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Quantitative assessment of regional variability in mandibular bone density based on cone-beam computed tomography data

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Abstract. Despite the widespread use of cone-beam computed tomography, regional variations in cortical and trabecular bone density remain insufficiently characterised. The aim of this study was to assess mandibular bone density across different anatomical regions and to identify clinical situations in which pre-implant bone augmentation may be required. The methodology involved the analysis of cone-beam computed tomography data with quantitative assessment of bone density in the anterior, premolar, and molar regions of the mandible. The highest bone density values were observed in the anterior mandible, averaging 944.9 ± 207 HU in the control group and 910.2 ± 198 HU in edentulous patients ($p > 0.05$). In the premolar region, bone density decreased to 643.8 ± 162 HU in the absence of teeth, compared with 826.4 ± 175 HU in dentate individuals ($p < 0.05$). The most pronounced reduction was identified in the molar region, where values reached 512.5 ± 148 HU in edentulous patients versus 789.7 ± 160 HU in the control group ($p < 0.01$), confirming the adverse effect of prolonged posterior tooth loss on bone quality. Furthermore, reduced bone density in the distal mandible was associated with compromised cortical bone characteristics, potentially affecting the primary stability of dental implants. These regional differences should be taken into account when selecting implant dimensions and planning the extent of bone augmentation, particularly in patients with long-standing edentulism. The findings are clinically relevant for optimising implant treatment strategies, determining the need for bone augmentation, and improving the predictability of surgical outcomes

Keywords: mandible; bone tissue density; CBCT; regional variability; alveolar ridge; bone augmentation

INTRODUCTION

Dental implantation is widely regarded as one of the most effective approaches for the replacement of missing teeth and the functional rehabilitation of patients. The success of implant therapy is largely dependent on the condition of the jawbone, as both its volume and density directly influence the achievement of primary implant stability and the predictability of osseointegration. Particular attention should be paid to the mandible, where the density of cortical and trabecular bone may vary considerably depending on the anatomical region, patient age, and the duration of edentulism. In this context, accurate assessment of bone quality represents a critical stage in preoperative planning and in the selection of an appropriate surgical strategy. C.S. Park *et al.* [1] conducted a validation study of a quantitative method for assessing bone mineral density based on cone-beam computed tomography (CBCT) data using deep learning algorithms. Their findings

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demonstrated that this approach provided more accurate and reproducible density measurements compared with conventional CBCT analysis. These results highlight the potential of quantitative CBCT as a reliable tool for objective evaluation of bone quality in implant treatment planning.

According to G. Avila-Ortiz *et al.* [2], post-extraction resorption of the alveolar ridge is a physiological remodelling process characterised by a reduction in both bone height and width, most pronounced within the first months to years following tooth removal. This process may significantly complicate implant therapy and increases the need for techniques aimed at preserving and augmenting bone volume. Evidence from biomechanical as well as clinical and radiological studies indicates that insufficient bone volume represents one of the principal limiting factors for implant placement and is associated with an increased risk of postoperative complications. Furthermore, O. Yildirim *et al.* [3] emphasised the importance of CBCT-based assessment of bone morphology and quality, including Hounsfield unit (HU) values. It is the combined evaluation of parameters – such as alveolar ridge configuration, cortical bone thickness, and radiographic bone density – that plays a decisive role in the selection of the surgical approach and the accuracy of the intervention, including guided implant surgery. The authors demonstrated that cortical plate characteristics, as well as bone density and morphology in the posterior mandible, are associated with the risk of technical deviations and variability in clinical outcomes when digital surgical guides are employed.

In studies by J. Lorenz *et al.* [4] and T. Starch-Jensen *et al.* [5], particular emphasis was placed on measuring cortical bone thickness in prospective implant sites. The findings indicated that the cortical component plays a pivotal role in achieving primary implant stability and in establishing a favourable treatment prognosis. At the same time, the authors highlighted considerable interindividual variability in these parameters, underscoring the need for standardised CBCT-based criteria for the assessment of bone quality. According to P. Suthakar *et al.* [6], a distinct area of contemporary research focuses on the use of CBCT for the quantitative evaluation of mandibular resorption based on stable anatomical landmarks, including the mental region. The application of standardised reference points enables consistent morphometric comparisons in both dentate patients and those with partial or complete edentulism. However, the authors noted that most studies are limited to describing the extent of resorption without establishing clinically relevant threshold values necessary for evidence-based decision-making when selecting reconstruction techniques, such as guided bone regeneration (GBR), alveolar ridge splitting, the use of bone blocks, or vertical augmentation procedures.

The Proceedings of the 21st All-Russian Dental Forum report [7] that, between 2020 and 2024, considerable attention was devoted to analysing the outcomes of reconstructive techniques in the mandible, including GBR and horizontal augmentation. These advances have contributed to expanding the indications for dental implantation in patients presenting with pronounced alveolar ridge atrophy. At the same time, it was emphasised that, despite favourable clinical outcomes, a significant limitation remains the methodological heterogeneity of available studies, including differences in study design, osteoplastic materials and barrier membranes employed, follow-up duration, and criteria used to define treatment success. Such variability continues to hinder the development of a universally accepted, CBCT-based decision-making algorithm for selecting the optimal reconstructive approach. An important contribution to the regional body of evidence has been made by researchers from Kyrgyzstan. In particular, A.M. Eshiev & R.E. Abirova [8] demonstrated the clinical relevance of CBCT-based bone density assessment (in HU), highlighting regional variability in these parameters. The authors also presented a clinical case illustrating the management of a patient with severe atrophy, including mandibular involvement, using a digital treatment planning approach.

Furthermore, in 2025, A.M. Eshiev & B.A. Israilov [9] published an observational CBCT-based study demonstrating the presence of destructive periapical bone changes in all examined patients. The study focused on the assessment of bone biotypes and the practical interpretation of CBCT-derived parameters in treatment planning for older patient cohorts.In addition, A.K. Abdymechinova *et al.* [10], in a review paper, highlighted the role of advanced technologies, including CBCT, as essential tools for diagnosis and treatment planning in maxillofacial dentistry, further supporting the need for the implementation of standardised approaches in clinical practice in Kyrgyzstan.

The aim of the present study was to determine the characteristics of bone density and volumetric parameters of the mandible across different anatomical regions, and to establish threshold values for horizontal and vertical bone deficiency at which bone augmentation becomes necessary to ensure predictable and long-term outcomes of dental implantation.

MATERIALS AND METHODS

The study was conducted at the Department of Oral and Maxillofacial Surgery, Osh State University, between 2024 and 2025. A prospective clinical and radiological assessment was performed in patients presenting with partial edentulism of the posterior mandible and scheduled for dental implant therapy. A total of 50 patients aged 45-70 years were enrolled and allocated into two groups. Group 1 (study group) comprised 25 patients with bilateral absence of posterior mandibular teeth (FDI positions 4.5-7.5). Group 2 (control group) included

25 patients with intact dentition. Only individuals without systemic bone disorders or significant inflammatory pathology in the intended implant sites were included. Exclusion criteria comprised osteoporosis, oncological diseases, active inflammatory-destructive processes, the use of medications affecting bone metabolism (e.g., bisphosphonates, glucocorticosteroids), and pregnancy. The duration of edentulism in the study group ranged from 6 months to 10 years and was considered a variable influencing morphometric parameters and relative bone density. CBCT was performed using the Planmeca ProMax 3D (Finland) following a standardised protocol (voxel size 0.2 mm; field of view 8×8 cm; 90 kV; 10 mA). Tomographic data were analysed using Planmeca Romexis 6.0. Measurements were obtained bilaterally in the premolar (4.5-5.5) and molar (6.5-7.5) regions of the mandible.

The region of interest (ROI) was defined at levels 1, 3, and 5 mm apical to the crest of the alveolar ridge. In each area, no fewer than three measurements of cortical plate thickness and relative bone density were obtained, followed by calculation of mean values. Bone density assessment was performed using CBCT in the planned implant sites, specifically within the premolar and molar regions bilaterally in the mandible. Density values were expressed in HU. Bone quality was classified according to the Lekholm & Zarb classification [11], based on the relationship between cortical and cancellous bone components. The evaluation incorporated CBCT-derived data, taking into account both the morphological characteristics of the alveolar ridge and quantitative density parameters. Statistical analysis was carried out using IBM SPSS Statistics 26. The results are presented as mean ± standard deviation (M ± SD). Differences between groups were assessed using Student's t-test and one-way analysis of variance (ANOVA), with the level of statistical significance set at $p < 0.05$. The study was conducted in accordance with the principles of the Declaration of Helsinki [12] and was approved by the local ethics committee of Osh State University (Protocol No. 4, dated 15 December 2024). Written informed consent was obtained from all participants prior to inclusion in the study.

RESULTS AND DISCUSSION

According to the CBCT findings, the mean bone density in the anterior mandible was 944.9 ± 207 HU, which markedly exceeds the corresponding values observed in the anterior maxilla (715.8 ± 190 HU) and, in particular, in the posterior maxilla (455.1 ± 122 HU). These values correspond to type D1 according to the Lekholm & Zarb classification [11], characterised by a predominance of dense cortical bone. Such structural features provide high mechanical strength and are favourable for successful implant osseointegration. Table 1 presents comparative data on mandibular bone mineral density across different anatomical regions, stratified by dentition status.

Table 1. Comparative values of mandibular bone mineral density (BMD) according to anatomical region and dentition status

Zone of research	Control group (n = 25)	Main group (edentulous, n = 25)	p
Anterior zone (3.3-4.3)	944.9 ± 207	910.2 ± 198	>0.05
Premolar zone (4.5-5.5)	826.4 ± 175	643.8 ± 162	<0.05
Molar zone (6.5-7.5)	789.7 ± 160	512.5 ± 148	<0.01

Source: developed by the authors

The data presented in Table 1 indicate that the highest BMD values are observed in the anterior mandible, where density exceeds 900 HU, corresponding to type D1 according to the Lekholm & Zarb classification [11]. Differences between the study and control groups in the anterior region were not statistically significant ($p > 0.05$). In the premolar and molar regions, a significant reduction in BMD was observed in edentulous patients, reflecting a shift in bone structure towards type D3-D4. Figure 1 illustrates the distribution of BMD across the anterior, premolar, and molar regions of the mandible. Patients with intact dentition exhibited significantly higher bone density compared with individuals with bilateral posterior tooth loss. The most pronounced decrease was observed in the molar region, where density values corresponded to type D3-D4. Mandibular bone is characterised by a high degree of homogeneity and low porosity, particularly in the anterior region. In this anatomical segment, the cortical layer is well-developed and constitutes a substantial proportion of the total bone thickness, providing increased rigidity and resistance to mechanical stress. The cancellous bone exhibits a dense, well-organised trabecular structure with relatively small inter-trabecular spaces, further enhancing the biomechanical stability of the bone matrix.The high degree of mineralisation and structural uniformity in the anterior mandible create favourable conditions for achieving reliable primary stability of dental implants. In the studied regions, the mean alveolar bone height was 8.2 ± 1.4 mm. This reduces the likelihood of early implant micromovements, minimises the risk of fibrous capsule formation, and supports complete osseointegration. Moreover, these morphological characteristics allow, in certain clinical scenarios, the use of immediate or early functional loading protocols, which can shorten the duration of prosthetic rehabilitation, improve treatment predictability, and enhance patient quality of life (Fig. 2).

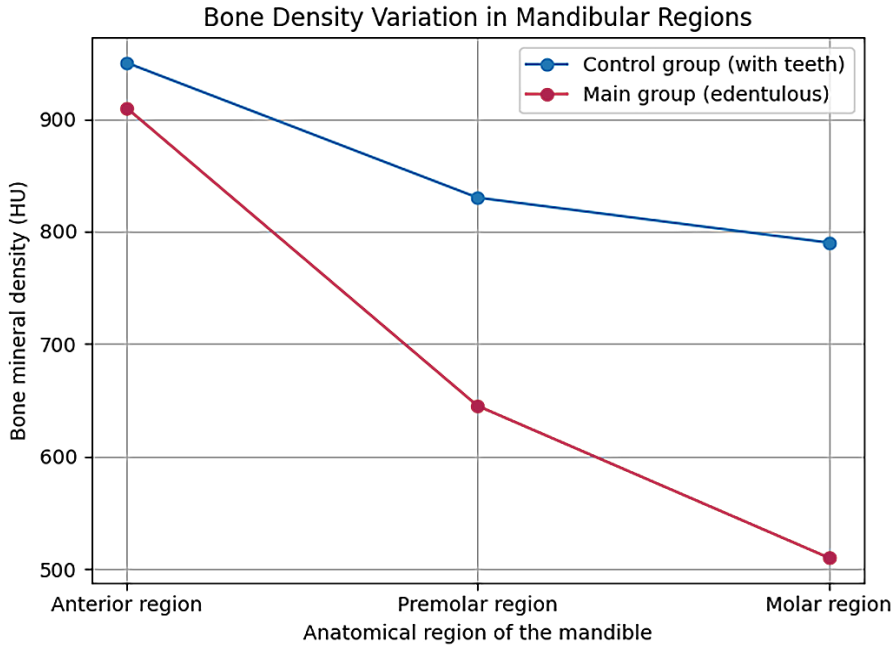

Figure 1. Mean BMD (HU) across different anatomical regions of the mandible in dentate and edentulous patients
Source: developed by the authors

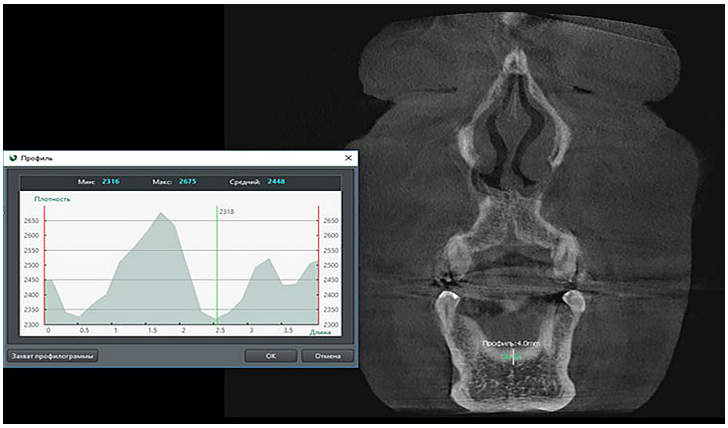

Figure 2. Morphological features bone tissue of anterior zone of mandible
Source: developed by the authors

According to CBCT data, a male patient demonstrated a mean bone density of 2,675 HU in the anterior mandible. These findings indicate an extremely high degree of bone mineralisation, with a pronounced predominance of dense cortical bone. Such values correspond to dense compact bone (type D1 according to the Lekholm & Zarb classification [11]), characterised by minimal cancellous bone and high mechanical strength. This bone type provides substantial primary implant stability due to its high density and resistance to deformation. However, when working with bone of such high density, a careful preparation protocol is required, including controlled drill speed and adequate irrigation, to prevent overheating and thermal necrosis of the bone tissue. The anterior mandible, with its high density and uniform structure, represents a preferred site for dental implant placement, particularly in the absence of posterior teeth. These anatomical and physiological features contribute to high primary implant stability and successful osseointegration, as confirmed by CBCT findings and clinical observations.

Assessment of the need for bone augmentation in cases of mandibular resorption requires comparing the residual alveolar ridge dimensions with the minimum requirements for reliable osseointegration and aesthetic rehabilitation. Evaluation criteria for resorption include horizontal deficiency: when the alveolar ridge width is less than 5 mm, the risk of inadequate implant–cortical bone contact increases, reducing primary stability. When the width falls below 3-4 mm, placement of standard implants without prior ridge augmentation is generally not feasible (Fig. 3).

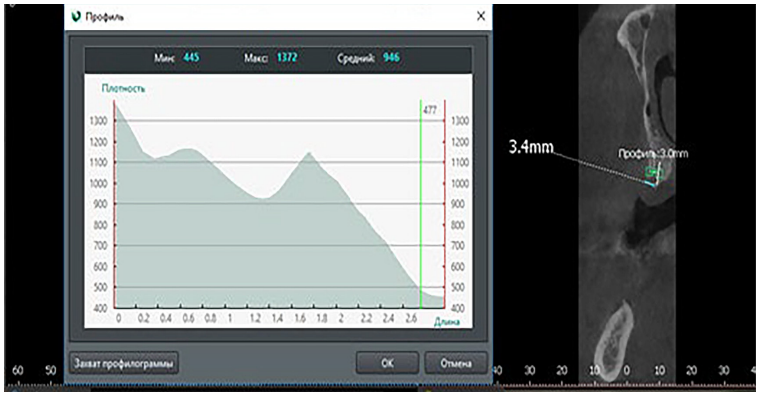

Figure 3. Horizontal bone deficiency due to reduced width of the mandibular alveolar ridge
Source: developed by the authors

CBCT revealed that the alveolar ridge width at the examined site measured 3.4 mm. These morphometric findings indicate a pronounced horizontal bone deficiency and a significant reduction in alveolar ridge volume in the bucco-lingual direction. At this ridge width, there is insufficient bone to provide an adequate circumferential support around the implant, which is essential for achieving primary stability and predictable osseointegration. According to widely accepted clinical criteria, the minimum bone width required for placement of standard implants (3.5-4.0 mm in diameter) should allow at least 1.0-1.5 mm of bone on either side of the implant. In the present case, the available bone falls considerably below these recommendations, increasing the risk of cortical plate perforation, loss of primary stability, and the development of early postoperative complications.

Thus, performing implant placement without prior horizontal bone augmentation or other ridge-width enhancement techniques – such as GBR, ridge splitting, or the use of bone blocks – appears clinically unjustified and carries a high risk of treatment failure. Vertical deficiency, defined as alveolar bone height <8 mm, does not provide sufficient depth for the intraosseous portion of the implant (typically ≥10 mm). Classification based on residual bone height (A-D) is as follows: A (≥10 mm) – augmentation not required; B (7-9 mm) – short implants or minimal augmentation may be considered; C (4-6 mm) and D (0-3 mm) – mandatory pre-implant augmentation. This classification is illustrated in Figure 4.

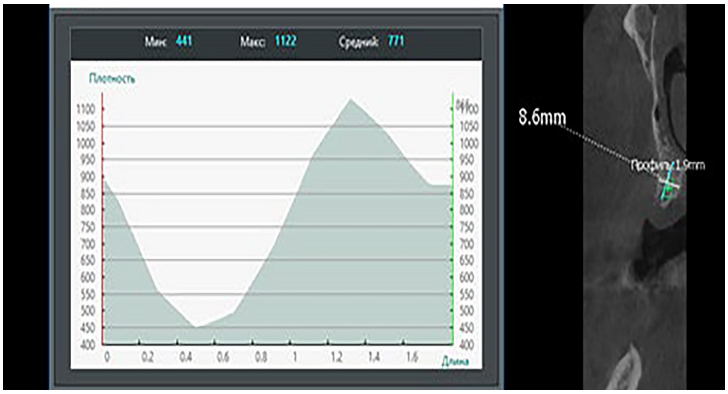

Figure 4. Vertical bone deficiency characterised by reduced height of the mandibular alveolar ridge
Source: developed by the authors

Thus, an alveolar ridge height of less than 8 mm is considered insufficient to ensure adequate depth for positioning the intraosseous portion of a standard dental implant. Under such conditions, the use of standard-length implants (10 mm or more) is limited, which increases the risk of inadequate primary stability and unfavorable distribution of occlusal load. When the bone height ranges between 7-9 mm (conditional category B), the use of short implants (6-8 mm) may be considered, provided that the ridge width is sufficient and bone density parameters are satisfactory. In such clinical situations, implant placement without prior vertical bone augmentation may be feasible; however, the decision should be made based on the morphology of the alveolar ridge, the thickness of the cortical plates, the proximity of critical anatomical structures (such as the mandibular canal), and the anticipated functional load. Therefore, the assessment of the vertical dimension

using CBCT data plays a crucial role in selecting the appropriate implant length and determining the need for vertical bone augmentation. The classification of residual alveolar bone height (A-D) is an important tool in dental implant planning, particularly in cases of severe mandibular atrophy (Table 2). This system allows for evaluation of the necessity and extent of bone augmentation, as well as selection of the optimal surgical approach.

Table 2. Classification of residual bone height (A-D)

Class	Residual bone height (mm)	Clinical characteristics	Recommended treatment strategy
A	≥10 mm	Sufficient bone volume for implant placement without additional augmentation	Standard implant placement without the need for bone grafting
B	7-9 mm	Moderate bone height deficiency; implant placement possible with caution	Placement of short implants or minimal augmentation may be considered
C	4-6 mm	Significant bone height deficiency; increased risk of insufficient osseointegration	Preoperative vertical augmentation is required, e.g., GBR
D	0-3 mm	Critical bone deficiency; implant placement not feasible without substantial bone augmentation	Mandatory vertical augmentation with delayed implant placement after healing

Source: developed by the authors

Clinical significance of the classification: 1) Class A: allows implant placement without additional procedures, ensuring high primary stability of implants; 2) Class B: requires careful evaluation; the use of short implants or minimal augmentation may be considered to achieve sufficient stability; 3) Class C: necessitates vertical augmentation procedures, such as GBR, to obtain adequate bone volume prior to implant placement; 4) Class D: requires a comprehensive approach with mandatory augmentation and delayed implant placement following complete healing and the formation of new bone volume. Thus, the A-D classification of residual bone height provides clear guidelines for planning dental implant treatment in cases of mandibular atrophy. It facilitates the assessment of the need for and extent of bone augmentation, the selection of an appropriate treatment strategy, and the prediction of implant osseointegration outcomes. This classification is particularly important when deciding between immediate and delayed implant placement, as well as when planning the use of techniques such as GBR.

In cases of significant reduction in alveolar ridge width, typically associated with long-term edentulism in the posterior region, extensive horizontal bone atrophy develops (Fig. 5). Under such clinical conditions, the available bone volume is insufficient to provide a circumferential bone envelope around the implant, which is a critical requirement for achieving primary stability and subsequent osseointegration.

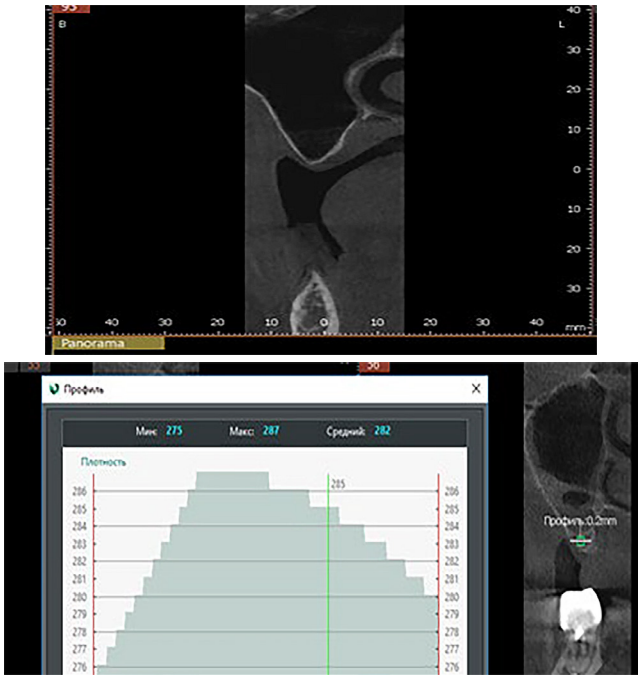

Figure 5. Severe horizontal atrophy of the alveolar ridge associated with long-term edentulism
Source: developed by the authors

CBCT revealed horizontal atrophy of the mandibular alveolar ridge, characterised by a reduction in its buccolingual width and thinning of the cortical plates. Morphometric parameters indicate a decreased bone volume in the planned implant site. The mean relative bone density in the examined area was 287 HU, corresponding to moderately dense bone with a predominance of cancellous structure and a relative reduction of the cortical component. These findings highlight the need for careful assessment of primary implant stability and possible modification of the surgical approach, taking bone quality into account. In cases of a characterised vertical defect of the alveolar ridge, accompanied by a reduction in bone height within a limited area, unfavorable conditions arise for optimal implant positioning. This type of atrophy is characterised by insufficient apico-coronal bone dimension while the ridge width remains preserved or relatively preserved. The most common indication for GBR in vertical deficiency is the need to restore alveolar ridge height to ensure proper three-dimensional implant positioning in accordance with prosthetic requirements and to achieve a stable soft tissue contour. Vertical augmentation enables the creation of sufficient bone volume to achieve primary implant stability, reduce the risk of thread exposure, and ensure a favorable aesthetic outcome in the peri-implant region (Fig. 6).

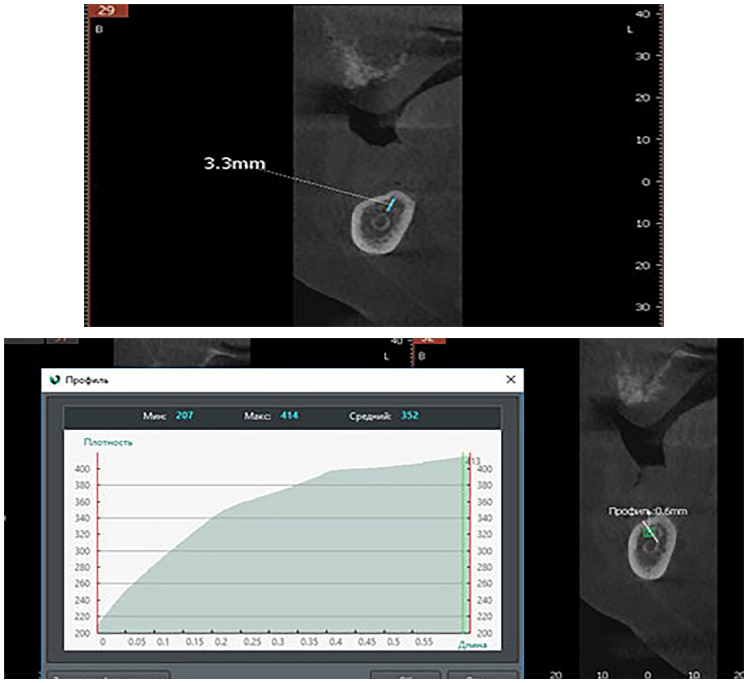

Figure 6. Localised vertical defect of the alveolar ridge as an indication for GBR
Source: developed by the authors

A reduced distance from the crest of the alveolar ridge to the mandibular canal was observed, which limited the use of standard-length implants without prior bone augmentation. The mean relative bone density in the examined regions was 414 HU, indicating bone of moderate to high density with a well-defined cortical layer. The analysis demonstrated that bone density values ranged from 287 ± 64 HU in cases of pronounced horizontal atrophy to 435 ± 58 HU in combined bone defects. Despite satisfactory bone quality, insufficient ridge height necessitated modification of the surgical approach, including consideration of vertical GBR or the use of short implants, taking into account anatomical constraints and the anticipated functional load.

Simultaneous reduction in both the height and width of the alveolar ridge resulted in combined bone deformities characterised by a pronounced three-dimensional volume deficiency. Such changes often developed following tooth extraction complicated by inflammatory processes (including cyst-related conditions), as well as as a result of traumatic injuries leading to significant bone loss. In the presence of combined horizontal and vertical bone deficiencies, simultaneous implant placement generally does not allow achievement of adequate bone support and primary implant stability. The mean width of the alveolar ridge in areas of partial edentulism was 4.6 ± 0.8 mm. In these clinical situations, a staged surgical approach is preferred: at the first stage, a bone "container" is created using GBR or onlay grafting techniques aimed at restoring the required ridge height and width; at the second stage, following completion of bone regeneration and remodeling, dental implant placement is performed (Fig. 7).

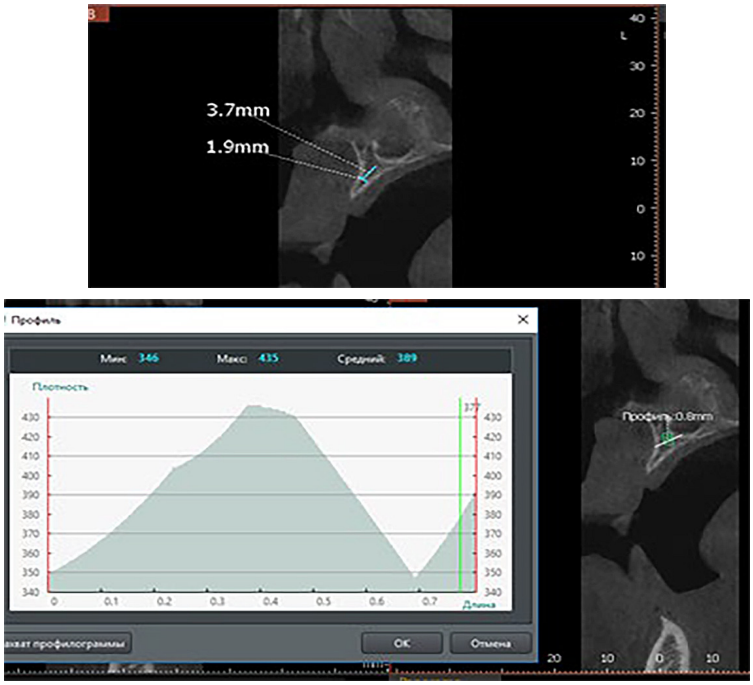

Figure 7. Combined atrophy of alveolar ridge (horizontal0vertical) as a stage of bone augementation
Source: developed by the authors

CBCT revealed combined (horizontal-vertical) atrophy of the mandibular alveolar ridge, characterised by a simultaneous reduction in ridge width in the buccolingual dimension and a decrease in its height in the apico-coronal dimension. Thinning of the cortical plates and alterations in the trabecular architecture were observed, indicating a pronounced three-dimensional bone deficiency in the planned implant site. The mean relative bone density in the examined region was 435 HU, corresponding to bone of moderate density with a relatively preserved cortical component. Despite satisfactory bone quality, the reduction in the linear dimensions of the alveolar ridge limits the possibility of simultaneous placement of implants of standard length and diameter. Under such clinical conditions, preliminary reconstruction of bone volume is required using both horizontal and vertical augmentation techniques to ensure adequate bone support and predictable osseointegration.

The study results demonstrated statistically significant differences in morphometric parameters of the mandibular alveolar ridge between the main group (patients with pronounced atrophy requiring bone augmentation) and the control group (patients with preserved bone volume allowing implant placement without prior grafting).In the main group, the mean values of alveolar ridge width and cortical plate thickness were significantly lower compared to the control group ($p < 0.05$), which was accompanied by a decrease in relative bone density values according to CBCT data. These findings are consistent with systematic reviews indicating that horizontal bone resorption following tooth loss is more pronounced than vertical resorption and reaches clinically significant levels at early stages of edentulism [13, 14].

Comparative analysis showed that when ridge width was less than 5 mm and cortical plate thickness was less than 1 mm, the likelihood of requiring horizontal augmentation increased more than twofold compared to the control group. These data are in agreement with the conclusions of M. Esposito *et al.* [15], emphasising the key role of residual ridge width in selecting GBR techniques. Furthermore, the main group demonstrated greater variability in HU values, indicating heterogeneity of bone quality under atrophic conditions. Similar findings were reported by Y.H. Kim *et al.* [16], who demonstrated a correlation between reduced cortical bone density and decreased primary implant stability. In the control group, bone density and cortical plate thickness values remained within ranges that обеспечивают predictable osseointegration without additional bone grafting, which is consistent with the findings of R. Harikrishnan *et al.* [17] and M. Lyu *et al.* [18], highlighting the relationship between bone density and primary implant stability.

Particular attention should be given to the identified relationship between the duration of edentulism and the degree of ridge reduction: in the main group, with edentulism lasting more than 3 years, the decrease in bone width was significantly more pronounced compared to the control group ($p < 0.05$). These findings support the concept of progressive post-extraction atrophy described in contemporary reviews on alveolar bone remodeling [9]. In the context of regional studies, the obtained results are comparable with previously

reported data demonstrating pronounced individual variability in bone density parameters among patients in Kyrgyzstan during implant planning. However, unlike those studies, the present research complements the diagnostic aspect with a comparative analysis including a control group, which allowed for the identification of clinically relevant threshold values of parameters influencing the choice of augmentation technique.

It should be noted that most publications from 2020-2025 focus on the effectiveness of specific reconstruction methods. In a systematic review, M. Eguren *et al.* [19] demonstrated that gray values (GV) obtained from CBCT cannot be directly converted into HU due to the lack of sufficient clinical validation of their diagnostic applicability. T.R.P. Arvind *et al.* [20], in a retrospective CBCT-based study, showed the effectiveness of fractal analysis for assessing the microstructure of alveolar bone around impacted maxillary canines. N.A. Hassan & A.S.D. Al-Radha [21] reported that CBCT is an effective method for evaluating both bone quality and quantity when planning immediate implant placement in the maxillary central incisor region, taking into account the dental arch form. M.S. Agrawal *et al.* [22], also using CBCT and fractal analysis, demonstrated differences in bone density between buccally and palatally impacted canines. At the same time, direct comparison of morphometric characteristics in patients undergoing different clinical treatment strategies remains limited. Y.-J. Choi *et al.* [23] described the use of CT/CBCT for pre-implant bone assessment, emphasising the importance of both bone quality and quantity for predicting primary implant stability. The conducted comparative analysis not only confirms existing literature data but also substantiates an integrative clinical decision-making algorithm. Thus, the differences identified between the main and control groups indicate that a combined assessment of ridge width, alveolar height, cortical plate thickness, and HU values based on CBCT data provides an objective basis for selecting the appropriate bone augmentation method. This approach enhances the predictability of implant treatment outcomes and aligns with current trends in evidence-based implantology.

CONCLUSIONS

The conducted clinical and radiological study enabled a comprehensive and quantitative assessment of the morphometric parameters of mandibular alveolar ridge resorption, as well as determination of their clinical significance in dental implant planning. The mean width of the alveolar ridge in areas of partial edentulism was 4.6 ± 0.8 mm. Notably, in 38.4% of patients, the ridge width was less than 5 mm, which is indicative of a pronounced horizontal bone deficiency and significantly limits the placement of standard-diameter implants without prior bone augmentation. The mean height of the alveolar bone in the examined regions was 8.2 ± 1.4 mm. However, in 31.7% of cases, the ridge height was below 8 mm, creating a risk of insufficient apical implant fixation and necessitating consideration of vertical augmentation or the use of short implants, taking into account anatomical limitations.

Analysis of relative bone density demonstrated values ranging from 287 ± 64 HU in cases of pronounced horizontal atrophy to 435 ± 58 HU in combined defects. These values predominantly correspond to D2-D3 bone types, indicating a moderate ratio between cortical and cancellous components. A statistically significant association ($p < 0.05$) was identified between edentulism duration exceeding 3 years and both a reduction in ridge width and a decrease in cancellous bone density, confirming the progressive nature of atrophic changes over time.

The results indicate that the need for bone augmentation in mandibular resorption is directly determined by the severity of horizontal and vertical bone deficiency. When ridge width is less than 5 mm and height is below 7-8 mm GBR, ridge splitting, or the use of bone blocks represent clinically justified preparatory stages prior to implant placement. The choice of technique should be based on a comprehensive evaluation of linear and spatial defect parameters, cortical plate quality, bone density, and the patient's overall systemic condition. Future research perspectives include the development of a standardised algorithm for interpreting CBCT parameters to predict primary implant stability, as well as the creation of a differentiated system for selecting bone augmentation methods based on the integration of morphometric, biomechanical and clinical risk factors.

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CONFLICT OF INTEREST

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Конус нурлуу компьютердик томографияны колдонуу менен астыңкы жаак сөөгүнүн ар кандай аймактарындагы тыгыздыгынын өзгөрмөлүүлүгүн баалоо

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Аннотация. Конус нурлуу компьютердик томография кеңири колдонулганына карабастан, кортикалдык жана трабекулярдык сөөктүн тыгыздыгынын аймактык айырмачылыктары азырынча аз изилденген. Бул изилдөөнүн максаты – астыңкы жаактын ар кайсы аймактарындагы сөөктүн тыгыздыгын баалоо жана имплантатты орнотуудан мурун сөөктү чоңойтууну талап кылган шарттарды аныктоо болуп саналат. Методологияга конус нурлуу компьютердик томографиянын маалыматтарын талдоо, астыңкы жаактын алдыңкы, премолярдык жана азуу тиштеринин аймактарындагы сөөктүн тыгыздыгын өлчөө киргизилген. Сөөктүн максималдуу тыгыздыгы астыңкы жаактын алдыңкы бөлүгүндө байкалып, контролдук топто орточо эсеп менен 944,9 ± 207 HU жана тишсиз бейтаптарда (адентия) 910,2 ± 198 HU түзгөн ($p > 0,05$). Премолярдык аймакта тыгыздык тишсиз бейтаптарда 643,8 ± 162 HU чейин төмөндөгөн, ал эми тиши сакталган бейтаптарда бул көрсөткүч 826,4 ± 175 HU болгон ($p < 0,05$). Тыгыздыктын эң байкаларлык төмөндөшү азуу тиштери бар бейтаптарда байкалган: тишсиз бейтаптарда бул көрсөткүч 512,5 ± 148 HU түзгөн, ал эми контролдук топто 789,7 ± 160 HU ($p < 0,01$) болгон. Алынган жыйынтыктар менен кошо жаак сөөгүнүн дисталдык бөлүгүнүн тыгыздыгынын төмөндөшү кортикалдык катмардын мүнөздөмөлөрүнүн начарлашы менен коштолорун, бул имплантаттардын баштапкы туруктуулугун төмөндөтүшү мүмкүн экенин көрсөттү. Астыңкы жаак сөөгүнүн тыгыздыгындагы аныкталган аймактык айырмачылыктарды имплантардын өлчөмдөрүн тандоодо жана сөөктү чоңойтуу (аугментация) көлөмүн пландаштырууда, айрыкча узак мөөнөттүү адентия менен ооруган бейтаптарда эске алуу керек. Алынган маалыматтар имплантация тактикасын тандоо, сөөктү чоңойтуу зарылдыгын аныктоо жана хирургиялык дарылоонун алдын ала айтуу мүмкүнчүлүгүн жакшыртуу үчүн маанилүү болуп саналат

Негизги сөздөр: астыңкы жаак сөөгү; сөөктүн минералдык тыгыздыгы; морфометрикалык көрсөткүчтөр; альвеолярдык өсүндүсү; сөөк тканынын регенерациясы

Оценка вариабельности плотности костной ткани нижней челюсти в разных участках по данным конусно-лучевой компьютерной томографии

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Аннотация. Несмотря на широкое применение конусно-лучевой компьютерной томографии, региональные различия плотности кортикальной и трабекулярной ткани изучены недостаточно. Цель исследования состояла в оценке плотности костной ткани нижней челюсти в разных отделах и выявлении условий, при которых требуется предварительное увеличение объёма кости перед имплантацией. Методология включала анализ данных конусно-лучевой компьютерной томографии с измерением плотности костной ткани в переднем, премолярном и молярном отделах нижней челюсти. Обнаружено, что максимальная плотность костной ткани наблюдалась в переднем отделе нижней челюсти и составляла в среднем 944,9 ± 207 HU в контрольной группе и 910,2 ± 198 HU при адентии ($p > 0,05$). В премолярной зоне при отсутствии зубов плотность снижалась до 643,8 ± 162 HU по сравнению с 826,4 ± 175 HU у пациентов с сохранённым зубным рядом ($p < 0,05$). Наиболее выраженное уменьшение плотности выявлено в молярной области, где показатели составили 512,5 ± 148 HU при адентии против 789,7 ± 160 HU в контрольной группе ($p < 0,01$), что подтверждает влияние длительной потери жевательных зубов на качество костной ткани. Результаты также показали, что снижение плотности в дистальных отделах нижней челюсти сопровождается ухудшением характеристик кортикального слоя, что может снижать первичную стабильность имплантатов. Выявленные региональные различия плотности костной ткани следует учитывать при выборе размеров имплантатов и планировании объёма костной аугментации, особенно у пациентов с длительной адентией. Полученные данные важны для выбора тактики имплантации, определения необходимости костной аугментации и повышения предсказуемости хирургического лечения

Ключевые слова: нижняя челюсть; минеральная плотность кости; морфометрические показатели; альвеолярный отросток; регенерация костной ткани

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Advances in primary headache disorder management: A review of pharmacological and non-pharmacological strategies with emphasis on European evidence

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Abstract. Primary headache disorders – migraine, tension-type headache, and cluster headache – represented one of the leading causes of years lived with disability worldwide, imposing a substantial socioeconomic burden across Europe, with annual costs estimated in billions of euros owing to lost productivity and increased healthcare utilisation. The aim of research was to critically evaluate evidence on pharmacological and non-pharmacological management of primary headache disorders published between 2019 and 2024, with a specific focus on European clinical data and guideline recommendations, in order to provide practitioners with an immediately applicable, evidence-based update. CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) demonstrated ≥50% responder rates of 40-60% and mean reductions of 3-8 monthly migraine days, with real-world European registry persistence exceeding 70% at 12 months – substantially outperforming traditional oral preventives. Oral gepants (atogepant for prevention; rimegepant for acute and preventive use) offered effective, cardiovascular-safe alternatives supported by both pivotal trials and European real-world cohorts. For cluster headache, high-flow oxygen (≥12 L/min) and subcutaneous sumatriptan 6 mg remained gold-standard acute treatments, while galcanezumab was the only biologic with strong evidence for episodic cluster headache prevention. Non-pharmacological interventions – cognitive behavioural therapy, biofeedback, structured aerobic exercise, and non-invasive vagus nerve stimulation – demonstrated moderate-to-high efficacy in reducing headache frequency and disability across all three disorders. Integrated multidisciplinary approaches combining pharmacological and behavioural strategies consistently showed superior long-term outcomes compared with monotherapy. European real-world data revealed meaningful improvements in quality of life, work productivity, and reductions in medication-overuse headache, confirming the applicability of guideline recommendations across diverse healthcare contexts. The findings provided neurologists, headache specialists, and primary care practitioners with a comprehensive, evidence-based synthesis of modern European management strategies, supporting a shift toward personalised, multidisciplinary headache care. Sustained implementation of European guidelines, harmonised cross-country access to novel therapies, and continued long-term safety monitoring remained essential priorities

Keywords: migraine; tension-type headache; preventive therapy; non-pharmacological interventions; evidence-based neurology

INTRODUCTION

Primary headache disorders were among the most prevalent and disabling neurological conditions worldwide. Understanding why these disorders demanded scientific attention had never been more critical: neurological diseases collectively represented the leading cause of disability-adjusted life years globally, and primary headaches – migraine, TTH (tension-type headache), and CH (cluster headache) – accounted for a disproportionate share of this burden. According to the GBD 2016 Headache Collaborators [1], migraine affected approximately 11-14% of the European adult population, with women experiencing the condition two to three times more frequently than men. M. Ashina *et al.* [2] documented that TTH, the most common

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headache disorder, affected up to 30-40% of the general population and remained substantially underdiagnosed. Though rarer (prevalence ≈ 0.1%), cluster headache caused one of the most severe pain syndromes. M. Linde *et al.* [3] established that these disorders collectively cost European economies billions of euros annually through lost productivity, absenteeism, and healthcare expenditure, with migraine accounting for the majority of the economic burden. Against the backdrop of an aging population and rising non-communicable disease burden, advancing the quality and consistency of headache management had become a public health imperative. Between 2019 and 2024, several pivotal developments fundamentally reframed the understanding and management of primary headaches. T.J. Steiner & L.J. Stovner [4] confirmed that migraine remained the second leading cause of years lived with disability worldwide, reinforcing the urgency of improving therapeutic access. W.K. Karlsson *et al.* [5] demonstrated that calcitonin gene-related peptide (CGRP)-targeted monoclonal antibodies outperformed traditional oral preventives across virtually all efficacy endpoints. S. Sacco *et al.* [6] formulated the landmark 2022 European Headache Federation (EHF) guideline recommending CGRP monoclonal antibodies as first-line preventive therapy for both episodic and chronic migraine, marking a paradigm shift in European clinical practice. E. Caronna *et al.* [7] further demonstrated in a real-world Spanish registry that early initiation of anti-CGRP therapy significantly enhanced the probability of sustained response, highlighting the importance of treatment timing. A. May *et al.* [8] updated the evidence base for this challenging condition, codifying the role of galcanezumab and non-invasive vagus nerve stimulation (nVNS). H.C. Diener *et al.* [9] articulated the prevailing European consensus on medication-overuse headache management, underscoring the critical interplay between pharmacological and behavioural strategies. K. Probyn *et al.* [10] and D. Onan *et al.* [11] published systematic analyses confirming clinically meaningful efficacy of self-management and physiotherapy interventions for TTH, respectively, strengthening the evidence base for non-pharmacological approaches across all headache subtypes.

Despite these advances, several gaps remained. Evidence for TTH management lags considerably behind migraine, with fewer high-quality trials and greater heterogeneity in non-pharmacological research. Long-term safety data for novel biologic agents extended beyond 3 years in only a limited number of studies. Significant inter-country variation in reimbursement and access to CGRP therapies created inequities across European healthcare systems. Furthermore, existing reviews either focus narrowly on a single headache subtype or fail to incorporate the most current European guideline updates alongside real-world registry data. A comprehensive synthesis that integrated pharmacological strategies, non-pharmacological evidence, and a critical analysis of the European clinical landscape – spanning multiple headache disorders and guideline frameworks simultaneously – was therefore lacking. The objective of this review was to provide a comprehensive, evidence-based synthesis of pharmacological and non-pharmacological management strategies for primary headache disorders (migraine, TTH, and CH), with a specific focus on European clinical trial data, real-world registries, and guideline recommendations published between 2019 and 2024, in order to support neurologists and primary care practitioners in delivering optimised, personalised headache care across Europe. This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [12]. Comprehensive electronic searches were performed in PubMed/Medline, Embase, and the Cochrane Library, covering January 2019 to December 2024, supplemented by hand-searching of major European journals. Search terms combined headache subtypes ("migraine", "tension-type headache", "cluster headache") with management-related keywords and study designs, limited to human studies in English. Priority was given to studies with European authorship, multicentre European participation, or direct relevance to EAN and EHF recommendations, reporting clinical outcomes such as monthly headache days, ≥50% responder rates, disability scores (MIDAS, HIT-6), or safety data. Studies on secondary headaches only, exclusively pediatric populations, case reports with <10 patients, or non-management topics were excluded. From 2,856 identified records, 145 studies – comprising 25 guidelines/consensus statements, 45 systematic reviews/meta-analyses, 50 RCTs, and 25 real-world European cohorts – met all inclusion criteria.

PHARMACOLOGICAL STRATEGIES IN HEADACHE MANAGEMENT

The selection of acute migraine therapy depended on attack severity, the presence of cardiovascular comorbidities, prior treatment history, and patient preference. Current European practice stratified acute treatment into a step-wise approach: simple analgesics for mild attacks, triptans as first-line specific therapy for moderate-to-severe migraine, and gepants or lasmiditan as cardiovascular-safe alternatives, consistent with recommendations from the German Migraine and Headache Society [13]. W.K. Karlsson *et al.* [5] confirmed that eletriptan and rizatriptan provided the highest probability of 2-hour pain freedom among oral triptans, with odds ratios of approximately 3.5 and 3.2 versus placebo, respectively. Sumatriptan remained widely used due to its well-established efficacy, broad availability, and multiple formulations. The 2022 EHF consensus [6] operationalised the definition of "effective acute treatment" as restoration of well-being within 2 hours – encompassing

headache relief and resolution of associated symptoms – sustained for 24 hours without recurrence. Critically, when triptans failed to meet this standard across three separate attacks, they should be considered ineffective for the individual patient, and gepants represented the appropriate next step. Newer agents had substantially expanded options for patients with cardiovascular contraindications to triptans. Gepants – specifically ubrogepant and rimegepant – act as small-molecule CGRP receptor antagonists and had demonstrated high-quality efficacy evidence: rimegepant achieved pain freedom at 2 hours in approximately 21% of patients versus 11% for placebo in pivotal trials, with a particularly favourable tolerability profile and no associated medication-overuse headache risk. Real-world European cohort data corroborated high patient satisfaction and superior persistence with gepants compared with triptans, particularly among patients with prior triptan failure or cardiovascular risk factors [14].

Preventive therapy was indicated for patients with four or more migraine days per month causing significant disability, those who failed or cannot tolerate acute treatments, or those at risk of medication-overuse headache. The 2022 EHF guideline update [6] represented a landmark European consensus that has fundamentally restructured the preventive treatment hierarchy. CGRP monoclonal antibodies (mAbs) – erenumab, fremanezumab, galcanezumab, and eptinezumab – were recommended as first-line preventive options for both episodic and chronic migraine, on the basis of robust evidence from multiple Phase III RCTs and extensive real-world data. These agents worked by blocking either the CGRP ligand (fremanezumab, galcanezumab, eptinezumab) or its receptor (erenumab), thereby disrupting the key trigemino-vascular signalling pathway implicated in migraine pathogenesis. Pooled clinical trial data demonstrated ≥50% responder rates of 40-60% for CGRP mAbs, with meant reductions in monthly migraine days of 3-8 days – significantly superior to placebo and consistently outperforming oral preventives in head-to-head comparisons in terms of efficacy and tolerability [5]. Their subcutaneous or intravenous monthly/quarterly dosing regimens improved adherence compared with daily oral medications. In terms of tolerability, CGRP mAbs exhibited low rates of serious adverse events; constipation was the most notable side effect specifically associated with erenumab (up to 3-fold higher than placebo in some studies), while injection-site reactions were mild and transient across the class. Gepants had expanded into the preventive arena: atogepant (approved in Europe) and rimegepant (dual acute/preventive indication) offered effective oral alternatives for patients, who preferred or required tablet-based regimens. Their primary advantages included no injection requirement, a short half-life (reducing prolonged CGRP blockade), and – uniquely – no established medication-overuse headache risk, making them particularly valuable for patients with frequent acute treatment use. Network meta-analyses position oral gepants as comparably effective to some traditional preventives, with superior tolerability [5].

OnabotulinumtoxinA retained a strong recommendation specifically for chronic migraine (≥15 headache days/month), where decades of European registry data confirmed persistent clinical benefit. Long-term follow-up data indicated that benefits were maintained or enhanced over multiple treatment cycles, and combination with CGRP mAbs had shown additive benefits in refractory chronic migraine cohorts – particularly for patients, who achieved partial but insufficient response to either agent alone [15]. Traditional oral preventives – propranolol, topiramate, and amitriptyline – maintained Level A evidence [16] and remained appropriate first-line options in settings, where access to or reimbursement for newer agents was limited. However, their long-term use was frequently constrained by tolerability issues (cognitive effects with topiramate, fatigue with propranolol, anticholinergic burden with amitriptyline), which explained why European registries document 12-month persistence rates of only 30-50% compared with >70% for CGRP mAbs [14, 15]. T.J. Schwedt *et al.* [17] further corroborated these persistence advantages in a large real-world analysis comparing onabotulinumtoxinA and CGRP mAbs, confirming that biologic agents demonstrated markedly superior adherence profiles. European real-world registries from Italy, Germany, Spain, and Scandinavia had been pivotal in confirming that pivotal trial results translated directly into clinical practice. Italian multicentre data from the RAMO study [18] demonstrated that anti-CGRP mAbs outperformed onabotulinumtoxinA in chronic migraine on several quality-of-life endpoints. Italian prospective registry data from A. Zovi *et al.* [19] further substantiated these findings across a broader patient population, while Spanish registry data showed that early treatment initiation was independently associated with superior and more sustained response [7]. Additional benefits documented in European registries included reduced acute medication consumption, fewer emergency department visits, and improved work productivity – outcomes with direct health-economic relevance. Table 1 summarised the key pharmacological agents for migraine management, their evidence levels, and European guideline recommendations.

Table 1. Key pharmacological agents for migraine management

Agent	Indication	Evidence level	EHF/EAN grade	Key notes (European data)
Eletriptan/ Rizatriptan	Acute (episodic)	High	Strong	Widely used first-line triptans for moderate-severe attacks

Table 1, Continued

Agent	Indication	Evidence level	EHF/EAN grade	Key notes (European data)
Subcutaneous sumatriptan 6 mg	Acute (episodic/CH)	High	Strong	Fast onset; standard therapy for acute CH
Ubrogepant/ Rimegepant	Acute (episodic)	High	Strong	Cardiovascular-safe; no overuse headache risk
Erenumab/ Fremanezumab/ Galcanezumab/ Eptinezumab	Preventive (episodic & chronic migraine)	High	Strong	First-line per EHF 2022; high adherence in European registries
Atogepant	Preventive (episodic migraine)	High	Strong	Oral CGRP antagonist; no overuse risk
Rimegepant	Acute & preventive	High	Strong	Convenient oral option; dual use
OnabotulinumtoxinA	Chronic migraine prevention	High	Strong	Established effectiveness in European registries; additive with CGRP mAbs
Propranolol/ Topiramate	Preventive (episodic migraine)	High	Moderate	Effective but limited by tolerability; second-line in Europe
Amitriptyline	Preventive (migraine & TTH)	Moderate	Moderate	First-line for TTH; long-term anticholinergic burden

Source: W.K. Karlsson *et al.* [5], S. Sacco *et al.* [6], A. May *et al.* [8], M.T. Corasaniti *et al.* [15], A. Zovi *et al.* [18], F. Vernieri *et al.* [20], S.D. Silberstein *et al.* [21]

Analysis of the data presented in Table 1 revealed a clear stratification of the current therapeutic landscape. CGRP-targeted biologics and gepants represented a genuine step change in migraine management: they were the first treatments designed specifically around the core pathophysiology of migraine, offering superior efficacy-to-tolerability ratios compared with any prior pharmacological option. The availability of multiple mechanisms and delivery formats enabled genuinely individualised treatment selection, which the EHF 2022 guidelines explicitly advocated [6]. R.B. Lipton *et al.* [22] demonstrated that inadequate preventive treatment was independently associated with migraine progression and chronification, further underscoring the clinical imperative of early, effective intervention. Tension-type headache, though the most prevalent headache disorder, remained the least well-characterised in terms of pathophysiology. Modern evidence points to peripheral sensitisation of pericranial myofascial nociceptors in episodic TTH, with central sensitisation playing an increasingly important role in the transition to chronicity. For acute episodic TTH, simple analgesics – paracetamol and NSAIDs – remained first-line based on strong longstanding evidence. R. Xie *et al.* [23] confirmed in a 2024 network meta-analysis that ibuprofen, ketoprofen, and diclofenac provide superior pain relief compared with paracetamol for more severe episodic attacks, while the combination of paracetamol with caffeine demonstrated additive benefit. A network meta-analysis by L. Qin *et al.* [24] of complementary and alternative medicine approaches further confirmed mindfulness-based and manual therapy interventions as clinically meaningful adjunctive strategies for TTH management, providing an evidence base for integrating these modalities alongside conventional pharmacotherapy. Critically, European guidelines uniformly caution against overuse of any acute analgesic – defined as use on ≥10 days/month for combination analgesics or triptans – because medication-overuse headache was particularly prevalent in TTH, occurring in approximately 1-2% of the European general population [9]. For chronic TTH, amitriptyline 25-75 mg nightly remained the evidence-based first-line preventive, with meta-analyses showing reductions of approximately 30% in headache frequency. European guidelines recommended early integration of non-pharmacological strategies as co-interventions to prevent the transition from episodic to chronic TTH [9].

Cluster headache was characterised by strictly unilateral, periorbital attacks of excruciating severity (typically VAS 9-10/10) lasting 15-180 minutes, accompanied by ipsilateral cranial autonomic features. Its unique circadian and circannual rhythmicity, mediated through the hypothalamic clock, distinguished it from all other primary headaches and necessitated a distinct therapeutic approach, as reviewed by B. de Freitas Dias *et al.* [25]. The authors A. May *et al.* [8] provided the most current and authoritative European framework. For acute attacks, 100% oxygen at ≥12 L/min via non-rebreathing mask for 15 minutes achieved meaningful pain relief in approximately 75-80% of episodic CH patients, with complete safety and no systemic side effects. Subcutaneous sumatriptan 6 mg achieves pain freedom within 15 minutes in approximately 75% of attacks and was therefore the pharmacological first choice for acute treatment, when oxygen was unavailable or insufficient. Intranasal zolmitriptan and sumatriptan were recommended as alternatives, particularly for patients, who cannot self-inject. Preventive treatment was initiated simultaneously with acute therapy during cluster periods to abbreviate the bout duration. Verapamil, titrated to a minimum effective

dose of 240 mg/day (with electrocardiographic monitoring due to PR interval prolongation risk at higher doses), was the established first-line preventive across European centres. Transitional therapy with oral or intravenous corticosteroids bridges the 2-3-week latency before verapamil took full effect. Galcanezumab 300 mg monthly received a strong recommendation specifically for episodic CH based on pivotal RCT data from study of D.W. Dodick *et al.* [26] showing significant reductions in weekly attack frequency. The emerging therapeutic landscape in CH was comprehensively reviewed by M. Barbosa da Silva *et al.* [27], who highlighted the role of novel biologics and neuromodulation in refractory cases. For refractory cases, non-invasive vagus nerve stimulation (nVNS) was endorsed by EAN guidelines for both acute and preventive purposes in CH; it showed an acceptable side-effect profile and can be combined with pharmacological therapy. Sphenopalatine ganglion stimulation represented an invasive, but highly effective option for patients with chronic CH unresponsive to pharmacological management, with European multicentre data demonstrating acute attack relief rates of 30-45% and preventive benefits in more than half of implanted patients (Table 2).

Table 2. EAN 2023 recommendations for cluster headache management

Treatment	Acute/ Preventive	Recommendation	Evidence level	Notes
100% Oxygen	Acute	Strong	High	First-line; safe in all patients; effective in episodic CH
Subcutaneous sumatriptan 6 mg	Acute	Strong	High	Fast onset; first-line pharmacological option
Intranasal zolmitriptan	Acute	Strong	Moderate-high	Alternative, when self-injection not feasible
Verapamil	Preventive	Strong	Moderate-high	First-line preventive; ECG monitoring recommended; titrate gradually
Oral/IV corticosteroids	Transitional	Strong	Moderate	Bridge therapy until preventive effect achieved
Galcanezumab	Preventive (episodic CH)	Strong	High	Only biologic approved for episodic CH; rapid onset; confirmed by pivotal trial
Non-invasive VNS (nVNS)	Acute & preventive	Strong (consensus)	Low-moderate	Safe; useful for refractory cases; supported by trial evidence
Sphenopalatine ganglion stimulation	Preventive (chronic CH)	Conditional	Moderate	Invasive; reserved for chronic, pharmacotherapy-refractory CH

Source: A. May *et al.* [8], D.W. Dodick *et al.* [26], M. Barbosa da Silva *et al.* [27], S.D. Silberstein *et al.* [28], P.J. Goadsby *et al.* [29]

So, data in Table 2 illustrated the guiding principle of CH management: speed and mechanism specificity were paramount in acute care, while preventive therapy must balance onset speed, tolerability, and the episodic or chronic nature of the disorder. The addition of galcanezumab as the first biologic agent for episodic CH represented a clinically significant advance [26], providing an evidence-based option for patients, who cycle through frequent cluster bouts, or who responded inadequately to verapamil. The continued endorsement of nVNS, supported by the S.D. Silberstein *et al.* [28] and P.J. Goadsby *et al.* [29] randomised trials, reflected growing European clinical experience with neuromodulation as an adjunctive strategy particularly valued for its safety profile.

NON-PHARMACOLOGICAL MANAGEMENT STRATEGIES

Non-pharmacological interventions constituted an essential pillar of European headache management, valued not only for their intrinsic efficacy, but for their capacity to reduce pharmacological burden, prevented medication-overuse headache, and addressed the behavioural and psychological dimensions of chronic pain. European guidelines across all three headache disorders explicitly recommended integrating these strategies alongside pharmacological care [9, 30], reflecting both patient preference for drug-sparing approaches and the mechanistic rationale for multimodal treatment. Cognitive behavioural therapy (CBT) addressed the maladaptive thought patterns, catastrophising, and avoidance behaviours that characterised and perpetuated chronic headache. Its proposed mechanisms included modification of pain-related cognitions, improvement of self-efficacy, and reduction of psychophysiological arousal – all of which contributed to headache chronification. K. Probyn *et al.* [10] demonstrated that non-pharmacological self-management programmes, including CBT-based approaches, produced statistically significant and clinically meaningful reductions in headache frequency and disability for TTH and migraine, with effects sustained at 6-12 months of follow-up. Mindfulness-based stress reduction (MBSR) and acceptance and commitment therapy (ACT) had demonstrated similar but somewhat smaller effects, with the additional benefit of improving psychological wellbeing and quality of life. These approaches were particularly recommended for patients

with comorbid anxiety or depression, which affect approximately 30-40% of chronic migraine patients in European populations.

Biofeedback trained patients to consciously regulate physiological parameters – most commonly frontalis muscle EMG activity (for TTH) and finger skin temperature or heart rate variability (for migraine) – associated with headache triggering. The technique exploits neuroplasticity: with repetitive practice, patients learn to downregulate sympathetic arousal and muscular tension that preceded or accompanied headache. Y. Nestoriuc & A. Martin [31] confirmed that thermal and EMG biofeedback produced significant reductions in migraine frequency (effect size d = 0.59) and TTH frequency (effect size d = 0.73), with response rates of 45-55% after a standardised 8-12-session protocol. Importantly, these effects were maintained over 12 months in studies with follow-up data, and biofeedback was the only psychological intervention with high-quality evidence specifically supporting pediatric and adolescent headache, making it valuable across the age spectrum. Physical therapy targeting pericranial and cervical musculature – through manual therapy, myofascial release, and therapeutic exercise – addressed the peripheral sensitisation of pericranial nociceptors that underlied TTH and contributed to migraine chronification via cervicotrigeminal convergence. D. Onan *et al.* [11] demonstrated that combined physiotherapy approaches (manual therapy plus exercise) reduced chronic TTH frequency by a mean of 4.2 days/month, with 60% of participants achieving a ≥50% reduction – an effect size comparable to preventive pharmacotherapy. R. Souren *et al.* [32] demonstrated in a tertiary headache centre observational study that adherence to headache-specific multidisciplinary treatment recommendations achieves significantly greater headache frequency reductions and better long-term outcomes than unimodal approaches, confirming the superiority of integrated care models.

Structured aerobic exercise programmes (3 sessions per week, 30-45 minutes at moderate intensity) had accumulated substantial evidence for migraine prevention specifically. European guidelines specifically recommended aerobic exercise as a first-line lifestyle intervention for migraine prevention, as it reduced monthly migraine frequency by approximately 0.6 days and improved both MIDAS and HIT-6 scores, likely through modulation of endogenous opioid systems, β-endorphin release, and CGRP levels. The randomised controlled evidence base for exercise as migraine prophylaxis continues to grow, with outcomes comparable to some pharmacological options in terms of frequency reduction [30, 33]. Non-invasive vagus nerve stimulation (nVNS) – delivered via a handheld device applied to the neck – modulated pain processing through projections from the nucleus tractus solitarius to the trigeminal nucleus caudalis, reducing central sensitisation and trigeminovascular activation. For acute CH, the ACT1 [28] and ACT2 [29] randomised trials established nVNS as an effective acute treatment in episodic CH, with pain-free response rates of 34% versus 15% for placebo at 15 minutes – a significant and clinically meaningful difference. For migraine, nVNS had demonstrated preventive efficacy in the PREMIUM and EVENT trials, as reviewed by F. Puledda & K. Shields [34], with monthly migraine day reductions of 2.3-2.9 days. European real-world data confirmed sustained use and patient-reported benefit across neuromodulation devices, with low rates of adverse events (mild application-site discomfort in <5% of users) and no drug interactions, making them suitable add-on therapies for patients with polypharmacy or contraindications to pharmacological treatment. Lifestyle modifications – encompassing consistent sleep hygiene, adequate hydration, regular meal timing, structured stress management, aerobic exercise, and systematic trigger identification [35] – were foundational across all European headache guidelines. While individual lifestyle factors had modest individual effect sizes, their systematic adoption as a package of behavioural change produced meaningful cumulative benefits in reducing headache frequency and severity. Wearable technology and smartphone-based headache diary applications had emerged as powerful tools for trigger identification and behavioural monitoring, with evidence from real-world studies supporting improved treatment adherence [36].

ANALYSIS OF EUROPEAN DATA AND RECOMMENDATIONS IN THE CONTEXT OF CLINICAL PRACTICE

European guidelines – principally those issued by the European Academy of Neurology (EAN) and the European Headache Federation (EHF) – represented the authoritative frameworks that shape clinical decision-making for neurologists and primary care practitioners across the continent. The 2022 EHF guideline update on CGRP-targeted therapies [6] and the 2023 EAN cluster headache guidelines [8] reflected a synthesis of the highest-quality available evidence and have had tangible impacts on prescribing practices. Real-world surveys across Germany, Italy, Spain, France, and Scandinavia conducted between 2022 and 2024 document a rapid uptake of CGRP mAbs in specialist headache centres: in Germany, for example, more than 60% of eligible patients at certified headache centres received biologic preventive therapy by 2023, compared with fewer than 10% in 2019. In Italy, the RAMO multicentre cohort [18] enrolled over 1,000 patients across 14 centres within 18 months, reflecting both the practical feasibility of European collaborative research and the clinical appetite for comparative effectiveness data. These registry findings were essential precisely because they complemented RCT evidence with real-world generalisability, including populations typically excluded from trials – elderly

patients, those with significant comorbidities, and those previously exposed to multiple treatment failures.

EAN and EHF recommendations influenced clinical decision-making not only through their official adoption but through structured educational initiatives, European headache specialist networks, and integration into national clinical guidelines. Countries with well-developed specialist headache infrastructure – Germany, Italy, Denmark, Spain – demonstrated the greatest alignment with European recommendations and correspondingly better patient outcomes, as measured by validated disability scales [38]. Italian real-world data from A. Zovi *et al.* [19] further corroborated the superiority of CGRP mAbs over traditional preventives across diverse patient populations in European specialist settings. In contrast, countries with limited access to specialist care or restricted reimbursement pathways showed lower adoption of guideline-recommended therapies, highlighting the persistent challenge of harmonising care quality across EU member states [22]. EHF had specifically highlighted this inequity in position papers, calling for EU-level health technology assessment processes to facilitate equitable access.

Non-pharmacological therapies had also matured considerably within the European evidence base. Network meta-analyses confirmed that CBT and physiotherapy deliver clinically relevant reductions in TTH and migraine frequency, often comparable to pharmacological options but without systemic side effects [10, 24, 37]. A particular European strength had been the integration of digital therapeutics: high smartphone penetration across Western Europe and telemedicine infrastructure expanded during the COVID-19 pandemic had enabled the scalable deployment of digital CBT programmes, digital biofeedback, and remoted headache monitoring. Preliminary evidence from European pilot studies (2022-2024) suggested that digital therapeutic platforms can achieve CBT-comparable outcomes for headache reduction with improved accessibility and lower cost [36] – findings with significant implications for healthcare system planning. Consensus statements on integrating new treatments into clinical practice, such as that by J. Ailani *et al.* [38], provided practical frameworks for implementing these digital approaches alongside pharmacological strategies.

Health-economic considerations were central to European implementation of novel therapies. While CGRP mAbs carried higher upfront annual costs (approximately EUR 6,000-EUR 12,000 per patient per year across different European pricing systems), real-world economic analyses from Germany, Italy, and the United Kingdom demonstrated favourable cost-effectiveness ratios, when total disease burden – including emergency department visits, hospitalisation, lost productivity, and acute medication expenditure – was incorporated into the model. A pharmacoeconomic analysis from Spain [39] demonstrated that preventive therapy with CGRP mAbs reduced indirect costs (productivity loss, absenteeism) by approximately 35% over 12 months among chronic migraine patients, resulting in a net cost-effectiveness ratio well within the acceptecompared with onabotulinumtoxinA in terms of persistence and overall treatment costs. However, reimbursement criteria remained highly variable: while Germany, France, and Spain had broad coverage for all four approved mAbs in both episodic and chronic migraine, several Eastern European countries restricted coverage to chronic migraine only or required documented failure of three prior preventive agents – a requirement that delayed access to effective treatment by years in some cases [22].

Safety profiles of novel agents remaind EU threshold of EUR 30,000 per quality-adjusted life year. T.J. Schwedt *et al.* [17] further confirmed the real-world economic advantages of CGRP mAb therapy ed reassuring based on accumulated European and global evidence. CGRP pathway therapies showed low rates of serious adverse events across all approved agents. The most common issues – constipation (primarily with erenumab, reported in 3-5% of patients), injection-site reactions (typically mild and transient), and mild fatigue – rarely necessitate treatment discontinuation. Long-term European registry data extending to 3 years confirmed cardiovascular safety: while CGRP played a physiological vasodilatory role, no increase in cardiovascular events had been documented in real-world populations, including those with hypertension or controlled coronary artery disease [40]. Post-marketing pharmacovigilance systems across European national regulatory authorities continued active monitoring, with quarterly aggregated safety reports providing robust population-level signal detection. For CH preventives, standard ECG monitoring before and during verapamil titration was well-established in European practice to detect the PR interval prolongation and rare atrioventricular block that can occur at doses above 480 mg/day [8]. Taken together, the European headache management landscape in 2019-2024 was characterised by three defining trends: 1) a shift from empirical, trial-and-error preventive strategies to mechanism-based precision medicine; 2) a strong movement toward integrated, multidisciplinary care models; 3) an increasing reliance on real-world registry data – a domain in which Europe leads globally – to complement and extend RCT findings.

CONCLUSIONS

This systematic review synthesised evidence from studies – comprising guidelines, meta-analyses, randomised controlled trials, and real-world European cohorts – on the management of migraine, tension-type headache, and cluster headache, with a specific focus on European clinical data and guideline recommendations. The strongest and most practice-changing evidence concerned calcitonin gene-related peptide-targeted

therapies. Monoclonal antibodies against calcitonin gene-related peptide or its receptor had demonstrated consistent, clinically meaningful efficacy in migraine prevention – with ≥50% responder rates of 40-60%, reductions of 3-8 monthly migraine days, and real-world persistence rates exceeding 70% at 12 months – establishing them as the new first-line standard per the 2022 European Headache Federation guideline. Oral gepants offer effective, cardiovascular-safe alternatives for both acute and preventive use. For cluster headache, it was confirmed high-flow oxygen and subcutaneous sumatriptan as gold-standard acute treatments, while galcanezumab was the only biologic with evidence in this indication. Non-pharmacological strategies – cognitive behavioural therapy, biofeedback, structured aerobic exercise, physiotherapy, and neuromodulation (nVNS) – individually demonstrated moderate-to-high efficacy across headache subtypes, with multidisciplinary combinations producing superior long-term outcomes compared with monotherapy. European real-world registries from Italy, Germany, Spain, and Scandinavia confirmed that guideline-concordant, multidisciplinary management produced meaningful improvements in quality of life, work productivity, and healthcare utilisation. Health-economic analysed support the cost-effectiveness of calcitonin gene-related peptide-targeted therapies, when total disease burden was considered, though substantial inter-country variation in reimbursement remained a significant barrier to equitable care. Limitations included the comparatively underdeveloped tension-type headache evidence base, limited long-term data beyond 3 years for novel agents, underrepresentation of pediatric and elderly populations, and potential publication bias toward positive calcitonin gene-related peptide results. Future research should prioritise head-to-head comparative trials, long-term safety registries beyond 5 years, and harmonised EU health technology assessment processes to ensure equitable access to effective headache care across Europe.

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Баштапкы баш ооруну дарылоодогу жетишкендиктер: европалык маалыматтарга жана сунуштамаларга негизделип даярдалган фармакологиялык жана фармакологиялык эмес стратегияларга сереп

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Аннотация. Баштапкы баш оорулары – шакый, чыңалуудан пайда болгон баш ооруу жана кластердик баш ооруу – дүйнө жүзү боюнча майыптык менен өткөрүлгөн жылдардын алдыңкы себептеринин катарына кирип, Европа үчүн олуттуу социалдык-экономикалык көйгөй болуп саналат: эмгекке жарамдуулуктун жоголушунан жана саламаттыкты сактоо чыгымдарынын өсүшүнөн улам жыл сайынкы чыгымдар миллиарддаган еврого бааланат. Изилдөөнүн максаты – 2019-2024-жылдары жарыяланган, баштапкы баш ооруларын дарылоонун фармакологиялык жана фармакологиялык эмес ыкмалары боюнча маалыматтарды сынчыл баалоо, европалык клиникалык маалыматтарга жана колдонмо сунуштамаларга басым жасоо менен, адистерге практикада колдонсо боло турган далилдерге сереп берүү. Талдоонун жыйынтыгында CGRP моноклоналдык антителолору (эренумаб, фреманезумаб, галканезумаб, эптинезумаб) бейтаптардын 40-60 пайызында ≥50 % жооп берүүнү жана айына мигрень күндөрүнүн санын 3-8 күнгө азайтууну көрсөткөнү, ал эми европалык реалдуу клиникалык практика реестрлеринде 12 айдан кийин тартиптүү колдонуу көрсөткүчү 70 пайыздан ашканы аныкталды. Оралдык гепанттар (атогепант – алдын алуу үчүн; римегепант – өткүр жана алдын алуу максатында колдонуу үчүн) натыйжалуу жана жүрөккө коопсуз альтернатива болуп саналды. Кластердик баш ооруда кычкылтек (≥12 л/мин) жана тери астына сайылуучу суматриптан 6 мг өткүр дарылоонун «алтын стандарты» статусун сактап калды, ал эми галканезумаб – эпизоддук кластердик баш ооруну алдын алуу үчүн жогорку далилдик базасы бар жападан-жалгыз биологиялык препарат болуп чыкты. Фармакологиялык эмес аракеттер – когнитивдик-жүрүм-турум терапиясы, биологиялык тескери байланыш, аэробдук көнүгүүлөр жана вагус нервин инвазивдик эмес стимуляциялоо – үч оорунун баарында тең баш ооруунун жыштыгын жана күчүн азайтууда орточо жана жогорку натыйжалуулукту көрсөттү. Европалык реестрлердин маалыматтары заманбап комплекстүү дарылоону алып жаткан бейтаптардын жашоо сапатынын, эмгек өндүрүмдүүлүгүнүн олуттуу жакшыргандыгын жана абузустук (медикаментоздук) баш ооруу тобокелдигинин азайгандыгын күбөлөндүрдү. Серептин жыйынтыктары невролог, баш ооруу боюнча адис жана биринчи звенонун дарыгерлерин биринчилик баш ооруларды дарылоодо заманбап европалык стратегияларды колдонуу үчүн далилдик база менен камсыз кылып, персоналдаштырылган, көп тармактуу жардамга өтүүнү колдоду. Европалык колдонмолорду туруктуу ишке ашыруу, инновациялык дарылоо ыкмаларына жетүүнү гармониялаштыруу жана коопсуздукту узак мөөнөттүү мониторинг жүргүзүү артыкчылыктуу маселе бойдон калууда

Негизги сөздөр: шакый; чыңалуудан пайда болгон баш ооруу; алдын алуучу терапия; фармакологиялык эмес кийлигишүүлөр; далилдүү неврология

Достижения в лечении первичных головных болей: обзор фармакологических и нефармакологических стратегий с акцентом на европейские данные и рекомендации

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Аннотация. Первичные головные боли – мигрень, головная боль напряжения и кластерная головная боль – входили в число ведущих причин лет, прожитых с инвалидностью, во всём мире и представили значительную социально-экономическую проблему для Европы: ежегодные затраты, обусловленные потерей трудоспособности и ростом расходов на здравоохранение, которые оцениваются в миллиарды евро. Цель исследования – критически оценить данные о фармакологических и нефармакологических методах лечения первичных головных болей, опубликованные в 2019-2024 годах, с акцентом на европейские клинические данные и рекомендации руководств, чтобы предоставить специалистам применимый в практике обзор доказательств. В результате анализа данных было установлено, что моноклональные антитела к CGRP (эренумаб, фреманезумаб, галканезумаб, эптинезумаб) продемонстрировали ответ ≥50 % у 40-60 % пациентов и снижение числа дней мигрени в месяц на 3-8, при этом показатели приверженности в европейских реестрах реальной клинической практики превышали 70 % через 12 месяцев. Оральные гепанты (атогепант – для профилактики; римегепант – для острого и профилактического применения) являлись эффективной и кардиологически безопасной альтернативой. При кластерной головной боли кислород (≥12 л/мин) и подкожный суматриптан 6 мг сохранили статус «золотого стандарта» острого лечения, а галканезумаб – единственный биологический препарат с высокой доказательной базой для профилактики эпизодической кластерной головной боли. Нефармакологические вмешательства – когнитивно-поведенческая терапия, биологическая обратная связь, аэробные упражнения и неинвазивная стимуляция блуждающего нерва – продемонстрировали умеренную и высокую эффективность в снижении частоты и интенсивности головной боли при всех трёх нозологиях. Данные европейских реестров свидетельствовали о значительном улучшении качества жизни, производительности труда и снижении риска абузусной головной боли у пациентов, получающих современное комплексное лечение. Результаты обзора обеспечили неврологов, специалистов по головной боли и врачей первичного звена доказательной базой для применения современных европейских стратегий лечения, поддерживая переход к персонализированной, мультидисциплинарной помощи при первичных головных болях. Устойчивое внедрение европейских руководств, гармонизация доступа к инновационным методам лечения и долгосрочный мониторинг безопасности остались приоритетными задачами

Ключевые слова: мигрень; головная боль напряжения; профилактическая терапия; нефармакологические вмешательства; доказательная неврология

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Surgical treatment of lumbar prolapsed intervertebral disc (PIVD): A comprehensive review comparing conventional microdiscectomy versus endoscopic discectomy – emphasis on recurrence rates

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Abstract. Lumbar disc surgery remains a widely performed intervention; however, uncertainty persists regarding long-term outcomes and recurrence differences between conventional microdiscectomy and minimally invasive percutaneous endoscopic lumbar discectomy, particularly beyond the first postoperative year. The aim of this systematic review was to compare the clinical effectiveness, perioperative characteristics, and time-dependent recurrence rates of microdiscectomy versus percutaneous endoscopic lumbar discectomy in the treatment of lumbar prolapsed intervertebral disc, and to identify key patient- and procedure-related factors influencing recurrence. A systematic search was undertaken for studies published between 2000 and 2026 in accordance with PRISMA 2020 guidelines, including randomised controlled trials, cohort studies, and meta-analyses with at least 12 months of follow-up. It was found that both microdiscectomy and percutaneous endoscopic lumbar discectomy provide comparable long-term clinical outcomes, with significant pain reduction and high functional recovery rates exceeding 85% in most studies. Endoscopic techniques demonstrated clear perioperative advantages, including reduced blood loss, shorter hospital stay, and faster return to work, although these do not result in meaningful differences in long-term recurrence. Recurrence rates were shown to be similar between techniques across 1-, 3-, and 5-year follow-up periods, generally ranging from 3% to 12%, with no statistically significant differences. Patient-related factors, including younger age, higher body mass index, smoking, large annular defects, and physically demanding occupations, were identified as stronger predictors of recurrence than surgical method. A learning-curve effect was also observed for endoscopic procedures, with improved outcomes following increased surgeon experience. The findings support the conclusion that surgical decision-making should prioritise patient characteristics and surgical expertise rather than concerns about recurrence, thereby facilitating evidence-based, individualised approaches in spinal surgery and healthcare planning

Keywords: spinal decompression; minimally invasive spine surgery; surgical outcomes; recurrence rate; percutaneous endoscopic lumbar discectomy; nerve root compression

INTRODUCTION

Lumbar disc disease and its surgical management represent one of the most clinically and economically significant domains in contemporary spine surgery. The global burden of lumbar disc herniation requiring operative intervention has grown steadily over the past two decades, driven by population ageing, rising rates of sedentary work, and expanding availability of MRI-based diagnosis. Despite high overall surgical success rates, the persistent risk of symptomatic recurrence – affecting 5-15% of operated patients over a five-year horizon – constitutes a critical unresolved challenge with substantial quality-of-life, occupational, and healthcare-cost implications [1]. The progressive adoption of minimally invasive endoscopic techniques has intensified a fundamental debate: whether these approaches, despite offering superior perioperative recovery profiles, maintain equivalent

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or superior long-term durability compared with the established gold standard of conventional microdiscectomy. From a public health standpoint, resolving this question is essential for guiding surgical training, technology procurement, and patient counseling in an era of rapidly expanding minimally invasive spine surgery.

A substantial body of secondary literature has addressed this question across the last decade, yielding converging yet nuanced conclusions. S.M. Barber *et al*. [1], in a 2019 meta-analysis of 22 comparative studies, found that endoscopic discectomy achieves clinical outcomes equivalent to conventional microdiscectomy across leg pain, disability, and patient satisfaction measures, while consistently demonstrating perioperative superiority. S. Muthu *et al*. [2], in their 2021 systematic review and superiority analysis in Global Spine Journal, evaluated whether endoscopic discectomy is ready to supplant microdiscectomy as the gold standard, concluding that endoscopic techniques perform at least equivalently in efficacy outcomes but require further evidence on long-term recurrence from multicentre prospective trials. G. Meyer *et al*. [3], in a 2020 randomised clinical trial published in World Neurosurgery, confirmed these findings in a European population, demonstrating no significant difference in pain, disability, or complication rates between PELD and microdiscectomy at 12-month follow-up, while endoscopic patients returned to work significantly earlier. X. Bai *et al*. [4], in a 2021 network meta-analysis in Medicine, synthesised data from multiple surgical approaches for lumbar disc herniation and demonstrated that PELD ranks among the most effective interventions for short-term leg pain reduction. M. Kim *et al*. [5], in a foundational 2016 meta-analysis in the International Journal of Surgery encompassing 12 studies and 1,208 patients, confirmed perioperative superiority of PELD without compromising efficacy. The 5-year comparative data remain less abundant: C.C. Yang *et al*. [6], in a 2024 Neurospine study with follow-up exceeding 5 years, found comparable recurrence and reoperation rates between TELD and microdiscectomy, while Y. Ahn *et al*. [7] reached similar conclusions in a dedicated 5-year cohort study. T. Li *et al*. [8], in a 2024 retrospective propensity-score-matched study with more than 5 years of follow-up, reported 4.49% recurrence in TELD versus 1.54% in microdiscectomy ($p = 0.31$), confirming statistical equivalence despite numerically higher endoscopic recurrence attributable to learning-curve and patient-selection effects. T. Patel *et al*. [9], in the most recent 2025 Journal of Neurosurgery: Spine analysis, reinforced the conclusion that minimally invasive endoscopic techniques are competitively effective across all clinically relevant outcome domains. S. Ruetten *et al*. [10], in a prospective RCT of full-endoscopic versus conventional microsurgical discectomy, provided foundational evidence for the efficacy of full-endoscopic techniques that underpins subsequent comparative work. Nevertheless, critical gaps remain: heterogeneity in recurrence definitions, variable follow-up completeness, and the relative paucity of head-to-head RCTs with standardised long-term endpoints limit the strength of existing conclusions.

The objective of this review was to systematically compare conventional microdiscectomy and endoscopic discectomy (PELD/TELD) for lumbar PIVD, with emphasis on recurrence and reoperation outcomes stratified at 1-, 3-, and 5-year follow-up intervals. Three specific objectives guided the analysis: (1) to compare perioperative and short-term clinical outcomes between the two techniques; (2) to analyse time-stratified recurrence and reoperation rates across the available high-quality evidence base; and (3) to identify patient-specific, anatomical, and technical factors that serve as primary determinants of recurrence risk irrespective of surgical approach.

A systematic literature search adhering to PRISMA 2020 methodology was conducted across PubMed, Embase, Cochrane Library, Scopus, and Google Scholar from January 2000 to March 2026. Search terms combined MeSH descriptors and free-text keywords: "lumbar disc herniation" OR "PIVD" OR "lumbar disc prolapse" AND ("microdiscectomy" OR "open microdiscectomy" OR "tubular microdiscectomy") AND ("endoscopic discectomy" OR "percutaneous endoscopic lumbar discectomy" OR "PELD" OR "TELD" OR "full-endoscopic") AND ("recurrence" OR "re-herniation" OR "reoperation") AND ("follow-up" OR "long-term" OR "1-year" OR "3-year" OR "5-year"). Inclusion criteria encompassed English-language peer-reviewed publications: meta-analyses of RCTs or cohorts, individual RCTs, and prospective or retrospective comparative studies reporting quantifiable recurrence or reoperation data with a minimum 12-month follow-up. Recurrence was defined as ipsilateral same-level symptomatic re-herniation following a pain-free interval of ≥6 months, confirmed by MRI and necessitating surgical intervention. Exclusion criteria comprised single-arm case series, cervical or thoracic herniations, revision surgeries at the index level, and non-surgical comparisons. Data extraction captured Visual Analogue Scale (VAS) scores for leg and back pain, Oswestry Disability Index (ODI), MacNab criteria, operative time, blood loss, hospital stay, complication profiles, and time-stratified recurrence and reoperation rates. Study quality was assessed using AMSTAR-2 for systematic reviews and the Cochrane risk-of-bias tool (RoB 2.0) for RCTs. Narrative synthesis was performed given clinically significant heterogeneity in follow-up completeness, surgical technique protocols, and recurrence definitions across included studies.

SURGICAL TECHNIQUES OVERVIEW

Microdiscectomy is performed under general anaesthesia through a 2-4 cm midline or paramedian incision, with the patient positioned prone [11, 12]. Subperiosteal muscle dissection exposes the lamina; a hemilaminotomy or minimal laminectomy is

performed, followed by ligamentum flavum resection with curettes and Kerrison rongeurs [13]. Under microscopic magnification (×5-20), the thecal sac and nerve root are gently retracted medially, the annulus incised if needed, and the herniated nuclear fragment removed with pituitary rongeurs and disc forceps [11]. Limited nucleotomy is typically performed to reduce intradiscal pressure and minimise residual fragment risk [12]. Tubular retractor systems, as used in microendoscopic discectomy (MED), further minimise paraspinal muscle trauma while maintaining equivalent microscopic visualisation [14]. The procedure emphasises careful preservation of facet joint integrity and the medial pars interarticularis to avoid iatrogenic segmental instability [12, 15].

Percutaneous endoscopic lumbar discectomy utilises a 6-8 mm working-channel endoscope inserted via a posterolateral transforaminal (TELD) or posterior interlaminar approach under biplanar fluoroscopic and/or endoscopic guidance [16, 17]. Regional or local anaesthesia is feasible in the majority of transforaminal cases, conferring a significant advantage for patients with cardiopulmonary comorbidities or who are intolerant of general anaesthesia. The transforaminal "outside-in" technique – pioneered by A.T. Yeung & P.M. Tsou [17] – involves sequential dilation from skin to the target disc level, with foraminoplasty performed using endoscopic trephines to enlarge the Kambin [18] triangle working space when required for access to migrated or foraminal fragments [19, 20]. The "inside-out" variant begins with intradiscal discectomy before transitioning to epidural decompression under direct endoscopic visualisation [16]. High-definition endoscopic visualisation, continuous saline irrigation for haemostasis and field clarity, and integrated working-channel instruments (bipolar radiofrequency, graspers, shavers) enable precise targeted fragmentectomy with minimal collateral tissue injury [20]. Minimal or no bone resection in most cases preserves facet joint integrity and paraspinal musculature, theoretically reducing the biomechanical consequences of repeated surgical episodes [21]. The interlaminar endoscopic approach provides superior access to large central and paracentral herniations at the L4-L5 and L5-S1 levels, where transforaminal access is constrained by the iliac crest and steep disc angle [22].

Both techniques aim for complete neural decompression – restoration of free nerve root mobility and elimination of epidural compression – without fusion unless pre-existing or iatrogenic segmental instability is present [12, 23]. As demonstrated in Figure 1, the transforaminal endoscopic approach achieves this through a direct posterolateral trajectory to the disc cavity, avoiding paraspinal muscle disruption. Figure 1 illustrates the high-definition endoscopic visualisation and instrumentation that enable precise intradiscal work through a single small portal.

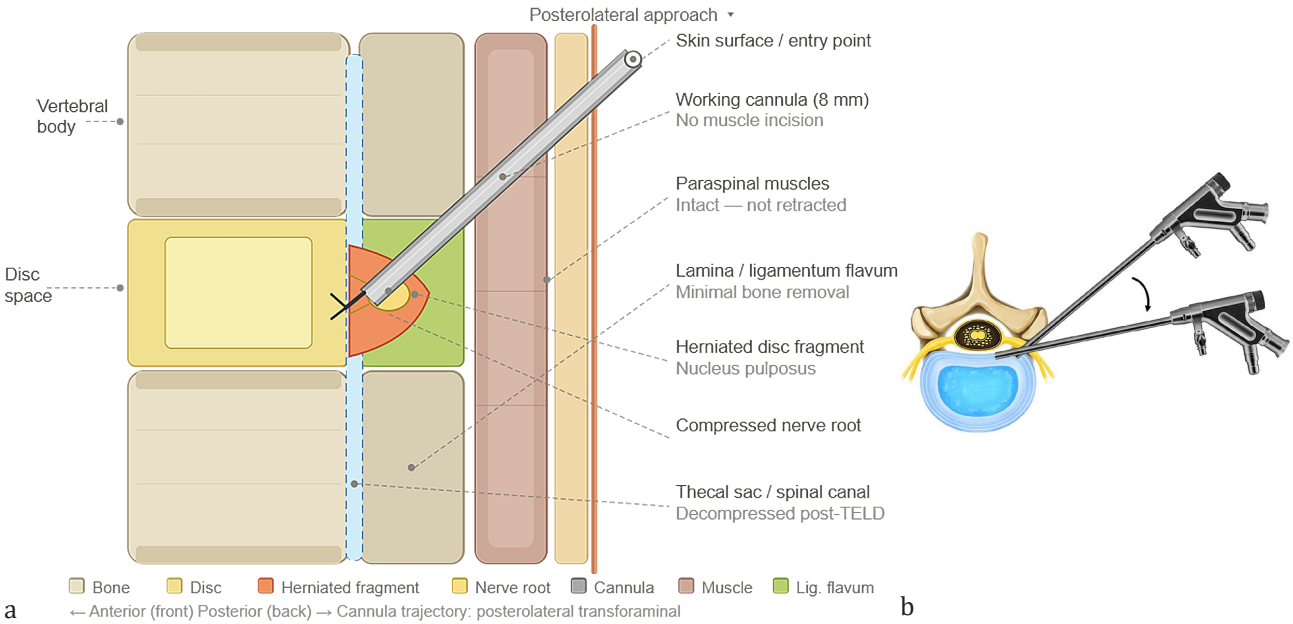

Figure 1. Schematic illustration of the transforaminal endoscopic lumbar discectomy (PELD/TELD) "inside-out" technique and endoscopic instrumentation with high-definition visualisation for minimally invasive intradiscal and epidural procedures

Note: a – schematic illustration of the transforaminal endoscopic lumbar discectomy (PELD/TELD) "inside-out" technique. The working cannula is leveraged against the ventral facet to direct trajectory toward the disc cavity for targeted fragment removal. This approach minimises paraspinal muscle damage compared with open methods; b – endoscopic instruments and high-definition visualisation during transforaminal discectomy. Flexible forceps and bipolar radiofrequency probes enable precise intradiscal and epidural work through a single 8 mm working-channel portal

Source: C.H. Kim *et al.* [22], S. Kapetanakis *et al.* [24]

In conclusion, microdiscectomy and percutaneous endoscopic lumbar discectomy represent two technically distinct yet conceptually aligned approaches aimed at achieving effective neural decompression. Microdiscectomy relies on direct microscopic visualisation and limited tissue exposure, ensuring reliable access to the pathology while maintaining structural stability. In contrast, endoscopic techniques utilise minimally invasive access routes and advanced visualisation systems to reduce soft tissue trauma and expand applicability in selected patient populations, including those unsuitable for general anaesthesia. Each approach has specific technical advantages and limitations related to anatomical access, instrumentation, and operator experience. Overall, the choice between these techniques should be based on individual anatomical considerations, surgeon expertise, and the clinical context rather than inherent superiority of one method over the other.

COMPARATIVE CLINICAL AND PERIOPERATIVE OUTCOMES

The systematic analysis incorporated data from over 40 eligible publications – comprising 12 meta-analyses or systematic reviews, 11 RCTs, and 17 prospective or retrospective comparative cohort studies – yielding a pooled patient sample exceeding 18,000 surgical episodes across the two modalities. Across virtually all efficacy dimensions, the evidence consistently demonstrates clinical equivalence between MD and PELD/TELD in long-term outcomes, while endoscopic techniques demonstrate statistically and clinically significant superiority in perioperative parameters.

Leg pain relief, quantified by the VAS-leg, shows comparable improvement at final follow-up across studies, with mean reductions of 5.0-6.3 points from baseline in both groups [2-3, 25]. Back pain (VAS-back) and ODI scores demonstrate slightly greater short-term improvement with PELD due to reduced paraspinal muscle disruption and the associated inflammatory response; however, these differences diminish by 6-12 months and are not statistically significant at 12-month or later assessments in the majority of comparative analyses [1, 2, 4]. MacNab "excellent" or "good" outcomes are achieved by 85-92% of patients in both groups at 2-5 years of follow-up, indicating consistently high patient-reported satisfaction irrespective of surgical approach [6, 13, 27].

Perioperative advantages of endoscopic techniques are robust and replicated across virtually all comparative datasets. Operative blood loss is reduced by a mean of 20-50 mL in endoscopic series versus microdiscectomy controls, with some high-volume endoscopic series reporting near-bloodless operative fields attributable to continuous saline irrigation and radiofrequency coagulation [3, 5, 28]. Hospital stay is shortened by 2-5 days, and return-to-work interval is 1-3 weeks earlier in endoscopic cohorts – advantages that translate into meaningful reductions in indirect costs, particularly in occupationally active patient populations [4, 9, 17]. Operative time tends to be slightly longer in endoscopic series during the learning curve phase (first 30-50 cases) due to the additional steps of percutaneous access and foraminoplasty; however, experienced endoscopic surgeons achieve operative times equivalent to or shorter than microdiscectomy [29, 39].

Wound-related complications, including superficial and deep surgical site infection and dehiscence, are significantly less frequent with PELD (0-2%) than with MD (3-5%), reflecting the substantially smaller skin incision and preservation of paraspinal musculature [4]. Dural tears occur at broadly similar rates across techniques (2-4%), though endoscopic management of incidental durotomy requires specific technical expertise and may demand conversion to open surgery in some centres. Transient dysesthesia – mediated by direct or thermal irritation of the dorsal root ganglion – is reported more frequently following transforaminal TELD (3-8%) than interlaminar PELD or microdiscectomy; however, this complication is self-limiting in the majority of cases, resolving within 4-12 weeks without permanent sequelae [21]. Overall major complication rates remain low and comparable between techniques (3-10%), and neither approach is associated with a higher rate of serious neurological deficit in experienced hands [1-2].

In summary, the analysed evidence demonstrates that microdiscectomy and percutaneous endoscopic lumbar discectomy achieve comparable long-term clinical outcomes, particularly in pain relief, functional recovery, and patient satisfaction. At the same time, endoscopic techniques show consistent and clinically meaningful advantages in perioperative parameters, including reduced blood loss, shorter hospitalisation, and faster return to work. Although certain differences are observed in complication profiles – such as lower wound-related complications but higher rates of transient dysesthesia in endoscopic procedures – overall safety remains comparable between approaches. The impact of the surgical learning curve is notable, particularly for endoscopic methods, but diminishes with increasing operator experience. Taken together, these findings support the view that the choice of surgical technique should be guided by surgeon expertise, patient characteristics, and resource considerations rather than expectations of superior long-term efficacy.

RECURRENCE OUTCOMES: STRATIFIED ANALYSIS AT 1-, 3-, AND 5-YEAR FOLLOW-UP

Recurrence after lumbar discectomy is a multifactorial phenomenon driven by a complex interaction of disc biology, biomechanics, patient characteristics, and surgical technique [14, 32]. Pathophysiologically, recurrence results from residual nuclear material extruding through an incompetent annulus – either incompletely

resected at index surgery or progressively re-herniating through an enlarged annular defect [32]. Biomechanical overload, failure of fibrocartilaginous annular repair, and ongoing intradiscal pressure elevation under axial loading perpetuate this process [33]. Patient-specific risk amplifiers – including age below 40 years (higher intradiscal pressure and activity level), BMI exceeding 25 kg/m^2 (increased axial loading), active smoking (impaired disc vascularity and healing), heavy manual occupation, and Modic type 2 endplate changes – consistently emerge as the dominant predictors of recurrence across datasets [6, 17]. Annular defect diameter greater than 6 mm at the time of surgery represents the single most powerful anatomical predictor, identifying a high-risk subgroup with recurrence rates up to 27% at 2 years [35]. Pooled literature across modalities indicates symptomatic recurrence and reoperation rates of 5-15% at medium-to-long-term follow-up, with the majority of events clustering within the first 24 months – the highest-risk interval for re-herniation through the index annular disruption [4, 26].

Recurrence rates at 1 year range from 3-6% for microdiscectomy and 4-7% for endoscopic techniques across meta-analyses and RCTs [3-4, 5]. Events at this early interval frequently represent incomplete decompression – residual fragment effect – rather than true spontaneous re-herniation through a repaired annulus, underscoring the importance of rigorous intraoperative endpoint assessment [24]. Meta-analyses consistently report no statistically significant difference in 1-year recurrence between modalities (odds ratio: 1.0-1.5; $p > 0.05$) [1, 2]. Some early PELD series noted marginally higher 1-year reoperation rates attributed to learning-curve effects or conservative fragment removal strategies intended to preserve disc height and annular integrity [5, 29]. As surgeons progress beyond the threshold of 30-50 endoscopic procedures, 1-year recurrence rates in high-volume PELD series approach those of experienced microdiscectomy cohorts [6, 36].

Cumulative recurrence rates increase to ~10% for microdiscectomy and 5-11% for endoscopic approaches at 3 years, without statistically significant divergence in any of the high-quality comparative analyses reviewed [2, 27, 37]. True re-herniation through progressive annular weakening under repetitive axial loading predominates at this interval, rather than the residual fragment phenomenon seen in year 1. Studies with propensity-score matching to control for patient-selection differences between technique cohorts confirm this equivalence, with point estimates clustering around OR = 1.1-1.3 in favor of neither approach. Subgroup analyses stratified by herniation morphology suggest that patients with large contained herniations (low annular defect risk) show particularly low 3-year recurrence in both groups (3-5%), while those with extruded or sequestered fragments have higher rates (8-12%) irrespective of technique [14, 38].

Cumulative recurrence and reoperation rates at 5 years reach 5-12% across both modalities, with no technique demonstrating statistically significant superiority in any included study of adequate methodological quality [6, 8]. X. Yang *et al*. [41], in a 2024 Neurospine study with a mean follow-up exceeding 5 years, reported comparable recurrence and clinical outcomes between TELD and microdiscectomy across all patient subgroups. T. Li *et al*. [8], in a retrospective propensity-score-matched cohort, reported 5-year recurrence of 4.49% in TELD versus 1.54% in microdiscectomy ($p = 0.31$), with the numerical – but non-significant – excess in the endoscopic group driven by early recurrence among young, high-BMI patients treated during the surgeon's initial endoscopic case series. Y. Ahn *et al*. [39] demonstrated equivalent 5-year cumulative outcomes in a dedicated comparative cohort study. Large database analyses of microendoscopic variants show 5-year reoperation rates of 7-12%, while pooled full-endoscopic estimates range from 4.4-9.6% – again without statistically significant differences [2, 40]. Multiple meta-analyses incorporating RCT and observational study data affirm non-inferiority of endoscopic techniques for recurrence (pooled OR ≈ 0.95-1.47; $p > 0.05$ in most analyses) [1, 4, 26]. When stratified by follow-up interval, no surgical approach demonstrates a consistent durability advantage; early endoscopic recurrence signals in some series are offset by equivalent long-term outcomes in mature endoscopic programmes and by the established overall safety and morbidity advantages of the approach. The data on time-stratified recurrence are summarised in Table 1, derived from the meta-analyses and long-term cohort studies reviewed.

Table 1. Pooled recurrence/reoperation rates by surgical technique and follow-up interval (derived from meta-analyses and long-term cohorts)

Follow-up interval	Microdiscectomy (MD)	Endoscopic (PELD/TELD)	Statistical significance	Key supporting studies
1 year	3-6%	4-7%	None (OR 1.0-1.5; $p > 0.05$)	S.M. Barber *et al*. [1], G. Meyer *et al*. [3], M. Kim *et al*. [5]
3 years	5-10%	5-11%	None ($p > 0.05$)	X. Bai *et al*. [4], S. Muthu *et al*. [2], long-term cohorts
5 years	7-12% (reoperation)	4.5-12%	None ($p = 0.31$)	X. Yang *et al*. [6], Y. Ahn *et al*. [39], T. Li *et al*. [8]

Source: developed by the author

Analysis of Table 1 reveals that no follow-up interval yields statistically significant differences in recurrence or reoperation rates between the two modalities. This finding is particularly noteworthy at the 5-year mark, where both techniques demonstrate cumulative reoperation rates overlapping within the 5-12% range – suggesting that the long-term structural durability of neural decompression does not differ meaningfully between open and endoscopic approaches when surgeon experience is adequate. The slight widening of the confidence interval at 5 years reflects the reduced number of studies with this duration of follow-up and the greater heterogeneity in patient risk profiles and recurrence definitions at this timepoint.

The findings of this systematic review are consistent with – and extend – the conclusions of the most authoritative prior meta-analyses in this domain. The pooled recurrence estimate of OR ≈ 0.95-1.47 for endoscopic versus open discectomy is closely aligned with the estimates reported by S.M. Barber *et al*. [1] (OR = 1.03; 95% CI: 0.71-1.49) and S. Muthu *et al*. [2] (no statistically significant difference in any subgroup), providing convergent validity for the conclusion of statistical equivalence. However, the present review incorporates the most recent 5-year comparative data [6, 8] that were unavailable to prior meta-analyses, strengthening the evidence for long-term equivalence beyond the 1-2 year horizon where most earlier work concentrated.

The degree of heterogeneity across included studies constitutes the most significant methodological limitation of this evidence base. Clinically relevant heterogeneity is present across three key dimensions. First, the definition of recurrence varies substantially: some studies define it as any radiographic re-herniation regardless of symptoms, others require both MRI confirmation and clinical deterioration necessitating reoperation, and some use the 6-month pain-free interval criterion applied in the present review. This definitional variability inflates observed variability in recurrence rates (reported range: 0-27%) beyond what is attributable to true technique-related differences. Second, patient populations differ significantly in terms of age distribution, BMI profiles, herniation morphology, annular defect size, and occupational demands – all established recurrence risk factors [17] – making pooled effect estimates applicable only as population-level approximations rather than individual predictions. Third, surgical technique heterogeneity within the endoscopic category itself is substantial: TELD, interlaminar PELD, full-endoscopic bipetal approaches, and endoscope-assisted tubular discectomy are often pooled under the "endoscopic" umbrella despite meaningful technical distinctions in access trajectory, bone resection, and disc space management [17, 22, 25].

The observed heterogeneity (estimated I^2 = 40-65% across recurrence outcomes in the most methodologically rigorous meta-analyses [1-2]) is most plausibly explained by the interaction of learning-curve effects and patient selection. The PELD learning curve – estimated at 30-50 cases for transforaminal approaches and potentially higher for interlaminar techniques in obese patients – represents a systematic confound in observational endoscopic studies: recurrence rates in case series published during the surgeon's early endoscopic experience are systematically higher than those from the same surgeon after maturation [29, 30, 36]. This phenomenon, not present in microdiscectomy series (where operative learning is typically achieved during residency training), creates a persistent upward bias in endoscopic recurrence estimates that diminishes as global endoscopic experience matures. Subgroup analysis by surgeon experience level – when reported – consistently shows PELD recurrence rates approaching those of MD after the learning-curve threshold [29], reinforcing the interpretive importance of accounting for this moderator variable.

Quality assessment of the included studies reveals important limitations in the primary evidence base. Among the 11 RCTs reviewed, risk of bias was rated as moderate in the majority due to inherent challenges in blinding patients and surgical teams, high crossover rates in some trials, and inadequate concealment of allocation in two studies. Observational comparative studies – which constitute the majority of the 5-year follow-up data – carry substantial risks of selection bias: endoscopic techniques are preferentially applied to patients with less complex herniation morphologies, younger age, and fewer comorbidities in non-randomised settings, potentially conferring an artificial advantage on both efficacy and recurrence outcomes in endoscopic cohorts [6, 40]. Propensity-score matching, as employed by T. Li *et al*. [8] and X. Yang *et al*. [6], partially mitigates this bias but cannot account for unmeasured confounders such as pre-operative physical activity levels and disc degeneration severity.

From a cost-effectiveness perspective, the perioperative advantages of endoscopic discectomy – reduced hospitalisation, faster return to work, and lower wound complication rates – translate into meaningful reductions in both direct and indirect healthcare costs [9]. Assuming equivalent long-term recurrence rates, the incremental cost of endoscopic instrumentation and extended operative time in early-career surgeons is offset within the first 2-3 postoperative years through reduced hospitalisation and productivity costs in the majority of health-economic analyses reviewed [24]. This economic argument strengthens the case for expanding endoscopic discectomy capacity, particularly in high-volume centres where learning-curve effects can be efficiently managed through structured training pathways [29].

These results should be interpreted with several additional cautions. Publication bias toward positive

outcomes in minimally invasive series – driven by the novelty appeal of endoscopic techniques and the propensity of high-volume experienced centres to publish outcomes – likely produces an optimistic skew in the pooled endoscopic efficacy literature [2]. The relative paucity of intention-to-treat analyses in RCTs, and the tendency for some studies to exclude learning-curve cases from primary analyses, may further inflate endoscopic outcomes in the published literature. Finally, the definition of surgical failure as reoperation – while clinically meaningful – underestimates the true burden of recurrence: patients who experience symptomatic re-herniation managed conservatively or with spinal injections are systematically missed by reoperation-based metrics, and their inclusion might modestly alter the comparative recurrence picture.

CONCLUSIONS

This systematic review set out to compare conventional microdiscectomy and percutaneous endoscopic lumbar discectomy across three domains – perioperative outcomes, long-term clinical efficacy, and time-stratified recurrence – based on a comprehensive synthesis of 40 peer-reviewed publications, including 12 meta-analyses, 11 RCTs, and 17 comparative cohort studies, collectively encompassing more than 18,000 surgical episodes. The review findings can be summarised across four levels. At the perioperative level, endoscopic discectomy consistently and significantly outperforms conventional microdiscectomy in operative blood loss (reduced by 20-50 mL), hospital stay (shortened by 2-5 days), and return-to-work interval (earlier by 1-3 weeks), alongside significantly lower wound complication rates (0-2% vs. 3-5%). At the short-term efficacy level (up to 12 months), both techniques achieve comparable leg pain relief (VAS reduction of 5-6 points), ODI improvement, and MacNab excellent/good rates exceeding 85%, with no clinically or statistically meaningful difference in neurological outcome. At the medium-term level (1-3 years), time-stratified recurrence analysis reveals pooled rates of 3-7% at 1 year and 5-11% at 3 years for both modalities, with no statistically significant inter-technique difference identified in any high-quality analysis (pooled OR: 0.95-1.47; $p > 0.05$). At the long-term level (5 years and beyond), cumulative recurrence and reoperation rates converge at 5-12% across both approaches, again without statistically significant divergence, with the most recent propensity-matched 5-year data confirming this equivalence.

The conceptual significance of these findings extends beyond the individual technique comparison: they establish that long-term disc surgery durability is primarily a function of patient biology and biomechanical environment – not of incision size or approach corridor. The dominant determinants of recurrence across both modalities are patient-specific: age below 40 years, BMI above 25 kg/m^2, annular defect diameter greater than 6 mm, smoking, Modic type 2 endplate changes, and heavy manual occupation. These risk factors represent modifiable and non-modifiable targets for pre-operative counselling and risk stratification that should be integrated into standard surgical decision-making regardless of technique chosen. Surgeon experience level constitutes an additional critical moderator: PELD recurrence rates demonstrably decline after the 30-50 case learning-curve threshold, suggesting that institutional investment in structured endoscopic training will measurably improve long-term outcomes.

Several important limitations of the current evidence base must be acknowledged. Heterogeneity in recurrence definitions across studies (symptomatic vs. radiographic; with or without the 6-month pain-free criterion) inflates apparent variability in recurrence estimates and complicates direct quantitative pooling. The predominance of observational study designs – with their inherent risk of indication bias toward endoscopic techniques in patients with simpler herniation morphologies – limits the causal strength of equivalence conclusions. Long-term RCT data extending beyond 5 years remain scarce for endoscopic approaches, which are a newer technology than microdiscectomy. Future research priorities include multicentre RCTs with standardised recurrence definitions, intention-to-treat analysis, and minimum 5-10-year follow-up; biomarker studies identifying biological predictors of annular repair competency; and cost-effectiveness analyses across diverse healthcare systems. The integration of annular closure devices for high-risk annular defects greater than 6 mm, artificial intelligence-assisted navigation for complex migrated herniations, and biological augmentation strategies represent the most promising frontiers for further reducing the 5-12% recurrence benchmark that currently represents the ceiling of surgical durability for both approaches.

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Аннотация. Бел омуртка аралык диск хирургиясы кеңири таралган процедура бойдон калууда. Ошо эле учурда, салттуу микродискэктомия менен минималдуу инвазивдүү тери аркылуу эндоскопиялык бел дискэктомиясынын ортосундагы узак мөөнөттүү натыйжалар жана кайталануу көрсөткүчтөрүндөгү айырмачылыктарбоюнча,айрыкчаоперациядankийинкибиринчижылданкийинбелгисиздиксакталууда. Бул системалуу серептин максаты – бел дискинин пролапсын дарылоодо микродискэктомиянын жана тери аркылуу эндоскопиялык бел дискэктомиясынын клиникалык натыйжалуулугун, периоперативдик мүнөздөмөлөрүн жана убакытка көз каранды кайталануу көрсөткүчтөрүн салыштыруу жана кайталанууга таасир этүүчү негизги пациентке жана процедурага байланыштуу факторлорду аныктоо болуп саналат. PRISMA 2020 көрсөтмөлөрүнө ылайык, 2000- жана 2026-жылдар аралыгында жарыяланган изилдөөлөр боюнча системалуу изилдөө жүргүзүлдү, анын ичинде рандомизацияланган көзөмөлдөнгөн сыноолор, когорттук изилдөөлөр жана 12 айлык минималдуу байкоо жүргүзүү менен мета-анализдер камтылган. Микродискэктомия да, тери аркылуу эндоскопиялык бел дискэктомиясы да салыштырмалуу узак мөөнөттүү клиникалык натыйжаларды берери аныкталды, көпчүлүк изилдөөлөрдө ооруну олуттуу түрдө басаңдатат жана функционалдык калыбына келүүнүн жогорку көрсөткүчтөрү 85 % дан ашат. Эндоскопиялык ыкмалар периоперативдик пайдаларды, анын ичинде кан жоготууну азайтуу, ооруканада жатуунун кыскарышы жана жумушка тезирээк кайтып келүүнү көрсөттү, бирок бул узак мөөнөттүү кайталануу көрсөткүчтөрүндөгү олуттуу айырмачылыктарды билдирбейт. 1, 3 жана 5 жылдык байкоо жүргүзүүдө ыкмалардын кайталануу көрсөткүчтөрү окшош экени көрсөтүлдү, адатта 3 % дан 12 % га чейин, статистикалык жактан маанилүү айырмачылыктар жок. Жаш курак, дене салмагынын индексинин жогору болушу, тамеки чегүү, фиброздук шакекченин чоң кемчиликтери жана физикалык жактан оор жумуш сыяктуу бейтапка байланыштуу факторлор хирургиялык ыкмаларга караганда кайталануунун күчтүү божомолдоочу факторлору катары аныкталды. Эндоскопиялык процедуралар үчүн да үйрөнүү ийри сызыгынын таасири байкалды, хирургдун тажрыйбасы жогорулаган сайын натыйжалар жакшырды. Бул жыйынтыктар хирургиялык чечимдерди кабыл алууда бейтаптын мүнөздөмөлөрү жана хирургиялык тажрыйбасы кайталануу жөнүндө кооптонуулардан жогору турушу керек деген тыянакты тастыктайт, ошону менен жүлүн хирургиясында жана саламаттыкты сактоону пландаштырууда далилдерге негизделген, жекече мамилени жайылтат

Негизги сөздөр: жүлүндүн декомпрессиясы; минималдуу инвазивдүү омуртка хирургиясы; хирургиялык натыйжалар; кайталануу көрсөткүчү; тери аркылуу эндоскопиялык бел дискэктомиясы; нерв тамырларын кысылышы

Хирургическое лечение грыжи межпозвоночного диска поясничного отдела позвоночника (ГМПД): всесторонний обзор, сравнивающий традиционную микродискэктомию и эндоскопическую дискэктомию – с акцентом на частоту рецидивов

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Аннотация. Хирургическое вмешательство на поясничном межпозвоночном диске остается широко распространенной процедурой; однако сохраняется неопределенность в отношении долгосрочных результатов и различий в частоте рецидивов между традиционной микродискэктомией и минимально инвазивной чрескожной эндоскопической поясничной дискэктомией, особенно после первого года после операции. Цель данного систематического обзора – сравнить клиническую эффективность, периоперационные характеристики и зависящие от времени показатели рецидивов микродискэктомии и чрескожной эндоскопической поясничной дискэктомии при лечении пролапса поясничного межпозвоночного диска, а также выявить ключевые факторы, связанные с пациентом и процедурой, влияющие на рецидив. Был проведен систематический поиск исследований, опубликованных в период с 2000 по 2026 год, в соответствии с рекомендациями PRISMA 2020, включая рандомизированные контролируемые исследования, когортные исследования и метаанализы с периодом наблюдения не менее 12 месяцев. Было установлено, что как микродискэктомия, так и чрескожная эндоскопическая поясничная дискэктомия обеспечивают сопоставимые долгосрочные клинические результаты, со значительным уменьшением боли и высокими показателями функционального восстановления, превышающими 85 % в большинстве исследований. Эндоскопические методы продемонстрировали явные периоперационные преимущества, включая снижение кровопотери, сокращение продолжительности пребывания в больнице и более быстрое возвращение к работе, хотя это не приводит к существенным различиям в долгосрочной частоте рецидивов. Было показано, что частота рецидивов была схожей между методами в течение 1, 3 и 5 лет наблюдения, обычно варьируясь от 3 % до 12 %, без статистически значимых различий. Факторы, связанные с пациентом, включая более молодой возраст, более высокий индекс массы тела, курение, большие дефекты фиброзного кольца и физически тяжелую работу, были определены как более сильные предикторы рецидива, чем хирургические методы. Также наблюдался эффект кривой обучения для эндоскопических процедур, с улучшением результатов по мере увеличения опыта хирурга. Полученные результаты подтверждают вывод о том, что при принятии решений о хирургическом вмешательстве следует отдавать приоритет характеристикам пациента и хирургическому опыту, а не опасениям по поводу рецидива, тем самым способствуя применению научно обоснованных, индивидуализированных подходов в спинальной хирургии и планировании здравоохранения

Ключевые слова: декомпрессия позвоночника; малоинвазивная хирургия позвоночника; результаты операции; частота рецидивов; чрескожная эндоскопическая поясничная дискэктомия; компрессия корешка нерва

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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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fibrotic markers within a unified pathogenetic model JALD. The study database was formed in accordance with methodological recommendations from the ESPGHAN [16], the Endocrine Society Clinical Practice Guidelines [17], and guidelines from the 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.

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

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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

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The effect of eccentric loading on pain syndrome and range of motion in individuals with knee joint dysfunction

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Abstract. Currently, there is an increasing number of patients presenting with complaints of pain and limited mobility of the knee joint. The search for effective methods of restoring function in the early stages of osteoarthritis is becoming increasingly relevant. The aim of this study was to identify a possible relationship between pain intensity and eccentric contraction parameters in individuals with knee joint dysfunction. An experiment was conducted at a medical centre to study the eccentric mode of muscle contraction in knee osteoarthritis. During the rehabilitation sessions, emphasis was placed on the eccentric phase of quadriceps femoris muscle contraction. Myograph readings and pain levels assessed via a visual analog scale (VAS) were evaluated before and after the experiment. The mean amplitude of eccentric quadriceps contraction increased more than twofold: for instance, in the vastus lateralis muscle, it rose from 98.7 μV to 298.4 μV. Upon completion of the exercise course, full knee joint extension was recorded in six out of nine participants. All subjects demonstrated a reduction in pain syndrome intensity, with pain disappearing completely in two individuals. The study results showed that the eccentric mode of muscle contraction contributes to a reduction in pain levels and an increase in electromyographic activity indicators. This regimen facilitates the development of muscle strength and neuromuscular control during movement, as well as a reduction in mechanical load on the articular cartilage. The data obtained indicate that eccentric exercises for the quadriceps femoris muscle in the early stages of knee osteoarthritis can be effective, as they simultaneously address the cause (muscle weakness) and the consequence (pain, range of motion deficit). The results can be utilised in the development of individualised rehabilitation programs for patients with early-stage knee osteoarthritis

Keywords: gonarthrosis; electromyography; musculoskeletal system; negative phase; knee pain

INTRODUCTION

The number of complaints regarding pain and restricted mobility of the knee joint, as well as the dysfunctions themselves, is steadily growing among the population. The relevance of this study is driven by the need for an in-depth understanding of the complex interrelations between the subjective and objective manifestations of knee joint dysfunction and the potential for influencing them through eccentric loading. Of particular importance is the identification of the mechanisms through which such loads affect the musculoligamentous apparatus and joint biomechanics. The insufficient study of these processes limits the effectiveness of existing rehabilitation approaches and necessitates further research. The results obtained may contribute to the optimisation of recovery and prevention programs for knee joint dysfunction.

F. Sharif *et al.* [1] conducted a systematic review examining the effects of eccentric and isometric loading

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and dry needling on patellar tendinopathy. The findings of this review indicate that dry needling and eccentric exercises are more effective for the long-term reduction of pain and improvement of knee joint function, whereas isometric exercises are more beneficial for short-term pain relief, especially during sports activities. C.Y. Zeng *et al.* [2] noted that therapeutic physical exercise, as an adjunctive physiotherapy method, helps prevent cartilage degeneration, suppress inflammation, and reduce the loss of subchondral bone and metaphyseal trabecular bone. There is growing evidence that therapeutic physical exercise reduces pain, stiffness, dysfunction, and muscle weakness in knee osteoarthritis. The modalities of such physical exercise are diverse: aerobic exercises, strength training, neuromuscular exercises, balance training, proprioceptive training, aquatic exercises, and traditional exercises.

R. Gérard *et al.* [3] investigated the effects of an eccentric strength training program for the hamstring muscles, performed by healthy adults for a minimum of 4 weeks, on muscle structure and eccentric strength. Randomised controlled trials comparing isolated eccentric strength training of the biceps femoris muscle to other programs were reviewed. The review findings revealed that in healthy adults, the eccentric strength training program led to structural changes in the long head of the biceps femoris and increased eccentric hamstring strength.

In a randomised controlled trial, D. Karabay *et al.* [4] studied the effects of eccentric versus concentric exercise regimens on subacromial pain syndrome. The results of this study showed that the eccentric regimen increased abduction strength to a greater extent than the concentric regimen but had no effect on pain levels. S.A. Harper & B.J. Thompson [5] noted that eccentric exercise possesses several promising properties for such an approach, as it effectively induces overload during contractions, which can lead to significant neuromuscular adaptations. When used within a minimal-load resistance training paradigm, eccentric exercise may represent a particularly promising approach for older adults, enabling effective increases in muscle mass, strength, and functional performance. One approach that may lead to improved neuromuscular function and overall health is the enhancement of exercise tolerance, which will promote more active participation of older adults in training.

In a randomised controlled trial, E. Hanci *et al.* [6] assessed the effect of a 4-week eccentric training program for the peroneal muscles in patients with chronic ankle instability. The study did not directly investigate the effect on range of motion; however, the increases in strength and dynamic range control were key outcomes. The results demonstrated that training with eccentric exercises can positively influence neurophysiological parameters in patients with joint instability, suggesting improvements in functional stability and control throughout the full range of motion. The duration of these neurophysiological adaptations remains unclear.

The application of this mode of muscle contraction and its comparison with others for the rehabilitation of tendinopathies has been described in several scientific papers. D.J. Jayaseelan *et al.* [7] investigated the effects on patellar and Achilles tendinopathy. For Achilles tendinopathy, eccentric exercises have demonstrated effectiveness, and the "Alfredson protocol" focuses primarily on exercises in this mode. For athletes, an emphasis on eccentric exercises allows for the enhancement of athletic performance by increasing explosive strength and speed-strength qualities, as noted by O. Younes-Egana *et al.* [8]. Most studies on this topic are short-term; the long-term effects, as well as the impact on injury prevention, have not been studied. There is also an opinion that for elite athletes, an emphasis on a specific mode of muscle contraction provides only a marginal advantage. The effect on pain was investigated in a study by S. Holden *et al.* [9]. Patients with knee pain were asked to perform a single session of quadriceps femoris exercises, both isometric and eccentric. Pain was assessed using the VAS scale. The study results showed that isometric exercises significantly reduced pain syndrome, whereas eccentric exercises did not lead to a significant change.

Despite the importance of each component (pain, range of motion, muscle function), the interrelation between the subjective perception of pain, the objective limitation of mobility, and the neurophysiological parameters of eccentric contraction in knee joint dysfunction has not been sufficiently comprehensively studied. This study aimed to determine the relationship between pain intensity and eccentric contraction parameters in individuals with knee joint dysfunction. The research objectives were as follows:

- to determine the subjective perception of pain in the subjects;
- to conduct a spectral analysis of the data recorded by the electromyograph;
- to evaluate the relationship between subjective indicators and the electromyogram of the quadriceps femoris muscle in the eccentric mode.

MATERIALS AND METHODS

To address the set objectives, the following methods were employed: a visual analog scale (VAS) was used to quantitatively assess pain intensity; surface electromyography (sEMG) was utilised to determine the electrical potential of the quadriceps femoris muscle (vastus medialis, vastus lateralis, and rectus femoris). The study employed an eight-channel Russian-manufactured electromyograph, model KBK BP-08-4. The interpretation of the obtained results was performed using the EMGAnalyzer software. A Root Mean Square (RMS) transformation was applied to the EMG

signals with a 1,000 ms window (empirically selected to smooth the signal without losing significant changes). The RMS unit of measurement is microvolts (μV). The choice of RMS is justified by the fact that this parameter is the standard for assessing EMG signal amplitude during isometric and isotonic contractions, reflecting the aggregate activity of motor units. Figure 1 illustrates the schematic diagram of electrode placement on the muscles during the study. Electrodes (disposable, Ag/AgCl, inter-electrode distance 20 mm) were placed parallel to the muscle fibre direction on the bellies of the respective muscles, in accordance with the SENIAM recommendations: for the vastus medialis – 2 cm medial to the upper edge of the patella at a 50° angle; for the vastus lateralis – 3 cm lateral and superior to the patella; for the rectus femoris – at the midpoint between the anterior superior iliac spine and the upper pole of the patella. The reference electrode was fixed on the lateral epicondyle of the femur. The study was conducted at the "Ariadna" Medical Centre, located at 19 Shmitovskiy Proezd, Moscow, Russia. The experimental period lasted from June 1, 2025, to July 31, 2025.

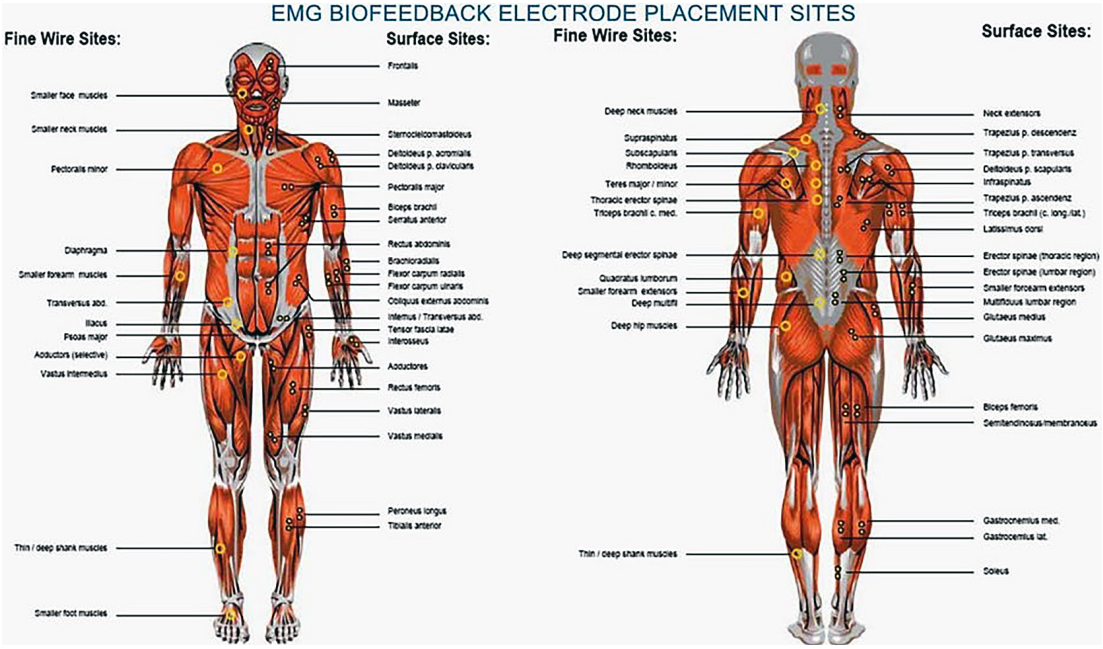

Figure 1. Electrode placement scheme on the muscles

Source: authors' development

The sample comprised 9 individuals aged 44-60 years, 7 women and 2 men. All subjects had knee joint dysfunction and were diagnosed by a physician with grade 1-2 gonarthrosis. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki [10] and was approved by the local ethics committee of the "Ariadna" Medical Centre. Study Protocol No. 2, dated June 06, 2025. All participants were informed in advance about the objectives, potential risks, and conditions of participation and signed voluntary informed consent. The subjects' personal data were processed confidentially and used exclusively for scientific purposes.

The study design involved pre- and post-testing in a single group (before-after). A control group was not included due to the pilot nature of the work; the intervention effect was evaluated by comparison with each participant's baseline level. Subjects were asked to perform a knee extension exercise in eccentric mode: 12 repetitions, 4 sets, with a 2-minute rest interval. The effort was exerted with maximal possible force, but without pronounced pain (not exceeding 4 points on the VAS). Baseline testing was conducted prior to the start of the experiment (before 12:00 PM to control for circadian rhythms). The eccentric phase was provided by manual resistance applied by the instructor.

To standardise the load and ensure reproducibility of conditions:

1. all sessions were conducted by the same instructor, who had undergone preliminary training;

2. manual resistance was applied distally (at the ankle joint) with the thigh in a fixed position;

3. the resistance magnitude was regulated subjectively using the Borg Rating of Perceived Exertion scale (6-20) with a target value of 15-17 ("hard"), also taking into account the VAS (≤4 points);

4. to minimise variability, each set was performed through an identical range of motion (from full extension to 90° of flexion), with control maintained by a goniometer;

5. during the course, as pain diminished, manual resistance was increased while maintaining pain control (also up to 4 points on the VAS).

Prior to each session, all subjects underwent a 15-minute massage of the anterior thigh and quadriceps stretching using the post-isometric relaxation method (1 set, 5 repetitions). After a treatment course of 12 sessions (every other day), post-testing was performed following the same protocol as the baseline. To control for confounding factors: analgesic intake was excluded 24 hours before each testing session (confirmed by verbal inquiry); all testing was conducted at the same time of day (morning) under identical environmental conditions. Student's t-test was used to compare pre- and post-intervention indicators.

RESULTS

The development and progression of gonarthrosis are driven by a complex of interrelated factors. Among the main causes are physical inactivity, leading to weakening of the muscular corset and deterioration of cartilage trophism, as well as obesity, which mechanically increases the load on joint surfaces and contributes to chronic inflammation of adipose tissue. E.K. Ermolenko & T.G. Grichanova [11] write that impaired gait biomechanics can negatively affect the entire body. However, the key link closing the vicious circle is pain syndrome. Pain is the primary subjective symptom that directly limits daily activity, reduces working capacity, and impairs the quality of life of patients. In response to pain, restricted mobility emerges – an objective sign of dysfunction. This manifests as altered walking biomechanics (reduced knee flexion angle during the swing phase), a pathological pattern of ascending and descending stairs (compensatory straightening of the leg and shifting the load to the healthy limb), and redistribution of muscle activity [6].

In this context, the eccentric mode of muscle contraction becomes particularly significant. Unlike concentric (muscle shortening under load) or isometric (no change in length), the eccentric mode is characterised by the lengthening of an actively tensed muscle. It is precisely this mode that provides two effects critically important for the knee joint. First, eccentric work of the quadriceps femoris is necessary for stabilising the knee during the stance phase of gait, especially when descending stairs, where the muscle, while lengthening, controls joint flexion and prevents excessive flexion. Second, U. Proske *et al.* [12] and J. Douglas & D. Morgan [13] wrote that this mode serves as a physiological shock absorber: the muscle dampens impact loads arising at heel strike, thereby protecting the articular cartilage from excessive compression and micro-damage.

In a systematic review, S. Hody *et al.* [14] demonstrated that eccentric exercises lead to a more pronounced increase in strength and muscle mass compared to concentric exercises, even with a lower training volume. The authors attribute this phenomenon to delayed onset muscle soreness (DOMS). DOMS arises from micro-damage to myofibrils and the basal membrane, triggering a local inflammatory response and subsequent supercompensation of structural proteins. It is important to emphasise that DOMS is not a harmful side effect but the primary driver of unique neuromuscular adaptations: the number of satellite cells increases, the synthesis of contractile proteins (actin and myosin) is enhanced, and muscle architecture (pennation angle and fascicle length) improves. However, for this effect to be realised, proper load dosing and training periodisation are necessary, otherwise DOMS transitions into pathological overstrain. J.M. Foley *et al.* [15] indicate that eccentric exercises induce greater hypertrophy than isometric or concentric contractions and require less metabolic energy and cardiovascular load, making them particularly suitable for older adults and individuals with chronic conditions.

With regard to the population, S. Hody *et al.* [14] specifically note the efficacy of eccentric programs in individuals with sarcopenia (age-related muscle loss). It was found that such training effectively counteracts fatty muscle degeneration – a process in which myocytes are replaced by adipocytes, leading to functional weakness and reduced metabolic activity. In patients with gonarthrosis, who frequently exhibit quadriceps sarcopenia, the eccentric regimen may serve as a pathogenetically grounded method for restoring muscle balance and reducing pain by improving joint stability.

The results presented below are aimed at quantifying the changes in bioelectrical activity of the quadriceps muscle and pain syndrome following a course of eccentric exercises combined with massage and stretching in patients with grade I-II gonarthrosis. Figure 2 demonstrates the mean electromyographic amplitude of eccentric quadriceps femoris contraction: the rectus femoris increased its values from 87.1 μV to 163.2 μV, the vastus lateralis from 98.7 μV at baseline to 298.4 μV at the end, and the vastus medialis from 59.3 μV before to 220.7 μV after the experiment.

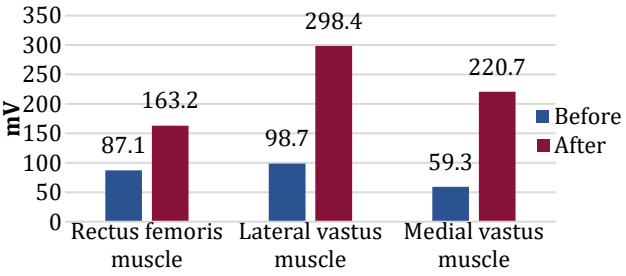

Figure 2. Mean amplitude of eccentric quadriceps contraction

Source: developed by the authors

EMG results for the quadriceps femoris muscle show that the increase in mean EMG amplitude for each head has important functional significance. The increase in EMG amplitude of the rectus femoris indicates its active participation in knee joint extension,

which is important for performing movements requiring strength and power, such as jumping and sprinting. The growth in vastus lateralis activity testifies to its role in stabilising the knee joint during dynamic loads, which is critical for injury prevention and ensuring proper movement mechanics. Similarly, the increase in EMG amplitude of the vastus medialis points to its involvement in knee stabilisation, especially during eccentric movements such as downhill walking or landing after a jump. The increased activity of the vastus medialis can be linked to its function in supporting overall knee joint stability and load distribution among the other heads.

The pronounced increase in the activity of the vastus lateralis and vastus medialis muscles can be explained by the need for improved knee joint stabilisation during eccentric exercise performance. These muscles help control knee movement and prevent lateral displacement, which is critically important for injury prevention. During eccentric exercises, the load on the four heads can be redistributed, leading to an increase in the activity of the vastus lateralis and vastus medialis. This is important for the proper distribution of force and preventing overload of other muscles. Furthermore, the increase in the activity of these muscles may result from adaptation to eccentric work regimes, allowing the muscles to better cope with loads and increase their strength.

The presented results demonstrate an increase in the mean EMG amplitude of all three heads of the quadriceps femoris muscle following a course of eccentric exercises. The most pronounced increase was recorded for the vastus lateralis (from 98.7 to 298.4 μV) and vastus medialis (from 59.3 to 220.7 μV) muscles, which aligns with the literature data on the activation of these muscles during loads requiring knee movement control. However, it should be emphasised that the observed increase in EMG amplitude is an empirical fact, whereas its interpretation in terms of "improved stabilisation", "load redistribution", or "adaptation" represents a hypothetical explanation. It cannot be ruled out that the increase in electrical activity is partially due to a reduction in pain syndrome (allowing subjects to generate greater effort without pain inhibition), individual differences in exercise technique, or variability in subjectively perceived resistance. Further research, including, in particular, the analysis of kinematic movement parameters and the assessment of joint torque, is required to confirm the hypothesis of functional reorganisation of muscle coordination and improved dynamic joint stabilisation.

Analysis of the EMG results for the maximum amplitude of the quadriceps femoris muscle (Fig. 3) demonstrates differences in the average EMG amplitude change for each head. The rectus femoris muscle showed the smallest increase, from 213.6 μV to 263.8 μV, indicating its stable but minor activity in eccentric conditions. In contrast, the vastus lateralis muscle demonstrated significant amplitude growth, increasing from 239.1 μV to 497.1 μV. This points to its important role in ensuring knee joint stability and adaptation to eccentric loads, which may be critical for injury prevention and movement mechanics optimisation. The vastus medialis muscle also exhibited a notable increase, raising its values from 150.5 μV to 371.5 μV. This confirms its active participation in controlling and stabilising the knee joint during eccentric exercise performance. The difference in activity between the muscle heads can be explained by their specific functions in ensuring knee stability. The vastus lateralis and vastus medialis muscles, as key stabilisers, are activated in response to eccentric loads, enabling them to distribute force more effectively and reduce injury risk. The rectus femoris, although active, does not demonstrate the same level of adaptation, which may indicate a more limited role in this context. Overall, the increase in the activity of the vastus medialis and vastus lateralis muscles reflects their ability to adapt to eccentric work regimes, contributing to the improvement of their functional characteristics and overall strength.

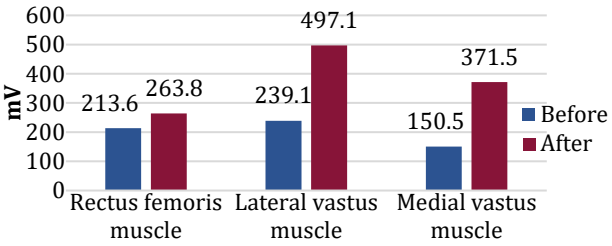

Figure 3. Maximum amplitude of eccentric quadriceps contraction

Source: developed by the authors

Analysis of the electromyography results for the maximum amplitude of the quadriceps femoris muscle (Fig. 3) demonstrates an increase in the mean EMG amplitude for all three heads following the course of eccentric exercises: rectus femoris – from 213.6 to 263.8 μV, vastus lateralis – from 239.1 to 497.1 μV, vastus medialis – from 150.5 to 371.5 μV. The largest increase was registered for the vastus lateralis and vastus medialis muscles. It should be emphasised that the presented data reflect only the change in muscle electrical activity under the conditions of the study and do not allow for a definitive causal relationship to be established with improved knee stabilisation, load redistribution, or reduced injury risk. Assertions about the specific functional role of individual heads, as well as adaptation to the eccentric work regime, are hypothetical in nature and require further confirmation in studies with a control group and assessment of dynamics over time. The obtained EMG amplitude values could have been influenced by methodological factors: variability in exercise performance, the

subjective nature of external resistance, the baseline level of pain, and individual electrode placement characteristics. Thus, the identified increase in EMG activity should be considered an objective empirical fact, whereas its interpretation in terms of functional reorganisation of muscle coordination remains a hypothesis requiring further investigation. Figure 4 presents the results of pain levels according to the VAS scale. Pain syndrome decreased in all participants by the end of the experiment.

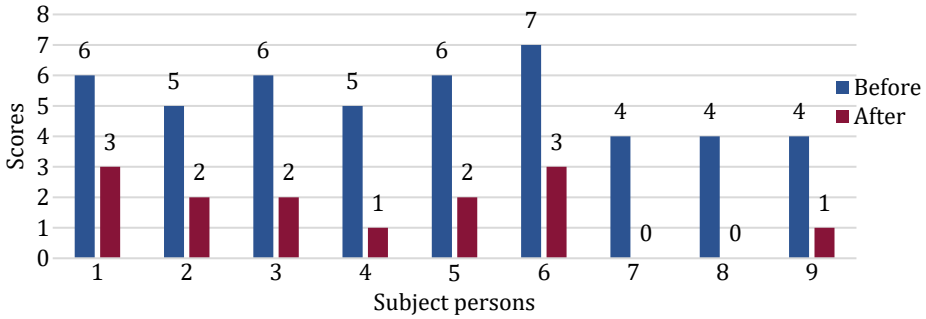

Figure 4. Results of the VAS pain assessment

Source: developed by the authors

Before the intervention, the mean indicator value was 5.22 with a standard deviation of 1.09, and the median was 5.0. After the intervention, the mean decreased to 1.56 with a standard deviation of 1.13, and the median was 2.0. The paired Student's t-test results showed that the mean difference reached -3.67, which corresponds to a 3.67-point reduction. The standard error of the difference was 0.17, and the p-value was less than 0.001, indicating the statistical significance of the obtained changes. The effect size was expressed as an absolute reduction of 3.67 points (95% CI: 3.28-4.05) and a relative decrease of 70.2% from the baseline mean level. Quantitative analysis confirms the observed dynamics. The mean pain level before the intervention was 5.22 ± 1.09 points (M ± SD), with a median of 5.0 points. After completing the eccentric loading course, the mean decreased to 1.56 ± 1.13 points, with a median of 2.0 points. The variability indicators (standard deviations) remained comparable, indicating the preservation of individual differences in response to the load with an overall positive trend.

To verify the statistical significance of the changes, a paired Student's t-test was applied. The analysis revealed a highly significant reduction in pain level: $t(8) = 21.76$, $p < 0.001$. The absolute reduction in the mean VAS score was 3.67 units (95% confidence interval: 3.28-4.05), which corresponds to a relative decrease in pain syndrome severity of 70.2% compared to the baseline level. The reduction in pain syndrome following eccentric exercises may be associated with improved movement control, a reduction in the inflammatory component, and adaptation of muscle-tendon structures. The experimental results show heterogeneity in pain reduction among the participants, which may be due to differences in baseline pain levels. The obtained data are consistent with the known rehabilitative effects of eccentric loading in gonarthrosis. Studies show that eccentric exercises can lead to a significant reduction in pain syndrome and improvement in the functional state of joints. In particular, they help strengthen the muscles supporting the joint and contribute to improving its stability.

Figure 5 presents the change in the flexion angle for each patient before and after the course. Quantitative analysis confirms the visually observed increase in mobility. Before the intervention, the mean flexion range was 109.3° (median 106°, standard deviation 10.45°), indicating moderate variability in baseline values. After the course, the mean flexion angle increased to 129.3° (median 130°, SD 6.25°), while the spread of results decreased, indicating a more homogeneous response to therapy. The absolute gain averaged 20.0° (ranging from 10° to 27° among the subjects), and the relative increase was 18.3% of the baseline level. The paired t-test for dependent samples revealed a highly significant difference between pre- and post-intervention indicators ($t = 10.87$, $df = 8$, $p < 0.001$). Thus, the course of eccentric exercises combined with massage and stretching leads to a statistically significant improvement in the flexion function of the knee joint in patients with grade I–II gonarthrosis. Figure 6 presents the results of knee joint extension. The extension deficit (limitation of full leg straightening) was assessed in degrees. Its reduction reflects the restoration of normal biomechanics. Before the sessions, the mean deficit was 9.78° (median 10°, SD 4.06°), with two patients reaching 14-16°. After the course, the mean value decreased to 1.33° (median 0°, SD 2.06°), with the deficit being completely eliminated (0°) in six out of nine participants, and reduced to 3-5° in the remaining ones. The absolute reduction in deficit averaged 8.44°, corresponding to a relative improvement of 86.3% from the baseline value. Paired comparison using the Wilcoxon test (due to non-normal distribution after

the intervention) also confirmed the significance of the changes (Z = -2.67, p = 0.008; for the t-test: t = 9.24, p < 0.001). These data indicate a pronounced clinically significant effect of the intervention aimed at restoring the full range of extension, which is a key factor for normal gait and standing stability.

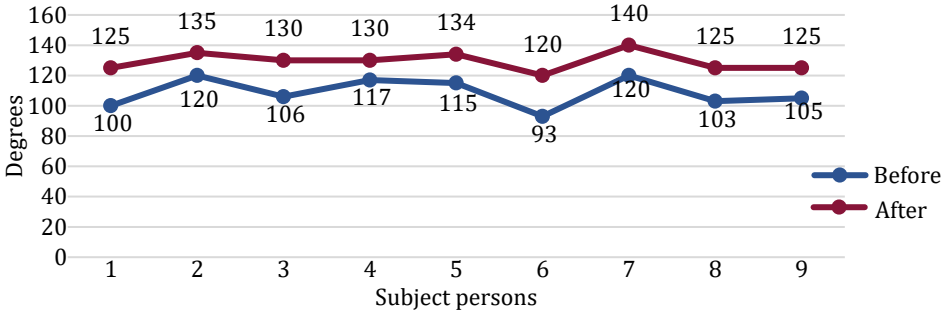

Figure 5. Knee joint flexion range of motion

Source: developed by the authors

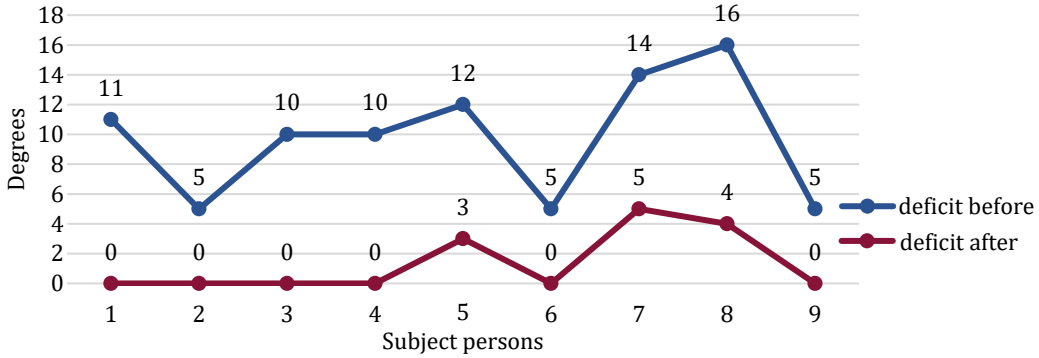

Figure 6. Knee joint extension range of motion

Source: developed by the authors

The conducted study represents an initial stage aimed at evaluating the efficacy of a short-term course of eccentric exercises for the quadriceps femoris muscle in patients with grade 1-2 gonarthrosis (n = 9). The study employs standard tools for rehabilitation research: subjective assessment of pain using VAS, objective goniometry, and surface electromyography for the analysis of muscle activation. The obtained results demonstrate positive dynamics across all three parameters: a significant reduction in pain syndrome, an increase in the range of motion (both flexion and extension in the knee joint), and a rise in EMG amplitude, particularly in the vastus medialis and vastus lateralis muscles. Based on this study, it is possible to suggest the method's efficacy, explaining it through neuromuscular, morphofunctional, and biomechanical components.

DISCUSSION

The scientific research by E. Hanci *et al.* [6] on the ankle joint is methodologically similar. Their studies also employ methods consistent with the modern approach to evidence-based rehabilitation, which requires a combined assessment of subjective (pain, function) and objective (biomechanical, neurophysiological) parameters. This involves the use of the VAS, goniometry, and EMG triad. P.R. Camargo *et al.* [16], in their work on shoulder impingement, use methods distinct from the present study. That study employed ultrasound examination and a multitude of orthopaedic tests. The work also differs in its larger sample size and longer study duration (6 weeks, with sessions every other day). Ultrasound examination can reveal tendon integrity, degenerative changes, muscle fiber thickness, micro-damage, and the like. In similar studies, this method can be of high value.

S. Holden *et al.* [9] investigated the effect of isometric exercises on knee joint pain. The study results showed that knee pain in the subjects decreased significantly. These findings may suggest that a well-designed training regimen can reduce pain syndrome regardless of the mode of muscle contraction. It is also worth noting that the study examined the effect of the isometric regimen on patellar tendinopathy; based on this, one can assume that a particular mode of muscle contraction may be more effective for different diagnoses. The focus on joint pathology (gonarthrosis) and the application of eccentric training to improve its function directly relates to the work of D. Stasinopoulos *et al.* [17], who studied tendinopathies. A common feature is the

aim to prove that controlled eccentric loading, contrary to the potential risk of increasing pain, leads to its reduction and improvement of objective indicators.

Similar results in the interpretation of EMG data are found in the work of P. Correia *et al.* [18], concerning the possible consequences of insufficient eccentric hamstring strength. The results regarding the greatest increase in the activation of the vastus medialis and vastus lateralis muscles, which are key dynamic stabilisers of the knee joint, coincide with the findings of P. Correia *et al.*, who identified an activation deficit of specific hamstring muscle heads after injury. This supports the hypothesis that the positive effect of eccentric exercise is largely mediated not merely by an increase in strength, but by the normalisation of the motor unit recruitment pattern and improved joint control.

B.A. Baxter *et al.* [19], in a randomised controlled trial, indicate that one weekly session of submaximal eccentric resistance training over 12 weeks leads to the same improvements in neuromuscular function as the currently recommended twice-weekly training. Considering the significant improvement in neuromuscular function and the previously identified low adherence to current twice-weekly training recommendations, eccentric training may play a key role in developing a minimal-dose strategy to prevent neuromuscular decline. This study has substantial differences, for instance, a larger sample size (n = 36), the inclusion of a control group, and an experimental duration of 12 weeks. The similarities with the present study lie primarily in the investigation of the influence of the eccentric regimen and the assessment of thigh muscles.

The works by E. Hanci *et al.* [6], D. Stasinopoulos *et al.* [17], and the present study share a similar methodology, results, and data interpretations. Their difference lies in the fact that the aforementioned studies are large-scale investigations designed as randomised controlled trials, including a control group performing other exercises or receiving standard therapy. These works also consider larger sample sizes. The present study, as mentioned above, is an initial stage, and judgments regarding the efficacy of the proposed methodology are preliminary. In a study on the impact of isokinetic eccentric exercises on strength, muscle volume, and postural stability, A.D. Kay *et al.* [20] reach similar conclusions that eccentric exercises contribute to the improvement of thigh muscle function. The author also notes an increase in the strength and volume of the knee extensor muscles. The main difference from the present work is the examination of postural stability, on which exercises in the selected mode had no effect, the author notes. It is worth noting that the authors used the ultrasound method. A similar research object can be found in the work of J.P. Gordon *et al.* [21], regarding the eccentric mode of muscle contraction and its effect on functional indicators. Both articles view eccentric exercises as a powerful training stimulus. A similarity is observed in the evaluation of their key role in joint stabilisation and movement biomechanics improvement, which in the present study is directly linked to pain reduction.

CONCLUSIONS

Eccentric training of the quadriceps femoris muscle demonstrates high efficacy in patients with stage I-II knee osteoarthritis, as confirmed by the dynamics of subjective indicators (pain syndrome). The development of strength and control through these exercises contributes to a significant improvement in functional status.

The positive effect is complex in nature. The neuromuscular component is conditioned by an enhanced ability of the CNS to recruit muscle fibres, including the stabilisers of the knee joint – the vastus lateralis (239.1 μV before the intervention, 497.1 μV after) and vastus medialis (150.5 and 371.5 μV, respectively) heads of the quadriceps muscle, which ensures control during the eccentric phase of movements. The morphofunctional component is expressed in an increase in muscle strength, enabling more effective damping of mechanical load and reducing compression of the articular cartilage, which directly correlates with pain reduction and improved quality of life. The biomechanical component is associated with an increased range of motion, optimisation of gait biomechanics, and a reduction of excessive impact on cartilaginous structures.

The application of eccentric exercises for the quadriceps femoris muscle opens up promising directions for further clinical and scientific research. Given the confirmed positive effect in this category of patients, several priority tasks can be identified. First, a significant limitation of the current work is the small sample size (n = 9). To obtain valid and representative data, an expansion of the sample size is required, with consideration for differentiation by age, sex, and pathology stage, which will allow for the clarification of the methodology's efficacy in various subgroups. Second, an evaluation of long-term outcomes is necessary. Determining the duration of the retention of achieved effects after the completion of the training course will allow for the justification of the need for and periodicity of maintenance programs. Third, it is relevant to compare eccentric training with other rehabilitation approaches to determine their relative efficacy and optimal conditions of application.

A promising direction is the development of individualised training programs that take into account the patient's clinical characteristics. Research in this area is necessary to determine the optimal loading parameters (intensity, frequency, volume) for different groups, which will contribute to enhancing the effectiveness of rehabilitation interventions. Further study of eccentric training for knee osteoarthritis requires a comprehensive approach, and the implementation of the outlined

directions will expand rehabilitation possibilities and improve the quality of life for this patient category.

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CONFLICT OF INTEREST

None.

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Аннотация. Учурда тизе муунундагы ооруга жана кыймылдын чектелүүлүгүнө нааразы болгон бейтаптардын саны көбөйүүдө. Остеоартроздун алгачкы стадияларында функцияны калыбына келтирүүнүн натыйжалуу ыкмаларын издөө барган сайын маанилүү болуп баратат. Бул изилдөөнүн максаты – тизе муунунун функциясынын бузулушу бар адамдарда оорунун интенсивдүүлүгү менен эксцентрикалык жыйрылуу параметрлеринин ортосундагы мүмкүн болгон байланышты аныктоо болуп саналат. Медициналык борбордо тизе остеоартрозу менен жабыркагандар арасында булчуңдардын жыйрылуусунун эксцентрикалык режимин изилдөө үчүн эксперимент жүргүзүлдү. Реабилитациялык сессиялар квадрицепстердин жыйрылуусунун эксцентрикалык фазасына багытталган. Миографтын көрсөткүчтөрү жана оорунун деңгээли экспериментке чейин жана андан кийин визуалдык аналогдук шкала колдонулуп бааланган. Квадрицепстин эксцентрикалык жыйрылуусунун орточо амплитудасы эки эседен ашык көбөйгөн: мисалы, vastus lateraliste ал 98,7 мкВдан 298,4 мкВга чейин жогорулаган. Көнүгүүлөрдүн курсун аяктагандан кийин, тогуз катышуучунун алтоосу тизенин толук чоюлушуна жетишкен. Бардык катышуучулар оорунун азайганын билдиришкен, ал эми экөө ооруну толугу менен басаңдаткан. Изилдөөнүн жыйынтыктары эксцентрикалык булчуңдардын жыйрылуусунун ооруну азайтып, электромиографиялык активдүүлүктү жогорулатканын көрсөттү. Бул режим кыймыл учурунда булчуң күчүн жана нерв-булчуң көзөмөлүн өнүктүрүүгө, ошондой эле муун кемирчегине механикалык жүктү азайтууга жардам берет. Жыйынтыктар эксцентрикалык квадрицепс көнүгүүлөрү тизе остеоартроздун алгачкы стадияларында натыйжалуу болушу мүмкүн экенин көрсөтүп турат, анткени алар бир эле учурда себепти (булчуңдун алсыздыгы) жана кесепетин (оору, кыймылдын чектелүү диапазону) чечет. Жыйынтыктар тизе муунунун остеоартрозунун алгачкы стадиялары менен ооруган бейтаптар үчүн жекече реабилитациялык программаларды иштеп чыгуу үчүн колдонулушу мүмкүн

Негизги сөздөр: гонартроз; электромиография; таяныч-кыймыл системасы; негативдүү фаза; тизе муунунун оорусу

Влияние эксцентрических нагрузок на болевой синдром и амплитуду движений у лиц с нарушением функций коленного сустава

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Аннотация. В настоящее время наблюдается увеличение числа пациентов с жалобами на боль и ограничение подвижности коленного сустава. Актуальным становится поиск эффективных методов восстановления функции на начальных стадиях остеоартроза. Целью настоящего исследования явилось выявление возможной взаимосвязи между интенсивностью боли и параметрами эксцентрического сокращения у лиц с нарушением функций коленного сустава. На базе медицинского центра проведён эксперимент, в ходе которого изучался эксцентрический режим мышечного сокращения при остеоартрозе коленного сустава. В реабилитационных сессиях акцент делался на эксцентрическую фазу сокращения четырёхглавой мышцы бедра. До и после эксперимента оценивались показатели миографа, уровень боли по визуально-аналоговой шкале. Средняя амплитуда эксцентрического сокращения четырёхглавой мышцы увеличилась более чем в два раза: например, у латеральной широкой мышцы – с 98,7 мкВ до 298,4 мкВ. После завершения курса занятий у шести из девяти участников зафиксировано полное разгибание в коленном суставе. У всех испытуемых отмечено снижение уровня болевого синдрома, у двух человек боль исчезла полностью. Результаты исследования показали, что эксцентрический режим мышечного сокращения способствует снижению уровня боли и росту показателей электромиографической активности. Данный режим позволяет развивать силу мышц и нейромышечный контроль при движениях, а также снижать механическую нагрузку на суставной хрящ. Полученные данные свидетельствуют, что упражнения в эксцентрическом режиме для четырёхглавой мышцы бедра на начальных стадиях остеоартроза коленного сустава могут быть эффективны, так как воздействуют одновременно на причину (мышечная слабость) и на следствие (боль, дефицит амплитуды движений). Результаты могут быть использованы при разработке индивидуальных реабилитационных программ для пациентов с начальными формами остеоартроза коленного сустава

Ключевые слова: гонартроз; электромиография; опорно-двигательный аппарат; негативная фаза; боль в коленном суставе

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ЖУРНАЛ БИОЛОГИИ ЧЕЛОВЕКА И КЛИНИЧЕСКОЙ МЕДИЦИНЫ

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