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Discoordination of the processes of activation and suppression of immunocompetent cells during mesotherapy with hyaluronic acid

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Objective. The study aimed to assess the dynamics of the systemic immune response in patients during mesotherapy with hyaluronic acid (HA). **Materials and methods.** The observation group included 26 women who received the first-time mesocorrection with drugs based on hyaluronic acid (HA). Injections of low molecular weight HA were carried out according to standard methods in a course of 5 procedures with an interval of 14 days. The parameters of the innate and adaptive immune response were studied before and two weeks after the end of the course. The skin condition was assessed by dermatoscopy (Aramo Smart Lite 300, Southern Korea). **Results.** The clinical effect of the course of procedures was reflected in the subjective improvement in the appearance. The improvement was confirmed by hardware analysis, which recorded an increase in hydration, a smoothing of the skin relief, and a decrease in the depth of wrinkles. At the end of the course, redistribution of lymphocyte populations towards natural killer cells and B-lymphocytes was revealed with a decrease in the total number of T cells. The antibody production of immunoglobulins of classes M and G was increased, the serum content of Ig A and IgE was reduced, the number of both T-effectors and T-lymphocytes with immunosuppressive activity increased. Changes in the neutrophil system were characterized by the inhibition of the production of reactive oxygen intermediates; the dynamics of the expression of Toll-like receptors by monocytes was ambiguous. **Conclusion.** The results of the study confirmed the active involvement of the factors of innate and adaptive systemic response in the cosmetic effect, which manifested itself immediately after mesotherapy as systemic dysregulatory immune changes.

Keywords: hyaluronic acid, innate and adaptive immune response, mesotherapy.

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Дискоординация процессов активации и супрессии иммунокомпетентных клеток при мезотерапии гиалуроновой кислотой

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Цель: оценить динамику системного иммунного реагирования пациентов при мезотерапии гиалуроновой кислотой (ГК). **Материалы и методы:** группу наблюдения составили 26 женщин, впервые выполняющих мезокоррекцию препаратами на основе гиалуроновой кислоты (ГК). Инъекции низкомолекулярной ГК проводились по стандартным методикам курсом 5 процедур с интервалом в 14 дней. До начала проведения и через две недели по окончании курса были исследованы параметры врожденного и адаптивного иммунного ответа. Состояния кожи оценивали методом дерматоскопии с использованием аппарата Aramo Smart Lite 300. **Результаты:** клинический эффект курса процедур отразился в субъективном улучшении внешнего вида и подтвержден аппаратным анализом, зафиксировавшим повышение увлажненности, выравнивание рельефа и уменьшение глубины морщин. По окончании курса процедур по сравнению с исходными данными выявлено перераспределение популяций лимфоцитов в сторону натуральных киллеров и В-лимфоцитов при снижении общего числа Т-клеток. При этом усилена антителопродукция иммуноглобулинов классов М и G и снижено сывороточное содержания Ig A и IgE, увеличено количество как Т-эффекторов, так и Т-лимфоцитов с иммуносупрессивной активностью. Изменения в системе нейтрофилов характеризуются угнетением продукции активных форм кислорода, а динамика экспрессии Toll-подобных рецепторов клетками моноцитарного ряда неоднозначна. **Заключение:** результаты исследования подтверждают активное вовлечение в реализуемый косметический эффект факторов врожденного и адаптивного системного ответа, что сразу по окончании процедур мезотерапии ГК проявляется в системных дисрегуляторных иммунных изменениях.

Ключевые слова: гиалуроновая кислота, врожденный и адаптивный иммунный ответ, мезотерапия.

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Introduction

Presently, esthetic medicine develops intensively. It aims to correct the appearance of a person with medical methods [1, 2]. A specific peculiarity of this type of medicine is not only the diversity of methods and technologies applied but also the fact that their practical application significantly advances the theoretical justification of the mechanism of action. In this aspect, one of the leading positions (from the point of view of vast practical application) is occupied by mesotherapy with hyaluronic acid (HA) [3, 4]. The technology is based on the disturbance of the skin by injections of HA that exerts expressed immune tropic effect and involves the immune system to have an effect. The ambivalence of HA effects is well-known. Its highly molecular variant exerts anti-inflammatory, wound-healing, and immune-suppressive effects, while its low molecular fragments exert stimulating effects due to the impact on pattern recognizing receptors, which leads to the activation of signaling pathways of the synthesis of anti-inflammatory mediators [5]. The available modern publications on this subject are not consistent and, as a rule, they are dedicated to the characteristics of single factors of the immune response, do not contain the multicomponent analysis, and interaction of the reactions of the congenital and adaptive immunity of patients. These facts provide the rationale for the present study.

The study aimed to assess the dynamics of the systemic immune response in patients during mesotherapy with HA.

Materials and Methods

The group of observation included 26 women aged 45±10 years old) that underwent mesocorrection with HA-based drugs for the first time. The criteria of exclusion included previous mesotherapy, hormonal replacement therapy, combined oral contraceptives, acute infectious pathology, comorbid somatic pathology at the stage of subcompensation or decompensation, pregnancy, and lactation. The clinical study complied with "The guidelines for clinical practice in the Russian Federation" approved by the Decree of the Ministry of the Russian Federation dated June 19, 2003 No. 266. All patients signed informed consent for participation in the study. The study was approved by the local ethical committee of the Rostov State Medical University (protocol No. 19/19 dated October 3, 2019).

The injection of low molecular HA was made by a standard method in a course of 5 procedures with a 14-day interval. Before the procedures and two weeks after the course, the parameters of the inborn and adaptive immunity were studied that included the evaluation of the expression of CD3, CD4, CD8, CD16, CD19, and CD25 by lymphocytes, intracellular levels of Foxp3, expression of TLR2, TLR4, and TLR9 on monocytes in the peripheral blood. The oxygen-dependent metabolic activity of neutrophils was evaluated by the nitroblue tetrazolium (NBT) test. The content of serum immunoglobulins A, M, and G was estimated by the reaction of radial immune diffusion in the gel according to the Manchini method, the level of IgE – by enzyme-linked immunosorbent assay. The evaluation of the skin condition (moisture content, the depth of folds and wrinkles) was performed using an apparatus Aramo Smart Lite 300. The study was carried out at the facilities of Ekaterininskaya Clinics, LLC and Chain of European Laboratories, LLC. Statistical analysis was conducted in the software R (version 3.2, R Foundation for Statistical Computing, Vienna, Austria). The results were presented as a central tendency for the median and interquartile range (25 and 75 percentile), in the text presented as Me [LQ; UQ]. The group medians were compared using Wilcoxon's test for linked samples. The differences were statistically significant at $p < 0.05$.

Results

The objective reflection of the subjective perception of the course of mesotherapy with HA was the analysis of the results of dermatoscopy using Aramo Smart Lite 300. The comparison of such parameters as moisture content and skin relief, evaluated before the procedures and two weeks after the therapy, showed an increase in the parameters of moisture content from 53% to 87% and a decrease in the relief of the skin folds and wrinkles from 74% to 45%. The changes in the immune response of patients were observed at the level of leukopoiesis as a statistically significant decrease in the total number of leukocytes (before injections – $6.65 \times 10^9/L$ [5.2;7.9]; after injections – $6.25 \times 10^9/L$ [5.2;7.4], $p = 0.003$) and an increase in the relative number of lymphocytes (before injections – 32.5% [27;35], after injections – 36.5% [30;42], $p = 0.005$). The analysis of the parameters that characterize the functioning of the factors of inborn immunity showed that in comparison with the data obtained before the procedures, the changes after a

course of mesotherapy were observed in all the parameters. In particular, an increase in the peripheral circulation of the number of natural killers was registered. This fact was confirmed by not only relative but also absolute values: CD16⁺ % before the therapy 11 [10;12], after the therapy – 12 [11;15], $p = 0.004$; CD16⁺, 10⁹/L before the therapy 0.25 [0.17;0.28], after the therapy – 0.27 [0.22;0.34], $p = 0.002$. The functional potential of neutrophils in the peripheral circulation decreased, indicating a decrease in the oxygen-producing activity, which was confirmed by the results of the NBT test. It was most evident in the case with a stimulated variant (NBT stim., CU 13 [11;7] and 11 [8;8], $p=0.0003$), while spontaneous production of active forms of oxygen changed less significantly (NBT spontaneous before the procedures – 9.5 [7;10], after – 8.0 [7;9], $p = 0.035$). The ambiguous effect of a course of mesotherapy with HA affected the expression of different variants of Toll-like receptor cells of monocyte series. Thus, for TLR 2 and TLR 9, an increase in the number of monocytes in the peripheral blood that carried these structures was revealed in relative and absolute variants of the evaluation: CD14⁺282⁺,% 3.31 [2.44;4.72] and 3.92 [2.73;4.54], $p = 0.016$; CD14⁺282⁺,10⁹/L 0.061 [0.045;0.11] and 0.069 [0.048; 0.11], $p = 0.008$; CD 14⁺289⁺,% 3.35 [2.8;5.6] and 3.9 [3.1;5.2], $p = 0.003$; CD 14⁺289⁺,10⁹/L 0.074 [0.06;0.11] and 0.091[0.067;0.12], $p = 0.004$. At the same time, on the contrary, the capacity of pattern recognition via TLR 4 decreased, which indicated a decrease in the relative number of TLR 4⁺-monocytes (CD14⁺284⁺,% 3.7 [2.2;5.1] and 3.15 [2.05;4.7], $p = 0.016$). The absolute values did not have statistically significant differences.

The dynamic in the changes of quantitative and functional parameters of the adaptive immunity after a course of mesotherapy with HA in comparison with the data obtained before manipulations was observed for both cellular and humoral components. Thus, there was a decrease in the relative number of mature T-lymphocytes (CD3⁺,% 69 [62;71] and 64.5 [57;70], $p < 0.0001$). However, the changes in the differentiation of the lymphoid lineage did not show significant changes in the absolute number of the peripheral T-lymphocytes (CD3⁺,10⁹/L 1.39 [1.11;1.66] and 1.38[1.12;1.6], $p=0.9$). The same peculiarity was observed also in the T-helper subpopulation: a statistically significant decrease in the relative number of total CD4⁺-lymphocytes (37 [35;41]% to 34 [32;37]% after the therapy, $p = 0.0004$) and a lack of significant changes in the circulating pool of immune-competent cells (CD4⁺,10⁹/L 0.76 [0.66;0.93] and 0.74 [0.62;0.91], $p = 0.65$). It should be noted that there was a significant increase in the relative and absolute number of T-lymphocytes that formed the CD8⁺-subpopulation and provided the realization of the cytotoxic effects of the cellular link of the adaptive protection: CD8⁺,% 32 [29;35] and 34 [32;37], $p = 0.0001$;

CD8⁺,10⁹/L 0.63 [0.53;0.84] and 0.74 [0.57;0.89], $p = 0.004$. Apart from the mentioned quantitative changes, there were dynamics observed in the functional parameters of T-cells of the immune response, in particular, an increase in the relative (CD3⁺CD25⁺,% 6 [5;7] and 7 [7;8], $p = 0.002$) and absolute values (CD3⁺CD25⁺,10⁹/L 0.13 [0.097;0.16] and 0.15 [0.12;0.19], $p = 0.001$) of the number of T-lymphocytes that express CD25, a receptor responsible for the activation of the intracellular signaling pathways mediated by a universal immune-stimulating IL-2. Another functional parameter associated with the regulation of the activation potential of the immune response showed dynamic changes during mesotherapy of HA. An increase in the fixed number of the relative number of peripheral T-regulatory lymphocytes with the phenotype CD4⁺CD25⁺Foxp3⁺ that are also responsible for immune suppression (4.75[4.1;6.1] and 4.9[4.3;6.7], $p = 0.038$) was observed. However, in absolute values, the observed dynamics were not statistically confirmed, although there was a certain tendency (CD4⁺CD25⁺Foxp3⁺,10⁹/L 0.11 [0.071;0.12] and 0.11 [0.085; 0.14], $p = 0.11$). In the humoral link of the adaptive immunity, an increase in the circulative pool of immune-competent cells was observed in the relative (CD19⁺,% 22.5 [22; 24] and 25 [23; 26], $p < 0.0001$) and absolute (CD19⁺,10⁹/L 0.49 [0.4; 0.57] and 0.52 [0.42; 0.65], $p = 0.001$) content in the number of B-lymphocytes. One should note not only the enhancement of the differentiation shift to precursors of anti-body production but also the activation of the synthesis of immunoglobulins M (IgM, g/L to 1.38 [1.13; 2.11], after the therapy – 2.13 [1.31; 2.76], $p = 0.004$) and G (IgG 15.4 [13.5; 18] and 17.1 [13.7; 19], $p = 0.007$). There was a statistically significant decrease in the serum levels IgA (IgA, g/L to – 2.42 [1.2;3.2], after the therapy – 1.39 [0.99;2.7], $p = 0.0002$) and IgE (IgE, IU/ml 12.8 [7;30] and 9[6;20], $p = 0.0009$). It should be mentioned that there was a statistically significant increase in the content of circulating immune complexes (CIC, CU. 11.9 [10.8;16] and 12.9 [11.1;18.8], $p = 0.019$).

Discussion

Mesotherapy is a course intradermal injection of different drugs. In the present study, low molecular HA was used for cosmetic effect due to the improvement of the skin properties at the site of injection. The obtained results showed that all the participants reached the desirable results. This was not only a subjective perception of the appearance improvement but was also proved instrumentally by the results of dermatoscopy, which showed an increase in the moisture level, smoothening of the relief, and a decrease in the depth of wrinkles. It can be suggested that the immune system of the skin is involved in the realization of the obtained effect due to the immune trophic properties of HA. Since skin-associated lymphoid tissue is one of the

components of multilevel functioning of the system of the immune response, the changes registered during the study of the properties of the immune-competent cells of the peripheral circulation reflect the effects of mesotherapy with HA. The obtained data confirmed the active involvement of the factors of inborn and adaptive systemic responses. Thus, two weeks after the end of the course, redistribution of differentiation inside lymphoid lineage to the side of natural killers and B-lymphocytes was observed. At the same time, antibody production of immunoglobulins M and G was enhanced. A certain decrease in the serum content of IgA can be explained by the activation of the local mucosal immune response. A decrease in the production of IgE can be associated with an enhancement of cytokine regulation of Th1 immune reactions. The latter suggestion was confirmed by the changes inside the T-cells population of lymphocytes, wherein the number

of T-effectors was increased, and the differentiation of the natural killers. It should be highlighted that the data were obtained that confirmed the association of two oppositely directed reactions of immune regulation: enhancement of the processes of activation of T-lymphocytes and a shift of differentiation of T-helpers to CD4⁺CD25⁺Foxp3⁺-lymphocytes with immune suppressive activity. It should be mentioned that the parameters of the inborn immunity at the systemic level were characterized by both an increase and a decrease in the functional potency. Along with the activation of natural killers, in the system of neutrophils, a suppression of oxygen-producing activity was registered, and the changes in the monocyte cells were ambiguous: an increase in the expression of TLR 2 and TLR 9 was associated with a tendency to a decrease in the number of TLR4⁺-monocytes (Figure 1).

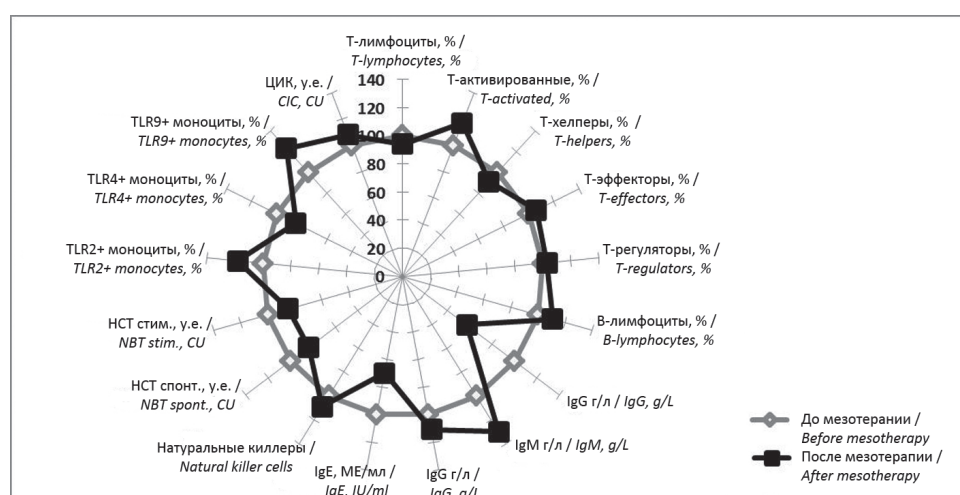


Figure 1. Changes in the parameters of the functioning of the immune system of patients after a course of mesotherapy with hyaluronic acid. Data before mesotherapy are taken as 100%.

Рисунок 1. Изменения параметров функционирования иммунной системы пациентов после курса мезотерапии гиалуроновой кислотой. Данные до мезотерапии приняты за 100%.

It should be mentioned that the obtained data agree with the results obtained by other authors that indicated a consecutive involvement of pro-inflammatory [6] and anti-inflammatory [7] cytokines in response to HA, an important role of Treg [8–10] in the recreation and maintenance of collagen, and involvement of Toll-like receptors in the initiation of immune tropic effects of HA [11, 12]. The presented publications are dedicated to the characteristics of single parameters, while the obtained data confirm the association of all the mentioned factors.

Conclusion

The results of the study reflect the dynamics of the systemic immune changes right after the end of the course of

mesotherapy with HA. Further observation after the development of these patients allowed defining the period of resolution of the appeared dysregulatory changes and establishing the character and degree of the expression of these changes with the duration and quality of the clinical effect.

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