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Changes in the Immune Status in Adult Patients with Diabetes Mellitus in the Postcovid Period

RUZIMURODOV Nodir Fazliddinovich
PhD, Scientific Secretary, Institute of Immunology and Human Genomics, Tashkent, Uzbekistan

ARIPOVA Tamara Uktamovna
DSc, Academican, Director, Institute of Immunology and Human Genomics, Tashkent, Uzbekistan

Annotation: Resume:

Background: This study presents the results of an investigation into the immune status of adult patients with diabetes mellitus during the post-COVID period. Key cytokine levels, such as VEGF-A, TGF-β, IGF-1, and IP-10, as well as adhesion molecules VCAM-1 and ICAM-1, were analyzed. The study includes a comparison between vaccinated and unvaccinated patients, allowing for an assessment of the impact of vaccination on inflammatory processes and metabolic indicators.

Objective: To assess the effect of vaccination on immunological parameters in patients with diabetes that developed in the post-COVID period and identify key markers of inflammation and angiogenesis.

Materials and Methods: The study was conducted with 98 patients divided into three groups: vaccinated, unvaccinated patients with diabetes that developed after COVID-19, and a control group. Levels of VEGF-A, TGF-β, IGF-1, and IP-10 were measured using ELISA.

Results: The level of VEGF-A was higher in the group of unvaccinated patients (257.98±15.55 pg/ml), indicating more pronounced inflammatory processes compared to the vaccinated group. TGF-β and IGF-1 levels were also significantly elevated in the unvaccinated group, indicating the development of fibrotic changes in tissues.

Keywords: Immune status, Diabetes Mellitus, Postcovid Period, Cytokines.

Relevance: COVID-19, caused by SARS-CoV-2, has become a focal point for studying the impact of acute viral infections on chronic metabolic disorders such as diabetes. The disease has highlighted the vulnerability of individuals with metabolic dysregulation to infectious diseases. The complex relationship between systemic inflammation, immune system dysregulation, and the development of comorbid conditions underscores the body's intricate response to illness. The connection between coronavirus infections and diabetes emphasizes the need for a comprehensive understanding of these mechanisms to develop effective treatment and management strategies. As research in this field continues, there is hope that new insights will improve outcomes for patients with diabetes and related conditions.

Immunological research in type 2 diabetes mellitus (T2DM) is crucial, as chronic inflammation and immune dysfunction play key roles in the pathogenesis and progression of the disease. Patients with T2DM are at higher risk of infections and inflammatory conditions, which worsen their health and lead to complications. During the COVID-19 pandemic, studying the immunological status of patients with T2DM has become even more critical, as coronavirus infection causes pronounced immune activation and can significantly worsen metabolic status, increasing the risk of complications in this patient population.

Objective of the study: Our study focused on evaluating the immunological parameters in patients with T2DM who had recovered from coronavirus infection and received vaccination against COVID-19.

Materials and Methods: Immunological assessments were carried out in two main patient groups and a control group of practically healthy individuals. The first group included 21 patients diagnosed with T2DM after the onset of the pandemic, who received vaccination against COVID-19. The second group consisted of 42 patients with T2DM that developed after recovering from COVID-19, but who had not been vaccinated. The control group included 15 practically healthy individuals, matched by age, gender, and the absence of chronic diseases, which minimized the impact of these factors on the study results.

Results: Our research focused on analyzing the immunological and metabolic parameters in patients whose diabetes developed after recovering from coronavirus infection. The study was conducted on two groups: the first group included 21 patients whose diabetes developed after COVID-19, and who were vaccinated, while the second group consisted of 42 patients with diabetes that developed after COVID-19, but who were not vaccinated. These groups allowed us to compare the impact of vaccination on the development and course of diabetes post-COVID-19, as well as to assess differences in immunological and metabolic parameters between vaccinated and unvaccinated patients. We examined how vaccination may have influenced key markers such as inflammatory markers, hormones, and other biochemical parameters, and what differences were observed between the two groups.

Table 1. Immunological parameters in patients with diabetes developed after COVID-19

	Control group, n=35	Group 1, n=21	Group 2, n=42
VEGF A (пг/мл)	80,21±2,87	125,71±8,78**	257,98±15,55*
TGF β (пг/мл	46,39±1,53	88,56±3,57***	102,51±3,06***
IGF-1 (нг/мл)	106,33±3,57	223,17±10,81***	464,69±22,10*
IP-10 (пг/мл)	208,98±6,91	300,21±14,01*	398,48±25,54**

*Note: * - significantly compared with the data of the control group (* - P<0.05, ** - P<0.01,*** - P<0.001). Me is the median, Q1(percentile) -25%, Q3 (percentile) – 75%.*

Analysis of VEGF-A levels, which plays a key role in regulating angiogenesis and vascular permeability, provides deeper insights into the pathogenic processes occurring in patients with diabetes mellitus after recovering from a coronavirus infection. VEGF-A is a marker that reflects the degree of angiogenesis activation and inflammatory processes, which is especially important in comorbid conditions where COVID-19 exacerbates the inflammatory response in the body. The results of VEGF-A level analysis in various groups of patients, including vaccinated and unvaccinated diabetic patients, as well as a comparison with the control group, are presented below (Table 1).

In the first group, where patients with diabetes who had recovered from COVID-19 were vaccinated, the VEGF-A level was significantly higher than in the control group. The mean VEGF-A value was 125.71±8.78 pg/ml, more than 1.5 times higher than the control group's mean value of 80.21±2.87 pg/ml. The median VEGF-A level in the first group was 108.37 pg/ml, also higher than the median in the control group (86.48 pg/ml). The interquartile range [97.85; 146.55] pg/ml in the first group indicates significant variability in VEGF-A levels among patients, which suggests a wide range of inflammatory and angiogenic reactions. The minimum VEGF-A level in the first group was 87.18 pg/ml, and the maximum was 211.51 pg/ml, also significantly higher than the control group, where the minimum was 41.23 pg/ml and the maximum was 100.29 pg/ml (Fig. 1).

In the second group, comprising unvaccinated patients whose diabetes developed after COVID-19, the VEGF-A level was even higher. The mean VEGF-A level was 257.98±15.55 pg/ml, more than three times higher than in the control group. The median VEGF-A level in the second group reached 244.10 pg/ml, significantly higher than both the first group and the control group. The interquartile range [194.78; 330.18] pg/ml in the second group was much broader, reflecting greater intensity and variability of inflammatory processes. The minimum VEGF-A level in the second group was 89.30

pg/ml, while the maximum reached 432.80 pg/ml, indicating more severe pathological processes compared to the control group.

Pathogenetically, the increase in VEGF-A levels is associated with the activation of angiogenesis in response to hypoxia and inflammation, which is characteristic of patients with diabetes and post-COVID syndrome. In the context of diabetes and COVID-19, VEGF-A stimulates the growth of new blood vessels and increases vascular permeability, which may contribute to the development of conditions such as diabetic retinopathy and tissue edema. A comparison between the groups shows that vaccination in the first group led to a decrease in VEGF-A levels compared to the second group, which may be explained by a more controlled inflammatory response and a reduced need for intense angiogenesis.

Moving on to the analysis of another key immunological marker, it is important to examine the role of TGF-β in the pathogenesis of diabetes, especially in patients who have recovered from COVID-19. Pathogenetically, TGF-β plays a crucial role in regulating immune responses, inflammation, and tissue remodeling. This cytokine promotes the differentiation of fibroblasts into myofibroblasts, leading to excessive accumulation of extracellular matrix and the development of tissue fibrosis. In the context of chronic inflammation, which is characteristic of diabetes, elevated levels of TGF-β exacerbate fibrosis, potentially resulting in irreversible changes in tissues such as nephropathy, cardiomyopathy, and lung fibrosis.

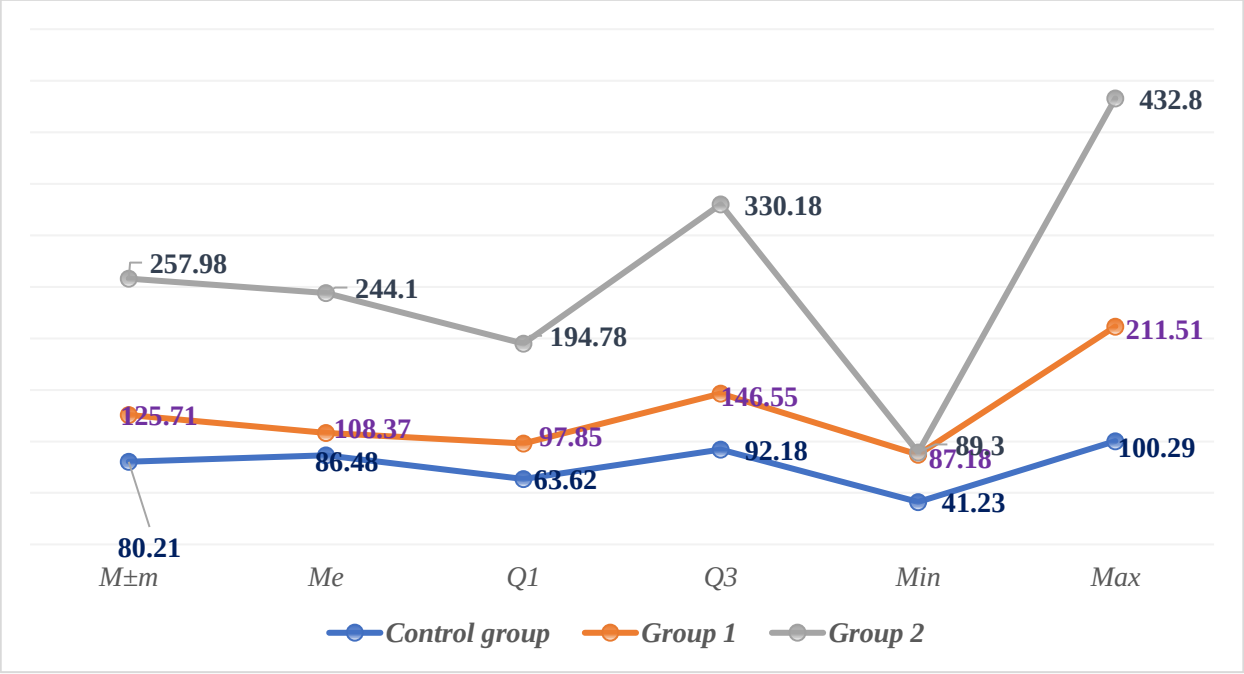

Figure 1. Comparative analysis of VEGF-A levels in the control and study groups.

In the first group, where patients with diabetes after COVID-19 were vaccinated, TGF-β levels were significantly elevated compared to the control group, though slightly lower than in the second group. The average TGF-β level was 88.56±3.57 pg/ml, which is more than 1.9 times higher than the control group's average of 46.39±1.53 pg/ml. The median in the first group was 83.20 pg/ml, which was also higher compared to the control group (49.24 pg/ml) (Fig. 2).

The interquartile range in the first group was [77.44; 103.30] pg/ml, indicating significant variability in TGF-β levels among the patients. The minimum TGF-β value in the first group was 67.04 pg/ml, while the maximum value reached 121.20 pg/ml, demonstrating a wide range of inflammatory and fibrotic processes in these patients.

In the second group, consisting of unvaccinated patients with diabetes that developed after COVID-19, the TGF-β level was significantly higher compared to the control group. The mean TGF-β value in this group was 102.51±3.06 pg/ml, more than twice the mean value in the control group, which was

46.39±1.53 pg/ml. The median TGF-β level in the second group reached 100.05 pg/ml, also significantly higher than in the control group, where the median was 49.24 pg/ml (Fig. 3).

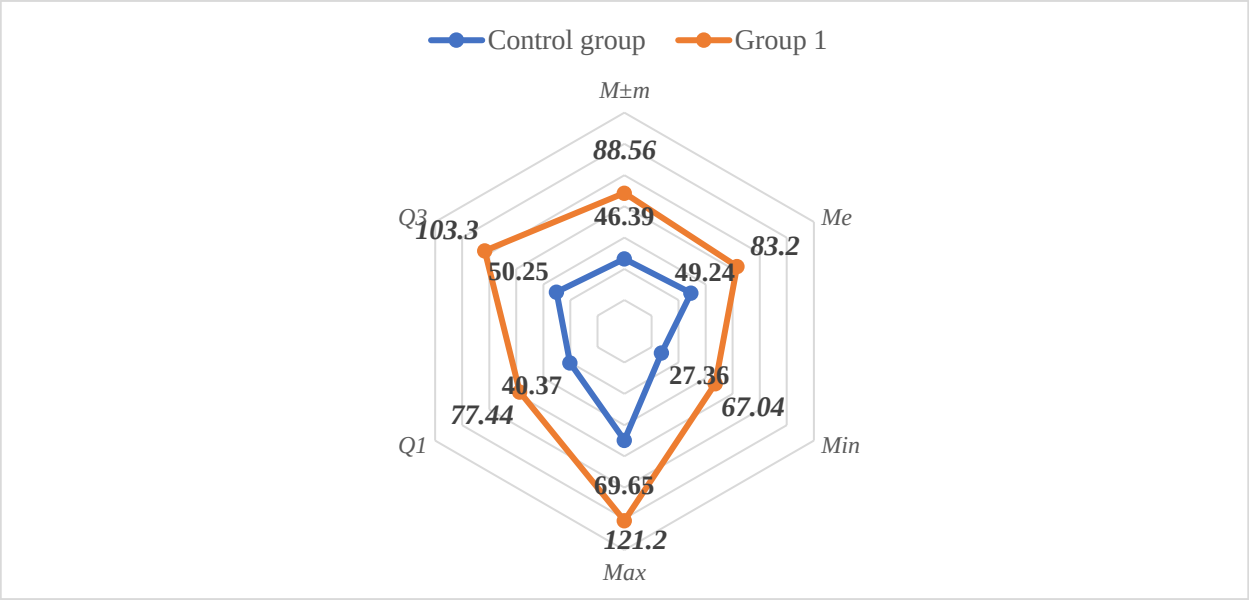

Figure 2. Comparative analysis of TGF-β levels in the control and first groups.

The interquartile range in the second group was broad, at [93.50; 120.90] pg/ml, indicating high variability in TGF-β levels among these patients. For comparison, in the control group, the interquartile range was much narrower—[40.37; 50.25] pg/ml—indicating more stable levels of this marker among healthy individuals.

The minimum TGF-β value in the second group was 53.89 pg/ml, and the maximum value reached 133.50 pg/ml. These values significantly exceed the minimum and maximum values recorded in the control group, where the minimum was 40.37 pg/ml and the maximum was 50.25 pg/ml.

These data confirm that in the second group, where patients were unvaccinated, the TGF-β level was significantly elevated compared to the control group, more than doubling the control values, indicating intense inflammation and active fibrotic processes.

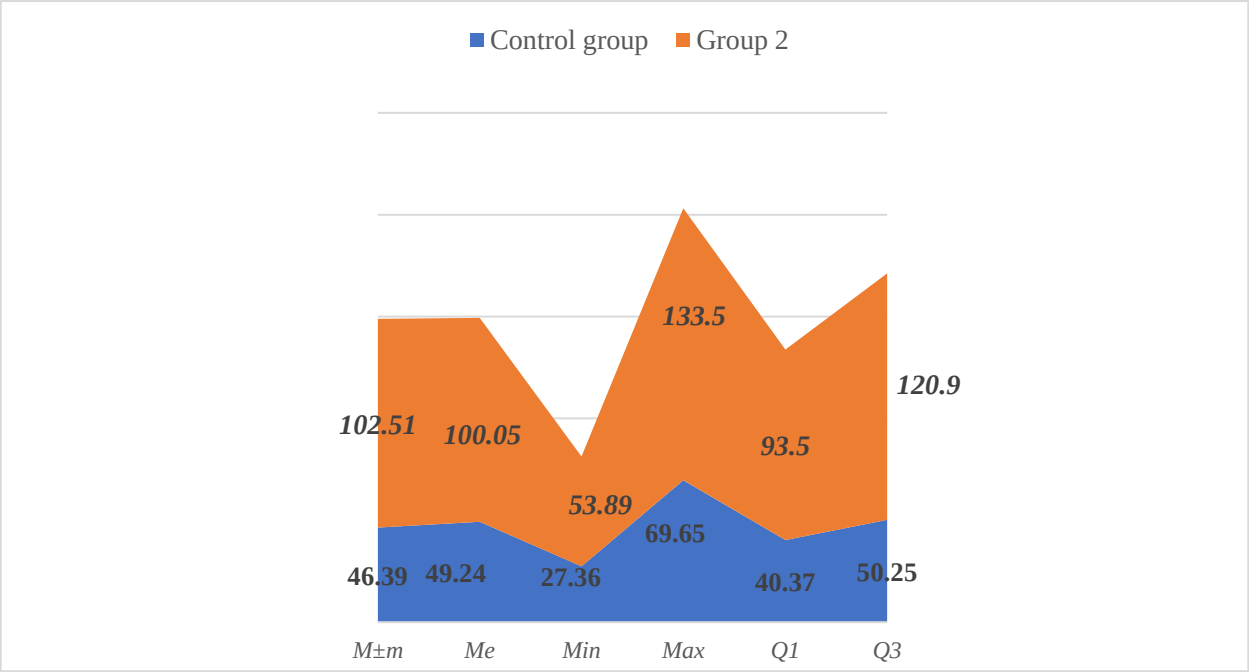

Figure 2. Comparative analysis of TGF-β levels in the control and second groups.

A comparison between the first and second groups shows that vaccination contributed to a reduction in TGF-β levels, decreased inflammatory reactions, and mitigated fibrotic processes, as evidenced by the lower average, minimum, and maximum values in the vaccinated group.

Analyzing IGF-1 concentrations provides deeper insight into the pathophysiological changes occurring in patients with diabetes that developed after recovering from a coronavirus infection. IGF-1 is an important regulator of cell growth and metabolism, and its levels can change significantly in response to tissue damage and metabolic disturbances, such as those seen in diabetes and post-COVID syndrome. The results of IGF-1 measurements in different groups of patients, including vaccinated and unvaccinated individuals, as well as a comparison with the control group, are presented below (Fig. 4).

In the first group, where patients with diabetes after COVID-19 were vaccinated, the IGF-1 concentration was significantly higher compared to the control group, though lower than in the second group. The mean IGF-1 value in the first group was 223.17±10.81 ng/ml, approximately twice as high as the control group, where the mean value was 106.33±3.57 ng/ml. The median IGF-1 level in the first group was 219.71 ng/ml, also higher than the control group, where the median was 103.14 ng/ml. The interquartile range in the first group was [193.54; 253.66] ng/ml, indicating significant variability in IGF-1 levels among patients.

The minimum IGF-1 values in the first group were 132.82 ng/ml, and the maximum reached 309.24 ng/ml, which is notably higher than in the control group, where the minimum was 69.70 ng/ml, and the maximum was 149.40 ng/ml.

In the second group, consisting of unvaccinated patients with diabetes that developed after COVID-19, IGF-1 levels were even higher. The mean IGF-1 value in the second group was 464.69±22.10 ng/ml, more than four times higher than the control group's mean.

The median IGF-1 level in the second group reached 478.44 ng/ml, significantly higher than in both the first group and the control group. The interquartile range [387.91; 584.58] ng/ml in the second group was much broader than in the other groups, reflecting a greater intensity of metabolic and regenerative processes. The minimum IGF-1 value in the second group was 121.51 ng/ml, while the maximum reached 790.73 ng/ml, demonstrating a wide range of fluctuations in this marker’s levels.

The next stage of the study focused on IP-10. Also known as CXCL10, IP-10 is a chemokine that plays a critical role in the immune response, especially during inflammation and viral infections. This protein attracts immune cells, such as T-lymphocytes and NK cells, to sites of inflammation, amplifying the immune reaction. In both diabetes and COVID-19, IP-10 levels can be significantly elevated, reflecting an active inflammatory process that may exacerbate metabolic disorders and tissue damage. Elevated IP-10 levels in these conditions are linked to immune system hyperactivation, which can contribute to chronic inflammation, organ dysfunction, and the progression of complications such as diabetic nephropathy and retinopathy.

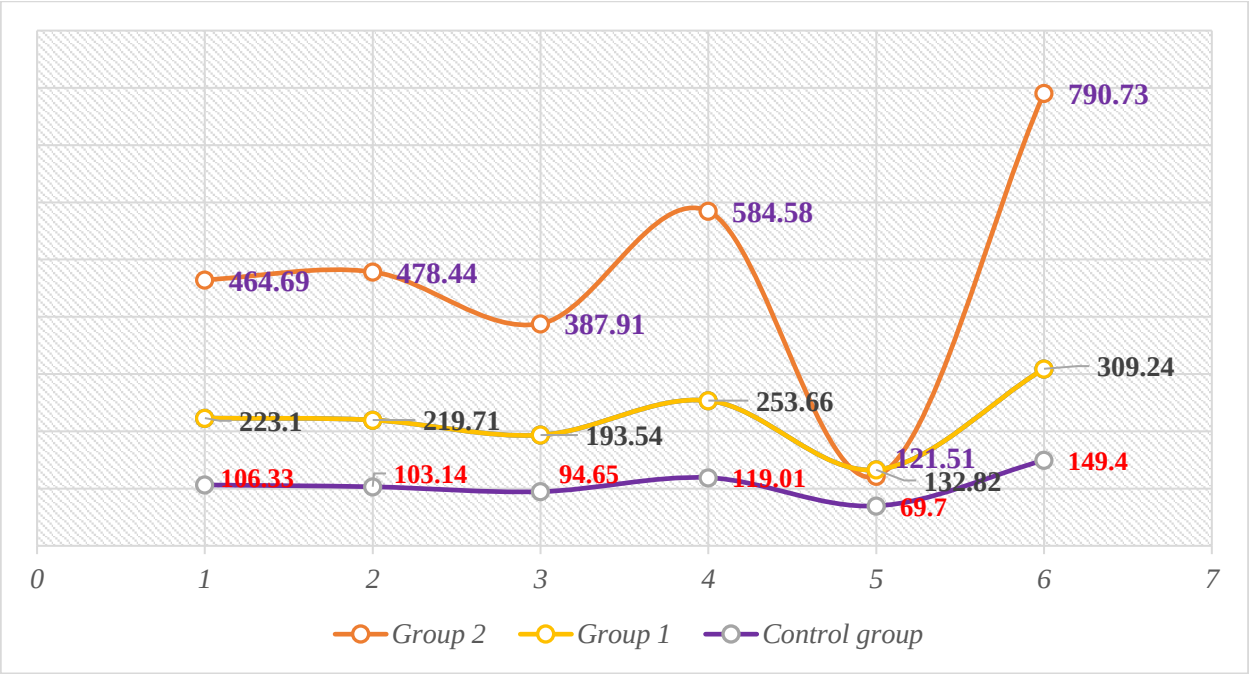

Figure 4. Comparative analysis of IGF-1 levels in the control and study groups.

In the control group, IP-10 levels remained relatively stable and significantly lower than in patients with diabetes and COVID-19. The average IP-10 level in the control group was 208.98±6.91 pg/ml, reflecting a normal level of inflammatory activity. The median IP-10 level in the control group was 202.40 pg/ml, with an interquartile range of [176.65; 246.65] pg/ml, indicating moderate variability and the absence of significant inflammatory responses. The minimum and maximum IP-10 values in the control group were 125.30 pg/ml and 285.60 pg/ml, respectively.

In the first group, consisting of patients with diabetes after COVID-19 who were vaccinated, the IP-10 level was higher than in the control group but lower than in the second group, indicating that vaccination had a mitigating effect on inflammation. The average IP-10 level in the first group was 300.21±14.01 pg/ml, significantly higher than the control values but lower than in the second group. The median IP-10 level in the first group reached 290.57 pg/ml, higher than the control group's median of 202.40 pg/ml. The interquartile range in the first group was [284.58; 321.64] pg/ml, indicating relatively stable but elevated inflammatory activity. The minimum IP-10 values in the first group were 187.91 pg/ml, while the maximum reached 421.78 pg/ml, suggesting significant, but less intense immune activation compared to the second group.

In the second group, comprising unvaccinated patients with diabetes after COVID-19, the IP-10 level was significantly higher, indicating more pronounced inflammatory processes. The average IP-10 level in this group was 398.48±25.54 pg/ml, nearly double that of the control group. The median IP-10 level in the second group was 389.81 pg/ml, highlighting a much more intense inflammatory response compared to the control group and vaccinated patients. The interquartile range in the second group was [293.44; 503.47] pg/ml, much broader, reflecting greater variability and intensity of inflammatory processes. The minimum IP-10 values in the second group were 117.62 pg/ml, while the maximum reached 791.71 pg/ml, demonstrating extremely high immune activation in these patients.

The analysis shows that IP-10 levels vary significantly between the groups, reflecting the extent of the inflammatory response and the impact of vaccination on this process. Vaccination in the first group contributed to a reduction in IP-10 levels, likely due to the modulation of the inflammatory response and a lower risk of severe inflammatory complications. In the second group, where patients were not vaccinated, IP-10 levels were significantly higher, indicating more severe pathological processes and the need for more aggressive control of inflammation.

Conclusion: The study demonstrated that in the first group, comprising vaccinated patients with diabetes after COVID-19, the levels of all immunological markers, including VEGF-A, IGF-1, and IP-10, were higher than in the control group but generally lower than in the second group. This indicates that vaccination helped to reduce inflammatory processes and improve metabolic health. In the second group, consisting of unvaccinated patients, higher levels of inflammatory markers and more pronounced metabolic disturbances were observed, emphasizing the importance of vaccination in mitigating inflammatory reactions and reducing the risk of complications in patients with diabetes after COVID-19.

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