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ИММУНОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА БОЛЬНЫХ ПЕРЕНЁСШИХ ЛИПОФИЛИНГ

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✓ ***Резюме***

Наиболее выраженные иммунологические нарушения отмечены при липофилинге молочных желез, что соответствует и высокой клинической частоте осложнений в этой зоне. Полученные данные подтверждают наличие иммунологической предрасположенности к неблагоприятному исходу вмешательства и могут служить основой для разработки системы прогнозирования риска

Ключевые слова: липофилинг, иммунитет, осложнение

LIPOFILLINGNINGNI BOSHIDAN KECHIRGAN BEMORLARNING IMMUNOLOGIK TAVSIFI

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✓ ***Rezyume***

Yaqqol ifodalangan immunologik buzilishlar sut bezlarini lipofilling paytida qayd etilgan, bu o‘z navbatida ushbu sohadagi asoratlarning yuqori klinik chastotasiga mos keladi. Olingan ma'lumotlar aralashuvning noqulay natijasiga immunologik moyillik mavjudligini tasdiqlaydi va xavfni bashorat qilish tizimini ishlab chiqish uchun asos bo'lib xizmat qilishi mumkin

Kalit so'zlar: lipofilling, immunitet, asorat

IMMUNOLOGICAL CHARACTERISTICS OF PATIENTS WHO UNDERWENT LIPOFILLING

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✓ ***Resume***

The most pronounced immunological disorders were noted during lipofilling of mammary glands, which corresponds to the high clinical frequency of complications in this area. The data obtained confirm the presence of an immunological predisposition to an unfavorable outcome of the intervention and can serve as a basis for developing a risk prediction system

Key words: lipofilling, immunity, complication

Relevance

The conducted analysis of literature sources regarding the problem of engraftment of adipose tissue after lipofilling showed that the study of the causes and mechanisms of complicated outcome of this operation requires a comprehensive analysis of not only clinical data, but also the immunological and morphological context in which the unfavorable result of the intervention is formed (1,3,5,8). At the same time, given that the lipofilling operation is associated with the movement and integration of

autologous tissue, the outcome of the intervention is determined not only by technical parameters, but also by the reactive capabilities of the body, primarily the immune system (2,4,6,7).

Violation of the engraftment of the fat graft with the formation of necrosis, cysts, seals and other complications, as clinical observations show, is not always explained by anatomical or surgical reasons, but may be associated with the individual immunological characteristics of the patient (3,4,8).

The aim of the study is a comprehensive study of systemic and local changes in the immune profile in patients who underwent lipofilling, with different clinical outcomes.

Materials and methods

The main leitmotif of this stage of the study was the assessment of immunological parameters of peripheral blood in patients who subsequently underwent lipofilling in order to identify deviations associated with the development of unfavorable aesthetic outcomes (fat necrosis, resorption, fibrosis), with subsequent comparison with reference values obtained in healthy individuals. The data obtained will serve as a basis for substantiating clinical and immunological risk factors for complications and forming a prognostic approach.

In the framework of the present study, the frequency of complications of lipofilling was assessed in the control group of patients, which included 93 patients who were not subjected to immunological prognosis and prevention methods. Analysis of the distribution of adverse outcomes by anatomical zones of intervention revealed a clear dependence of the frequency of complications on the localization of fat graft administration. The lowest percentage of complications was recorded during facial lipofilling in the amount of 4 cases out of 24 (16.7%). In this case, as a rule, it was a question of partial fat resorption or minor formation of compaction in the area of the zygomatic arch or nasolacrimal groove, which was defined as an aesthetic defect of the operation. In most of these cases, patients did not present any complaints, and the reason for repeated treatment was a subjective feeling of insufficient volume of the intervention. A significantly higher frequency of complications was recorded during mammary gland lipofilling. They were noted in 17 cases out of 37 (45.9%). Clinically, such patients were observed to have the formation of dense masses, edema, and shape asymmetry. In a number of women, formations such as cysts or lipogranulomas were verified by ultrasound; in some cases, aspiration biopsy was performed. Comparable rates of complications were also obtained with gluteal lipofilling. Thus, out of 21 interventions on the gluteal region, complications were noted in 9 cases (42.9%). In this segment, the main complaints were the formation of dense areas, pain on palpation, and volumetric asymmetry. Thus, in patient Sh., 33 years old, after lipofilling of the upper lateral parts of the buttocks, the formation of a dense node was noted in the projection of the upper outer quadrant on the left, with subsequent detection of areas of fat necrosis by ultrasound and morphological analysis of the removed fragment. In areas classified as “other” (including the back of the hands, anterior abdominal wall, and pubic area), complications were observed in 4 of 11 cases (36.4%). In these cases, it was more often a matter of surface deformation, formation of asymmetrical lumpy areas, or partial volume resorption, which led to patient dissatisfaction with the aesthetic result. At the same time, pronounced inflammatory reactions or cyst formation were less typical for this category of interventions. Overall, the frequency of adverse outcomes in the control group was 36.6%. The data obtained serve as the initial clinical picture, against which the immunological characteristics of patients and the types of morphological changes in complicated cases will be compared in the future.

At the first stage, a comparative analysis of the cellular immune status in patients who underwent lipofilling, depending on the clinical outcome of the intervention, as well as in relation to the reference group of healthy individuals, showed that the level of $CD3^+$ T-lymphocytes, reflecting the general T-cell component of the immune system, did not demonstrate statistically significant differences between the groups, which may indicate the preservation of the total T-cell pool both in patients without complications and in individuals who subsequently developed unfavorable outcomes of lipofilling.

Similarly, the content of $CD19^+$ B-cells remained within the physiological norm in all subgroups, without significant fluctuations, which suggests a limited involvement of the humoral link of adaptive immunity in the pathogenesis of outcomes.

The greatest attention was attracted by the differences in the ratio of $CD4^+$ and $CD8^+$ T-cells. In patients with complications, $CD4^+$ values significantly increased (45.6±5.9%) compared to both the reference group (39.2±3.8%; $p<0.01$) and patients without complications (41.3±4.6%; $p<0.01$). At the

same time, a decrease in the $CD8^+$ T-cell content was observed in the group with complications (20.1±3.3%) compared to other groups ($p<0.05$), which together led to a significant increase in the immunoregulatory index $CD4^+/CD8^+$. In patients with an unfavorable outcome, it reached 2.27±0.41 units, which significantly exceeded the values both in the reference group (1.58±0.23 units; $p<0.001$) and in patients with a favorable outcome (1.83±0.36 units; $p<0.01$). The obtained data may directly indicate the presence of an imbalance with a predominance of the helper link with a relative deficiency of cytotoxic lymphocytes, which may be associated with insufficient regulation of the local inflammatory process in the transplantation area. Such changes may indicate a reduced functional capacity of the innate immunity to control sterile inflammation that occurs in the lipofilling area in response to local hypoxia, fatty detritus and mechanical tissue damage. Patients with severe NK cell deficiency subsequently demonstrated a more severe course of complications with the formation of dense infiltrates and fibrous capsules.

Thus, in patients with an unfavorable outcome of lipofilling, reliable immunological shifts were revealed in the form of an increase in $CD4^+$, a decrease in $CD8^+$ and NK cells, as well as an increase in the $CD4^+/CD8^+$ ratio, which can be regarded as markers of subclinical immune dysregulation.

To assess the prognostic value of systemic inflammatory markers and cytokines before lipofilling, a comparative analysis of the levels of IL-6, IL-10, TNF-α, TGF-β1 and CRP in the blood serum of patients with different clinical outcomes, as well as in healthy reference individuals, was performed.

The key difference in the group of patients with a subsequent complicated outcome of lipofilling was a significant increase in the level of IL-6, one of the central cytokines of acute and subclinical inflammation. If in healthy individuals the median IL-6 level was 1.8±0.5 pg/ml, and in patients with a favorable outcome it increased to 2.4±0.7 pg/ml, then in individuals who subsequently developed complications (fat necrosis, compactions, cysts), the IL-6 level reached 4.9±1.1 pg/ml. The differences in these patients were highly statistically significant both in comparison with the reference data ($p<0.001$) and in comparison with the subgroup without complications ($p<0.001$). Particularly pronounced IL-6 values were observed in patients who underwent lipofilling of the mammary glands. The level of TNF-α, as a key proinflammatory cytokine of innate immunity, was also elevated in patients with a complicated outcome. The average TNF-α level in this group was 9.2±2.7 pg/ml, which significantly exceeded the values both in the reference group ($p<0.01$) and in patients without complications ($p<0.01$), which directly indicated the background activation of the proinflammatory cascade, predisposing to a hyperreaction to local changes in the transplantation area. For example, in patient B., 44 years old, with TNF-α at a level of 10.6 pg/ml before surgery, painful infiltration occurred 6 weeks after buttock lipofilling, requiring aspiration and subsequent surgical drainage. Of interest are the values of TGF-β1, one of the key regulators of fibrosis and tissue remodeling. In the group with complications, its level was 3.8±1.0 ng/ml, which is significantly higher than in the reference individuals ($p<0.05$) and higher than in patients without complications ($p<0.05$). Such changes may indicate a predisposition to fibrosis, excessive healing, and the formation of dense tissue structures in the fat injection area. In contrast, the level of IL-10 (anti-inflammatory regulatory cytokine) did not have significant differences between the groups. In patients with complications, IL-10 was lower than in healthy patients, but did not reach statistical significance ($p>0.05$), which may indicate insufficient anti-inflammatory compensation in some patients, but requires further analysis on larger samples.

The CRP level also demonstrated a consistent trend. Thus, with normal values in healthy individuals at the level of 1.2±0.4 mg/l and moderately elevated in patients without complications, in the group with an unfavorable outcome, CRP increased more than 2 times ($p<0.001$), which may indicate the presence of subclinical inflammation before the intervention. In some cases, this was accompanied by a systemic sluggish infectious load (recurrent sinusitis, chronic tonsillitis).

Thus, preoperative increase in IL-6, TNF-α, TGF-β1 and CRP can be regarded as an immunological predisposition to the development of complications of lipofilling. The data obtained showed the potential to be included in a prognostic model aimed at early detection of patients with a high risk of fat necrosis and fibrosis. Analysis of the nature of the correlation relationship between cellular and humoral indices of the immune system in patients with aesthetically complicated lipofilling outcomes allowed us to identify patterns reflecting the development of systemic immune imbalance at the stage preceding clinically manifest impairment of fat graft survival.

Results and discussions

The most pronounced and statistically significant relationships were recorded between the CD4+/CD8+ index and a number of key humoral markers. Thus, the correlation coefficient between CD4+/CD8+ and the IL-6 level was r=0.610 (p <0.001), with TNF-α r=0.460 (p <0.01), with TGF-β1 r=0.330 (p <0.05) and with CRP - r=0.670 (p <0.001). The listed values reflect a close relationship between the immunoregulatory imbalance towards the predominance of helper T cells and the activation of the proinflammatory cascade, accompanied by an increase in both acute phase and fibrogenic mediators. In fact, a high CD4+/CD8+ index can be considered as a systemic predictor of severe sterile inflammation in response to intervention, in particular lipofilling. A high positive correlation was also found between the level of $CD4^+$ T helpers and CRP (r=0.610; p <0.001) and a moderate positive relationship with IL-6 (r=0.540; p <0.01) and TNF-α (r=0.420; p <0.05). The data obtained allow us to interpret the activation of the $CD4^+$ link as a component of the systemic inflammatory background in patients prone to complicated healing. For example, in patient K., 37 years old, with initial $CD4^+$=47.2%, IL-6=5.1 pg/ml and CRP=3.4 mg/l, within 2 months after buttock lipofilling, an infiltrate with lipogranulomatosis developed, confirmed morphologically. The inverse correlation between NK cells and proinflammatory markers, especially with CRP (r=-0.420; p <0.05) and IL-6 (r=-0.370; p <0.05), deserves special attention. A decrease in the content of natural killers can be regarded as a decrease in innate immune control over local inflammation, which creates conditions for the persistence of sterile inflammation in the transplantation area. For example, in patient Z., 45 years old, with NK=6.8%, IL-6=4.9 pg/ml and TNF-α=9.7 pg/ml, 3 months after lipofilling of the mammary gland, a cyst with signs of capsular fibrosis was detected.

$CD8^+$ T lymphocytes, on the contrary, demonstrated negative correlations with IL-6 (r=-0.310; p <0.05) and CRP (r=-0.280; p> 0.05), which can be interpreted as insufficient cytotoxic regulation of inflammation under unfavorable immune conditions. Together with $CD4^+$ hyperactivity, this forms a functionally unbalanced adaptive response, potentially predisposing to necrosis, aseptic inflammation, and fibrosis.

Other cell populations, including $CD3^+$ and $CD19^+$, had less pronounced and statistically insignificant correlations with cytokines, which confirms the limited participation of the common T-cell and B-cell link in the development of a complicated outcome. Thus, the conducted correlation analysis revealed regular functional relationships between cellular immunity disorders (especially $CD4^+$/$CD8^+$, $CD4^+$, NK) and increased inflammatory cytokine response (IL-6, TNF-α, CRP). The obtained data confirm that immune imbalance present before surgery may be a key predictor of unfavorable outcome of lipofilling and requires consideration when planning preventive measures.

The greatest severity of changes was demonstrated by patients who underwent lipofilling of the mammary glands. In this group, the highest levels of IL-6 and CRP were noted, which significantly differed from similar indicators in facial lipofilling (p<0.05). The obtained differences indicate the most pronounced systemic proinflammatory activity in patients in whom adipose tissue was injected into the mammary glands, which is probably associated with both the peculiarities of the vascular bed and tissue resistance in this area, and with hormonal-mediated reactivity.

Also in this subgroup, the greatest increase in $CD4^+$ T-helpers and the immunoregulatory index CD4+/CD8+ was recorded, which significantly exceeds similar values in facial lipofilling (p<0.05). An increase in these indicators confirms the presence of a background of T-helper hyperactivation, which can play a role in enhancing sterile inflammation, especially in conditions of delayed vascular incorporation of the fat transplant.

Also noteworthy is the detected decrease in the content of NK cells in the mammary gland lipofilling group, compared to patients who underwent facial lipofilling (p<0.05). In turn, the obtained data indicate a reduced ability of the innate immune system to regulate the local inflammatory response, including due to a decrease in the level of cytotoxic control.

Patients with gluteal lipofilling occupied an intermediate position in most parameters, among which IL-6, CD4+/CD8+ and the level of NK cells stood out, suggesting that the immunological risk of developing aesthetic complications in this area is moderate, but in the presence of an additional provoking background (large volume, technical violations) it can be quite realized.

In the group of other anatomical zones (hands, abdomen, pubis), immune parameters also demonstrated moderate deviations, but statistically significant differences in most parameters between this category and the face, buttocks were not revealed, which may be due to the small number of observations.

Thus, the most pronounced deviations in significant immunological parameters in complicated lipofilling outcomes are observed in the mammary gland area. The data obtained may directly indicate a high anatomical and functional vulnerability of this zone to impaired engraftment of the fat graft under conditions of subclinical immune activation. Thus, the conducted clinical and immunological study showed that patients with complicated outcome of lipofilling already at the preoperative stage had pronounced signs of subclinical immune imbalance. The most significant differences in the group of complicated cases were the increase in the level of IL-6, TNF-α, CRP, TGF-β1, an increase in the content of $CD4^+$-lymphocytes and the $CD4^+/CD8^+$ index with a simultaneous decrease in $CD8^+$ and NK cells. Also, reliable positive correlations were established between the cellular and cytokine links of immunity, increasing in the direction from the reference values to complicated outcomes.

The most pronounced immunological disorders were noted during lipofilling of the mammary glands, which corresponds to the high clinical frequency of complications in this area. The data obtained confirm the presence of immunological predisposition to an unfavorable outcome of the intervention and can serve as a basis for developing a risk prediction system.

Conclusion

1. The conducted clinical and immunological study showed that patients with complicated outcome of lipofilling already at the preoperative stage had pronounced signs of subclinical immune imbalance.
2. The most significant differences in the group of complicated cases were the increase in the level of IL-6, TNF-α, CRP, TGF-β1, an increase in the content of $CD4^+$-lymphocytes and the $CD4^+/CD8^+$ index with a simultaneous decrease in $CD8^+$ and NK cells. Also, reliable positive correlations were established between the cellular and cytokine links of immunity, increasing in the direction from the reference values to complicated outcomes.
3. The most pronounced immunological disorders were noted during lipofilling of the mammary glands, which corresponds to the high clinical frequency of complications in this area. The obtained data confirm the presence of an immunological predisposition to an unfavorable outcome of the intervention and can serve as a basis for the development of a risk prediction system.

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