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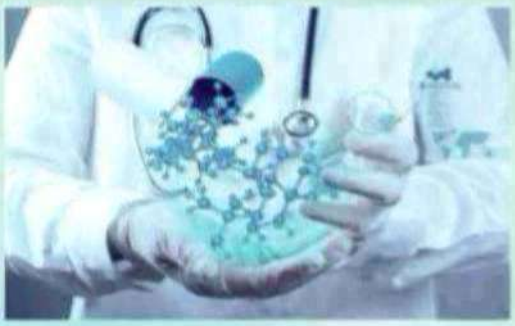

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IMMUNO - METABOLIC CORRELATIONS IN DELAYED CONSOLIDATION OF LONG BONE FRACTURES IN THE POST-COVID PERIOD

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✓ ***Resume***

The study investigates the correlation between lipid and carbohydrate metabolism indicators and immune-inflammatory markers in patients with delayed consolidation of long bone fractures after COVID-19. A total of 126 patients were analyzed using clinical, biochemical, and immunological parameters. Elevated total cholesterol and LDL were positively associated with increased levels of IgA, IgG, IgE, and pro-inflammatory cytokines (IL-1β, IL-6), and negatively correlated with the osteogenic marker lactoferrin. Hyperglycemia and insulin resistance showed strong positive correlations with humoral immunity markers and systemic inflammation (CRP, IL-6), while inversely correlating with INF-γ, reflecting immune dysregulation. HDL demonstrated a protective role by showing inverse relationships with inflammatory markers. These findings emphasize the pathophysiological significance of immune-metabolic interactions in post-COVID bone healing impairments

Keywords: delayed bone consolidation, lipid profile, carbohydrate metabolism, immunological markers, inflammation, COVID-19, cytokines, lactoferrin, HOMA-IR, immune dysregulation

ИММУННО - МЕТАБОЛИЧЕСКИЕ КОРРЕЛЯЦИИ ПРИ ЗАМЕДЛЕННОЙ КОНСОЛИДАЦИИ ПЕРЕЛОМОВ ДЛИННЫХ ТРУБЧАТЫХ КОСТЕЙ В ПОСТКОВИДНОМ ПЕРИОДЕ

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✓ ***Резюме***

В исследовании рассматривается взаимосвязь показателей липидного и углеводного обмена с иммуновоспалительными маркерами у пациентов с замедленной консолидацией переломов длинных трубчатых костей после перенесённого COVID-19. Было проанализировано 126 пациентов с использованием клинических, биохимических и иммунологических методов.

Повышенные уровни общего холестерина и ЛПНП (липопротеинов низкой плотности) положительно коррелировали с увеличением концентрации иммуноглобулинов A, G, E (IgA, IgG, IgE) и провоспалительных цитокинов (IL-1β, IL-6), а также отрицательно — с остеогенным маркером лактоферрином. Гипергликемия и инсулинорезистентность демонстрировали выраженные положительные корреляции с маркерами гуморального иммунитета и системного воспаления (СРБ, IL-6), одновременно показывая обратную связь с ИФН-γ (интерферон-гамма), что отражает дисрегуляцию иммунного ответа. ЛПВП (липопротеины высокой плотности) проявляли защитную роль, обратно коррелируя с воспалительными маркерами. Полученные данные подчеркивают патофизиологическую значимость иммунно-метаболических взаимодействий при нарушениях заживления костной ткани после COVID-19

Ключевые слова: замедленная консолидация костей, липидный профиль, углеводный обмен, иммунологические маркеры, воспаление, COVID-19, цитокины, лактоферрин, HOMA-IR, иммунная дисрегуляция

KOVIDDAN KEYINGI DAVRDA UZUN NAYSIMON SUYAKLAR SINISHIDAN SO‘NGI SEKINLASHGAN KONSOLIDATSIYASINING IMMUNNO - METABOLIK KORRELYATSIYASI

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✓ ***Rezyume***

Tadqiqot lipidlar va uglevodlar almashinuvi parametrlari va COVID-19 dan keyin uzun suyak sinishlarining konsolidatsiyasi sekinlashgan bemorlarda immun-yallig'lanish belgilari o'rtasidagi munosabatni o'rganadi. Klinik, biokimyoviy va immunologik usullar yordamida jami 126 bemor tahlil qilindi. Umumiy xolesterin va LDL (past zichlikdagi lipoproteinlar) darajasining oshishi immunoglobulinlar A, G, E (IgA, IgG, IgE) va proinflamatuar sitokinlar (IL-1b, IL-6) kontsentratsiyasining ortishi bilan ijobiy bog'liq va osteogen markyori laktoferin bilan salbiy.

Giperglikemiya va insulinorezistent gumoral immunitet va tizimli yallig'lanish belgilari (CRP, IL-6) bilan sezilarli ijobiy korrelyatsiyani ko'rsatdi va bir vaqtning o'zida IFN-g (interferon-gamma) bilan teskari bog'liqlikni ko'rsatdi, bu esa immunitetning disregulyatsiyasini aks ettiradi. HDL (yuqori zichlikdagi lipoprotein) yallig'lanish belgilari bilan teskari korrelyatsiya qiluvchi himoya rolini o'ynadi.

Olingan ma’lumotlar COVID-19 dan keyin buzilgan suyaklarni davolashda immun-metabolik o'zaro ta'sirlarning patofiziologik ahamiyatini ta'kidlaydi

Kalit so'zlar: sekinlashgan suyak konsolidatsiyasi, lipid profili, uglevod almashinuvi, immunologik belgilar, yallig'lanish, COVID-19, sitokinlar, laktoferrin, HOMA-IR, immun disregulyatsiya

Relevance

In recent years, the issues of prevention and treatment of traumatic diseases accompanied by bone fractures remain among the priority areas of modern medicine. Cases of impaired osteogenesis are particularly difficult, especially with fractures of long tubular bones, since they are accompanied by a persistent decrease in the functionality of the affected limb, emotional and psychological discomfort and a high risk of disability. According to clinical observations, “… the formation of incompetent bone fusion, including pseudoarthroses, is detected on average in 2% of patients with fractures, and with certain types of injuries this figure can reach 20%” (2, 6, 8, 11).

The severity of the consequences of closed fractures, the complexity of bone regeneration processes, as well as the significant socio-economic burden necessitate an in-depth study of pathogenesis, the introduction of early clinical and immunological diagnostic methods, and the development of effective therapeutic and preventive approaches. COVID-19 has a systemic effect on immune, vascular, and metabolic regulation, which can significantly alter bone tissue regeneration processes (1, 4, 5, 9). Lipid and carbohydrate disturbances, often observed in patients after COVID-19, can affect the immune response and inflammatory processes that are critical for reparative osteogenesis (3, 7, 10). At the same time, altered biochemical parameters, including markers of inflammation and tissue damage, can reflect the depth of systemic disorders associated with delayed fracture healing. Analysis of the relationships between these parameters allows for a deeper understanding of the pathogenetic mechanisms of impaired bone consolidation.

To assess the nature of the correlation relationships between lipid and carbohydrate metabolism indices and immunological markers of inflammation and immune dysregulation in patients with metabolic and inflammatory disorders.

Materials and methods

Clinical and anamnestic features of the course of diseases of 126 examined patients were clarified through our own observations, medical documentation data, namely clinical medical history, and data from the opinions of specialists.

Biochemical parameters (TC, LDL, HDL, glucose, glycated hemoglobin, insulin) were collected from the medical records of the examined patients. The HOMA (Homeostasis Model Assessment) index was determined using the standard formula: HOMA-IR = (Fasting glucose, mmol/l × Fasting insulin, μU/ml) / 22.5. This formula allows us to assess the degree of insulin resistance: the higher the HOMA-IR value, the more pronounced the insulin resistance.

Immunobiochemical analyzes (IgA, IgG, IgM, IgE, LF, CRP, INFy, IL-1β, IL-4, IL-6) were carried out by enzyme-linked immunosorbent assay (VectorBest).

The direction and closeness of the correlation between two quantitative indicators were assessed using the Pearson correlation coefficient (with a normal distribution of the compared indicators). The direction and closeness of the correlation between two quantitative indicators were assessed using the Spearman rank correlation coefficient (with a non-normal distribution of indicators) using the Chaddock method. Differences were considered statistically significant at $P<0.05$.

Results and discussions

The objective of this article is to determine whether there are statistically significant correlations between lipid profile parameters (total cholesterol, lipoproteins of different densities) and carbohydrate metabolism (glucose, glycated hemoglobin, insulin, HOMA-IR index) with the level of the main immunological markers of inflammation and immune dysregulation (IgA, IgG, IgM, IgE (Xema), LF, CRP, INFy, IL-1β, IL-4, IL-6 (Elisa-kid)).

The conducted correlation analysis showed the presence of many statistically significant relationships between lipid metabolism parameters and immunological markers of inflammation in patients with delayed fracture consolidation after COVID-19 infection (Fig. 1).

Total cholesterol (TC) and low-density lipoproteins (LDL) showed a direct moderate correlation with the levels of IgA (r=0.52), IgG (r=0.52 and r=0.47, respectively), IgE (r=0.53 and r=0.57, respectively), as well as with the levels of C-reactive protein (CRP) (r=0.64 and r=0.63), interleukin-1β (IL-1β), interleukin-4 (IL-4), and interleukin-6 (IL-6).

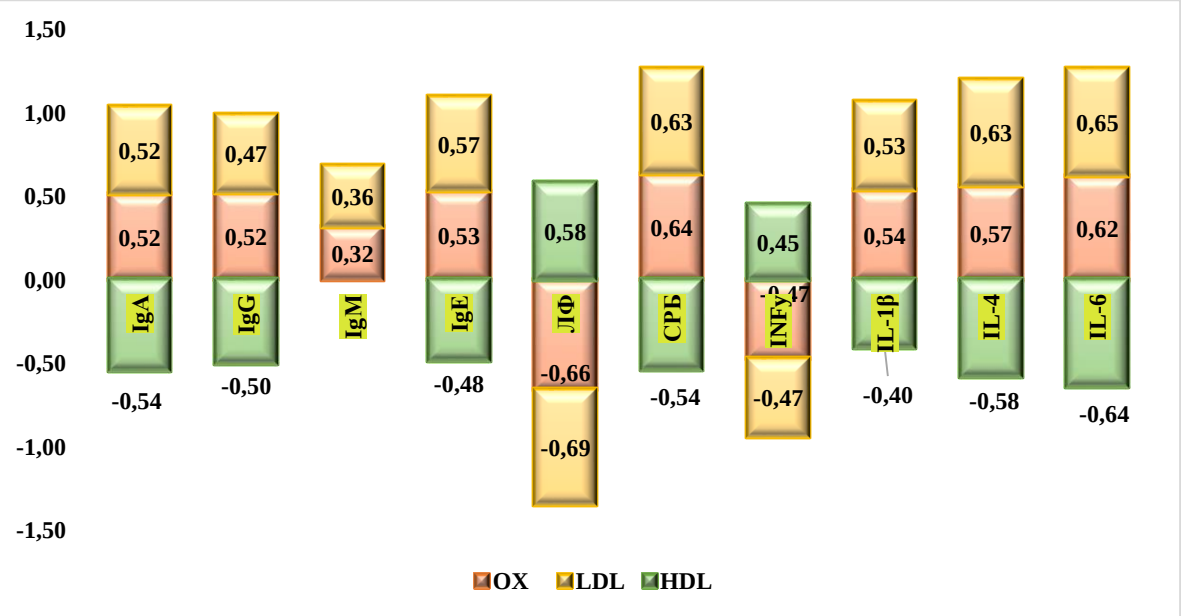

Fig. 1. Correlation relationships between lipid profile and immunological markers (P≤0.05)

These results indicate that dyslipidemia is accompanied by an increase in the humoral immune response and inflammatory processes.

Increased TC and LDL promote macrophage activation via modified lipoprotein recognition receptors, which stimulates the production of proinflammatory cytokines, including IL-1β and IL-6. In the context of post-COVID immune imbalance, this can increase chronic inflammation, preventing normal bone tissue regeneration.

In addition, an increase in IgE in combination with dyslipidemia may reflect a tendency to an allergic or atypical immune response, which also contributes to the disruption of reparative osteogenesis processes.

Negative correlations between TC and LDL with lactoferrin (LF) levels (r=-0.66 and r=-0.69, respectively) indicate a decrease in osteoblast activity under hypercholesterolemia conditions. It is known that oxidized LDL can inhibit osteoblast differentiation and stimulate bone cell apoptosis, which leads to impaired bone matrix mineralization and delayed fracture consolidation.

Interferon-gamma (IFN-γ) demonstrated an inverse relationship with TC and LDL (r=-0.47). Since IFN-γ plays a role in stimulating antibacterial defense and regulating bone resorption, a decrease in its level against the background of dyslipidemia may additionally contribute to the formation of a chronic inflammatory background and disruption of the balance between osteoblastic and osteoclastic activity.

Particular attention is drawn to the role of high-density lipoproteins (HDL). They showed inverse correlations with the levels of IgA, IgG, IgE, CRP, IL-4 and IL-6. This confirms their known anti-atherogenic and anti-inflammatory role: HDL inhibits the expression of adhesion molecules on the endothelium, reduces the activation of macrophages and suppresses the synthesis of pro-inflammatory cytokines.

Thus, high HDL levels contribute to a reduction in the inflammatory response and potentially improve the processes of reparative osteogenesis.

The obtained data indicate that lipid metabolism disorders that increase inflammation and suppress osteogenic activity are an important link in the pathogenesis of delayed fracture consolidation in patients after COVID-19. These results substantiate the need to control the lipid profile and modulate the inflammatory response to improve treatment outcomes in this category of patients.

Correlation analysis showed the presence of significant relationships between carbohydrate metabolism parameters (glucose, insulin, HOMA-IR index) and immunological inflammation indices in patients with delayed fracture consolidation after COVID-19. It should be noted that glycated hemoglobin showed weak relationships with immunological markers, and therefore we did not consider it necessary to display their values in this subchapter.

Glucose, insulin levels and the insulin resistance index significantly positively correlated with the concentrations of immunoglobulins A (IgA) (r=0.60–0.63), G (IgG) (r=0.56–0.59), M (IgM) (r=0.44–0.46) and E (IgE) (r=0.63–0.67).

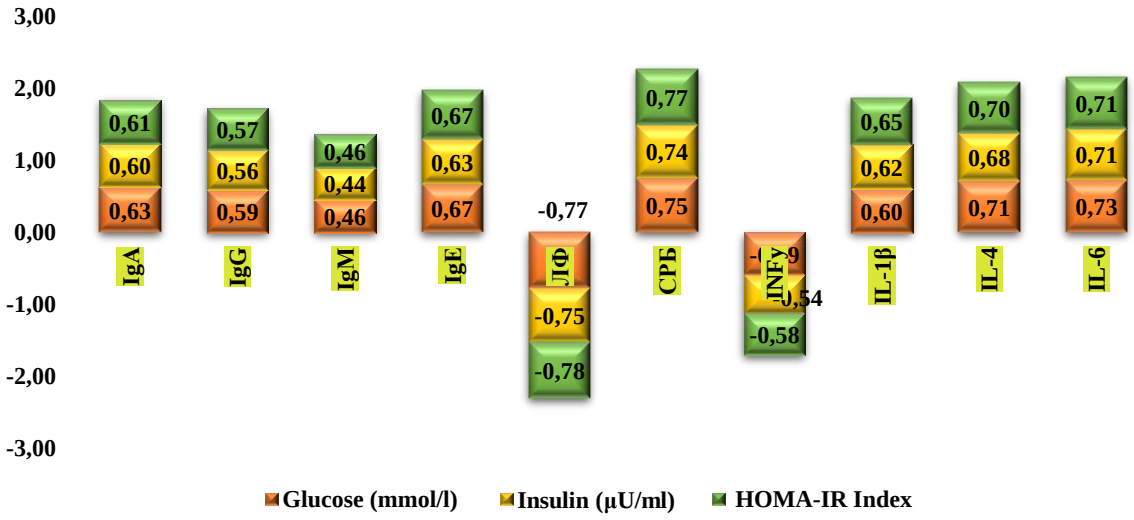

Fig. 2. Correlation links between carbohydrate metabolism and immunological markers, (P≤0.05)

This indicates the involvement of the humoral link of immunity in pathological processes occurring against the background of hyperglycemia and insulin resistance (Fig. 2).

At the molecular level, hyperglycemia increases the synthesis of proinflammatory cytokines by activating NF-κB signaling pathways, and hyperinsulinemia additionally stimulates chronic inflammation, which leads

to hyperproduction of immunoglobulins. An increase in IgE is especially characteristic of a shift in the immune response towards the Th2 type, which is typical for post-COVID immune disorders.

Lactoferrin (LF) showed significant negative correlations with glycemic disturbances (r=-0.75 to -0.78).

Lactoferrin is a key component of innate immunity, with anti-inflammatory, antioxidant and antimicrobial effects. A decrease in its levels against the background of hyperglycemia and insulin resistance may indicate a disruption of innate defense functions [2, 4].

The mechanisms for this include glycation of lactoferrin molecules and a decrease in its binding capacity to iron, which weakens antibacterial activity and promotes the development of secondary infections and persistent inflammation.

C-reactive protein (CRP) positively correlated with carbohydrate metabolism parameters (r=0.74–0.77), reflecting chronic systemic inflammation accompanying insulin resistance.

The negative correlation of interferon-gamma (INF-γ) with glucose and insulin levels (r=-0.54 to -0.59) indicates suppression of antiviral and antifibrotic protection in patients with carbohydrate metabolism disorders.

Since INF-γ is critical for macrophage activation and clearance of viral infections, its reduction promotes chronic inflammation and fibrotic changes in regenerating bone tissue.

Proinflammatory cytokine levels interleukin-1β (IL-1β), interleukin-4 (IL-4) and interleukin-6 (IL-6) showed significant positive correlations with glucose, insulin and HOMA-IR levels (r=0.60–0.73).

This reflects the activation of inflammatory cascades, with IL-6, being a potent mediator of acute inflammation, also stimulating osteoclastogenesis and bone resorption, which aggravates delayed fracture healing.

Conclusion

Thus, metabolic disorders, primarily insulin resistance and hyperglycemia, are closely associated with the activation of inflammatory responses, depletion of innate immunity (lactoferrin) and increased humoral immune activity, which is an important pathogenetic mechanism of delayed bone consolidation in patients after COVID-19.

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