessive inflammation. Group 3 animals, under extended high-altitude hypoxia, showed a subdued leukocyte response with lower cytokine levels, indicating immune exhaustion. Chronic hypoxia reduces inflammatory cytokine production and impairs immunity via HIF activation, metabolic stress, and oxidative stress [32,33]. This exhaustion undermines pathogen clearance, angiogenesis, and matrix remodeling, which are essential for wound healing [34].

The immune responses in Groups 2 and 3 highlight the influence of altitude exposure duration on wound healing. Group 2 animals showed significant immune imbalance after a 3-day stay at high altitude, with heightened IL-1β responses and inadequate IL-10 levels, suggesting extended inflammation. Brief exposure to low oxygen can activate inflammatory pathways without triggering compensatory mechanisms, leading to increased proinflammatory states at normal oxygen levels [31,35]. In contrast, Group 3 rabbits, which spent 30 days at high altitude before descending, showed reduced IL-1β and IL-10 responses, suggesting immune suppression. This aligns with "altitude memory," where prolonged adaptation through HIF-mediated signaling, erythropoietin stimulation, and metabolic changes prepares the system for lower immune activation upon returning to sea level [36,37].

Makhmudova et al. highlighted the role of oxidative stress and inflammation in impeding tissue repair, showing that inadequate antioxidant defenses can exacerbate chronic wounds and increase the risk of infection [38]. Alymkulov et al.'s [39] research emphasized environmental and host-related immunological factors in delayed healing and infection vulnerability, particularly in populations exposed to fluctuating oxygen levels. When considered with our findings, which showed that altitude deadaptation amplifies IL-1β-driven inflammation and disrupts IL-

10-mediated resolution, these studies confirm that wound healing is influenced by systemic oxidative, infectious, and immunological stressors. This underscores the importance of incorporating antioxidant, antimicrobial, and immune-modulating strategies into wound care protocols for individuals recovering from hypoxia-reoxygenation transitions.

Deadaptation from chronic hypoxia to normoxia initiates oxidative bursts that reactivate inflammatory pathways without re-establishing immunological balance. The increase in reactive oxygen species during reoxygenation enhances innate immune responses and disrupts cytokine regulation [40,41]. This challenges tissue repair because oxidative stress inhibits IL-10 secretion and alters macrophage polarization away from the reparative M2 phenotype^14. Lower IL-10 levels in Group 3 indicated a compromised resolution phase, increasing wound susceptibility to infection [40,42]. These findings align with studies linking hypoxia-reoxygenation cycles to immune imbalances and impaired healing [36,41]. Both short- and long-term altitude exposure modify immune responses, necessitating altitude-specific postoperative protocols.

5. Limitations

This study has some limitations. First, it focused only on IL-1β and IL-10, neglecting other cytokines such as IL-6, TNF-α, TGF-β, VEGF, or IL-16. This limited focus restricts our understanding of the immune network's behavior during wound healing at various altitudes. Second, the study analyzed systemic plasma levels rather than cytokine levels at the wound site, which may not accurately represent the local tissue environment. Third, factors such as nutrition, iron levels, and metabolic status were not considered, despite their impact on immune function, oxidative stress management, and tissue repair. Fourth, the study lacked pathogen characterization in purulent wounds, limiting the correlation between microbial load and immune response. Finally, although the rabbit model offers experimental control, caution is needed when applying these findings to human physiology because of differences in comorbidities, genetic backgrounds, and environmental exposures.

6. Clinical Implications

The findings show that altitude deadaptation impacts immune dynamics, leading to extended pro-inflammatory responses (IL-1β) and delayed anti-inflammatory processes (IL-10). These imbalances may impede wound healing and increase complications in patients descending from high altitudes. Tracking leukocyte profiles and cytokine responses after descent could help identify those at risk of delayed healing or infection. Potential interventions include oxygen therapy (topical oxygen delivery or oxygen-releasing biomaterials), pharmacological modulation of IL-1β using receptor antagonists (such as anakinra), boosting IL-10 signaling with analogs, or stabilizing hypoxia-inducible pathways with prolyl hydroxylase domain enzyme inhibitors to enhance outcomes. However, these strategies remain theoretical in the context of altitude-induced immune dysregulation. This study did not evaluate the dosage, timing, or effectiveness of these drugs, and no clinical evidence supports their routine use in patients recovering from high-altitude exposure. Future research should broaden cytokine profiling beyond IL-1β and IL-10 to include IL-6, TNF-α, TGF-β, and VEGF. Explore the influence of nutritional status, iron levels, and metabolic health on wound healing during deadaptation. Conduct clinical trials to assess the safety, timing, and therapeutic potential of cytokine-targeted agents and oxygen-based therapies. This study underscores the need for improvements in perioperative and postoperative care for patients transitioning from hypoxic to normoxic environments.

7. Conclusions

This study revealed that altitude deadaptation affects the immune response during wound healing. Short-term exposure enhances IL-1β–driven inflammation, whereas prolonged exposure results in immune exhaustion with diminished IL-10 activity. These imbalances in cytokine levels and leukocyte behavior emphasize the role of hypoxia and reoxygenation in determining the wound healing outcomes.

These results highlight the need to adjust perioperative and postoperative strategies for patients returning from high altitudes. Although oxygen therapy, cytokine modulation, and stabilization of hypoxia-inducible pathways appear promising, their effectiveness, dosage, and timing in altitude-related wound healing require validation through clinical trials. Addressing factors such as nutrition, metabolic status, and iron levels is crucial for applying these findings in practice.

8. Recommendations

Given the observed imbalance in cytokine levels during altitude deadaptation, several strategies can be explored. Oxygen therapy using topical delivery systems or oxygen-releasing biomaterials may alleviate stress during reoxygenation. Pharmacological interventions, such as IL-1 receptor antagonists, such as anakinra, can modulate pro-inflammatory signaling, or IL-10 analogs to boost anti-inflammatory responses, potentially helping to restore immune balance. Another strategy involves stabilizing hypoxia-inducible pathways using prolyl hydroxylase domain enzyme inhibitors to promote angiogenesis and enhance reparative macrophage activity.

However, these therapeutic options were not experimentally tested in this study. This study did not provide information on the dosage, timing, or clinical effectiveness of these interventions for altitude-related wound healing. These suggestions should be viewed as hypothesis-generating. Future translational research, including cytokine profiling, assessment of nutritional and metabolic factors, and controlled preclinical and clinical trials, is necessary to confirm their therapeutic potential and ensure safe application.

Author Contributions

Conceptualization, M.K.; methodology, A.E.; software, U.Y.; validation, N.B.; formal analysis, Y.V.; investigation, M.K., A.E., U.Y., and N.B.; data curation, M.T.; writing—original draft preparation, M.K., M.T., and Y.V.; writing—review and editing, Y.V. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The Institutional Bioethics Committee of I.K. Akhunbaev Kyrgyz State Medical Academy approved this study (Protocol No. 3, dated June 13, 2025).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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