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## **THE EXPRESSION OF THE SYSTEMIC INFLAMMATORY RESPONSE IN PATIENTS WITH ANTERIOR ABDOMINAL WALL HERNIAS FOLLOWING THE USE OF ENDOPROSTHESES**

**Kuldashev G. N.**

**Abdurakhmanov M. M.**

**Bukhara, Uzbekistan, Postal Code 200118**

**Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan,  
A. Gijduvani Street, Bukhara Tel.: +998(65) 223-00-50 e-mail: info@bsmi.uz**

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### **Abstract**

In the presented study, a comprehensive analysis of the systemic inflammatory response in patients with postoperative ventral hernias is conducted, aiming to assess the bioinert properties and the impact on the cytokine profile of two different types of endoprotheses: polypropylene "Esfil" and titanium "Titan Mesh." Based on their physicochemical characteristics and interactions with biological tissues, the study extensively describes the mechanisms of implant interaction with the immune system, with a particular focus on the roles of key cytokines, including TNF- $\alpha$ , IL-6, IL-8, and IL-4, in the processes of healing and scar formation following surgery. The results revealed that the use of titanium Mesh is associated with reduced inflammatory activity and a lower frequency of complications compared to polypropylene prostheses, indicating its superior bioinert properties and potential to improve clinical outcomes. The importance of the micro-porous structure of titanium Mesh and its promoting effect on cell adhesion and regeneration is also discussed as a key factor in accelerating the healing processes. The study's concluding recommendations emphasize the need for further research into the influence of different endoprotheses on the inflammatory response and regenerative processes, as well as the development of new materials with optimized biocompatible characteristics to enhance the treatment of postoperative ventral hernias and improve the quality of life for patients.



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**Keywords.** Inflammation, Ventral Hernia, Biocompatibility, Prosthetic Implants, Cytokine Profile, TNF- $\alpha$ , IL-6, IL-8, IL-4, Scar Formation.

### **Relevance**

Since the inception of abdominal surgery, the issue of ventral hernias occurring after surgeries has remained significant and is still not completely resolved. Studies indicate that anywhere from 5% to 40% of surgical interventions on abdominal organs lead to the formation of such hernias [1,2]. Recurrent hernias occurring on the anterior wall of the abdomen account for up to 30% of all surgical procedures in this area [3]. Modern medicine recognizes that the best treatment method for these hernias involves the use of endoprosthesis with various types of synthetic implants. Sublay or inlay techniques are common methods for these surgeries. However, in cases where postoperative hernias reach significant sizes, causing distortions in the structure of the anterior abdominal wall and subcutaneous tissue, the 'onlay' method is often required to reduce the operation time [4,5]. These circumstances emphasize the potential and, above all, the necessary need to study the conditions under which the implantation of endoprosthesis occurs, including the investigation of changes in the cytokine profile over time.

The variety of available synthetic endoprosthesis and herniorrhaphy techniques necessitates a critical approach when selecting a specific type of implant, taking into account the expected size of the hernia, potential complications, and other relevant factors [6]. The issue of immunoreactivity, which depends on the structural and chemical components of endoprosthesis, as well as their physical properties such as thickness and rigidity, remains at the forefront of modern herniology. Underestimating the immunological aspects of endoprosthesis can significantly complicate the interpretation of surgical outcomes in the context of wound dynamics [7,8].

This need for a selective approach is compounded by the complexity arising from the diversity of hernioplasty outcomes, including postoperative exudative complications and optimal timing and methods of wound drainage [9].

The study of immunological reactivity, especially considering the chemical



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composition of endoprostheses, is critically important for assessing treatment effectiveness [10]. Ignoring the immunological properties of the endoprosthesis can be a barrier to achieving reliable treatment outcomes, as the body's immune response to the prosthesis directly affects the wound healing process.

The fundamental principle that certain cytokines promote inflammation while others modulate it is of critical importance for both cytokine biology and practical clinical practice [11,12]. It provides the basis for predicting the body's response to the introduction of artificial materials. The outcome of the inflammatory response depends on the balance of activity between cytokines with pro-inflammatory and anti-inflammatory properties [13]. In the initial phase of inflammation, pro-inflammatory cytokines activate the inflammatory process, causing vasodilation, increased local blood flow, and vascular wall permeability, leading to the formation of exudate in the inflamed area.

At the initial stage of inflammation, pro-inflammatory cytokines serve a protective function by recruiting effector cells, such as neutrophils and macrophages, to the site of inflammation, enhancing their phagocytosis and bactericidal activity, and stimulating the onset of a specific immune response [14]. Cytokines-chemokines, especially IL-8, produced by activated macrophages, endothelial cells, and fibroblasts, regulate the migration of leukocytes to the site of inflammation, acting as chemotactic agents and recruiting them to the site of injury.

It is important to emphasize that the protective effect of pro-inflammatory cytokines is manifested only when they act locally in the inflammatory zone. Excessive and systemic production of these mediators, on the other hand, can lead to the development of hyperthermia and deterioration of the overall condition of the organism [15].

Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) is classified as a cytokine with pro-inflammatory properties. Its main function is through the activation of the endothelium and subsequent induction of intercellular adhesion molecule-1 (ICAM-1), which promotes transendothelial migration of granulocytes to the site of inflammation. TNF- $\alpha$  can be secreted not only by neutrophils but also by activated lymphocytes, and it acts as an endogenous pyrogen, affecting the



thermoregulatory centers of the hypothalamus and causing hyperthermia. TNF- $\alpha$  also initiates the early phase of the immune response, catalyzing the release of IL-8 in response to the transplantation of foreign materials [16,17]. Interleukin-8 (IL-8) is synthesized by activated macrophages, as well as fibroblasts, epithelial cells, and hepatocytes in response to stimulation by IL-1 or TNF- $\alpha$  [18]. It facilitates the degranulation of neutrophils and can contribute to tissue damage. As a pro-inflammatory agent, IL-8 is involved in the process of leukocyte extravasation from the bloodstream into tissues and belongs to the family of chemokines with the ability to induce directed leukocyte migration to the inflammatory focus.

To prevent excessive systemic inflammatory responses in the body, regulatory mechanisms are activated, including the synthesis of anti-inflammatory cytokines such as IL-4 and IL-10, which exert negative control over the inflammation process.

Interleukin-4 (IL-4) plays a key role in regulating the body's anti-inflammatory responses, acting as an immunosuppressive agent and promoting the enhanced proliferation of B-lymphocytes. This cytokine facilitates the growth and differentiation of B-cells in cooperation with interleukins 5 and 6, thereby enhancing their functional activity [19]. Additionally, IL-4 inhibits the activation of macrophages and effectively blocks the actions of other cytokines, including IL-1, as well as the synthesis of nitric oxide and prostaglandins, thus limiting the development and progression of inflammatory reactions. The outcome of the inflammatory process, therefore, is a direct result of the balance between the activity of pro-inflammatory and anti-inflammatory cytokines, where excessive pro-inflammatory responses are controlled through the production of anti-inflammatory cytokines, particularly IL-4 and IL-10 [20]. These dynamic underscores the importance of further research in the field of cytokine profiles at the implantation site, as well as the analysis of morphological changes in this area.

Modern surgical practices involve the use of numerous implants made from various materials. Titanium, characterized by its low molecular weight and high biocompatibility, has long established itself as one of the preferred materials in



medicine due to its neutral interaction with biological tissues [21]. In Russia, a unique titanium mesh implant known as 'Titan Mesh' (NPV 'Temp') has been developed for the reconstruction of the aponeurosis in cases of anterior abdominal wall hernias.

This study aimed to conduct a comparative analysis of clinical outcomes using two different types of synthetic endoprostheses: polypropylene 'Esfil' from the company 'Lintex' (Saint Petersburg) and 'Titan Mesh' (NPV 'Temp,' RUSSIA).

### **Materials and Methods**

The scientific study conducted in the surgical departments of the Bukhara branch of the National Research Center for Emergency Medicine from 2019 to 2022 aimed to compare the effectiveness of two different types of synthetic endoprostheses: polypropylene 'Esfil' from the 'Lintex' company (Saint Petersburg) and 'Titan Mesh'. During the study, which involved 112 patients divided into two groups, the outcomes of surgeries performed using the 'onlay' technique were evaluated. The patients were divided into two groups: in the first group (58 patients), a polypropylene mesh implant 'Esfil' was used as the endoprosthesis, while in the second group (54 patients), a mesh implant made from 'Titan Mesh' was used. This analysis provided valuable data on the clinical effectiveness and safety of these endoprostheses, contributing to a more informed choice of implant for the treatment of anterior abdominal wall hernias.

Within the scope of this study, an analysis of the cytokine profile was conducted in two groups of patients using polypropylene and titanium Mesh, each group consisting of 20 individuals. To ensure the accuracy of the comparison, demographic and clinical characteristics, including gender, age, body mass index, and assessment of operative-anesthesiological risk, were strictly standardized between both groups. The study only included patients who presented with giant and extensive hernia defects, excluding small and medium-sized hernias due to their low statistical representativeness and short duration of patient stay in the hospital.

The collection of wound exudate samples began on the third day after surgical intervention when the material was no longer saturated with erythrocytes. The



extended use of drains was dictated by the necessity to perform cytokine studies on the 3rd, 5th, 7th, and 10th days after the surgeries. However, when exudation ceased, the drains were removed before the previously indicated 10-day period. The first phase of the study included the analysis and comparison of clinical data and cytokine indicators in aspirates from the area of endoprosthesis. Subsequently, key clinical parameters, including temperature reaction, leukocyte count, volume, and organoleptic characteristics of the fluid drained through the drains, were correlated with the cytokine profile.

Active ultrasound monitoring of the postoperative wound was conducted for all study participants. In case of seroma or hematoma detection, ultrasound-guided puncture drainage was performed.

The analytical process of studying cytokines involved the analysis of exudate collected through drainage systems and punctures of exudative formations detected using ultrasound diagnostics. The study focused on determining the characteristics of the fluid, such as color and volume, as well as on the levels of cytokines, including IL-8, IL-6, TNF- $\alpha$ , IL-10, and IL-4, the selection of which was based on their role in the development of the immune response.

### **Research results and their discussion**

We found that postoperative formation of exudative formations in the implantation area is typical. Data on the frequency of exudative complications depending on the type of implant used were systematized and presented in Table 1-3

**Table 1-3 The frequency of exudative complications depending on the type of implant used**

Complications	«Esfil» n=58	«Titan Mesh» n=54
<b>Seroma</b>	18 (31%)	<b>9 (16,6%)</b>
<b>Hematoma</b>	9 (15,5%)	<b>1 (1,8%)</b>
<b>Infection</b>	<b>3 (5,2%)</b>	-





It was observed that seromas more frequently occurred when using implants in patients with large and giant hernias. In patients with small and medium-sized hernias, seromas were detected as a limited accumulation of fluid around the implant, confirmed by ultrasound. Seromas were found in 18 (31%) patients who used the polypropylene mesh "Esfil" and in 9 (16.6%) patients who used the "Titan Mesh" implant, which is twice as low as when using the polypropylene endoprosthesis.

Hematomas were also detected through ultrasound examination and, when necessary, were removed by diagnostic punctures and drainage under ultrasound control. When using polypropylene endoprostheses, hematomas occurred much more frequently – in 9 (15.5%) patients, due to the greater stiffness of the polypropylene threads and the presence of sharp edges from cut threads when forming the prosthesis size, which increased the risk of tissue injury and hematoma formation. Meanwhile, titanium prostheses resulted in hematoma in only 1 (1.8%) patient, reducing this complication by 8 times due to their better mechanical properties, characterized by softer and more elastic edges.

The study of cytokine dynamics demonstrates the sequence of phases of the local inflammatory response in the body. On the second day after surgery, there is a transition from the stage of primary and secondary tissue damage to the exudation phase. This stage is characterized by the migration of monocytes to the area of the implanted endoprosthesis and their subsequent transformation into phagocytic cells and macrophages. Macrophages, in turn, produce a range of powerful inflammation mediators, among which TNF- $\alpha$ , IL-6, and IL-8 are characterized by increased activity.

In the course of the study aimed at analyzing immunological changes associated with cytokine production, it was reliably determined that the expansion of the hernia defect correlates with increased secretion of pro-inflammatory cytokines, such as interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF- $\alpha$ ), when using different types of prostheses. This phenomenon is substantiated by logical biological mechanisms, indicating a direct relationship between the size of the hernia defect and the intensity of the immune response. The concentration of

TNF- $\alpha$  for "Esfil" already on the 3rd day of the study is at a higher level compared to "Titan Mesh" (Figure 1).

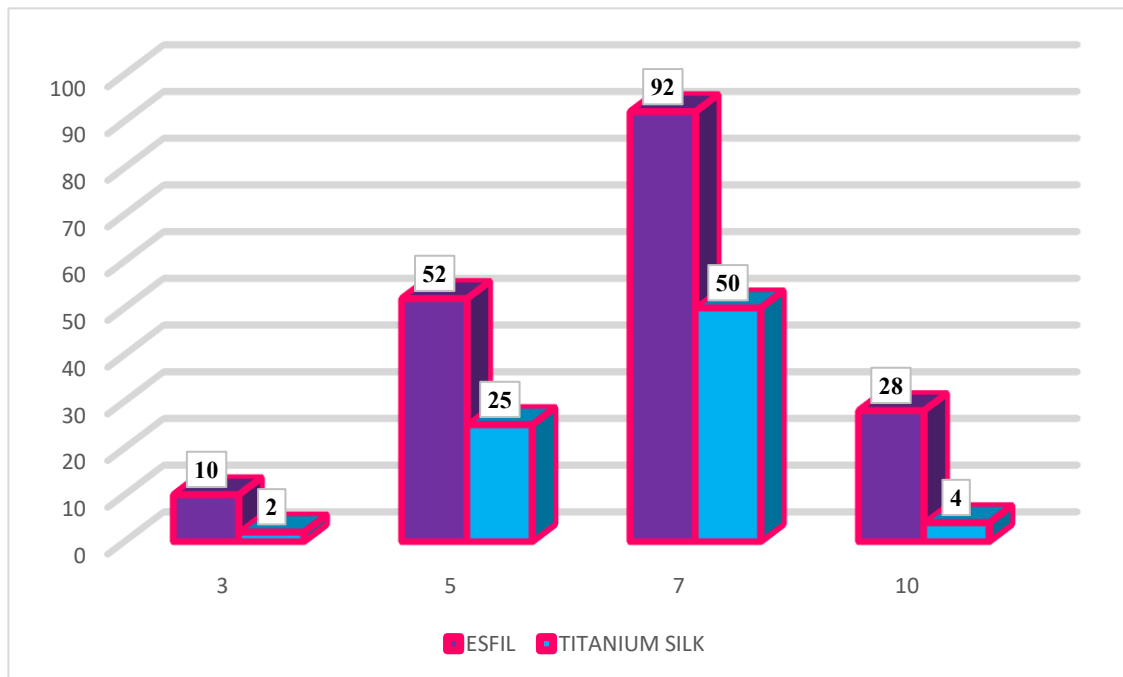


Fig. 1. The dynamics of changes in TNF- $\alpha$  concentration from day 3 to day 10 (pg/ml)

This information suggests that the concentration of the cytokine tumor necrosis factor-alpha (TNF- $\alpha$ ) is significantly higher in patients who received the "Esfil" endoprosthesis compared to those who received the "Titan Mesh" endoprosthesis in the days following surgery. The trend of higher TNF- $\alpha$  levels with the "Esfil" endoprosthesis continues over the subsequent days, reaching a peak concentration on the 7th day after surgery, which is significantly higher compared to the "Titan Mesh" endoprosthesis.

This indicates that the choice of endoprosthesis material may have an impact on the immune response and the production of pro-inflammatory cytokines, such as TNF- $\alpha$ , in the postoperative period. The study suggests that the "Esfil" endoprosthesis may lead to a more pronounced inflammatory response compared to the "Titan Mesh" endoprosthesis, at least in terms of TNF- $\alpha$  concentration.

If you have any specific questions or need further information on this topic, please feel free to ask.

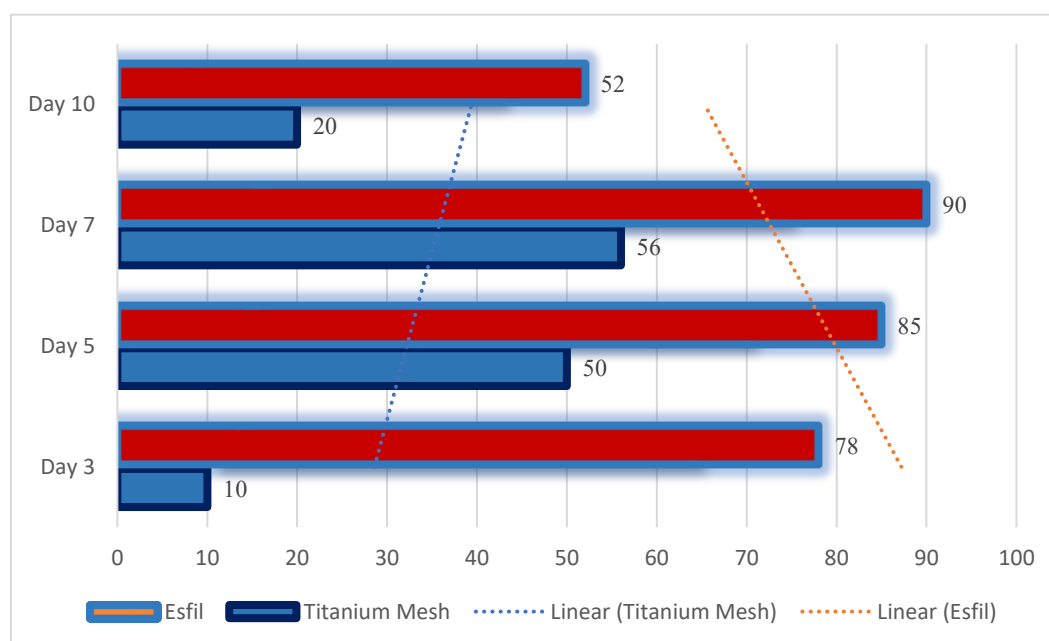




From the seventh to the tenth day, there is a gradual decrease in concentration, and the level of TNF- $\alpha$  stabilizes, corresponding to the initial values recorded on the third day after the surgery.

In conclusion, it should be noted that the use of the "Esfil" endoprosthesis is accompanied by a noticeable and intensive increase in the level of TNF- $\alpha$ , while the use of a polypropylene mesh maintains these indicators at a level 7 times higher compared to the "Titan Mesh," where a decrease in TNF- $\alpha$  concentration is observed, reaching symmetry with the latter and emphasizing its effectiveness compared to alternative methods.

By studying changes in the level of IL-8, which stimulates the migration of leukocytes to the inflammatory focus, significant differences in the dynamics of these changes can be noticed, depending on the type of endoprosthesis used. Similar to TNF- $\alpha$ , the concentration of IL-8 is significantly increased by the third day after the surgery, especially when using "Esfil," where it significantly exceeds the levels observed with "Titan Mesh," 78.1 $\pm$ 0.9 pg/ml versus 10.0 $\pm$ 0.5 pg/ml ( $p < 0.01$ ). On the seventh day after the surgery, this elevated level of IL-8 is maintained when using "Esfil," surpassing the "Titan Mesh" indicators by 1.7 times (Figure 2).



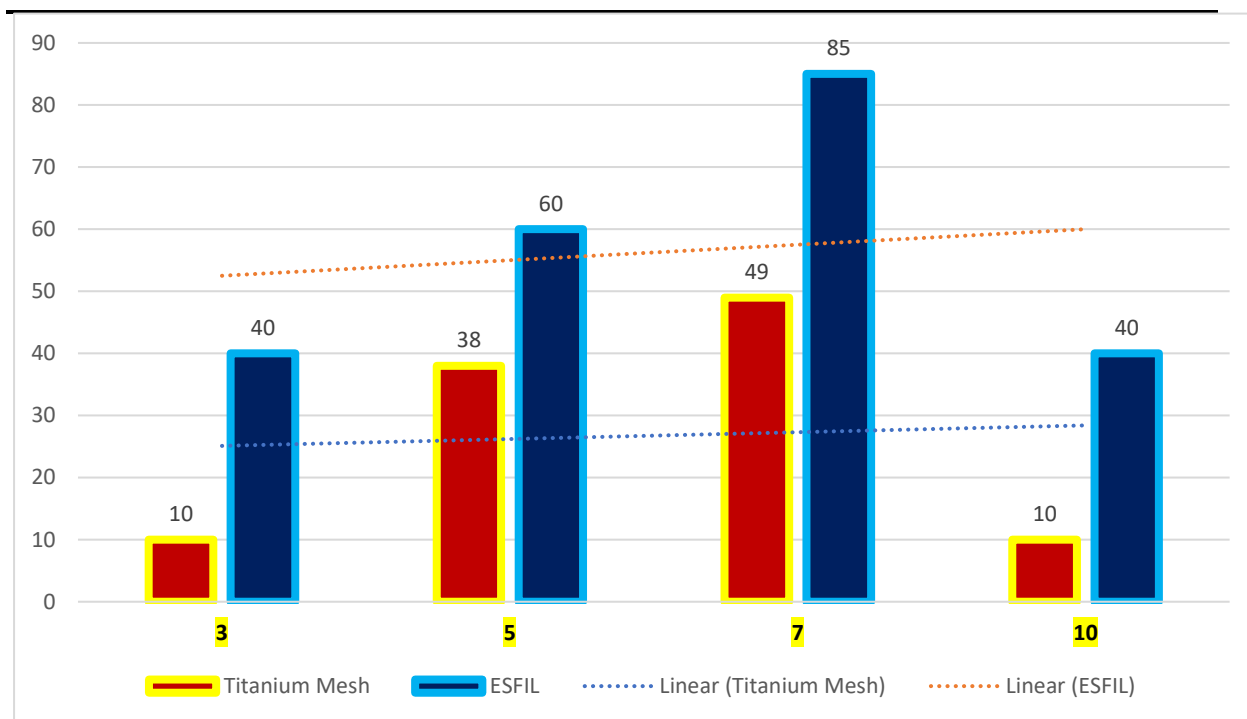
**Fig. 2.** Dynamics of changes in IL-8 concentration from day 3 to day 10 (pg/ml)



Studying the concentration of IL-8, it is evident that when using "Esfil," the concentration of this cytokine is already high on the 3rd day after the operation. With the use of "Esfil," the concentration of IL-8 remains high, reaching its peak on the 7th day after the operation, after which the IL-8 concentration gradually begins to decrease, reaching a value of  $52.2 \pm 1.8$  pg/ml by the 10th day, while with the use of the "Titan Mesh" endoprosthesis, the IL-8 concentration on the 10th day was 1.5 times lower, amounting to  $20.6 \pm 2.8$  pg/ml.

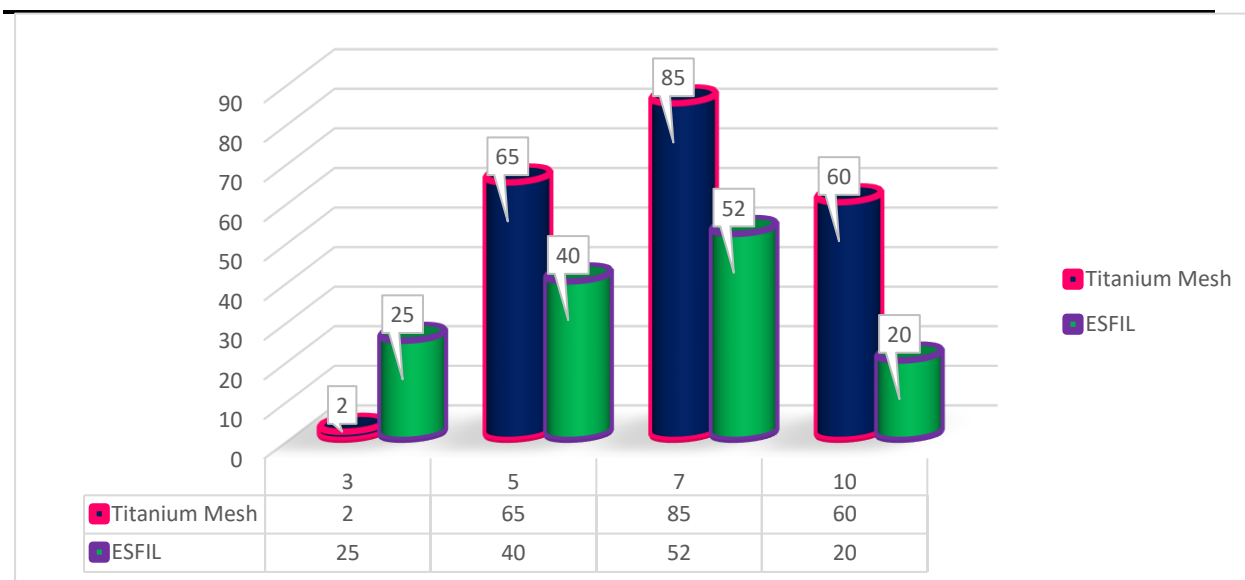
It is worth noting separately that when using "Esfil," there is no clear "peak" in the concentration of IL-8 during the observation period, which complicates determining the moment of maximum inflammation, especially in the period from the 5th to the 7th day ( $p > 0.05$ ). IL-8 is a product of macrophage activation, fibroblasts, and epithelial cells produced in response to  $\text{TNF-}\alpha$ . We assume that in the area of the endoprosthesis when using "Esfil," there are more macrophages and fibroblasts, which is due to the structural features of the endoprosthesis.

When analyzing changes in the concentration of IL-6, in the case of using "Titan Mesh," there was a slow increase from the third day until the seventh day, from  $10.1 \pm 0.3$  pg/ml to  $49.6 \pm 2.1$  pg/ml. Starting from the seventh day, there was a decrease, and by the tenth day, the values reached the level of the third day ( $10.4 \pm 1.3$  pg/ml). As for the "Esfil" endoprosthesis, the concentration of IL-6 was already high on the third day after the operation ( $40.2 \pm 1.1$  pg/ml), which served as the starting point for further growth, reaching its peak on the seventh day at  $85.4 \pm 1.8$  pg/ml. Then, by the tenth day, the IL-6 level gradually started to decrease, returning to the levels observed on the third day ( $40.1 \pm 2.3$  pg/ml). However, it is worth noting that the concentration levels after using titanium threads significantly differ from the levels after using Esfil. Prolonged high levels of IL-6 when using "Esfil," reaching their maximum on the seventh day after the operation, indicate a more prolonged maintenance of an active inflammatory response (Figure 3).



**Fig. 3.** Dynamics of changes in IL-6 concentrations from day 3 to day 10 (pg/ml) On the third day after using "Esfil," there is a statistically significant increase in the concentration of the cytokine IL-4, as confirmed by the data presented in Figure 3. Furthermore, when compared to "Titan Mesh," the concentration of IL-4 when using "Esfil" continues to increase, reaching its peak on the seventh day ( $85.2 \pm 1.4$  pg/ml). In the case of patients where the "Titan Mesh" endoprosthesis was used, there was a gradual increase from the third day to the seventh day ( $52.0 \pm 3.4$  pg/ml), followed by a sharp decrease in concentration until the tenth day ( $20.4 \pm 0.9$  pg/ml).

In the group where "Esfil" was used, the concentration of the anti-inflammatory cytokine IL-4 remains at a high level for the subsequent four days after reaching its peak, remaining equally high on the tenth day. In our opinion, this effect correlates with the initially high and prolonged concentration of the pro-inflammatory cytokine IL-8, indicating its influence on the dynamics of IL-4 concentration. (Figure 4).



**Fig. 4.** Dynamics of changes in IL-4 concentrations from day 3 to day 10 (pg/ml). Studying the dynamics of IL-10, an anti-inflammatory cytokine, allows us to track stage-wise changes in the concentration of other anti-inflammatory cytokines. When using "Titan Mesh" prostheses, there is a slow and steady decrease in the level of IL-10, from  $17.2 \pm 0.6$  on the third day to  $10.01 \pm 0.3$  on the tenth day after the operation. In the case of "Esfil," the concentration levels on the third day were  $20.1 \pm 0.3$ , and by the tenth day, they had decreased to  $15.0 \pm 0.4$  (Table 4).

**Table 4** Changes in the concentration levels of cytokines in wound exudate when using polypropylene and titanium Mesh endoprotheses (pg/ml)

«ESFIL»				
TNF-a	10,2±0,5	52,3±1,2	92,1±2,1	28,2±0,3
IL-6	40,2±1,1	60,3±1,6	85,4±1,8	40,1±2,3
IL-8	78,1±0,9	85,5±1,5	90,2±1,9	52,2±1,8
IL-4	25,2±0,7	65,4±0,5	85,2±1,4	60,1±1,1
IL-10	20,1±0,3	19,0±0,6	18,1±0,5	15,0±0,4
«TITAN MESH»				
TNF-a	2,1±0,1	25,6±1,0	50,4±2,3	4,01±0,3
IL-6	10,1±0,3	38,4±0,5	49,6±2,1	10,4±1,3
IL-8	10,0±0,5	50,4±1,6	56,4±2,1	20,6±2,8
IL-4	2,0±0,1	40,4±1,7	52±3,4	20,4±0,9
IL-10	17,2±0,6	15,1±1,3	14,2±0,9	10,01±0,3



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This process exacerbates the disruption of the integrity of biological tissues, especially in critical early periods (7-8 days), weakening wound healing processes and contributing to the development of exudative complications. Studying the cytokine profile in this context requires careful consideration of the architecture of different implants. In particular, the "Esfil" prosthesis is made of polypropylene monofilaments, while the "Titan Mesh" is formed from titanium fibers. The outer layers of the latter have a porous structure that allows various cells and microorganisms to penetrate, but at the same time limits accessibility to immune cells and their mediators. These features make "Titan Mesh" more bioinert, which is preferable for hernioplastic surgeries.

The increased bioinertness of titanium-containing material can be explained by its unique physicochemical characteristics. The titanium fibers that form the material's structure give it exceptional strength and flexibility, minimizing the risk of tissue damage during and after surgery. It is important to emphasize that the architecture of titanium Mesh promotes a more even distribution of stress, reducing the likelihood of new hernia formations.

The micro-porous structure of titanium Mesh also creates favorable conditions for cell adhesion and regeneration, thereby accelerating the healing processes and reducing the chances of developing infectious complications, facilitating a more harmonious integration of the implant into the surrounding biological tissues. However, it should be noted that a high degree of biological inertness can delay the immune response.

In the context of the cytokine profile, the use of titanium Mesh has a positive impact on the levels and changes in cytokines in wound fluid. The absence of a pronounced inflammatory response reduces the content of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, IL-8, IL-4, and IL-10, unlike the reaction to a polypropylene prosthesis, where such a reaction is more noticeable. This affects the reduction in the likelihood of chronic inflammation and improves overall healing indicators.

Titanium's inertness prevents the development of aggressive immune reactions, contributing to the formation of strong connective tissue that replaces defects in the muscular-aponeurotic layer. The choice of material for implantation is largely



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determined by its unique chemical properties, molecular weight, conditions and location of implantation, as well as the morphofunctional and mechanical characteristics of the material itself.

In conclusion, it can be said that the key difference of the titanium-containing implant is its ability to integrate physiologically, which contributes to the formation of a durable and functional postoperative scar and does not significantly affect the duration of regenerative processes.

## **Conclusions**

The impact of the material on healing: The research demonstrates a noticeable difference in the healing process and inflammatory response between polypropylene "Esfil" and titanium "Titanium Mesh" implants. Titanium implants, thanks to their biologically inert properties, induce a milder inflammatory response, as evidenced by lower levels of inflammatory cytokines such as TNF- $\alpha$ , IL-6, IL-8, IL-4, and IL-10 compared to polypropylene implants. Dynamics of cytokine profiles: The dynamics of cytokine profiles, especially TNF- $\alpha$ , IL-6, IL-8, IL-4, suggest a more aggressive inflammatory response when polypropylene implants are used. The study implies that the chemical composition of the implant plays a significant role in modulating the local inflammatory environment.

Complications with the use of different implants: It has been observed that postoperative complications, such as seroma and hematoma, occur more frequently when polypropylene implants are used compared to titanium implants. This indicates that the physical and chemical properties of "Titanium Mesh" contribute to a reduced risk of certain postoperative complications.

The role of cytokines in wound healing: The study underscores the critical role of cytokines in the wound healing process. Balanced interaction between pro- and anti-inflammatory cytokines is crucial for effective healing, and the choice of implant material significantly influences this balance.

The importance of implant selection: The results highlight the need for a careful approach when selecting the appropriate implant. Factors such as the biological inertness of the material, mechanical properties, and interaction with the immune





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system should be considered to minimize complications and optimize outcomes for the patient.

Prospects for future research: The study points to the necessity of further investigating the long-term consequences of these findings. It also emphasizes the importance of developing targeted therapeutic strategies for inflammation management and tissue regeneration tailored to the type of implant used.

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