Российский
иммунологический журнал
2024, Т. 27, № 4, стр. 1065-1070

Краткие сообщения
Short communications

Russian Journal of Immunology /
Rossiyskiy Immunologicheskiy Zhurnal
2024, Vol. 27, № 4, pp. 1065-1070

НЕКОТОРЫЕ ПАРАМЕТРЫ ИММУННОЙ СИСТЕМЫ У ЖЕНЩИН С ГИПЕРАНДРОГЕНИЕЙ

Юлдашев У.К.[1], Музафарова С.А.[2]

[1] *Институт иммунологии и геномики человека Академии наук Республики Узбекистан, г. Ташкент, Республика Узбекистан*

[2] *Центр женского здоровья AyolCare, г. Ташкент, Республика Узбекистан*

Резюме. Статья посвящена изучению некоторых параметров иммунной системы, что имеет большое значение в акушерстве и гинекологии. Изучение параметров иммунной системы позволяет установить нарушения при гиперандрогении у женщин репродуктивного возраста, что имеет важное практическое значение. Авторами проведено иммунологическое исследование женщин с гиперанндрогенией и женщин без данной патологии. Цель исследования: изучение состояния иммунной системы у женщин, страдающих гиперандрогенией. Обследованы 58 женщин репродуктивного возраста с установленным диагнозом «гиперандрогения», которые находились под наблюдением в Центре здоровья женщин AyolCare г. Ташкента. Всем женщинам осуществлялось комплексное клинико-лабораторное обследование. Контрольную группу составили 35 практически здоровых женщин репродуктивного возраста.

Полученные результаты свидетельствуют о том, что у женщин с измененным гормональным балансом, включая состояние ГА, происходят специфические изменения в иммунной системе. Проведенные исследования показали, что уровень Т-лимфоцитов и Т-хелперов/индукторов снижается, в то время как количество Т-киллеров, $CD25^+$ клеток (несущих рецептор к IL-2) и $CD95^+$ клеток (несущих рецептор сигналов к апоптозу) увеличивается. Повышенное содержание $CD95^+$ клеток свидетельствует о возросшей активации процессов апоптоза, которые выполняют защитную функцию Т-киллеров. Это увеличение активации лимфоцитов, вероятно, связано с повышением уровня зрелых активированных макрофагов и ряда цитокинов, которые они вырабатывают и которые непосредственно стимулируют лимфоциты. Обнаруженный дисбаланс иммунологических параметров, вероятно, указывает на то, что при гиперандрогении либо отсутствует, либо нарушена элиминация активированных клонов Т-хелперов, что обычно приводит к формированию супрессии иммунного ответа. Увеличение числа активированных клонов Т-лимфоцитов наблюдается при сниженном процессе их апоптоза, который, вероятно, усиливается воздействием андрогенов.

Ключевые слова: гиперандроения, женщины, кровь, лимфоциты, сыворотка, дисбаланс

Адрес для переписки:
Музафарова Салима Асхадовна
Центр женского здоровья AyolCare
Республика Узбекистан,
г. Ташкент, ул. Махтумкули, 15.
Тел.: +998 (93) 182-91-19.
E-mail: salima-m@list.ru

Address for correspondence:
Salima A. Muzafarova
AyolCare Women's Health Center
15 Magtymguly St
Tashkent
Republic of Uzbekistan
Phone: +998 (93) 182-91-19.
E-mail: salima-m@list.ru

Образец цитирования:
У.К. Юлдашев, С.А. Музафарова «Некоторые параметры иммунной системы у женщин с гиперандрогенией» // Российский иммунологический журнал, 2024. Т. 27, № 4. С. 1065-1070.
doi: 10.46235/1028-7221-16656-SPO

For citation:
U.K. Yuldashev, S.A. Muzafarova "Some parameters of the immune system in women with hyperandrogenism", Russian Journal of Immunology/Rossiyskiy Immunologicheskiy Zhurnal, 2024, Vol. 27, no. 4, pp. 1065-1070.
doi: 10.46235/1028-7221-16656-SPO

DOI: 10.46235/1028-7221-16656-SPO

SOME PARAMETERS OF THE IMMUNE SYSTEM IN WOMEN WITH HYPERANDROGENISM

Yuldashev U.K.[a], Muzafarova S.A.[b]

[a] *Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan, Tashkent, Republic of Uzbekistan*
[b] *AyolCare Women's Health Center, Tashkent, Republic of Uzbekistan*

Abstract. The article is dedicated to studying certain parameters of the immune system, which holds great significance in obstetrics and gynecology. Examining immune system parameters allows for identifying disruptions in reproductive-aged women with hyperandrogenism, which holds crucial practical implications. The authors conducted an immunological study of women with hyperandrogenism and women without this pathology. The aim of the study was to investigate the immune system status in women suffering from hyperandrogenism. Materials and methods of the study: 58 reproductive-aged women diagnosed with hyperandrogenism, under observation at the Women's Health Center "AyolCare" in Tashkent, were examined. Comprehensive clinical and laboratory examinations were conducted for all women. The control group comprised 35 practically healthy reproductive-aged women. The obtained results indicate that women with altered hormonal balance, including those with hyperandrogenism, experience specific changes in the immune system. The conducted research revealed that the levels of T lymphocytes and T helper/inducer cells decrease, while the number of T killer cells, $CD25^+$ cells (carrying IL-2 receptor), and $CD95^+$ cells (carrying apoptosis signaling receptor) increases. The elevated levels of $CD95^+$ cells indicate increased activation of apoptosis processes, which serve as a protective function of T killer cells. This increase in lymphocyte activation is likely associated with elevated levels of mature activated macrophages and a range of cytokines they produce, which directly stimulate lymphocytes. The detected imbalance in immunological parameters likely indicates that in hyperandrogenism, either the elimination of activated clones of T helper cells is absent or disrupted, which usually leads to the formation of immune response suppression. The increase in the number of activated clones of T lymphocytes is observed in the decreased process of their apoptosis, which is likely intensified by the influence of androgens.

Keywords: hyperandrogenism, women, blood, lymphocytes, serum, imbalance

Introduction

Hyperandrogenism (HA) is a medical condition characterized by excessive levels of androgens, in a woman's blood. Major androgens that may be elevated include testosterone, dihydrotestosterone, androstenedione, and others. This imbalance of hormones can occur for a variety of reasons and have different consequences for a woman's body [1, 3, 5, 6].

HA occurs in 17-18% of women of childbearing age. The disease affects 16-22% of patients with infertility and 55-62% – with endocrine disorder of reproductive functions, which determines the urgency of this problem in modern gynecology since the frequency of this pathology continues to be quite high and does not have a clear tendency to decrease [4].

The study of menstrual and generative function in hyperandrogenic female patients has significance in the context of scientific, social and clinical aspects of women's health care. This investigation is important for maintaining reproductive health, secondary prevention of reproductive dysfunction, and identification of patients at increased risk for such dysfunction in the future. According to the literature, the character of generative function in women with hyperandrogenism is closely related to their age, the specific causes of this condition, the effectiveness of therapy and other factors [8, 9].

Such patients often have altered psychoemotional status, increased risk of hyperplastic processes in target organs and endocrine diseases [4]. One of the main challenges is to identify the source of excessive androgen secretion, develop pathogenesis, diagnostic methods, and select effective rehabilitation measures [9]. Several obstetric aspects of this problem, taking into account the form of hyperandrogenism, need scientific substantiation, and their solution is of great practical importance: for predicting the features of reproductive function and hormone-dependent organs in women in the distant periods of observation [6, 9].

According to modern data, immunocompetent cells are equipped with receptors to hormones, which determines the possibility of their modulating effect on the functions of immunocompetent cells. According to the literature, the results obtained about the effect of androgens on immune processes are quite controversial [7].

The present study aimed to investigate the state of the immune system in women suffering from hyperandrogenism.

Materials and methods

Within the framework of this study, 58 women of reproductive age, diagnosed with hyperandrogenism, who were under observation at the Women's Health Center "AyolCare" in Tashkent were examined. All of the women underwent a comprehensive clinical and laboratory examination. The control group consisted of 35 practically healthy women of reproductive age. Immunological examinations were carried out in the Laboratory of Reproduction Immunology of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan.

Immunologic research was performed by quantitative determination of lymphocytes with $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD20^+$, $CD25^+$, CDHLA-DR, $CD95^+$ phenotype in peripheral blood using monoclonal antibodies of LT series ("Sorbent", Moscow, Russia). The level of immunoglobulins IgA, IgM, and IgG in blood serum was determined by solid-phase enzyme-linked immunosorbent assay using test systems of CJSC "Vector-Best" (Russia) by the manufacturer's recommendations.

Statistical processing of the results of the studies was carried out by methods of variation statistics, implemented by the standard package of applied programs "BioStat LE 7.6.5". The data were processed using conventional approaches and the results are presented as sample mean (M) and standard error of the mean (m). The reliability of the differences between the means (P) of the compared indicators was assessed by Student's criterion (t).

Results and discussion

As is widely known, cellular immunity is represented by different populations of T and B lymphocytes, the ratio of which plays an important role in assessing the state of this link of immunity. Immunologic researches revealed the following peculiarities of immune status [7].

The analysis of the relative number of mature T lymphocytes established the suppression of the immune system in the studied group of HA women compared to that of the control group. Thus, the total pool of T lymphocytes ($CD3^+$), «responsible» for the reactions of cellular immunity and carrying out immunological surveillance of antigenic homeostasis in the group of women with GA revealed a slightly reduced level of the relative number of $CD3^+$ lymphocytes compared to control values (48.5±2.24% *vs* 59.9±1.01%) ($p < 0.001$) (Figure 1).

T helper cells ($CD4^+$) are inducers that regulate the strength of the body's immune response to foreign antigen, control antigen homeostasis and cause increased antibody production. T helper/inducers ($CD4^+$) are regulatory cells, without which the transformation of B lymphocytes into antibody-producing plasma cells is impossible. They are also capable of enhancing cellular responses of the immune system [6].

When studying the number of subpopulation composition of T lymphocytes, a tendency to decrease $CD4^+$ lymphocytes was revealed in women with HA of the main group 29.3±2.09%, while in women of the control group, this indicator amounted to 38.2±0,97% ($p < 0.001$) (Figure 1).

Another group of regulatory T lymphocytes – T suppressors ($CD8^+$) are able to inhibit immunologic reactions that are too strong and too prolonged. T suppressors inhibit the production of antibodies (of various classes) due to delayed proliferation and differentiation of B lymphocytes, and the development of delayed-type hypersensitivity [7].

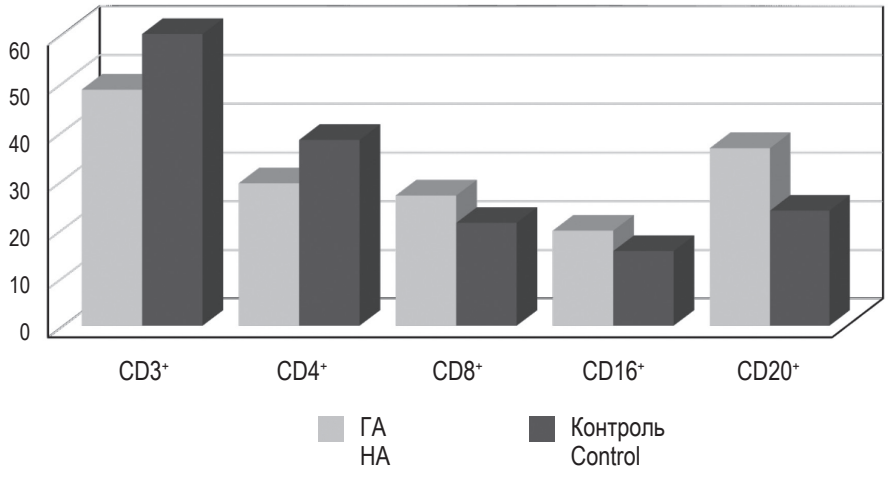

Figure 1. Certain immune system parameters in women with hyperandrogenism
Note. *, statistically significant compared to the control group data (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

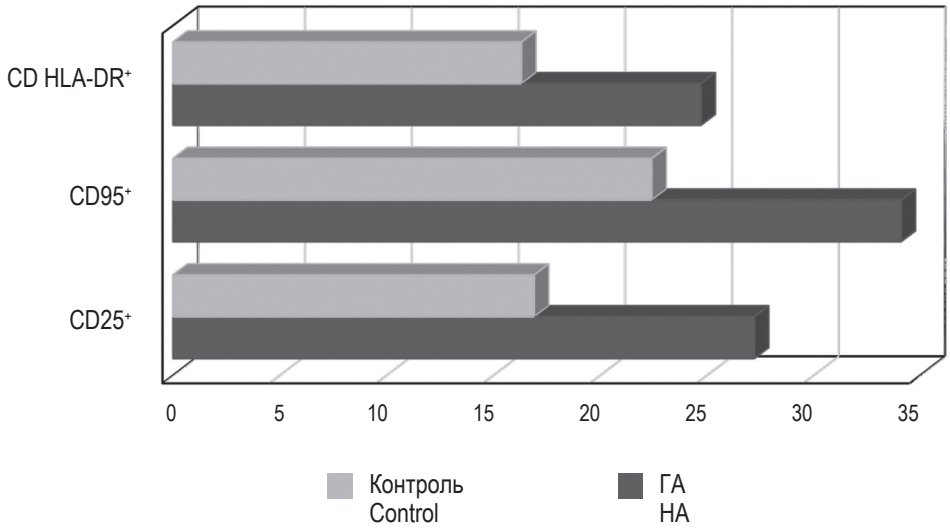

Figure 2. Level of lymphocytes with activation marker in women with a history of hyperandrogenism
Note. As for Figure 1.

At the same time, the content of the relative number of $CD8^+$ lymphocytes in women with HA was significantly increased with an average of 26.8±1.73% compared to the data of the control group 21.2±0.83% ($p < 0.01$).

NK cells are distinguished as a special class of lymphocytes due to their unique ability to rapidly and without prior immunization lysate foreign or their own altered cells in the absence of major histocompatibility complex class I molecules, regardless of antibodies and complement, which confirms their name "natural killer cells" [7].

It was also found that the percentage of $CD16^+$ cells in the peripheral blood of women with a history of HA amounted to 19.6±1.84, while in women of the control group, it was determined 15.4±0.52% ($p < 0.01$) (Figure 1).

$CD20^+$ lymphocytes are cells of humoral immunity responsible for antibody synthesis [5]. Analysis of the content of the number of circulating $CD20^+$ cells in the peripheral blood tended to increase compared to the control group. So the relative quantity. Thus, according to the obtained data, the estimate of the relative content of $CD20^+$ in the group of women with HA averaged 36.5±2.12 % *vs* 23.7±0.47% ($p < 0.001$) (Figure 1).

The number of lymphocytes expressing activation markers $CD25^+$, CDHLA-DR, indicating the activity of the process was higher in women with a history of hyperandrogenism.

The number of cells with receptor to interleukin 2 (IL-2)-$CD25^+$, a marker of autocrine cell proliferation suppressor cells, was increased in the group of women with hyperandrogenism So the percentage of $CD25^+$ in the group of women with GA averaged 27.2±1.33% against controls 16.9±1.04% ($p < 0.001$) (Figure 2).

In women of the main group the number of $CDHLA\text{-}DR^+$ cells was significantly higher than the values of the control group (24.7±2.09% *vs* 16.3±0.58%) ($p < 0.001$). The quantitative study of lymphocytes expressing the apoptosis antigen $CD95^+$ showed a tendency to increase them in the peripheral blood of women with hyperandrogenism compared to the values of healthy women (34.1±0.97% *vs* 22.4±0.94% in controls) ($p < 0.001$).

The level of serum immunoglobulins is an integral indicator of humoral immunity. Synthesis of IgG ($p < 0.001$) and IgA ($p < 0.05$) in women with a history of hyperandrogenism was significantly higher than in the control group, and the level of IgM did not differ from that of practically healthy women and was not significant ($p > 0.05$) (Figure 3).

Therefore, the results suggest that women with altered hormonal balance, including HA status, have specific changes in the immune system. Studies have shown that the levels of T lymphocytes and T helper/inducers decrease, while the number of T killers, $CD25^+$ cells (carrying receptor for IL-2) and $CD95^+$ cells (carrying apoptosis signaling receptor) increase. The increased content of $CD95^+$ cells indicates increased activation of apoptosis processes, which fulfill the protective function of T killers. This increase in lymphocyte activation is likely due to increased levels of mature activated macrophages and several cytokines they produce that directly stimulate lymphocytes. The observed imbalance of immunologic parameters probably indicates that

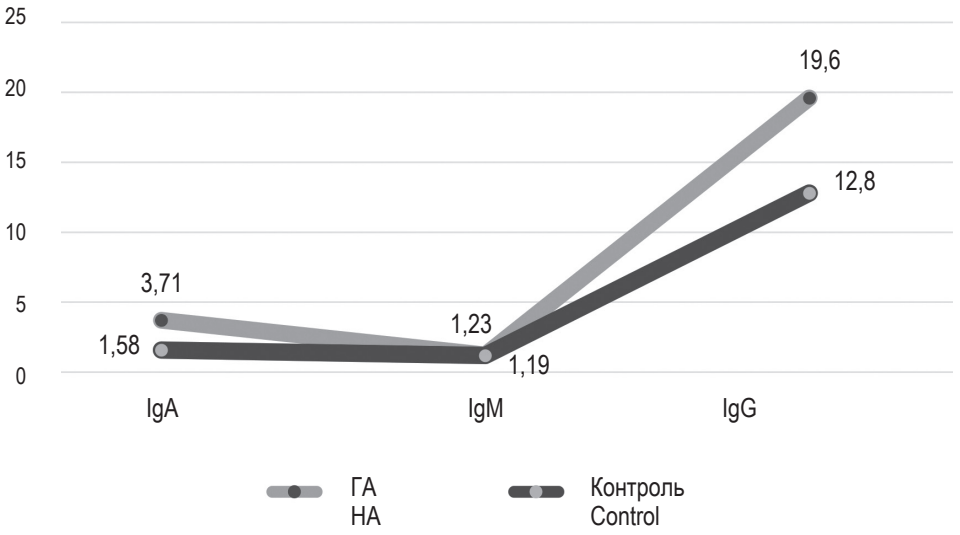

Figure 3. Humoral immunity indicators in women with hyperandrogenism
Note. As for Figure 1.

in hyperandrogenism the elimination of activated T helper clones is either absent or impaired, which usually leads to the formation of immune response suppression. An increase in the number of activated T lymphocyte clones is observed with a reduced process of their apoptosis, which is probably enhanced by androgen exposure.

Conclusions

1. A significant decrease in the number of T lymphocytes ($p < 0.001$), T helper/inducers ($p < 0.001$) in women with hyperandrogenism compared to the similar indicators of the control group was established.

2. A considerable increase of $CD8^+$ suppressor cells ($p < 0.001$) and $CD16^+$ ($p < 0.001$) in the group of women with GA, compared to those of the control group, was determined.

3. Substantial increase in the level of activation markers $CD25^+$ ($p < 0.001$), $CDHLA\text{-}DR^+$ ($p < 0.001$), and $CD95^+$ lymphocytes ($p < 0.001$) in women with hyperandrogenism compared to the parameters of healthy women in the control group was revealed.

4. Comparative analysis of humoral immunity indicators revealed a significant increase in the level of IgG ($p < 0.001$) and IgA ($p < 0.05$) in women with hyperandrogenism.

Список литературы / References

1. Bogdanova E.A., Telunts A.V. Hirsutism in girls and young women. Moscow: Medpress-Inform, 2002. 96 p.
2. Dobrohotova Yu.E., Dzhobava E.M., Ragimova Z.E., Gerasimovich M.Yu. Hyperandrogenism syndrome in the practice of obstetrician-gynecologists, dermatologists, and endocrinologists: modern aspects of pathogenesis, diagnosis, and therapy. Moscow: GEOTAR-Media, 2009. 112 p.
3. Endocrinology. National guidelines / Ed. by I.I. Dedov, G.A. Melnichenko. Moscow: GEOTAR-Media, 2020. 832 p.
4. Handelsman D.J., Hirschberg A.L., Bermon S. Circulating testosterone as the hormonal basis of sex differences in athletic performance. *Endocr. Rev., 2018, Vol. 39, no. 5, pp. 803-829.*
5. Khaitov R.M. Immunology: Structure and functions of the immune system. Textbook. Moscow: GEOTAR-Media, 2013. 230 p.
6. Kozlovene D., Kazanavichus G., Kruminis V. Concentrations of testosterone, dehydroepiandrosterone sulfate, and free androgen index in the blood of women with hirsutism. *Problems of Endocrinology, 2008. Vol. 54, no. 2, pp. 42-45.* (In Russ.)
7. Manukhin I.B., Tumilovich L.G., Gevorkyan M.A. Gynecological endocrinology: Clinical lectures: a guide for physicians. 2nd edition, revised and enlarged. Moscow: GEOTAR-Media, 2010. 280 p.

8. Ovsyannikova T.V. Hyperandrogenism in gynecology // Gynecological endocrinology / Serov V.N., Prilepskaya V.N., Ovsyannikova T.V. Moscow: MEDpressinform, 2008, pp. 125-158.

9. Wei D.M.. Effect of hyperandrogenism on obstetric complications of singleton pregnancy from in vitro fertilization in women with polycystic ovary syndrome. Zhonghua Fu Chan Ke Za Zhi, *2018, Vol. 53, no. 1, pp. 18-22.* (in Chinese)

Авторы:

Юлдашев У.К. *– самостоятельный соискатель, Институт иммунологии и геномики человека Академии наук Республики Узбекистан, г. Ташкент, Республика Узбекистан*

Музафарова С.А. *– д.м.н., ведущий специалист, Центр женского здоровья AyolCare, г. Ташкент, Республика Узбекистан*

Authors:

Yuldashev U.K., *Independent Researcher, Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan, Tashkent, Republic of Uzbekistan*

Muzafarova S.A., *PhD, MD (Medicine). Leading Specialist, AyolCare Women's Health Center, Tashkent, Republic of Uzbekistan*

Поступила 26.03.2024
Отправлена на доработку 03.04.2024
Принята к печати 25.04.2024

Received 26.03.2024
Revision received 03.04.2024
Accepted 25.04.2024