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The role of vitamin D in modulating immune response and inflammatory markers in paediatric autoimmune liver disorders

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Abstract. Given the high prevalence of hypovitaminosis D among the paediatric population in Ukraine, a need has emerged to explore its role in regulating hepatic fibrogenesis in juvenile autoimmune liver diseases. The aim of this study was to determine the effectiveness of long-term vitamin D supplementation in modifying serological and imaging markers of fibrosis in children with autoimmune hepatitis and autoimmune sclerosing cholangitis. The research was based on a prospective cohort observation conducted from March 2024 to March 2025, involving patients from specialised medical centres in Ukraine, and applying laboratory testing, two-dimensional shear wave elastography (2D-SWE), and statistical analysis. The results indicated that with a high cumulative annual dose of vitamin D exceeding 500,000 IU, the mean 25-hydroxyvitamin D level increased to 111.3 ± 19.9 nmol/L, while the level of hyaluronic acid decreased to 9.2 ± 7.1 ng/mL, in contrast to the control group where the respective figures were 63.5 ± 19.9 nmol/L and 20.7 ± 9.2 ng/mL ($p < 0.0001$ and $p = 0.001$, respectively). A statistically significant inverse correlation between these biomarkers was established ($r = -0.49$; $p = 0.018$) in the high-dose group, confirming a dose-dependent effect of the nutritional intervention. Liver tissue stiffness parameters according to elastography remained stable, showing no significant changes after 12 months of therapy. It was concluded that high-dose vitamin D supplementation was associated with a reduction in fibrogenesis activity, as evidenced serologically, though not accompanied by morphological changes in tissue stiffness. The study's findings may be applied in clinical practice to facilitate non-invasive monitoring of treatment efficacy and improve personalised nutritional support protocols for children with chronic autoimmune liver diseases

Keywords: fibrosis; parenchymal stiffness; hyaluronic acid; nutritional therapy; two-dimensional shear wave elastography; paediatric population; calcium-phosphate homeostasis

INTRODUCTION

Disorders of hepatic fibrogenesis in children with chronic autoimmune liver diseases form a distinct clinical and scientific domain requiring a comprehensive pathogenetic analysis and the refinement of therapeutic monitoring approaches. Among such conditions, juvenile autoimmune liver diseases (JALD), including autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC), are marked by early fibrosis progression, persistent inflammation, and limited effectiveness of immunosuppressive therapy, especially under coexisting metabolic disturbances. Deficiency of 25-hydroxyvitamin D (25(OH)D), frequently observed in these patients, is associated with enhanced systemic inflammation, impaired hepatic tissue regeneration, and activation of cellular fibrogenesis. In this context, nutritional status is increasingly being considered not merely as a background indicator but as a factor directly influencing the course of autoimmune pathology.

A review of current literature has revealed growing scientific interest in the role of 25(OH)D in systemic inflammation, metabolism, and liver fibrosis. N. Grygorieva *et al.* [1] substantiated national approaches to diagnosing and treating vitamin D deficiency in Ukraine's adult population; however, paediatric considerations were lacking. S. Shatylo *et al.* [2] conducted a multicentre study on vitamin D deficiency across Ukraine, without

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differentiating the metabolic peculiarities of patients with chronic liver diseases. A.M. Shulhai *et al.* [3] described the association between hypovitaminosis D and metabolic syndrome in adolescents, partly overlapping with hepatology but not addressing fibrogenesis specifically.

Epidemiological features of vitamin D deficiency in Ukraine were highlighted by N. Grygorieva *et al.* [4], who noted insufficient provision across age groups, yet did not categorise results by nosological forms or clinical complications. V. Theiler-Schwetz *et al.* [5] examined the influence of vitamin D on blood pressure, demonstrating systemic effects, but findings could not be extrapolated to tissue remodelling in fibrosis. S. Karahan & F. Katkat [6] discussed the correlation between 25(OH)D levels and COVID-19 mortality, though their focus was confined to immune response mechanisms. W.B. Grant *et al.* [7] summarised evidence on non-skeletal effects of vitamin D, without considering its impact on hepatic tissue.

A randomised study by M. Cojic *et al.* [8] showed vitamin D's effects on metabolic and oxidative parameters in diabetes mellitus, aligning with the organ-protective concept, yet excluded fibrosis markers. M. Coskun *et al.* [9] assessed biochemical and ultrasound features in acromegaly, but their methodology was unsuitable for paediatric hepatology. K. Zachou *et al.* [10] proposed the FibroMeter to assess fibrosis in autoimmune liver diseases, but it has not been validated for children. S. Lee *et al.* [11] evaluated the accuracy of shear-wave elastography in children, without considering vitamin therapy. Finally, S.C. Nagamani *et al.* [12] focused on biomarkers in hereditary metabolic liver disorders but did not analyse inflammatory or fibrotic markers in autoimmune conditions.

Hence, none of the aforementioned studies combined the analysis of serum HA levels, 2D-SWE parameters, and vitamin D status in paediatric patients with JALD. This national study is the first to integrate these elements. The proposed approach stands apart by dynamically correlating biochemical and imaging markers under standardised high-dose nutritional therapy, enabling evaluation of both functional and morphological changes in fibrogenesis. Thus, the study's relevance lies not only in meeting the clinical needs of paediatric hepatology but also in addressing the limited informativeness of certain non-invasive methods at early disease stages. Evaluating the potential of vitamin D to affect biochemical and structural fibrosis markers, notably HA and liver parenchymal stiffness according to 2D-SWE, presents a promising direction for developing a multiparametric model of non-invasive therapy monitoring.

The aim of this study was to assess the effect of long-term high-dose vitamin D supplementation on the dynamics of serum 25(OH)D levels, HA concentration as a biochemical marker of fibrosis, and liver parenchymal stiffness based on 2D-SWE data in children with JALD. Specific objectives included: to characterise the baseline 25(OH)D status in paediatric patients with autoimmune liver diseases, based on disease type, duration, and age; to analyse changes in 25(OH)D and hyaluronic acid (HA) levels over a 12-month period in relation to vitamin D supplementation dosage and to establish their correlation; to assess the effectiveness of non-invasive fibrosis monitoring through liver stiffness parameters and a multiparametric approach, including 2D-SWE and biochemical markers.

MATERIALS AND METHODS

The study period covered March 2024 to March 2025 inclusive. Inclusion criteria were: age between 6 and 18 years, confirmed diagnosis of AIH or ASC according to ESPGHAN criteria, and written informed consent from parents or legal guardians. Exclusion criteria included: presence of severe comorbidities (e.g., malignancies, decompensated endocrinopathies), use of other vitamin D preparations in the preceding 6 months, malabsorption syndromes, nephrotic syndrome, or refusal to participate. The study employed a prospective observational design with repeated measurements of biochemical markers and elastographic parameters over a 12-month supplementation period.

Clinical data were collected at specialised paediatric medical institutions in Ukraine, specifically within departments managing children with chronic liver diseases. Selection of centres was based on their specialisation, geographic distribution, and access to modern laboratory and imaging technologies. Participating centres included the Centre for Paediatric Hepatology at the Western Ukrainian Specialised Children's Medical Centre (Lviv) [13], National Children's Specialised Hospital "Okhmatdyt" [14], and the State Institution "Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine" (Dnipro) [15]. Clinical data were collected in gastroenterology departments specialising in the treatment of AIH and ASC. The inclusion of such patients was justified by the need to objectively evaluate the impact of vitamin D on fibrotic markers within a unified pathogenetic model of JALD. The study database was formed in accordance with methodological recommendations from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [16], the Endocrine Society Clinical Practice Guidelines [17], and guidelines from the European Association for the Study of the Liver (EASL) [18], adapted for paediatric hepatology. The use of serological markers, elastography techniques, and nutritional status indicators was based on interdisciplinary approaches outlined in methodological documents on biomarker stratification of fibrosis, laboratory morphology, cytokine biology, and fibrogenesis genetics.

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The total study sample comprised n = 43 patients diagnosed with JALD, divided into two nosological groups: AIH (n = 24) and ASC (n = 19). Stratification by vitamin D dose was based on actual daily and annual intake as recorded in medical records and nutritional therapy plans. Patients receiving over 500,000 IU annually were assigned to the high-dose group (n = 24); the remainder, with doses ≤ 290,000 IU, formed the low-dose group (n = 19). For a separate analysis of biochemical parameters (e.g. calcium and phosphorus), a high-dose group (n = 21) and a control group (n = 22) were established. The control group included both low-dose recipients and those receiving only baseline supportive therapy without additional vitamin D supplementation. The administered form was oral cholecalciferol (vitamin D3) in oil-based drops. Supplementation was provided daily. Adherence was monitored via monthly parental surveys, residual drug checks, periodic phone reminders, and clinical visits to verify compliance. To comprehensively compare the therapeutic response in both stratified groups, a descriptive analysis of the changes in 25(OH)D, hyaluronic acid (HA), and 2D-SWE values over the 12-month period was performed, allowing generalisation of supplementation efficacy differences.

Serum 25(OH)D levels were measured using electrochemiluminescence immunoassay (ECLIA) with a Cobas e411 analyser (Roche Diagnostics, Germany). The sensitivity threshold was 10 nmol/L, and the intra-laboratory coefficient of variation (CV%) was 4.2%. HA concentrations were determined via enzyme-linked immunosorbent assay (ELISA) using the Hyaluronic Acid Quantikine® ELISA Kit (R&D Systems, USA). Optical density was measured with a Multiskan FC microplate photometer (Thermo Fisher Scientific, USA). Biomarker selection was based on their sensitivity to active phases of fibrogenesis, suitability for routine diagnostics, and EASL recommendations for non-invasive fibrosis stratification. Liver parenchymal stiffness was evaluated using 2D-SWE on Aixplorer Ultimate ultrasound systems (SuperSonic Imagine, France) with elastography functionality and a convex probe (3.5-5.0 MHz). Examinations were performed before supplementation and after the 12-month observation period, with patients in the supine position, fasting, and in accordance with the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology [19]. All measurements were conducted by a single operator with over five years of paediatric elastography experience, ensuring consistency in interpretation. Each patient underwent at least five representative measurements in the right liver lobe, from which the mean value was used for analysis.

Statistical analysis was performed using Statistica 12.0. Normality was assessed using the Shapiro-Wilk test. Parameters were described using mean values and standard deviations. Within-group changes were evaluated using the paired Student's t-test; between-group comparisons employed the unpaired t-test. Associations between 25(OH)D and HA levels were assessed using Pearson's correlation coefficient (r), with statistical significance set at $p < 0.05$. No adjustments were made for covariates (age, sex), which is acknowledged as a methodological limitation. The study complied with principles of voluntariness, anonymity, and confidentiality in accordance with the Declaration of Helsinki [20] and ethical standards adopted by local bioethics committees, specifically those outlined in Good Clinical Practice (GCP) [21]. Ethical approval was granted by the ethics committee of the State Institution "Institute of Gastroenterology of the NAMS of Ukraine" (Protocol No. 12/2023 dated 02.12.2023). Identifying information was not retained; data were used solely in aggregated form for scientific purposes. Interpretation of results followed evidence-based medicine principles and considered the biological plausibility of marker changes. Relationships between serological and elastographic indicators were evaluated, as well as changes according to vitamin D dosage. Conclusions were drawn from generalised quantitative data without reliance on subjective clinical criteria.

RESULTS

The biological role of vitamin D in the pathogenesis of liver fibrosis in juvenile autoimmune diseases

The pathophysiological basis for using HA as a biomarker of liver fibrosis lies in its close association with cellular and molecular mechanisms involved in extracellular matrix formation. A central role is played by hepatic stellate cells (HSC), which, upon activation during chronic inflammation, transform into fibrogenic effector cells. Activated HSC produce numerous matrix components, including HA, due to upregulated expression of HAS2, regulated by transforming growth factor-beta (TGF-β). In paediatric patients with juvenile autoimmune liver diseases, this interaction is particularly relevant due to the heightened activity of the immune component in the fibrotic cascade. To systematise the roles of the main biological agents involved in HA synthesis during hepatic fibrosis, Table 1 summarises the relationships among HSC, TGF-β, and HAS2, outlining their functional characteristics and pathophysiological mechanisms in fibrosis progression. This structured format offers a comprehensive view of the molecular cascade underlying fibrogenesis in children with JALD.

Table 1. Illustrative scheme of the pathophysiological involvement of HSC, TGF-β, and HAS2 in HA synthesis during liver fibrosis

Component	Biological role	Mechanism of action in liver fibrosis	Relationship with HA synthesis
HSCs	Principal cells responsible for fibrosis development	In a quiescent state, they store retinoids; upon activation, they transform into myofibroblasts that produce extracellular matrix	Activated HSCs produce HA through upregulation of HAS2 expression
TGF-β	Cytokine regulating fibrogenesis	Activates HSCs and stimulates expression of fibrotic genes, particularly HAS2, via SMAD-dependent signalling pathways	Indirectly promotes HA synthesis by inducing HAS2
HAS2	Enzyme involved in HA biosynthesis	Catalyses HA formation from monosaccharides; predominantly expressed in activated HSCs	Directly determines HA accumulation levels in liver tissue and serum

Note: HSC – hepatic stellate cells; TGF-β – transforming growth factor beta; HAS2 – hyaluronan synthase 2; HA – hyaluronic acid. The table illustrates the cellular activation sequence and enzymatic pathways leading to increased HA synthesis – a key non-invasive marker of liver fibrosis

Source: developed by the author based on [18]

The analysed Table 1 illustrates the key stages of cellular fibrogenesis activation, within which HSCs, under the influence of TGF-β, transition into an activated state. This activation is accompanied by increased expression of the enzyme HAS2, which directly catalyses the synthesis of HA. HA, as one of the products of the fibrotic cascade, accumulates in tissues and the bloodstream, reflecting the intensity of fibrogenesis. Its level correlates with fibrosis progression, which justifies the use of this marker for non-invasive monitoring of changes in liver parenchyma. This pathophysiological model, comprising HSC-TGF-β-HAS2-HA, forms the basis of the study and substantiates the rationale for a multiparametric approach to assessing therapeutic intervention effectiveness.

Considering these mechanisms, the study was aimed at evaluating the effect of long-term vitamin D supplementation on HA levels as an indicator of active fibrogenesis in children with JALD. For this purpose, a comparative analysis of 25(OH)D and HA concentrations was conducted over a 12-month observation period. Participants were stratified according to their cumulative nutrient dose, allowing the formation of two groups – high-dose and low-dose supplementation. This approach provided a basis for analysing the dose-dependent effect of vitamin D on fibrotic markers. The results of the intergroup comparison of biochemical parameters are presented in Table 2, reflecting the potential antifibrotic effect of vitamin D in the study cohort.

Table 2. Comparison of mean levels of 25(OH)D and HA depending on the cumulative dose of vitamin D in children with JALD

Indicator	High-dose vitamin D (> 500,000 IU/12 months)	Low-dose vitamin D (≤ 290,000 IU/12 months)	p-value
Number of patients (n)	21	22	-
25(OH)D, nmol/L (after 12 months)	111.3 ± 19.9	63.5 ± 19.9	< 0.0001
25(OH)D >75 nmol/L, % of patients	100%	32%	< 0.0001
HA, ng/mL (after 12 months)	9.2 ± 7.1	20.7 ± 9.2	0.001
Correlation between 25(OH)D and HA (r)	-0.44	-	$p < 0.05$

Note: 25(OH)D – 25-hydroxyvitamin D (the main circulating metabolite of vitamin D); HA – hyaluronic acid (a molecular marker of fibrosis); IU – international units. All values are presented as mean ± standard deviation. The threshold of > 500,000 IU per year for high-dose supplementation was selected in accordance with Endocrine Society clinical guidelines, which recommend a safe daily intake of up to 2,000 IU for children aged 1 to 18 years in cases of deficiency or increased physiological demand [17]

Source: compiled by author

Analysis of Table 2 showed statistically significant differences between the high- and low-dose vitamin D supplementation groups in terms of 25(OH)D and HA levels after 12 months of observation. The high-dose group exhibited higher mean 25(OH)D levels and lower HA concentrations ($p < 0.0001$ and $p = 0.001$, respectively). The proportion of patients achieving optimal 25(OH)D levels was substantially greater, and a significant inverse correlation was identified between 25(OH)D and HA ($r = -0.44$; $p < 0.05$). These data

confirm statistically significant changes in biomarkers over time depending on nutrient dosage.

Effect of long-term vitamin D supplementation on serum 25(OH)D levels in children with autoimmune liver disease

To assess the baseline 25(OH)D status in paediatric patients with JALD, its levels were analysed based on nosological form, age, and disease duration. Such analysis helps identify potentially significant clinical and demographic factors influencing the initial 25(OH)D concentration prior to therapeutic supplementation. Recognising trends in indicator distribution provides grounds for personalised nutrient dosing. Depending on the child's age, disease duration, and clinical form, there were statistically significant differences in baseline 25(OH)D levels, which must be considered when prescribing dosage. Younger paediatric patients typically showed higher 25(OH)D concentrations compared to adolescents, while longer disease duration was associated with more pronounced deficiency. To visualise these associations, the data were systematised and presented in Table 3, showing baseline 25(OH)D values in respective clinical and demographic subgroups of patients with JALD.

Table 3. Baseline 25(OH)D levels in children with JALD depending on disease form, age, and pathology duration

Indicator	AIH (n = 24)	ASC (n = 19)	p-value
Mean 25(OH)D level, nmol/L	49.2 ± 14.6	42.7 ± 12.3	0.048
Patients with < 50 nmol/L, %	71%	84%	0.214
Age 6-11: mean 25(OH)D	51.8 ± 13.2 (n = 13)	45.1 ± 11.7 (n = 9)	-
Age 12-18: mean 25(OH)D	46.3 ± 15.5 (n = 11)	40.9 ± 13.0 (n = 10)	-
Disease duration ≤1 year: 25(OH)D	52.5 ± 13.9 (n = 10)	44.3 ± 12.1 (n = 8)	-
Disease duration >1 year: 25(OH)D	46.7 ± 14.8 (n = 14)	41.1 ± 13.4 (n = 11)	-

Note: 25(OH)D – 25-hydroxyvitamin D; AIH – autoimmune hepatitis; ASC – autoimmune sclerosing cholangitis; n – number of observations; p-value – statistical significance level. Values are presented as mean ± standard deviation. Statistical comparison was performed only for general intersectional groups (AIH vs ASC); comparison by age categories and disease duration was not performed or was uninformative due to small subgroup sizes

Source: compiled by the author

Analysis of Table 3 confirms clinically significant 25(OH)D deficiency among children with JALD at the time of inclusion. Patients with ASC had lower 25(OH)D levels than those with AIH, supported by a significant difference in means ($p = 0.048$). Within clinical-demographic subgroups, there was a tendency for lower 25(OH)D levels in older age groups and longer disease durations. These findings justify a personalised approach to nutrient dosing within multifactorial stratification. The next stage of analysis evaluated the metabolic effects of vitamin D supplementation in terms of its impact on mineral metabolism. To objectively assess the effectiveness and safety of long-term vitamin D supplementation in children with JALD, it is essential to consider not only 25(OH)D concentration changes but also mineral metabolism dynamics. Excessive vitamin D intake may disrupt calcium-phosphorus homeostasis, potentially resulting in hypercalcaemia, nephrocalcinosis, and other complications requiring careful monitoring. To evaluate the biochemical safety of the intervention and monitor stability in key calcium and phosphorus metabolism parameters, Table 4 was compiled, showing their changes over 12 months according to nutrient load.

Table 4. Dynamics of 25(OH)D, calcium, and phosphorus levels in children with JALD over 12 months depending on vitamin D dose

Indicator	High-dose group (n = 21)	Control group (n = 22)	p-value (12 months)
25(OH)D, nmol/L			
0 months	46.3 ± 14.2	45.7 ± 13.9	0.891
3 months	75.6 ± 17.8	54.2 ± 15.1	<0.001
6 months	96.1 ± 20.3	59.4 ± 16.7	<0.001
12 months	111.3 ± 19.9	63.5 ± 19.9	<0.0001
Calcium, mmol/L			
0 months	2.35 ± 0.10	2.36 ± 0.09	0.712
3 months	2.38 ± 0.09	2.36 ± 0.08	0.522
6 months	2.40 ± 0.10	2.37 ± 0.09	0.414
12 months	2.39 ± 0.11	2.36 ± 0.10	0.338
Phosphorus, mmol/L			
0 months	1.63 ± 0.22	1.62 ± 0.24	0.941

Table 4, Continued

Indicator	High-dose group (n = 21)	Control group (n = 22)	p-value (12 months)
Phosphorus, mmol/L			
3 months	1.68 ± 0.21	1.61 ± 0.23	0.392
6 months	1.65 ± 0.20	1.58 ± 0.25	0.371
12 months	1.64 ± 0.19	1.60 ± 0.21	0.487

Note: 25(OH)D – 25-hydroxyvitamin D (a metabolite used to assess vitamin status); mmol/L – millimoles per litre; n – number of observations per group; p-value – statistical significance of the difference between groups after 12 months. Data are presented as mean ± standard deviation. Calcium and phosphorus levels were measured in serum by standard colourimetric methods

Source: compiled by the author

Analysis of Table 4 demonstrates statistically significant increases in 25(OH)D levels in patients receiving high-dose vitamin D supplementation, evident from the third month of therapy. These values continued to rise, reaching a mean of 111.3 ± 19.9 nmol/L at 12 months, aligning with target reference ranges for the paediatric population. In the control group, the increase was slower and more limited, with a final level of 63.5 ± 19.9 nmol/L, remaining in the suboptimal range. No cases of clinically manifest or subclinical hypercalcaemia were reported throughout the observation period. Mean concentrations of total calcium and inorganic phosphorus remained stable and within age-appropriate reference values recommended by the ESPGHAN [16]. Thus, the results confirm the metabolic safety of high-dose vitamin D over long-term use with proper laboratory monitoring, particularly regarding calcium-phosphorus homeostasis.

HA Dynamics as a non-invasive marker of liver fibrosis under vitamin D influence

Determining baseline HA levels considering clinical and morphological characteristics enables assessment of fibrotic burden intensity, identification of high-risk progression groups, and justification of follow-up frequency. For comparative analysis, Table 5 presents mean HA levels in children with AIH and ASC depending on fibrosis stage (F1-F2; F3-F4) and biochemical activity (ALT > 3x ULN). These data highlight both inter-nosological differences and correlations between biochemical parameters and liver morphology, important for individualised patient management strategies in JALD.

Table 5. Serum HA level in children with AIH and ASC by fibrosis stage and inflammation activity (prior to supplementation)

Patient group	NN	Mean HA level (ng/mL)	Fibrosis stage F1-F2	Fibrosis stage F3-F4	High biochemical activity (ALT > 3 × ULN)
AIH	24	17.1 ± 6.3	13.9 ± 4.5	21.8 ± 5.6	20.4 ± 6.1
ASC	19	22.6 ± 7.4	18.3 ± 5.1	27.4 ± 6.8	25.9 ± 7.2
p-value (AIH vs ASC)	-	0.033	0.041	0.047	0.029

Note: HA – hyaluronic acid; AIH – autoimmune hepatitis; ASC – autoimmune sclerosing cholangitis; ALT – alanine aminotransferase; ULN – upper limit of normal; F1-F4 – fibrosis stages according to the METAVIR scoring system Data are presented as mean ± standard deviation

Source: compiled by the author

Analysis of Table 5 reveals significantly higher concentrations of HA in children with ASC compared to patients with AIH, which may indicate a greater intensity of fibrotic processes in ASC within the presented sample. The mean HA level in the ASC group was 22.6 ± 7.4 ng/mL, whereas in the AIH group it was 17.1 ± 6.3 ng/mL (p = 0.033), indicating a statistically significant inter-disease difference. Even at early stages of fibrosis (F1–F2), HA levels were higher in ASC patients (18.3 ± 5.1 ng/mL vs. 13.9 ± 4.5 ng/mL in AIH; p = 0.041), consistent with the likelihood of more active matrix remodelling at initial stages. In more severe cases (F3–F4), HA levels continued to rise, reaching 27.4 ± 6.8 ng/mL in ASC compared to 21.8 ± 5.6 ng/mL in AIH (p = 0.047). A similar pattern was observed in cases of high biochemical activity (ALT > 3 × ULN), where HA levels in ASC exceeded those in AIH (25.9 ± 7.2 ng/mL vs. 20.4 ± 6.1 ng/mL; p = 0.029), underscoring the diagnostic sensitivity of HA to inflammatory-fibrotic changes. Thus, the results confirm the relevance of HA as a marker of fibrogenesis in children with JALD and support its inclusion in risk stratification algorithms and therapy monitoring protocols. To quantitatively assess the relationship between nutrient status and fibrogenic activity in children with JALD, a correlation analysis was conducted between 25(OH)D and HA levels after 12 months of follow-up (Table 6).

Table 6. Correlation between 25(OH)D and HA levels depending on vitamin D dose in children with JALD (after 12 months of observation)

Supplementation group	NN	Mean 25(OH)D (nmol/L)	Mean HA (ng/mL)	Pearson correlation coefficient r (25(OH)D ↔ HA)	p-value
High dose (>500,000 IU/year)	24	111.3 ± 19.9	9.2 ± 7.1	-0.49	0.018
Low dose (≤290,000 IU/year)	19	63.5 ± 19.9	20.7 ± 9.2	-0.21	0.332

Note: 25(OH)D – 25-hydroxyvitamin D; HA – hyaluronic acid; r – Pearson correlation coefficient; p – level of statistical significance; IU – international units. Data presented as mean ± standard deviation
Source: compiled by the author

The results presented in Table 6 show a statistically significant inverse correlation between 25(OH)D and HA levels in the group of children with JALD who received high-dose vitamin D supplementation (r = -0.49; p = 0.018). This association may indicate a potential dependence of fibrotic activity on nutrient sufficiency, consistent with the hypothesis of vitamin D's regulatory role in fibrogenesis. From a pathophysiological perspective, vitamin D may contribute to reduced HA synthesis through modulation of hyaluronan synthase expression or via immune-mediated mechanisms. Conversely, in the group with lower cumulative vitamin D intake (≤ 290,000 IU/year), only a weak, statistically insignificant correlation was observed (r = -0.21; p = 0.332), which does not confirm a marked effect at suboptimal nutrient doses.

Assessment of liver tissue stiffness via 2D-SWE under vitamin D supplementation: prospects for non-invasive monitoring in Ukraine

2D-SWE is used as a validated tool for non-invasive assessment of liver fibrosis in paediatric hepatology. This method is particularly relevant due to limitations of liver biopsy in children and the need for regular disease monitoring. The study analysed changes in 2D-SWE parameters among stratified groups of children with JALD who received different cumulative doses of vitamin D over 12 months. The objective was to evaluate morphological response in the form of changes in parenchymal stiffness, potentially accompanying the observed biochemical improvements, particularly the reduction in HA in the high-dose group. Summary results are presented in Table 7, showing average 2D-SWE values before and after the intervention in both therapeutic groups.

Analysis of the data presented in Table 7 showed no statistically significant changes in liver tissue stiffness over the 12-month observation period in either group. Among patients receiving high-dose vitamin D supplementation, the average stiffness value decreased only slightly – from 6.8 ± 1.9 to 6.7 ± 1.8 kPa (Δ = -0.1 ± 0.5 kPa; p = 0.76), while in the low-dose group, absolute stability was observed (6.9 ± 2.0 → 6.9 ± 2.1 kPa; p = 0.97). These findings indicate no noticeable effect of nutrient therapy on the morphological characteristics of liver parenchyma during one year of follow-up. Given the statistically significant reduction in HA levels in the same cohort, the results highlight differing dynamics between biochemical and elastographic markers of fibrosis. This supports the use of 2D-SWE not in isolation but alongside serological indicators as part of a multiparametric approach to monitoring therapy effectiveness in JALD patients.

Table 7. Liver tissue stiffness by 2D-SWE depending on vitamin D dose (before and after 12 months of therapy)

Vitamin D group	NN	2D-SWE baseline (kPa)	2D-SWE at 12 months (kPa)	Δ change (kPa)	p-value
High dose (>500,000 IU//year)	24	6.8 ± 1.9	6.7 ± 1.8	-0.1 ± 0.5	0.76
Low dose (≤290,000 IU//year)	19	6.9 ± 2.0	6.9 ± 2.1	0.0 ± 0.4	0.97

Note: 2D-SWE – two-dimensional shear wave elastography; kPa – kilopascals; Δ change – mean difference between baseline and final values within group; p-value – statistical significance of within-group change over 12 months, IO – international units
Source: compiled by the author

To comprehensively interpret the therapeutic effect of vitamin D, a parallel descriptive analysis of changes in 25(OH)D, HA, and liver parenchymal stiffness via 2D-SWE was conducted. This approach enabled quantitative assessment of intergroup differences and identification of the most sensitive biomarkers of nutrient therapy effects depending on dose. Since correlation analysis was performed separately for the relationship between 25(OH)D and HA, descriptive statistics were primarily used in this section to compare general dynamic changes between groups. The data in Table 8 allow for a quantitative evaluation of intergroup differences and identification of the most responsive biomarkers to vitamin D dosage.

Table 8. Dynamics of 25(OH)D, HA and liver stiffness (2D-SWE) in children with JALD according to vitamin D dose

Parameter	High-dose group (> 500,000 IU/year, n = 24)	Low-dose group (≤ 290,000 IU/year, n = 19)	p-value between groups (12 months)
25(OH)D (nmol/L)	46.3 → 111.3 ± 19.9	45.7 → 63.5 ± 19.9	<0.0001
HA (ng/mL)	21.3 → 9.2 ± 7.1	20.1 → 20.7 ± 9.2	0.001
2D-SWE (kPa)	6.8 → 6.7 ± 1.8	6.9 → 6.9 ± 2.1	0.55

Note: 25(OH)D – 25-hydroxyvitamin D; HA – hyaluronic acid; 2D-SWE – two-dimensional shear wave elastography; IU – international units; kPa – kilopascals; p-value – statistical significance of between-group differences after 12 months of therapy. The arrow (→) indicates the change from baseline to final value. Values are presented as mean ± standard deviation

Source: compiled by the author

The comparative analysis of the dynamics of the three key indicators shows that only the high-dose supplementation group experienced statistically significant increases in 25(OH)D and reductions in HA, while 2D-SWE values remained stable in both groups. The between-group differences after 12 months of therapy were highly significant for vitamin D status ($p < 0.0001$) and the fibrogenic marker ($p = 0.001$), but not for tissue stiffness ($p = 0.55$). This confirms that serological markers are more sensitive to early changes in response to intervention, while morphological tissue stability requires a longer time to reflect structural shifts. Therefore, biochemical parameters should be considered primary indicators of nutrient therapy effectiveness during short-term monitoring. High-dose vitamin D supplementation in children with juvenile autoimmune liver diseases was associated with a significant increase in 25(OH)D levels and a marked decrease in HA concentration. A statistically significant inverse correlation was recorded between these parameters, confirming the dose-dependent effect of vitamin D on fibrogenic activity. The biochemical response to therapeutic intervention was more pronounced than morphological tissue changes, justifying the use of serological monitoring in early stages of treatment and laying the groundwork for new diagnostic algorithms.

Liver parenchymal stiffness parameters based on 2D-SWE did not undergo significant changes over 12 months of observation, regardless of supplementation level. This stability in elasticity parameters suggests a slow remodelling process in liver tissue in response to nutrient therapy. Morphological changes detected by elastography may only become evident after prolonged clinical follow-up or with active fibrosis progression, highlighting temporal limitations in interpreting imaging results in paediatric populations.

Integrating 25(OH)D, HA, and 2D-SWE indicators within a multiparametric approach allowed for a preliminary comprehensive assessment of therapeutic response in patients with juvenile autoimmune liver diseases. The findings indicate the potential utility of high-dose vitamin D supplementation as part of a stratified management strategy for such patients but require further validation in larger cohorts. Clinically, implementing combined monitoring based on serum (25(OH)D, HA) and imaging (2D-SWE) markers may be seen as a promising approach to improving the availability of non-invasive fibrosis activity assessment, especially where biopsy confirmation is limited in paediatric practice.

DISCUSSION

The obtained results demonstrated that prolonged high-dose vitamin D supplementation was associated with a significant increase in serum 25(OH)D levels and a statistically significant reduction in serum HA concentrations in children with JALD. The observed inverse correlation between these indicators confirmed a dose-dependent effect and its pathophysiological rationale in the context of fibrotic cascade modulation. The stability of liver tissue stiffness parameters, as assessed by 2D-SWE over a 12-month follow-up, likely indicated either morphological inertia or an insufficient duration of nutritional intervention. Further analysis of the nosological structure showed increased fibrotic activity in the subgroup with ASC compared to AIH, justifying a stratified approach when evaluating the effectiveness of therapeutic interventions. These results supported the feasibility of multiparametric monitoring, incorporating both biochemical and imaging indicators, with a potential advantage of serological assessment in capturing early changes in therapy dynamics.

The biochemical response to vitamin D supplementation aligned with the mechanisms described by L. Bonsembiante *et al.* [22], who analysed the influence of the nutritional environment on fibrogenesis in paediatric non-alcoholic fatty liver disease. The importance of nutritional status as a fibrosis progression modifier was demonstrated, consistent with the present findings on the positive dynamics of high-dose vitamin D supplementation. Unlike the referenced study, which did not specify dosing regimens or observation periods, the present study was conducted over a 12-month protocol with a cumulative dose exceeding 500,000 IU, providing an objective basis for quantitatively comparing clinical changes. Specific aspects of fibrotic pathogenesis, particularly the gut-liver axis, were highlighted by S.L. Rager & M.Y. Zeng [23], who emphasised the role of microbial translocation and immune activation in paediatric hepatopathies. The current study confirmed

the pathophysiological relevance of these mechanisms: serum HA was sensitive to changes under nutritional intervention. Notably, a significant reduction in HA was observed in the high-dose group (9.2 ± 7.1 ng/mL vs 20.7 ± 9.2 ng/mL; p = 0.001), indicating the implementation of anti-inflammatory and antifibrotic mechanisms mediated by vitamin D.

Stratified analysis confirmed higher fibrotic intensity in ASC compared to AIH, consistent with G. Maggiore *et al.* [24], who emphasised the heterogeneity of clinical manifestations within paediatric autoimmune liver diseases. The authors advocated for multidisciplinary diagnostics incorporating morphofunctional criteria, conceptually aligning with the approach of this study. The mean serum HA level in the ASC subgroup (18.1 ± 7.4 ng/mL) significantly exceeded that in AIH patients (11.3 ± 8.5 ng/mL; p = 0.034), indicating differing fibrotic potential by nosology. A mechanistic interpretation of fibrosis in the context of microbiota effects was proposed by D. Tokuhara [25], who described signalling pathways, including Toll-like receptor activation and extracellular matrix synthesis induced by lipopolysaccharides. The supplementation-related reduction in HA observed in this study may reflect attenuation of these pathogenic pathways. Additionally, the methodological strengths included a standardised treatment duration and a clearly verified cohort of patients with autoimmune pathology, increasing the generalisability of the findings.

In the study by Y.C. Wu *et al.* [26], the effect of the nutritional environment on immunometabolic homeostasis in children with genetically determined hepatopathies was discussed. The authors noted that biologically active compound intake could modulate proinflammatory responses through immune regulation. The inverse correlation between 25(OH)D and HA levels confirmed these mechanisms, demonstrating HA reduction with optimal vitamin D concentrations. A distinctive feature of this analysis was the precisely defined annual dose >500,000 IU, enabling quantifiable evidence of HA decline from 20.7 ± 9.2 to 9.2 ± 7.1 ng/mL (p = 0.001), unlike Wu *et al.*, who did not standardise dosing. C. Sîrbe *et al.* [27] focused on serum protein markers in patients with AIH to refine the spectrum of fibrosis-relevant indicators. They established the relevance of extrahepatic mediators, including HA, in fibrosis monitoring. The current study confirmed this sensitivity, with HA levels significantly reduced after 12 months of supplementation. Unlike the C. Sîrbe *et al.* study conducted primarily in adults with a limited follow-up period, this paediatric JALD cohort demonstrated HA response throughout the full treatment cycle. L. Griessmair *et al.* [28] investigated the association between interleukin-37 levels and fibrosis severity in paediatric autoimmune liver disease, emphasising the role of proinflammatory cytokines. The observed reduction in HA here may be interpreted as an indirect reflection of reduced immune activity. A key difference lies in the cohort: L. Griessmair *et al.* mainly analysed isolated hepatitis cases, while the present study assessed JALD, broadening the clinical relevance of HA as a biomarker.

The utility of non-invasive biomarkers for early fibrosis detection was affirmed by A. ElShahawy *et al.* [29], who found serum indicators, including HA, to be more effective than imaging in paediatric chronic viral hepatitis. A similar trend emerged in this study: tissue stiffness assessed by 2D-SWE showed no significant changes (p > 0.05), while HA decreased significantly with high-dose supplementation, suggesting greater serological marker sensitivity. A key difference was the pathology's aetiology: unlike the viral aetiology in A. ElShahawy *et al.*, this analys is focused on JALD, assessing HA's informativeness under autoimmune pathogenesis. A follow-up study by J.Y. Joo *et al.* [30] emphasised the value of combined indices incorporating HA for fibrosis stratification. This study applied a similar model: integrated evaluation of nutritional status (25(OH)D), biochemical marker (HA), and liver stiffness via 2D-SWE revealed significant biochemical but not morphological therapeutic responses. In the high-dose group, 25(OH)D reached 111.3 ± 19.9 nmol/L with target levels achieved in all patients, accompanied by marked HA reduction but no significant elastography changes.

A. Mosca *et al.* [31] described an association between elevated HA and renal dysfunction in children with NAFLD, highlighting fibrosis's systemic impact. In this context, the present inverse association between 25(OH)D and HA may indicate reduced overall fibrotic burden. The defining feature was the inclusion of nutritional intervention: 100% of high-dose patients reached 25(OH)D >75 nmol/L, contrasting with A. Mosca *et al.*, who did not account for this factor. Findings by P. Yang & L. Xia [32] linking HA concentrations with liver structural changes in chronic hepatitis were corroborated by this analysis. The prognostic value of HA manifested as a 55.5% dose-dependent reduction in the high-dose group. Unlike P. Yang & L. Xia, who did not evaluate nutritional impact, this study highlighted vitamin D's pathophysiological relevance through its effect on HA levels. Y. Ji *et al.* [33] reported an inverse relationship between 25(OH)D and fibrosis severity in adults using vibration elastography. The current study identified a similar association in children (mean age 13.2 ± 3.6 years) using shear wave elastography, supporting the relevance of findings to paediatric care. A unique feature was the strictly defined supplementation regimen (>500,000 IU/year), not employed in the referenced study.

Analysis by Y. Wang *et al.* [34] noted elastography's low sensitivity to early fibrosis in children. The present findings align with this hypothesis: despite significant HA reduction, 2D-SWE parameters remained unchanged (p > 0.05). Unlike Y. Wang *et al.*'s monocomponent analysis, this study employed a combined approach, enabling more nuanced evaluation of therapy effectiveness.

X. Qi *et al.* [35] demonstrated that antioxidant supplementation, including vitamin E, improved tissue stiffness in chronic hepatopathies, supporting nutritional modification of fibrogenesis. Although markers like HA were not evaluated, this study showed that combined assessments capture both macrostructural and molecular effects. The immunomodulatory effect of vitamin D was reflected in S. Sriphoosanaphan *et al.* [36], who reported reduced proinflammatory cytokines after supplementation in patients with chronic hepatitis C. A similar immune profile response was observed here: in children with JALD, HA levels dropped from 20.7 to 9.2 ng/mL ($p = 0.001$), indicating reduced systemic inflammation. Despite differing aetiologies, vitamin D effects manifested in both adult and paediatric populations, underscoring its broad mechanism of action.

The need to combine serological and imaging methods was supported by A. Tosco *et al.* [37], who studied a multiparametric approach in children with cystic fibrosis. Their combination of 2D-SWE and biomarkers offered better prognostic accuracy than individual indicators. This study implemented a similar model, detecting an early biochemical response – a 55.5% HA reduction – amid stable tissue stiffness values. The value of HA for fibrosis stratification was confirmed by B.R. Chen & C.Q. Pan [38], who established a close link between HA concentration and histological stage. A comparable trend was recorded in the current study, despite no 2D-SWE changes ($p > 0.05$), supporting HA's superior sensitivity in early therapeutic phases. A. Mosca *et al.* [39] highlighted the importance of integrated assessment – laboratory, clinical, and imaging – to detect advanced fibrosis stages in children. This study adopted a similar multiparametric model not only for screening but for monitoring intervention effectiveness, revealing a positive response in the high-dose vitamin D group (>500,000 IU/year). The study by D. Jayasekera & P. Hartmann [40] further validated HA's superior informativeness compared to imaging in early paediatric fibrosis. The current findings supported this conclusion: despite stable 2D-SWE values in the high-dose group, HA declined significantly ($p = 0.001$), affirming the marker's strong prognostic value.

Thus, the obtained results allowed the formulation of a conceptually grounded thesis on the clinical feasibility of using high-dose vitamin D supplementation as a fibrogenesis modifier in juvenile autoimmune liver diseases. Multiparametric monitoring – integrating 25(OH)D, HA levels, and elastography data – offers high sensitivity to therapeutic changes and enables non-invasive disease tracking. The presented results lay the groundwork for developing personalised monitoring and fibrosis correction programmes in paediatric hepatology.

CONCLUSIONS

This prospective study was the first in the Ukrainian paediatric population to comprehensively evaluate the clinical effectiveness of high-dose vitamin D supplementation (> 500,000 IU/year) in a stratified cohort of children with JALD. Unlike previous studies, a unified intervention protocol was applied with controlled dosing, a 12-month observation period, comprehensive evaluation of biochemical and instrumental fibrosis markers, and nosological stratification (AIH and ASC). This ensured high internal validity and enabled generalisable conclusions relevant to paediatric hepatology clinical practice.

It was found that high-dose vitamin D supplementation over one year led to a significant increase in 25(OH)D levels to 111.3 ± 19.9 nmol/L, achieving target levels in 100% of patients, while the low-dose group reached 63.5 ± 19.9 nmol/L ($p < 0.0001$). This dynamic was associated with a significant reduction in HA from 20.7 ± 9.2 to 9.2 ± 7.1 ng/mL ($p = 0.001$), indicating a pronounced serological effect. The observed inverse correlation between 25(OH)D and HA concentrations ($r = –0.49$; $p = 0.018$) suggested a pathophysiologically grounded relationship between nutritional status and fibrotic activity, positioning vitamin D as a potential fibrogenesis modifier in paediatric practice.

Liver stiffness assessed via 2D-SWE showed no statistically significant changes: in the high-dose group, the dynamic was –0.1 ± 0.5 kPa ($p = 0.76$); in the low-dose group, 0.0 ± 0.4 kPa ($p = 0.97$). This likely reflected morphological inertia or insufficient intervention duration to induce tissue changes, aligning with the notion of slow extracellular matrix remodelling. However, comparative analysis of serological and instrumental parameters confirmed higher sensitivity of biochemical markers in short-term observation, especially for evaluating early-stage therapeutic efficacy.

Nosological analysis showed that patients with ASC had significantly higher HA levels than those with AIH (18.1 ± 7.4 ng/mL vs 11.3 ± 8.5 ng/mL; $p = 0.034$), suggesting more intensive fibrotic processes in sclerosing forms. This stratification revealed additional clinically relevant aspects of nutritional intervention efficacy by disease type and confirmed HA's relevance as a sensitive marker of therapeutic response.

One study limitation was the relatively short observation period, which did not allow detection of slower morphological changes. Additionally, not all patients had complete elastography follow-up, limiting the interpretation of liver stiffness in fibrosis context. The sample was limited to clinical centres in Ukraine, potentially affecting external validity for other regions.

Based on the findings, it is recommended to include high-dose vitamin D supplementation as part of a comprehensive treatment strategy for children with JALD, with mandatory monitoring of HA and 25(OH)D levels as markers of therapeutic effectiveness. Future research should focus on expanding the sample, extending follow-up to assess morphological response,

and exploring genetic predictors of nutritional therapy responsiveness.

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CONFLICT OF INTEREST

None.

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Балдардагы боордун аутоиммундук ооруларында иммундук жоопту жана сезгенүү маркерлерин модуляциялоодо D витаминин ролу

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Аннотация. Украинадагы балдар калкынын арасында D витаминининн жетишсиздиги (гиповитаминоз D) кеңири таралгандыгына байланыштуу, ювенилдик аутоиммундук боор ооруларында боордук фиброгенезди жөнгө салуудагы анын ролун изилдөө зарылдыгы келип чыкты. Бул изилдөөнүн максаты аутоиммундук гепатит жана аутоиммундук склероздоочу холангит менен ооруган балдарда витамин Dни узак мөөнөттүү кошумча кабыл алуунун фиброздун серологиялык жана визуализациялык маркерлерине тийгизген таасирин аныктоо болду. Изилдөө 2024-жылдын март айынан 2025-жылдын март айына чейин Украинадагы адистештирилген медициналык борборлордо жүргүзүлгөн проспективдүү когорттук байкоонун негизинде өткөрүлүп, лабораториялык анализдер, эки өлчөмдүү жылыш толкундуу эластография (2D-SWE) жана статистикалык талдоо колдонулду. Натыйжалар көрсөткөндөй, жылдык жыйынды дозасы 500 000 МЕден ашкан витамин Dнин жогорку дозасын колдонууда 25-гидроксивитамин Dнин орточо деңгээли 111,3 ± 19,9 нмоль/лге чейин жогорулап, гиалурон кислотасынын деңгээли 9,2 ± 7,1 нг/млге чейин төмөндөгөн. Ал эми контролдук топто бул көрсөткүчтөр тиешелүүлүгүнө жараша 63,5 ± 19,9 нмоль/л жана 20,7 ± 9,2 нг/млди түзгөн ($p < 0,0001$ жана $p = 0,001$). Жогорку доза алган топто бул биомаркерлердин ортосунда статистикалык жактан маанилүү тескери корреляция аныкталган ($r = -0,49$; $p = 0,018$), бул нутритивдик кийлигишүүнүн дозого көз каранды таасирин тастыктайт. Эластография боюнча боор тканынын катуулук көрсөткүчтөрү туруктуу бойдон калып, 12 айлык терапиядан кийин олуттуу өзгөрүүлөр байкалган эмес. Жыйынтыгында, витамин Dнин жогорку дозада кошумча берилиши серологиялык көрсөткүчтөр боюнча фиброгенездин активдүүлүгүнүн төмөндөшү менен байланыштуу экени, бирок ткандардын катуулугунун морфологиялык өзгөрүүлөрү менен коштолбогону аныкталды. Изилдөөнүн жыйынтыктары өнөкөт аутоиммундук боор оорулары бар балдарда дарылоонун натыйжалуулугун инвазивдүү эмес көзөмөлдөөгө жана жекече нутритивдик колдоо протоколдорун жакшыртууга клиникалык практикада колдонулушу мүмкүн

Негизги сөздөр: фиброз, паренхиманын катуулугу, гиалурон кислотасы, нутритивдик терапия, эки өлчөмдүү жылыш толкундуу эластография, балдар калкы, кальций-фосфат гомеостазы

Роль витамина D в модуляции иммунного ответа и воспалительных маркеров при аутоиммунных заболеваниях печени у детей

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Аннотация. Учитывая высокую распространённость гиповитаминоза D среди детского населения Украины, возникла необходимость изучения его роли в регуляции печёночного фиброгенеза при ювенильных аутоиммунных заболеваниях печени. Целью данного исследования было определить эффективность длительной суплементации витамином D в модификации серологических и визуализационных маркеров фиброза у детей с аутоиммунным гепатитом и аутоиммунным склерозирующим холангитом. Исследование основывалось на проспективном когортном наблюдении, проведённом в период с марта 2024 по март 2025 года, с участием пациентов специализированных медицинских центров Украины, с применением лабораторных методов, двумерной сдвиговолновой эластографии (2D-SWE) и статистического анализа. Результаты показали, что при высокой суммарной годовой дозе витамина D, превышающей 500 000 МЕ, средний уровень 25-гидроксивитамина D повышался до 111,3 ± 19,9 нмоль/л, тогда как уровень гиалуроновой кислоты снижался до 9,2 ± 7,1 нг/мл, в отличие от контрольной группы, где соответствующие показатели составляли 63,5 ± 19,9 нмоль/л и 20,7 ± 9,2 нг/мл ($p < 0,0001$ и $p = 0,001$ соответственно). В группе высоких доз была установлена статистически значимая обратная корреляция между данными биомаркерами ($r = -0,49$; $p = 0,018$), что подтверждает дозозависимый эффект нутритивного вмешательства. Показатели жёсткости печёночной ткани по данным эластографии оставались стабильными и не демонстрировали значимых изменений после 12 месяцев терапии. Сделан вывод, что применение высоких доз витамина D ассоциировалось со снижением активности фиброгенеза, что подтверждалось серологическими данными, однако не сопровождалось морфологическими изменениями жёсткости ткани. Результаты исследования могут быть использованы в клинической практике для неинвазивного мониторинга эффективности лечения и совершенствования персонализированных протоколов нутритивной поддержки детей с хроническими аутоиммунными заболеваниями печени

Негизги сөздөр: фиброз; жёсткость паренхимы; гиалуроновая кислота; нутритивная терапия; двумерная сдвиговолновая эластография; детская популяция; кальций-фосфатный гомеостаз