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Staged treatment of ovarian cancer in a patient: Therapeutic strategy and outcomes

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Abstract. Epithelial ovarian cancer remains one of the most aggressive gynaecological malignancies, which in most cases is diagnosed at advanced stages. The aim of the study was to present a staged treatment of a patient with advanced high-grade serous ovarian carcinoma, demonstrating the value of multimodal diagnostics, laparoscopic determination of the peritoneal carcinomatosis index, assessment of morphological response, and integrated chemo-surgical tactics in accordance with the ESGO/ESMO 2023 recommendations. A 45-year-old patient with bilateral ovarian lesions, ascites, and a high carcinomatosis index (24) underwent a comprehensive examination that included ultrasound, computed tomography, magnetic resonance imaging, endoscopic methods, laparoscopy with biopsy, and in-depth morphological analysis (histology, immunohistochemistry, assessment of Ki-67, estrogen receptor expression, and angiogenic markers). Pathohistological examination demonstrated a high degree of therapeutic pathomorphosis: a sharp decrease in Ki-67 (up to 2-5%), single tumour cells against a background of pronounced fibrosis, a decrease in microvascular density and the presence of xanthoma cells in areas of previous necrosis. Postoperative adjuvant treatment provided a stable response without signs of progression. The treatment results demonstrated the effectiveness of a staged treatment strategy for advanced ovarian cancer, which combined laparoscopic assessment of resectability, neoadjuvant polychemotherapy, interval cytoreduction and morphological verification of the response. The results obtained confirmed the high prognostic informativeness of the carcinomatosis index, Ki-67 and morphological markers of regression. The findings of the work can be used by gynaecological oncologists, chemotherapists, and pathologists in specialised oncology and university clinics when planning and assessing the effectiveness of staged treatment of advanced epithelial ovarian cancer

Keywords: neoadjuvant chemotherapy; cytoreduction; peritoneal carcinomatosis; adenocarcinoma; paclitaxel; carboplatin

✦ INTRODUCTION

Ovarian cancer remains one of the most aggressive oncogynaecological diseases, occupying a leading place among

the causes of cancer mortality in women. As stated by G. Caruso *et al.* [1], it is the most lethal gynaecological cancer,

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and the average age of diagnosis in developed countries is about 63 years. The prevalence and mortality from ovarian cancer traditionally remain higher in highly developed regions, which partly reflects the age structure of the population and the characteristics of cancer registration. Meanwhile, under the epidemiological analysis summarised by P. Gaona-Luviano *et al.* [2], during 2015-2025 in Western Europe and North America, there was a tendency to stabilise or moderately decrease in standardised morbidity and mortality rates. Despite this, the overall mortality rate remains significant and on average corresponds to approximately 3.5-4.0 cases per 100,000 women, which keeps ovarian cancer among the leading causes of death from cancer in women. Along with epidemiological features, the role of hereditary factors in the pathogenesis of ovarian cancer is gaining increasing attention.

As noted by U.M. Zamwar & A.P. Anjankar [3], more than 21 thousand new cases of ovarian cancer are registered annually, which is approximately 1.2% of all malignant neoplasms in women. The authors emphasised a sharp decrease in 5-year survival from 91.8% in the case of local process to 29.7% in the case of metastatic lesion, which once again confirmed the critical role of timely diagnosis. The authors also stated that up to 90% of carcinomas are epithelial, and the serous subtype dominates the structure of the disease. Clinical outcomes in ovarian cancer largely depend on the stage and biological characteristics of the tumour. S. Nag *et al.* [4] pointed out that despite the progress of surgical approaches and the development of supportive therapy, 5-year survival remains below 50%. The authors explained this by a combination of factors: late detection, chemoresistance and high recurrence rate, which significantly complicate the management of such patients. In turn, A.T. Ali *et al.* [5] highlighted the age-related characteristics of survival, stating that women younger than the average age of diagnosis have better long-term results, which determines the importance of taking into account the age factor in clinical decisions. Morphological and pathogenetic differences are no less significant. In the work, L. Zhou *et al.* [6] demonstrated that endometrioid and clear cell histotypes of ovarian cancer have different clinicopathological characteristics and are often associated with endometriosis. The researchers proved that patients with endometriosis more often have concomitant endometrial lesions and hormone receptor-positive tumours. The authors also indicated a worsening prognosis in patients with extensive disease and concomitant endometriosis, which requires special vigilance when interpreting pathological material.

In addition to pathomorphological features, therapeutic approaches play a major role. The standard of first-line treatment has remained unchanged for many years. V. Tavares *et al.* [7] put an emphasis on the fact that the primary strategy in most cases is cytoreductive surgery followed by platinum-containing chemotherapy in combination with taxanes for six cycles. The authors noted that the sequence from surgery to chemotherapy is a key factor in long-term disease control. However, the treatment strategy is significantly stage-dependent. In accordance with the recommendations of the European Society of Gynaecologic Oncology (ESMO), A. González-Martín *et al.* [8] pointed out that chemotherapy may not be indicated in patients with

early stages and low-grade malignancy, which emphasises the importance of accurate histopathological assessment. For advanced cases, when complete tumour removal is not possible, J.S. Berek *et al.* [9] proved that the use of neoadjuvant chemotherapy followed by interval cytoreduction is a reasonable alternative that allows reducing the volume of the tumour mass and increasing the effectiveness of further treatment. Although the role of radiotherapy in ovarian cancer is limited, G. Macchia *et al.* [10] noted that its use remains critical in palliative situations, especially in the control of local symptoms, when systemic therapy is exhausted or insufficiently effective. The peculiarities of the course, prevalence, and difficulties of early detection of ovarian cancer are also characteristic of Ukraine. R.A. Chyzhma *et al.* [11] noted that the disease is most often registered in the age group of 60-79 years, which correlates with world trends. The histological structure is also similar: about 91% of neoplasms are epithelial-stromal tumours, mainly serous adenocarcinomas (approximately 75%). At the same time, almost half of the cases are diagnosed already at stage III, which indicates problems of early diagnosis and limited vigilance regarding early symptoms.

A literature review demonstrated that, despite the presence of clear international recommendations, the actual clinical pathways of patients with ovarian cancer differ significantly. Such differences are due to the initial stage of the process, the extent of peritoneal involvement, the carcinomatosis index, the histological variant, the degree of malignancy, the general somatic condition of the patient, as well as the nature of the response to neoadjuvant chemotherapy. Special attention is required in cases where primary surgery is impossible due to a large tumour mass or a high Peritoneal Cancer Index (PCI), which requires neoadjuvant polychemotherapy (NAPHT) and further assessment of the possibility of interval cytoreduction. It is such clinical situations that allow tracing how the theoretical principles of evidence-based medicine are applied in real practice – from the moment of initial tumour detection, PCI determination and morphological verification to the assessment of pathomorphosis and decision-making regarding further treatment strategy. The aim of the work was to provide a detailed explanation of the sequence of treatment decisions, the validity in accordance with modern evidence-based approaches, and to demonstrate the effectiveness of staged treatment in a patient with a complex and widespread tumour process.

✦ MATERIALS AND METHODS

As part of the preparation of the clinical observation, an analysis of current global and national epidemiological data on the incidence, mortality, and survival rates of ovarian cancer for the period 2020-2025 was conducted. For this purpose, generalised data from international review publications, materials from population-based oncology registries, as well as official statistics from the National Cancer Registry of Ukraine [12] were used. The information obtained was used to contextualise the case, compare the individual course of the disease with modern epidemiological trends, and justify the choice of a staged multimodal treatment strategy. The study was conducted at the clinical base of Dnipro State Medical University in accordance with the principles of good clinical practice and the WMA

Declaration of Helsinki [13]. The treatment strategy was determined at a meeting of the multidisciplinary oncology committee on 2024 June 24, taking into account the patient's clinical condition. When making its clinical decision, the commission was guided by the current regulatory framework of Ukraine, in particular Order No. 845 of the Ministry of Health of Ukraine [14], which regulates the application of clinical guidelines and standards of medical care. The treatment regimen used was not prescribed as part of a clinical trial, but as individualized antitumor therapy in accordance with the principles of evidence-based medicine, international clinical guidelines, and the current regulatory framework of Ukraine. The patient gave written informed consent for the use of clinical, radiological, and morphological data for scientific purposes with a guarantee of confidentiality and anonymity.

The assessment of the effectiveness of the staged treatment tactics was based on a set of radiological response criteria, PCI dynamics, intraoperative assessment of the completeness of cytoreduction and morphological signs of therapeutic pathomorphosis in the resected material. The results obtained were analysed in the context of the current recommendations of the European Society of Gynaecological Oncology/European Society of Medical Oncology (ESGO/ESMO) 2023 [15], which allowed comparing the individual clinical course with modern standards of management of patients with advanced ovarian cancer. The course of the disease in a 45-year-old patient with bilateral ovarian tumour lesions, ascites and widespread peritoneal carcinomatosis was analysed. The patient was in a state of surgical menopause for 11 years. Comorbidities included stage II arterial hypertension, metabolic cardiomyopathy, stage I aortic valve insufficiency and stage II obesity. Allergic history is not burdened, heredity for oncological diseases is not noted. The first clinical manifestations were nonspecific discomfort in the lower abdomen and episodic bloating.

The initial assessment of the pelvic organs was performed using ultrasound on the Voluson E8 device (GE Healthcare, USA) with subsequent risk stratification according to the Ovarian-Adnexal Reporting and Data System (O-RADS). To clarify the prevalence of the process, computed tomography (CT) of the abdominal cavity and pelvic organs was performed on a Siemens multispiral tomograph (Germany), as well as magnetic resonance tomography (MRI) on a device with a magnetic field strength of 1.5 T (GE Healthcare, USA). In order to exclude primary gastrointestinal neoplasia, fibrogastroscopy and colonoscopy were performed using the Olympus EVIS EXERA III video endoscopic system (Olympus Medical Systems, Japan). In order to accurately assess the extent of the tumour process, determine resectability and justify the choice of primary or interval surgical tactics, the patient underwent diagnostic laparoscopy. During the intervention, a systematic examination of all anatomical areas of the abdominal cavity and pelvis was performed pursuant to the standard PCI calculation scheme, with a quantitative assessment of the extent and size of tumour implants in each region. At the same time, a targeted biopsy of macroscopically changed areas of the peritoneum was performed for morphological verification of the diagnosis and assessment of the biological characteristics of the tumour. After completion of neoadjuvant

polychemotherapy, in order to re-evaluate the response to treatment and clarify the possibility of radical surgery, a control diagnostic laparoscopy was performed with repeated PCI calculation.

At the next stage, a median laparotomy was performed with complex interval cytoreduction, which included bilateral salpingo-oophorectomy, pelvic peritoneumectomy, anterior rectal resection, omentectomy and drainage of the abdominal cavity, in order to remove macroscopic tumour foci as completely as possible. Morphological examination of the biopsy material included standard histological staining and immunohistochemical analysis with determination of the Ki-67 proliferative index, estrogen receptor expression and angiogenesis markers. Immunohistochemical reactions were performed using certified antibodies in accordance with the manufacturer's protocols (Dako, Agilent, Denmark). Given the high primary PCI and the inability to achieve optimal primary cytoreduction, the patient was prescribed NAPHT in line with the standard regimen of paclitaxel in combination with carboplatin. After completing three courses of NAPHT, a reassessment of the response was performed, which included a control CT scan of the chest, abdomen and pelvis, MRI of the pelvis, as well as a repeat diagnostic laparoscopy with determination of PCI dynamics. MRI of the pelvis was used as one of the key methods for assessing the response to NAPHT and stratifying the patient for the possibility of performing interval cytoreductive surgery.

After confirming the reduction of PCI and achieving resectability, interval cytoreductive surgery was performed with subsequent histopathological and immunohistochemical analysis of the resected material to assess the degree of therapeutic pathomorphosis. Proliferative activity, hormone receptor expression and changes in microvascular density were analysed in relation to the clinical and radiological response. Therefore, diagnostic laparoscopy was performed to determine the PCI, which was 24 in the protocol. For this purpose, a course of PCT was performed and re-evaluation was performed immediately after the end of the course of PCT, which established almost complete regression of pathological formations. The limitations of the study include the nature of a single clinical observation, the lack of long-term follow-up of survival indicators and the impossibility of statistical extrapolation of the results.

RESULTS AND DISCUSSION

Pursuant to the global epidemiological estimates for the period 2020-2025, ovarian cancer accounts for about 3.7% of all malignant neoplasms in women and is associated with approximately 4.7% of cancer deaths, with a total number of deaths exceeding 200 thousand worldwide [16]. Despite the introduction of modern combined treatment approaches, the overall 5-year survival rate remains limited and in high-income countries does not exceed 46%, demonstrating a clear dependence on the stage of the disease at the time of diagnosis [17]. In Ukraine, ovarian cancer is among the most common malignant neoplasms of the female reproductive system. Pursuant to national oncological statistics, in 2022, about 28.3 thousand women with this diagnosis were registered, and a significant proportion of cases are detected at later stages, which necessitates the

use of staged multimodal approaches to treatment in real clinical practice [11, 12]. In this context, detailed documented individual observations are of particular clinical value, which allow tracking the implementation of modern recommendations in practice, taking into account the prevalence of the process, the patient's somatic status and morphological characteristics of the tumour. Below are the results of clinical observation of a patient with advanced ovarian cancer, in whom a staged diagnostic and treatment strategy was applied. At the initial stage of clinical examination, within the framework of the primary diagnostic algorithm, during an ultrasound examination of the pelvic organs, bilateral cystic-solid ovarian masses were detected, classified in consonance with the O-RADS system as 5, as well as the presence of ascites. Pathomorphological examination revealed serous adenocarcinoma with signs of moderate differentiation, however, extended histological analysis revealed a predominance of poorly differentiated solid-papillary areas with extensive foci of necrosis and haemorrhage (Fig. 1).

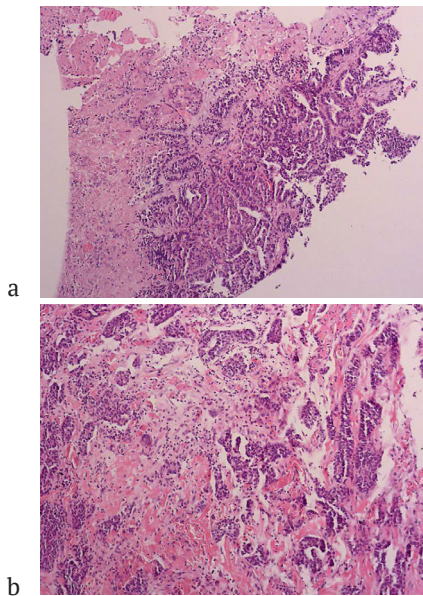


Figure 1. Primary histological material

Note: a – serous adenocarcinoma of the ovary with signs of moderate differentiation; b – poorly differentiated solid-papillary areas of the tumour with extensive foci of necrosis and haemorrhage

Source: compiled by the authors

For further risk stratification and clarification of the extent of the process, a CT scan of the pelvic organs and abdominal cavity was performed, which revealed a massive pelvic tumour, most likely of ovarian origin, with signs of peritoneal carcinomatosis, ascites and microlymphadenopathy of the retroperitoneal space. To exclude primary local gastrointestinal neoplasia, fibrogastrosocopy and colonoscopy were performed, no pathology was detected. In order to assess resectability, a diagnostic laparoscopy was performed: PCI was 24, which corresponded to a significant spread of the tumour process. A biopsy of the metastatically affected areas was performed. Pathomorphological examination revealed a moderately

differentiated serous adenocarcinoma of glandular-papillary structure with the presence of vascular invasion. Immunohistochemical study of the primary biopsy material confirmed the pronounced nuclear expression of estrogen receptors in the majority of tumour cells, which is consistent with the serous phenotype of high malignant potential and supports the assumption of an ovarian origin of the process (Fig. 2).

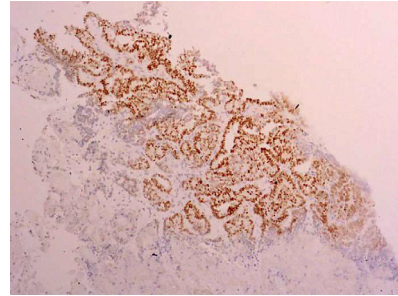


Figure 2. Immunohistochemistry of the primary tumour
Source: compiled by the authors

The presence of a developed microvascular network with numerous small vessels in the tumour stroma was also established, which is a characteristic feature of the high angiogenic activity of serous carcinomas (Fig. 3).

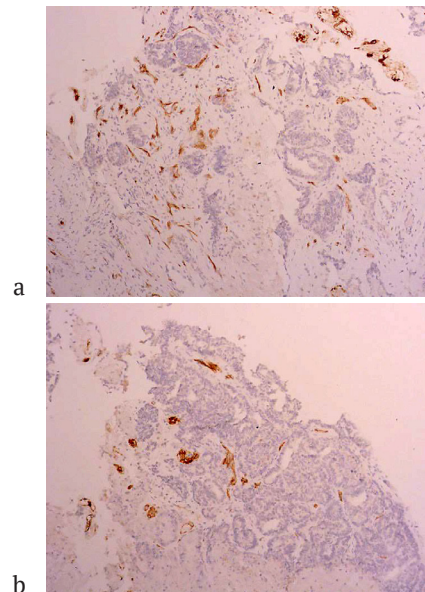


Figure 3. Histological structure of the primary tumour
Note: a – diffusely developed microvascular network in the tumour stroma of serous carcinoma; b – accumulation of small-calibre vessels in solid-papillary areas of the tumour
Source: compiled by the authors

Additional histological analysis confirmed that the primary tumour was characterised by a low degree of differentiation with a predominantly solid-papillary architecture, the presence of extensive areas of necrosis and haemorrhage, a significant microvascular network, and high proliferative potential (Ki-67 about 30%) (Fig. 4).

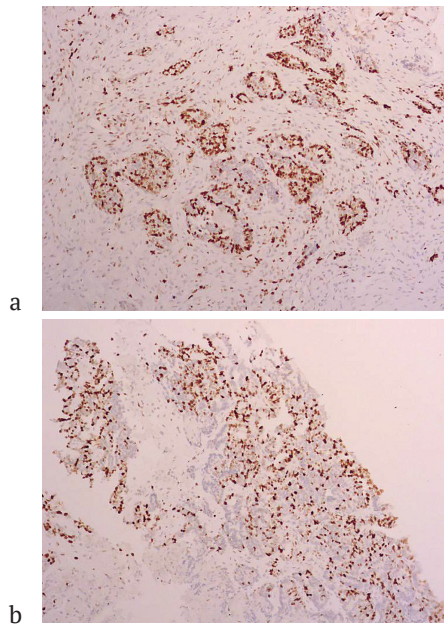


Figure 4. Immunohistochemical determination of Ki-67 in the primary tumour

Note: a – Ki-67 expression in tumour cells of serous carcinoma; b – foci of increased proliferative activity with a high Ki-67 index

Source: compiled by the authors

Given the high PCI index, the presence of carcinomatosis and the extent of the lesion, the patient was prescribed NAPHT in conformity with the paclitaxel in combination with carboplatin regimen. After three courses of NAPHT, a control CT scan of the chest, pelvis and abdominal cavity was performed, which demonstrated clear positive dynamics: a decrease in the size of the peritoneal nodes, a reduction in ascites and regression of retroperitoneal lymphadenopathy. MRI data of the pelvic organs confirmed a partial, sometimes complete response to treatment, which allowed considering the patient as a candidate for interval cytoreduction. Importantly, achieving such a response with an initially high PCI confirms the sensitivity of the tumour to platinum-containing chemotherapy and creates the basis for surgical intervention with potentially complete cytoreduction.

Additionally, a repeated diagnostic laparoscopy was performed, which showed a decrease in PCI to 4. This became the basis for performing a median laparotomy with complex interval cytoreduction: bilateral salpingo-oophorectomy, pelvic peritoneumectomy, anterior rectal resection, omentectomy, and abdominal drainage. The tumour tissue obtained after chemotherapy and radical surgery was pathohistologically determined as small foci of tumour cells with pronounced dystrophic changes among fields of fibrous tissue and foci of accumulation of xanthoma cells in areas of tumour necrosis (Fig. 5).

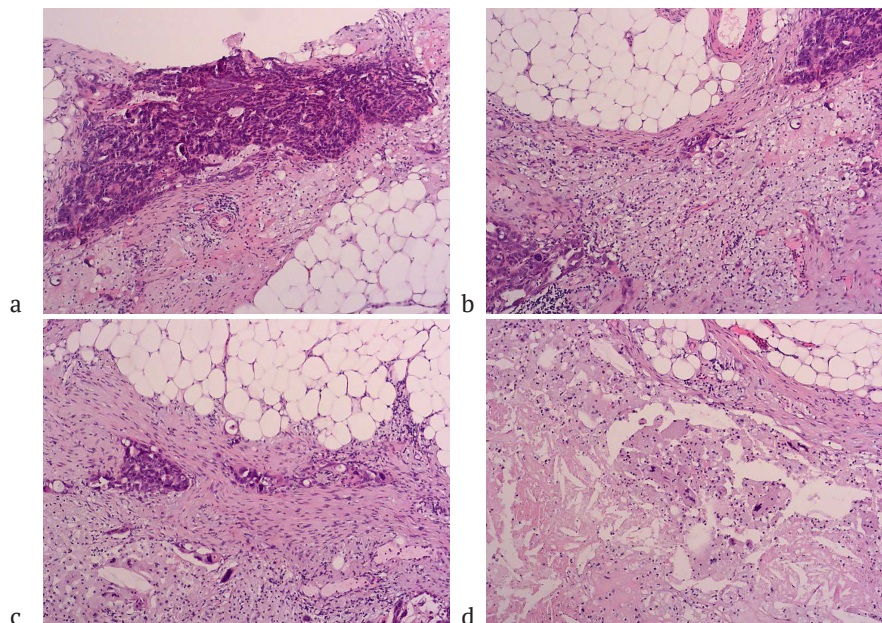


Figure 5. Pathohistological picture after treatment

Note: a – small residual foci of tumour cells with pronounced dystrophic changes on the background of fibrosis; b – fields of dense fibrous tissue with single atypical cells; c – foci of tumour necrosis with accumulation of xanthoma cells; d – areas of post-treatment stromal remodelling without signs of active tumour growth

Source: compiled by the authors

Postoperative histopathological examination revealed poorly differentiated adenocarcinoma with signs of therapeutic pathomorphosis of grade I-II in the right ovary, small residual foci of growth in the left ovary, preserved tumour growth in the pelvic peritoneum, focal lesion of the omentum and superficial lesion of the colonic serosa

without invasion into the wall. The proximal and distal resection margins were “clean”. In-depth morphological analysis of the resected material recorded a high degree of therapeutic pathomorphosis. Tumour cells retained clear nuclear expression of estrogen receptors, but were solitary (Fig. 6a, 6b). A significant part of the tumour tissue and

adjacent fibro-fatty tissue showed a decrease in the number of vessels (Fig. 6c). Xanthoma cells are present in areas of previous necrosis. Vascular density was significantly

reduced, and CD31 labelling mainly reflected macrophage structures (Fig. 6d). Proliferative activity was dramatically reduced to 2-5% by Ki-67.

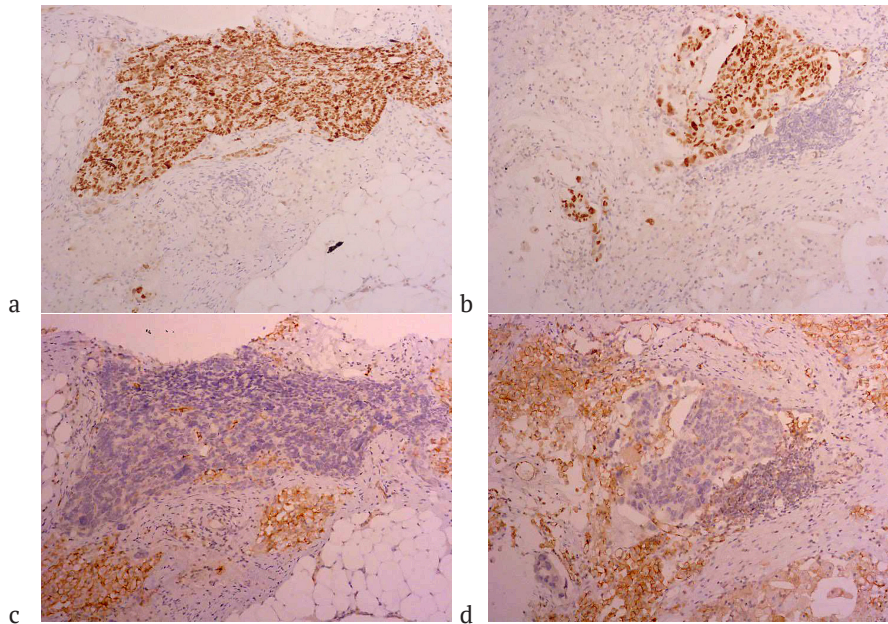


Figure 6. In-depth morphological analysis of resected material after chemotherapy and radical surgery

Note: a – intense nuclear expression of estrogen receptors in residual tumour cells; b – tumour cells with estrogen receptor expression; c – reduced vascular density in tumour and fibro-adipose tissue; d – CD31 labelling of macrophage structures in areas of previous necrosis

Source: compiled by the authors

These changes confirmed the high efficacy of NAPHT, which is consistent with the clinical and radiological dynamics. After the surgical stage, the patient received three more courses of adjuvant chemotherapy with the same regimen (paclitaxel + carboplatin). The final response assessment showed an excellent therapeutic effect without signs of progression. Thus, the obtained results reflected a consistent and methodologically justified interaction of diagnostic, morphological, and therapeutic stages with coordinated radiological, laparoscopic, and histological assessment of treatment response, which made it possible to achieve maximal tumour burden reduction and an optimal clinical outcome. The presented results illustrated a modern evidence-based approach to the management of patients with advanced high-grade serous ovarian carcinoma, based on staged diagnostics, risk stratification, and the personalisation of treatment strategy. The initial examination included multimodal imaging – ultrasound, CT and MRI, as well as diagnostic laparoscopy with determination of the PCI index. This combination of methods allowed to obtain the most accurate characterisation of the prevalence of the tumour process, which is a key element in the formation of the correct treatment tactics.

The scientific evidence base presented by J.A. Ledermann *et al.* [15] demonstrated that laparoscopic determination of PCI is the most accurate method for predicting resectability and allows minimising the risk of suboptimal primary cytoreduction. This became the foundation for making a decision on the appointment of NAPHT. This approach was fully consistent with the ESGO/ESMO

guidelines, according to which the stratification of patients with stages III-IV should be based on a combination of radiological and laparoscopic assessment. After three courses of NAPHT based on paclitaxel and carboplatin, a pronounced complex of positive changes was obtained. Pursuant to CT/MRI, a significant decrease in the volume of peritoneal implants, reduction of ascites, and PCI decreased from 24 to 4, which became a relevant argument in favour of the transition to the surgical stage of treatment. Morphological analysis of the material obtained during surgery demonstrated significant therapeutic pathomorphosis: fibrosis, the presence of xanthoma cells, a sharp decrease in the proliferative index (Ki-67 < 5%) and structural reorganisation of the microvascular network. These observations are consistent with the results of W.P. Tew *et al.* [18], who affirmed that a comprehensive assessment of the response, including both morphological and radiological markers, is one of the most reliable predictors of overall and relapse-free survival. In addition, the correspondence between the severity of the morphological response and the decrease in PCI is fully consistent with the results published by J. Hayek *et al.* [19], who proved that the combination of these parameters indicates high chemosensitivity of the tumour.

Surgical intervention was performed after confirmation of resectability based on laparoscopic data and positive dynamics after NAPHT. This algorithm corresponds to the approach proposed by J.A. Ledermann *et al.* [15], in which interval cytoreduction was considered the optimal standard of treatment for patients with high PCI in the presence

of other favourable factors. S. Piedimonte *et al.* [20] noted that it is the combination of a significant decrease in PCI and morphological signs of chemosensitivity that determines the likelihood of achieving complete or optimal cytoreduction. In the presented observation, R0 status was achieved – the absence of macroscopic tumour after surgery. Such a result has a crucial prognostic value, which is confirmed by the data of J.M. Porter *et al.* [21], who established that complete resection is the most critical driver in long-term improvement in survival regardless of whether it is a primary or interval surgery. This trend is also confirmed by N. Norppa *et al.* [22], which further strengthens the significance of the results obtained.

Histological analysis of the resected tissue confirmed a high degree of therapeutic response – single tumour cells against a background of dense fibrosis and a decrease in Ki-67. Similar morphological profiles were defined as favourable in the study by S. Wan *et al.* [23], where a direct relationship between the depth of the pathomorphosis and the duration of the relapse-free period was established. S. Böhm *et al.* [24] highlighted the significance of the Chemotherapy Response Score (CRS) classification, in line with which patients with CRS 3 have better overall and relapse-free survival rates. In the presented study, the morphological picture after NAPHT (pronounced fibrosis, single tumour cells, a sharp decrease in Ki-67 to 2-5%) corresponds to a high degree of therapeutic response, which functionally approaches CRS 3 and confirms the prognostically favourable nature of the obtained pathomorphosis. K.I. Kim *et al.* [25] further confirmed that a decrease in Ki-67 by >25% after NAPHT is an independent predictor of long-term disease control, which was even more pronounced in this patient, with a more than six-fold decrease in the proliferative index compared to baseline, highlighting the high chemosensitivity of the tumour.

The efficacy of the combination of paclitaxel/carboplatin in patients with disseminated serous carcinoma was confirmed by the SCORPION study by A. Fagotti *et al.* [26], which found that NAPHT in patients with a high risk of suboptimal cytoreduction significantly increased the frequency of complete resection and reduced the frequency of postoperative complications. A similar clinical effect was demonstrated in the presented observation: with initially high PCI (24), NAPHT provided a significant reduction in tumour burden (PCI 4) and created the conditions for achieving complete macroscopic cytoreduction (R0). I. Vergote *et al.* [27] obtained similar results in the CHORUS and EORTC-55971 studies, where NAPHT provided comparable survival rates to primary cytoreduction, but was characterised by better tolerability.

Thus, the obtained results showed that a sequential strategy, including initial laparoscopic evaluation, NAPHT administration, assessment of therapeutic response, interval cytoreduction, and subsequent adjuvant therapy, was optimal for patients with a high index of peritoneal

involvement. The results obtained are fully consistent with the data of leading international studies and demonstrated the high effectiveness of modern multimodal treatment tactics. Such an approach not only increases the likelihood of achieving R0 resection, but also enhances the long-term prognostic outlook through precise alignment of surgical and systemic therapeutic interventions.

★ CONCLUSIONS

The presented work summarised the results of the staged management of a patient with advanced high-grade serous ovarian carcinoma with a high primary index of peritoneal carcinomatosis, focusing on the integration of clinical, radiological, laparoscopic and morphological criteria for assessing the response to treatment. The study found that the use of primary diagnostic laparoscopy with PCI determination allows for a reasonable abandonment of suboptimal primary cytoreduction and a timely transition to neoadjuvant polychemotherapy. Three courses of NAPHT according to the paclitaxel/carboplatin regimen provided a pronounced clinical and radiological response, which was quantitatively manifested by a decrease in PCI from 24 to 4 and created conditions for performing interval cytoreduction with the achievement of R0 status. Morphological analysis of the resected material confirmed a high degree of therapeutic pathomorphosis, which was characterised by a sharp decrease in proliferative activity (Ki-67 to 2-5%), fibrous remodelling of the stroma, reduction of microvascular density and the presence of xanthoma cells in areas of previous necrosis. The combination of these qualitative and quantitative indicators indicated high chemosensitivity of the tumour and a favourable prognostic profile.

The results obtained confirmed that a comprehensive assessment of the response, which includes the dynamics of PCI, morphological markers of regression and proliferative indices, has significant practical value for personalising the treatment strategy in patients with advanced ovarian cancer. Based on the analysis, it is recommended to introduce laparoscopic stratification and standardised morphological assessment of the effectiveness of NAPHT in clinical practice more widely. Further studies should be directed at accumulating case series with a unified assessment of PCI, CRS, and molecular markers, which will allow for a deeper understanding of the prognostic significance of morphological response and optimise treatment algorithms for patients with high tumour burden.

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★ CONFLICT OF INTEREST

None.

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Етапне лікування раку яєчника у пацієнтки: терапевтична стратегія та результати

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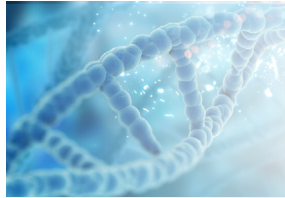
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Анотація. Епітеліальний рак яєчників залишається одним із найбільш агресивних гінекологічних злоякісних новоутворень, що у більшості випадків діагностується на пізніх стадіях. Метою дослідження було представити етапне лікування пацієнтки з поширеною високоградуальною серозною карциномою яєчників, продемонструвавши значення мультимодальної діагностики, лапароскопічного визначення індексу перитонеального канцероматозу, оцінки морфологічної відповіді та інтегрованої хіміо-хірургічної тактики відповідно до рекомендацій ESGO/ESMO 2023. Пацієнтка 45 років із двобічним оваріальним ураженням, асцитом і високим індексом канцероматозу (24) пройшла комплексне обстеження, що включало ультразвукове дослідження, комп'ютерну томографію, магнітно-резонансну томографію, ендоскопічні методи, лапароскопію з біопсією та поглиблений морфологічний аналіз (гістологія, імуногістохімічне дослідження, оцінка Ki-67, експресії естрогенових рецепторів та ангіогенних маркерів). Патогістологічне дослідження продемонструвало високий ступінь лікувального патоморфозу: різке зниження Ki-67 (до 2-5%), поодинокі пухлинні клітини на фоні вираженого фіброзу, зменшення мікросудинної щільності та наявність ксантомних клітин у зонах попередніх некрозів. Післяопераційне ад'ювантне лікування забезпечило стабільну відповідь без ознак прогресування. Результати лікування продемонстрували ефективність етапної стратегії лікування поширеного раку яєчників, що поєднувала лапароскопічну оцінку резектабельності, неоад'ювантну поліхіміотерапію, інтервальну циторедукцію та морфологічну верифікацію відповіді. Отримані результати підтвердили високу прогностичну інформативність індексу канцероматозу, Ki-67 та морфологічних маркерів регресії. Результати роботи можуть використовуватися лікарями-онкогінекологами, хіміотерапевтами та патоморфологами у спеціалізованих онкологічних і університетських клініках під час планування та оцінки ефективності етапного лікування поширеного епітеліального раку яєчників

Ключові слова: неоад'ювантна хіміотерапія; циторедукція; перитонеальний карциноматоз; аденокарцинома; паклітаксел; карбоплатин



Neurobiological aspects of hearing deprivation and its impact on quality of life in old age

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Abstract. Age-related changes in the body can cause functional limitations that make it difficult for older people to maintain their lifestyle and fulfil their social and personal roles, affecting their ability to live a full life. This article explored the main mechanisms by which hearing loss affects the quality of life in older people. Scientific publications from 2016-2025 in the MEDLINE/PubMed biomedical research database were reviewed. The analysis showed that age-related hearing loss is primarily caused by neurodegenerative processes. It was found that the degeneration of neurons in the auditory pathway – from the hair cells of the cochlea to the neurons of the neocortex – occurs in a reduction in the cell population, morphological alteration of neurons, and a decrease in the number of synaptic contacts. These changes are accompanied by disturbances in biochemical and electrophysiological homeostasis, dysregulation of intracellular calcium signalling, and decreased levels of key neurotransmitters, including glutamate, glycine, and γ -aminobutyric acid. Further analysis showed that these neurobiological disorders lead to a decrease in impulse activity and a weakening of inhibitory processes, which clinically manifests itself in auditory dysfunction, impaired perception of acoustic signals, and a decrease in the ability to spatially localise sound. The study determined that concomitant microangiopathy is characterised by inhibition of angiogenesis, decreased density of functioning capillaries, thickening of the basement membrane, and endothelial dysfunction, which leads to decreased tissue perfusion. It was found that microcirculatory insufficiency contributes to secondary ischaemic cell damage through the activation of oxidative stress and inflammatory cascades. Generalised age-related degeneration of neurons and microvessels is also evident in the brain structures responsible for cognitive functions. As a result, a recurrent pathophysiological mechanism is formed: auditory deprivation increases cognitive load and accelerates the depletion of neural resources, which in turn exacerbates neurodegenerative processes and structural changes in the brain. Analysis has shown that these processes mutually potentiate each other, causing progressive deterioration of cognitive functions and a decrease in physical and social activity in older people

Keywords: presbycusis; sensorineural hearing loss; dementia; cognitive function; neurodegeneration; angiopathy

★ INTRODUCTION

Quality of life is one of the key integral indicators of health status. It is a composite multifactorial concept that reflects not only medical aspects, but also functional, psycho-emotional and social components. It is used as one of the leading indicators of the level of social development of countries, which confirms the gradual shift in the global paradigm from a predominantly economic focus and technological progress to a people-oriented priority. Quality of life assessment reflects a person's subjective perception of their psychophysiological state and is based on a system of individual values, life experience, expectations and

standards. Given the global ageing of the world's population, research into the factors that affect the quality of life of this age group is of scientific and clinical importance.

The review by Q. Zheng *et al.* [1] emphasised that presbycusis is one of the most common geriatric diseases, second only to cardiovascular disease and degenerative joint disease in terms of frequency. It is reported that approximately two-thirds of people with age-related hearing loss are patients aged 60 and older, with a significant proportion of them having severe or profound hearing loss. The authors analysed in detail the key pathogenetic mechanisms

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of age-related hearing loss, focusing on mitochondrial dysfunction, energy metabolism dysregulation, histopathological changes in the structures of the inner ear, chronic inflammation and other mechanisms of damage to the cells of the auditory analyser. Considering presbycusis as a common sensory disorder in older adults, the researchers proposed differentiated rehabilitation strategies depending on the leading link in age-related transformation. It is emphasised that the use of an etiopathogenetically sound approach to rehabilitation, including hearing aids, increases its clinical effectiveness and contributes to improving the psychological well-being and functional independence of older people in their daily activities.

At the same time, the literature remains controversial and ambiguous. A.R. Huang *et al.* [2] conducted a secondary analysis of data from a randomised clinical trial to assess the impact of hearing loss correction on eight domains related to quality of life during a three-year follow-up of nearly 1,000 individuals over the age of 70. The study found no statistically significant improvement in physical and mental health indicators as a result of the use of hearing aids and other audiological interventions. The data obtained may indicate that the problem of age-related hearing loss is more complex and systemic in nature and is not limited to a decrease in acoustic perception, and therefore cannot be completely solved solely by increasing sound stimulation of the sensory apparatus.

The study by N. Henderson *et al.* [3] summarised data from 22 studies involving approximately 450 participants. The study determined that the quality of life of adults depends on the functional capabilities of the auditory system. Hearing impairment negatively affects not only its physical component (difficulties with speech recognition, sound localisation, or physical fatigue), but also reduces social (isolation, communication difficulties, reduced confidence and independence) and mental parameters. A cross-sectional study by S. Dedeoglu *et al.* [4] demonstrated that among people aged 18 to 65 with hearing impairment, the prevalence of anxiety disorders is higher, and the severity of psycho-emotional manifestations increases depending on the degree and clinical type of hearing dysfunction. At the same time, it has been established that the subjectively assessed severity of hearing loss has greater prognostic value for the development of psychological distress than objective audiometric indicators. B.J. Lawrence *et al.* [5] also reported a statistically significant correlation between hearing impairment and depression in older adults, with the presence of hearing dysfunction associated with an approximately 1.5-2-fold increase in the likelihood of developing depressive disorders.

A. Shukla *et al.* [6] demonstrated a consistent link between hearing loss and increased levels of loneliness and social isolation in adults and older adults. Hearing impairment limits effective interpersonal communication, contributing to reduced social engagement and poorer psychosocial well-being. The authors emphasised the significance of timely diagnosis and rehabilitative audiological interventions as potential strategies for reducing the risk of social isolation and its associated adverse health outcomes. Hearing deprivation in geriatric practice is reliably associated with a decline in cognitive function. M.L. Cantuaria *et al.* [7] found in a cohort study that a decline in auditory

perception increases the risk of developing dementia. The use of hearing aids, i.e. effective correction of existing audiological disorders, significantly reduces this risk, i.e. it can prevent or delay the onset and progression of dementia. The report by G. Livingston *et al.* [8] stated that if risk factors are corrected in a timely and effective manner, almost 40% of all cases of this disease can be prevented or delayed. Among the 14 pathological conditions ranked by their significance in the development of cognitive impairment, hearing loss occupies one of the leading places (7%), second only to low education and social isolation and exceeding several metabolic, mental and behavioural factors in terms of contribution. Unlike hyperlipidaemia, which was only included in the list of risk factors in 2024, hearing loss has been considered one of the most significant and potentially modifiable factors in the development of cognitive dysfunction for more than five years.

Recognising the possibility of effective correction of audiological disorders as one of the measures to prevent the development of dementia and improve the quality of life in elderly people encourages active action at all stages of medical care, from primary care physicians to specialised otolaryngological and audiological practices. This, in turn, requires determination of mechanisms of onset and development of audiological disorders. In this regard, the study aimed to identify the key mechanisms of the impact of hearing loss on the quality of life of elderly people based on a synthesis of global experience and analysis of available scientific and information sources.

✦ MATERIALS AND METHODS

To achieve this goal, scientific publications with a high citation index, published in English between 2016 and 2025, were analysed. The search was conducted in September-October 2025 using the MEDLINE/PubMed electronic database of medical and biological publications. To find potentially relevant materials, the following keywords in English were used: "Quality of Life" and "Hearing Loss" (2,481 publications) or "Cognitive Function" and "Hearing Loss" (1,811 publications). Based on the content of their abstracts, 44 studies that met the selected objective were selected for review. Nine articles did not pass the initial screening and were added during the process of explaining the pathogenesis of certain disorders. The study included systematic reviews and meta-analyses; observational epidemiological studies (cross-sectional, prospective/longitudinal, analytical) and experimental studies. The main criteria for inclusion of studies in the systematic review and meta-analysis were established sensorineural hearing loss and cognitive dysfunction of varying severity in older adults, a possible temporal correlation between the two events, and their potential impact on physical, mental, social, and other components of quality of life. The review did not include studies in which: the study population did not include elderly people; the subjects were diagnosed with conductive hearing loss; the relationship between hearing impairment and quality of life indicators was not analysed; the studies were descriptive in nature or were abstracts, comments or publications without full text.

The analysis of scientific sources devoted to the impact of hearing loss on the quality of life of older people was conducted using an integrated analytical approach aimed

at identifying the key mechanisms of the relationship between hearing deprivation and changes in quality-of-life indicators. The review included publications that highlighted the pathogenetic aspects of presbycusis or sensorineural hearing loss and the ways and mechanisms of their impact on the physical, psycho-emotional and social components of quality of life. The selected sources were evaluated according to the criteria of relevance to the research topic, design and methodology, characteristics of the study population, methods used to assess hearing function and quality of life indicators, as well as the analytical significance of the results obtained. The publications were classified and systematised by topic, which made it possible to structure the scientific data according to the main areas of research on the problem. A comparative analysis of the results of various studies made it possible to identify the leading pathophysiological, psychosocial, and functional mechanisms of the impact of hearing loss on the physical, cognitive, emotional, and social components of the quality of life of older people, assess the degree of consistency and inconsistency of scientific conclusions, and identify both the main trends and insufficiently studied aspects of the problem. The results obtained create a conceptual basis for further research and the development of effective strategies for the prevention and rehabilitation of elderly people with hearing loss.

◆ RESULTS AND DISCUSSION

Age-related neurodegenerative processes as a common pathogenetic basis for auditory and cognitive disorders. Impaired sound perception and speech comprehension, which develops with age, is defined as progressive, bilateral, symmetrical age-related sensorineural hearing loss, which mainly manifests itself at high acoustic frequencies [9]. This gradual loss of functionality is the result of genetically determined changes in the neurons of the auditory pathway. The development of presbycusis is associated with the influence of about 300 genes. S. Lee *et al.* [10] identified atonal homolog 1 (Atoh1) as a key transcription factor in the specification, differentiation, and survival of mechanosensory hair cells (both cochlear and vestibular). It coordinates the development, differentiation and functioning of sensory hair cells in the cochlea. The authors showed that Atoh1 plays a central role in the formation of the auditory apparatus during embryogenesis and in maintaining the structural integrity of the sensory epithelium. In addition, the activation of Atoh1 was considered a promising mechanism for the regeneration of hair cells after damage, confirming the importance of Atoh1 as a substantial molecular regulator of pathogenesis and a potential therapeutic target in sensorineural hearing loss.

K.L. Elliott *et al.* [11] demonstrated that the formation of sensory and neuronal components of the auditory system depends not only on Atoh1, but also on the structural and functional state of other transcription factors: Neurogenin 1 (Neurog1) and Neuronal Differentiation 1 (Neurod1), and their direct or indirect interdependent influence. According to them, Neurog1 is a key regulator of neurogenesis and differentiation of spiral ganglion neurons, while Neurod1 ensures their further specialisation, survival and formation of neural connections in the auditory nuclei. Atoh1, whose expression increases from the

cochlear base to the apex, determines the development and differentiation of sensory hair cells in the cochlea, ensuring the functional integrity of the peripheral auditory analyser. Accordingly, dysregulation of these genes leads to impaired neurosensory integration, forming the molecular basis for the development of neurosensory hearing loss.

K.L. Elliott *et al.* [12] demonstrated age-related cochlear degeneration by comparing different profiles of sensory deficits in elderly people and in experiments. The researchers compared age-related changes in a 70-year-old person with similar changes in an old 2-year-old mouse. Progressive age-related hearing loss, mainly at frequencies above 4 kHz, was established using tonal audiometry and confirmed histologically by delayed and progressive loss of inner (IHCs) and outer hair cells (OHCs). Based on changes in the cellular expression of related basic helix-loop-helix (bHLH) genes: Atoh1, Neurog1, the authors found that for outer hair cells, the vector of degeneration is directed from the base to the apex, while for inner hair cells, the morphological and functional changes are characterised by an apical-basal direction, leading to age-related auditory sensory deprivation at high frequencies. However, this is not a simple linear mechanism. The process of age-related degeneration begins with the outer hair cells and subsequently spreads to the inner hair cells. Therefore, the rate of cell loss is uneven: at the age of 75, the number of inner hair cells at the base of the cochlea decreases by about half, while in the same area, the number of outer hair cells decreases by 40%. In addition, degenerative processes spread to the central parts of the auditory analyser. With age, not only does the number of cells in the inner ear, cochlear nucleus, superior olivary cells, dorsal cochlear nucleus, medial nucleus of the trapezoid body, and other neurons of the auditory pathway decrease, but the number of synaptic terminals also decreases, along with other morphological changes. The study emphasised the role of glutamate excitotoxicity, mitochondrial dysfunction, and oxidative stress in the development of cochlear synaptopathy and neuronal degeneration. In other words, the interaction of sensory and neural biochemical disorders determines the progressive nature of presbycusis and the heterogeneity of its pathophysiology and clinical manifestations.

J.B. Dewey *et al.* [13] demonstrated the decisive role of the active mechanical response of outer hair cells in the mechanisms of cochlear amplification, which ensures high sensitivity and accuracy of auditory perception. The central molecular component of this process is the motor protein prestin, which is specifically expressed on the membranes of outer hair cells and provides rapid electromechanical conversion in response to changes in membrane potential. The cells rapidly change their length and stiffness, converting electrical energy into mechanical energy, i.e., acting as a physiological electromechanical transducer. The authors showed that prestin activity causes amplification of the movements of the organ of Corti at each sound wave cycle, especially in the high-frequency range. Accordingly, prestin dysfunction leads to a decrease in the efficiency of mechanical amplification of the sound signal and impaired frequency selectivity of hearing. J. Zheng *et al.* [14] explained the electromechanical activity of prestin by the fact that it is accompanied by a specific “gating current”, which reflects voltage-dependent conformational

changes in the molecule and its charge movements in the membrane. The detection of gating current confirmed the molecular mechanism of converting electrical signals into mechanical contractions of outer hair cells. Thus, prestin dysfunction is considered by scientists to be one of the key molecular links in the pathogenesis of age-related and neurosensory hearing loss.

R.H. Asli *et al.* [15] confirmed in a case-control study the role of prestin as a molecular link in the disruption of cellular and biochemical processes underlying the pathogenesis of sensorineural hearing loss. Studying the relationship between serum prestin concentration in individuals younger and older than 50 years with varying degrees of sensorineural hearing loss, it was determined that in both groups, serum prestin levels were significantly higher than in the control group, which may indicate a biochemical basis for functional insufficiency of outer hair cells. In addition, as prestin concentration increases, so does the severity of audiological disorders (odds ratio was 1.009 with a 95% confidence interval of 1.005-1.013). The authors emphasised that changes in the expression and functional activity of prestin, as a key motor protein, affect cell electromobility and calcium-dependent mechanisms of cochlear amplification. Therefore, the study proposed considering prestin levels as a quantitative biomarker of the severity of hearing disorders.

Y.J. Hu *et al.* [16] systematised role of Ca²⁺ signalling in the molecular and cellular mechanisms of sensorineural hearing loss. The study demonstrated that disturbances in intracellular Ca²⁺ regulation, dysfunction of voltage-gated calcium channels, pumps, and Na⁺/Ca²⁺ exchangers lead to changes in synaptic transmission, neurotransmitter balance, and energy metabolism in hair cells. Outer hair cells are connected to efferent neurons and amplify incoming sound signals, while inner hair cells, innervated by afferent nerve fibres, form synapses with 90-95% of the auditory nerve fibres and transmit virtually all acoustic information to the central nervous system. Given this, changes in Ca²⁺-dependent intracellular processes lead to impaired cochlear amplification and neural transmission of acoustic signals.

D.A. Godfrey *et al.* [17] emphasised that ageing causes a significant restructuring of the neurochemical profile not only in the peripheral cells of the auditory analyser. Structural changes in the neurons of the central auditory system are also accompanied by disturbances in intracellular biochemical and electrophysiological processes. Disturbances in glutamatergic neurotransmission manifest themselves in changes in glutamate concentration and metabolism, leading to a decrease in the efficiency of excitatory transmission and the potential development of excitotoxic processes. At the same time, there is a dysregulation of

inhibitory mediator systems, GABAergic and glycinergic, which causes an imbalance between excitatory and inhibitory influences and a degradation in the accuracy of neural encoding of acoustic information. Along with this, age-related modification of cholinergic neuromodulation, associated with changes in acetylcholine metabolism, limits the adaptive capabilities of auditory neural networks, reduces the level of synaptic plasticity and the efficiency of central processing of sound signals. In addition, the restructuring of the amino acid profile (aspartate, taurine, serine and other biologically active compounds) reflects systemic dysregulation of neurochemical homeostasis, which forms the biochemical basis for progressive dysfunction of the auditory pathways and the pathogenesis of age-related hearing loss.

A study by J.K. Mittelstadt *et al.* [18] also found that age-related audiological changes in ageing are the result of auditory cortex dysfunction. Therefore, the disruption of spectral and temporal processing of acoustic signals is caused not only by the weakening of inhibitory neural mechanisms, but also by a profound reorganisation of cortical neural networks. Magnetic resonance spectroscopy determined that the reduction of inhibitory neurotransmission in the auditory cortex is reliably associated with impaired speech perception in conditions of acoustic noise, reflecting age-related dysregulation of the balance between excitatory and inhibitory processes in cortical neural networks. Changes in neurotransmitter activity and receptor expression (modification of acetylcholine receptor subunit expression, decreased glutamate decarboxylase activity, decreased serotonin, increased acetyl transferase enzyme, impaired norepinephrine and dopamine activity, etc.) have been detected in auditory cortex neurons.), which, in combination with the restructuring of cortical neural networks, leads to a deterioration in the spectral and temporal processing of sound signals. Together, these processes form the neural basis for age-related decline in auditory discrimination and speech perception.

Systematic analysis of the experimental and clinical data presented reconstructed a generalised pathogenetic cascade of intracellular disorders (Table 1) underlying progressive neurosensory degeneration. Conceptually, it can be represented as a sequence of interrelated processes: genetic dysregulation → disruption of ion homeostasis and ion-dependent signalling → neurotransmitter imbalance → metabolic and mitochondrial dysfunction → energy deficiency, oxidative stress and impaired cellular signalling → cochlear synaptopathy → apoptosis of sensory and neuronal cells. The combination of intracellular metabolic, energy and regulatory changes is activated in stages at different levels of the auditory analyser, leading to the formation of a multicomponent, mutually potentiated pathological cascade.

Table 1. Key aspects of the pathophysiology of neurodegeneration in presbycusis

Level of damage	Key mechanisms	Pathophysiological effects	Functional audiological consequences for hearing
Genetic	Dysregulation of genes involved in auditory system development; deficiency of transcription factors.	Changes in the expression of Atoh1, Neurog1, Neurod1, deficiency of transcription factors and disruption of their regulation.	Impaired differentiation and specification of hair cells (HC), reduced neurogenesis, regeneration and plasticity of sensory and neuronal cells, defects in the formation of neural connections in the auditory nuclei.

Table 1. Continued

Level of damage	Key mechanisms	Pathophysiological effects	Functional audiological consequences for hearing
Intracellular	Dysregulation of Ca ²⁺ signalling.	Disruption of Ca ²⁺ -dependent regulation, cellular homeostasis, synaptic transmission, etc.	Decreased speed and accuracy of perception, transmission and analysis of acoustic information.
	Prestine dysfunction.	Electromechanical transduction disorders; gating current; decreased electromotility of OHCs.	Loss of cochlear amplification, decreased frequency selectivity.
	Imbalance of mediators: glutamate, gamma-aminobutyric acid, glycine, etc.	Excitotoxicity, disruption of excitation-inhibition processes.	Development of cochlear synaptopathy; neurodegeneration.
	Mitochondrial dysfunction.	Decreased production of adenosine triphosphate, accumulation of active forms of oxygen.	Energy deficiency of the brainstem, auditory pathway neurons, and auditory cortex.
	Oxidative stress.	Excess free radicals damage membranes, proteins, and DNA.	Apoptosis of hair cells and neurons.
Cochlear (sensory)	Reduction in number, structural and functional degeneration of OHCs.	Decreased cochlear amplification.	Decreased cochlear amplification and frequency selectivity.
	Decrease in number, structural and functional degeneration of IHCs.	Disruption of synaptic transmission to neurons in the spiral ganglion.	Decreased speed and accuracy of acoustic information transmission.
Retrocochlear (auditory pathway)	Decrease in the number, structural and functional degeneration of neurons in the auditory pathway, synaptic terminals, etc.	Decreased neural transmission efficiency, impaired synaptic integration and neuroplasticity.	Impaired neurosensory integration.
Central	Structural and functional degeneration of neurons in the auditory cortex.	Changes in neurotransmitter activity and receptor expression, impaired synaptic integration and neuroplasticity.	Changes in neuroplasticity, increased spontaneous neural activity, decreased inhibitory neural activity, imbalance between excitation and inhibition processes, decreased synaptic plasticity, etc.

Source: compiled by the author

Neurodegenerative processes are not limited to the structures of the auditory analyser. The nonspecific nature of age-related cellular and molecular changes gives reason to interpret them as a manifestation of pan-neuronal involution. A study by Z. Jafari *et al.* [19] highlighted the pathophysiological mechanisms linking presbycusis with cognitive decline based on magnetic resonance imaging and cellular studies. Based on the integration of neuroimaging and cellular neurobiology data, the authors demonstrated that auditory deprivation is associated with neuroanatomical and functional changes in the central nervous system, in particular, remodelling of the auditory cortex with impaired integration of sensory and cognitive networks, as well as a reduction in grey and white matter volume. The pooled data indicated that age-related hearing loss may be an independent and potentially modifiable risk factor for cognitive decline and dementia, justifying the need for early detection of hearing impairment and the implementation of multidisciplinary preventive and therapeutic strategies.

Thus, the combination of generalised age-related neurodegeneration of the auditory analyser, which causes the development of presbycusis, with progressive neurodegenerative changes in the parts of the brain responsible for cognitive functions, forms a clinically significant sensory-cognitive deficit. This recurrent pathophysiological mechanism, which consists of auditory perception and deprivation, decreased cognitive performance, limited functional autonomy of patients and other related processes, collectively manifests clinically as a degradation of integral indicators of quality of life in the ageing process. Thus, the decline in auditory function in older adults not only impairs

their social integration but also significantly limits their ability to perform daily tasks independently, which further exacerbates their psycho-emotional stress and leads to an increased risk of developing depressive disorders.

Age-related changes in microcirculation as a systemic pathogenetic factor in neuronal and tissue involution. Age-related metabolic transformation extends beyond neurons. X. Lu *et al.* [20] called ageing a systemic multi-organ process based on changes in cellular metabolism, mitochondrial dysfunction, inflammation, oxidative stress, and other pathological mechanisms triggered by energy homeostasis disruption. This work systematised current ideas about the role of exergines as key molecular mediators of a whole range of anti-ageing effects in gerontological practice. It has been proven that physical exercise induces the secretion of biologically active molecules such as brain-derived neurotrophic factor, Irisin, Fibroblast growth factor 21, Phospholipase D1 and a number of others, which trigger molecular cascades aimed at increasing cell resistance to oxidative stress and slowing down the processes of biological ageing. A leading role in this is played by the signalling systems of adenosine monophosphate-activated protein kinase, calcium/calmodulin-dependent protein kinases (CaMKs) and sirtuins, which ensure the induction of mitochondrial biogenesis, optimise energy metabolism, activate autophagic mechanisms of cell repair, and suppress NF- κ B-mediated inflammation, while improving endothelial function and microcirculation. Therefore, optimisation of microcirculatory blood flow, including through physical activity, ensures effective delivery of oxygen and metabolic substrates to neuronal and sensory cells, which contributes to the stabilisation of

mitochondrial function, maintenance of ionic and redox homeostasis, regulation of neurotransmitter activity and activation of cellular adaptation mechanisms, resulting in the normalisation of intracellular metabolic processes and increased functional resistance of neural structures.

B.S. Tsai Do *et al.* [21] also showed that the development of bilateral presbycusis is caused by degenerative changes in the structures of the inner ear and auditory nerve. However, among the main pathogenetic involutional mechanisms, in addition to damage to the hair cells of the cochlea and impaired function of the spiral ganglion, they emphasised age-related changes in the vascular strip, which normally produces endolymph with a characteristic high concentration of acetylcholine and potassium ions and a low sodium content. The vascular strip of the inner ear is the only epithelial tissue in the body that contains blood vessels. Therefore, impaired blood supply can also be considered a factor which, in combination with neurodegeneration, indirectly leads to a decrease in the efficiency of transduction and neural transmission of sound signals. The authors emphasised the multifactorial nature of age-related hearing loss and noted that its rate of progression is influenced by genetic factors, cumulative noise exposure, systemic metabolic disorders and concomitant diseases.

Neurons are characterised by high energy requirements and limited internal energy reserves, so their functioning is critically dependent on a continuous and efficient blood supply [22]. Therefore, it would be logical to assume that impaired tissue perfusion may be a common aetiological factor or catalyst for the progression of sensory and cognitive impairments in older adults. In support of this, Y. Uchida *et al.* [23] presented vascular brain damage, including stroke and microvascular infarction, as one of the pathophysiological mechanisms linking sensory and cognitive decline. In particular, a statistically significant association between moderate and severe hearing loss and stroke was found in elderly participants in a population study. The authors emphasised the importance of microcirculatory disorders (atherosclerotic, metabolic or other) in the development of auditory analyser dysfunction and cognitive decline, reflecting the commonality of vascular-metabolic mechanisms in their pathogenesis.

K. Połtyn-Zaradna *et al.* [24] consider age-related hearing loss to be a potentially modifiable risk factor for dementia, pathogenetically linked to vascular insufficiency and haemodynamic disorders. The study showed that sensorineural hearing loss is associated with an increased prevalence of vascular and metabolic pathology, in particular arterial hypertension, ischaemic heart disease, angina pectoris, myocardial infarction, and metabolic syndrome, confirming its role in the formation of vascular-mediated mechanisms of cognitive decline. The ageing process is accompanied by the risk of not only sensory and cognitive changes. Older people are prone to multimorbidity, when metabolic disorders intensify, and cardiovascular and degenerative geriatric diseases appear [25]. The risk of developing age-related audiological changes in individuals with a cardiometabolic profile was explained by D.W. Maidment *et al.* [26] as being due to common microvascular disorders characteristic of these diseases. Microangiopathy is manifested by inhibition of angiogenesis, a decrease in the number of functioning capillaries, thickening of their

basement membrane, endothelial dysfunction, and other structural changes that limit the perfusion of the metabolically active cochlea.

Vascular alteration leads to chronic tissue hypoperfusion, impaired transport of oxygen and metabolites, local hypoxia, and activation of inflammatory-oxidative cascades, which together contribute to the progression of organ dysfunction and neurodegenerative changes [27]. Y. Li *et al.* [28] described in detail the molecular mechanisms of metabolic vascular damage, which cover both the macro- and microcirculatory beds. They described their key pathogenetic links: endothelial dysfunction, chronic low-grade inflammation, oxidative stress, activation of the polyol and hexosamine pathways, as well as dysregulation of angiogenesis and vascular wall remodelling, which together lead to chronic hypoxia, metabolic failure and progressive organ dysfunction. The authors emphasised that diabetic microangiopathy is a universal mechanism of damage to various organs and systems and a substantial therapeutic target for strategies aimed at restoring vascular function and preventing neurodegenerative and sensory disorders.

Hemodynamic disturbances occur not only in peripheral areas. A study by O.Y. Bang *et al.* [29] showed that cerebral microangiopathy and macroangiopathy have common risk factors and biomarkers, indicating the unity of the pathogenetic mechanisms of vascular damage to the brain. The authors found that arterial hypertension, diabetes mellitus, dyslipidaemia, and inflammation are associated with both microvascular damage and large artery pathology, and that the key biological markers are indicators of endothelial dysfunction, oxidative stress, and systemic inflammation. The study determined that micro- and macrovascular disorders form a continuum of vascular pathology, which determines the progression of structural and functional changes in brain tissue, including ischaemic damage, neuronal dysfunction, and cognitive decline. The results confirm the concept of the systemic nature of vascular mechanisms of neurodegeneration and substantiate the role of microcirculatory insufficiency as a key link in the pathogenesis of age-related sensory and cognitive disorders.

Impaired blood flow is accompanied by activation of the coagulation cascade and the development of hypercoagulable syndrome, which further exacerbates microcirculatory disorders and tissue hypoxia. Increased blood clotting in the veins is clinically manifested mainly by pulmonary embolism, deep vein thrombosis, usually in the legs, and arterial thrombosis, which leads to ischaemia and tissue necrosis. Since the hair cells of the inner ear and the neurons of the auditory pathway and cortex are very sensitive to ischaemia, macro- and/or microthrombosis, for example, in the terminal capillary bed, which originates from the labyrinthine artery and provides vascularisation of the inner ear, leads to cochlear sensorineural hearing loss, and in the basin of the middle cerebral or anterior temporal arteries, i.e., the vessels that supply the upper auditory pathways, it can lead to central perceptual hearing loss [30].

Morphological changes in the capillary wall and hypercoagulation lead to hypoxic changes in cells, disrupting the transport of glucose, proteins, ions, and other metabolites necessary for electrophysiological processes. This pathophysiological cascade can cause direct damage to

metabolically active cells in the inner ear. Even temporary hypoxia has a stressful effect on cochlear cells. Changes in molecular transport are exacerbated by the accumulation of products of concomitant inflammation and oxidative stress, causing additional damage to cochlear cells [31]. C.Y. Förster *et al.* [31] showed that age-related hearing loss and Alzheimer's disease have a common vascular pathogenetic basis caused by dysfunction of the cerebrovascular system and microcirculation disorders. The authors substantiate the role of endothelial dysfunction, oxidative stress, and neuroinflammation as key mechanisms contributing to the simultaneous degeneration of the auditory analyser and cognitive structures of the brain. C.Y. Förster *et al.* noted that in older adults, cardiovascular disease, diabetes mellitus and other metabolic disorders, and hearing loss, among other things, are modified risk factors for cognitive disorders, with possibly identical mechanisms of development. During the search for common pathogenetic mechanisms in patients with Alzheimer's disease and presbycusis, MRI data revealed cortical microhaemorrhages, signs of cerebral hypoperfusion, and impaired blood-brain barrier permeability. Given the functional and structural similarity of the blood-brain and blood-labyrinth barriers, the study suggested that their damage is caused by the accumulation of β -amyloid or other neurotoxic metabolites, in particular active forms of oxygen, which contribute to the progression of neurosensory and cognitive disorders.

Potential dysmetabolic molecular mechanisms of hearing impairment associated with decreased microcirculation and neurodegeneration were demonstrated by R. Mittal *et al.* [32] using the example of hearing loss in the context of diabetes mellitus. The pathogenesis of changes caused by hyperglycaemia includes processes that are typical of atherosclerotic, vascular and metabolic microangiopathies, neuropathies and oxidative stress. These pathological reactions can damage sensory structures in the cochlea, including the vascular strip, spiral ganglion neurons, and hair cells, and may be the result of cochlear synaptopathy, microangiopathy, neuropathy, oxidative stress, mitochondrial abnormalities, and apoptosis-mediated cell death.

The multi-organ nature of this condition is accompanied by a decline in the function of the affected organs and, consequently, the entire body. H. Zhang *et al.* [33] conducted a cohort study in Dongfeng-Tongji, China, observing 18,625 individuals over a period of 5.5 years. They found that the adjusted mortality risk ratio, including cardiovascular problems, increased with the progression of hearing deprivation. In addition, the risk increased even more when combined with above-average hearing loss, noise exposure, diabetes or hypertension.

Thus, micro- and macroangiopathies in older individuals may, on the one hand, be the result of physiological changes in the ageing body, i.e., one of the causes of presbycusis, and, on the other hand, they may be the result of concomitant age-related metabolic and cardiovascular diseases that contribute to sensory deprivation. The question of which of these is primary and which is secondary is debatable. However, it is an indisputable fact that the combination of these processes has a mutually aggravating effect, reducing quality of life and increasing the risk of death. In addition, these changes significantly

complicate clinical management and require a comprehensive approach to treatment.

Hearing deprivation as a determinant of reduced physical and social activity. A systematic review by P. Martinez-Amezcuca *et al.* [34] analysed the relationship between hearing impairment and physical activity levels, measured using objective methods, in an elderly population. The authors included five studies based on data from the National Health and Nutrition Examination Survey and used accelerometry to quantify physical activity. The pooled results show that hearing impairment, especially moderate to severe, is associated with reduced physical activity and increased sedentary behaviour. D.S. Chen *et al.* [35] indicated that the presence of hearing dysfunction is associated with a deterioration in mobility, strength, and functional independence, which increases the risk of disability in women by 30%. Therefore, hearing deprivation is an independent predictor of functional decline, indicating its systemic impact on the processes of age-related decline in physical reserve. According to B.S.Y. Yeo *et al.* [36], the presence of presbycusis is significantly associated with an increased risk of falls in older adults. The identified relationship is due to a complex of pathogenetic mechanisms, in particular, impaired sensory integration between the auditory, vestibular and proprioceptive systems, decreased postural stability and compensatory redistribution of cognitive resources for processing acoustic information. Concomitant neurodegenerative and vascular processes contribute to functional vulnerability and impaired motor control. Fear of falling and feelings of helplessness force people to lead a more sedentary lifestyle [21].

The recommendations published by the World Health Organisation [37] stated that to achieve optimal health benefits, older adults need moderate-intensity aerobic physical activity for 150-300 minutes per week or high-intensity activity for at least 75-150 minutes. However, according to a longitudinal study of ageing conducted by M.V. Goodwin *et al.* [38], British people over the age of 50 with hearing loss move significantly less, and the decline in this activity occurs faster in them compared to those who did not report hearing loss. Decreased physical activity may also be a consequence of age-related reduction in skeletal muscle mass and strength. In addition, alteration of their capillary network contributes to reduced blood flow and oxygen delivery to contracting muscle fibres. C.M. Hearon & F.A. Dinunno [39] described an age-related impairment of "functional sympatholysis", the ability of muscles to contract despite sympathetic vasoconstriction, leading to reduced blood flow and oxygen delivery during physical exertion. This process is critically relevant for the proper regulation of tissue blood flow distribution and oxygen transport. A decrease in physical activity during ageing is accompanied by a reduction in the oxygen demand for muscle contraction due to a slowdown in oxidative metabolism, which in turn leads to a weakening of the haemodynamic response and a decrease in the stimulation of muscle blood flow.

The progressive decline in cognitive and physical functions contributes to the deterioration of mental health and increases the risk of developing depressive disorders and psychological distress. J.S. Golub *et al.* [40] found that more than a third of the 5,328 participants in a cross-sectional study had clinically significant depressive symptoms.

According to J.A. Holman *et al.* [41], hearing loss causes increased fatigue, which in turn affects the level of physical activity and subjective well-being of people with hearing impairment. The study established that hearing dysfunction is indirectly associated with decreased activity and impaired quality of life due to increased cognitive load and energy expenditure on auditory perception. Fatigue associated with auditory load is a relevant mediator between hearing impairment and psychophysical state.

Emotional well-being is a fundamental component of human life and a relevant determinant of mental and physical health. A positive emotional state, formed through feelings of confidence, involvement, satisfaction and the achievement of personally meaningful goals, contributes to maintaining psychophysiological balance. Harmonious interpersonal interaction and positive emotions are central in shaping social activity and the adaptive potential of the individual [42]. With age, the cumulative effect of exogenous and endogenous factors on auditory function is primarily manifested by an increase in hearing thresholds in the high-frequency range of the sensorineural type, which progresses at an individually variable rate, involving the frequencies of the main speech spectrum and the low-frequency range. As the degree of hearing loss increases, speech intelligibility deteriorates, which significantly complicates communication, especially in conditions of background noise. According to B.H.B. Timmer *et al.* [42], in such conditions, people with hearing impairments more often experience feelings of insecurity, discomfort and frustration, which leads to avoidance of socially complex situations, in particular interaction in large groups or noisy environments. The fear of social stigmatisation limits involvement in interpersonal interaction, reduces motivation to communicate and communicative activity, which negatively affects the social well-being of people with audiological impairments.

Studying the impact of hearing loss on communication, A. Shukla *et al.* [6] described an increased risk of loneliness and social isolation. Social isolation is described as a decrease in the number of social contacts and the frequency of interaction between them, i.e. it is a kind of measure of a person's social network. Loneliness, on the other hand, is a subjective emotional response to a perceived mismatch between the actual and desired levels of social connections. P.L. Ramage-Morin [43] found that hearing deprivation in people aged 45 and older is significantly associated with increased levels of social isolation. The study found that people with hearing impairments are more likely to report limited social contacts, reduced involvement in interpersonal interactions, and emotional alienation compared to people without hearing problems. According to A. Chern & J.S. Golub [44], hearing loss causes feelings of emotional distance and complicates communication in a social environment, forming persistent communication barriers. To adequately perceive speech, people with hearing impairments are forced to engage additional cognitive resources, which is accompanied by increased cognitive load and the development of hearing-induced fatigue. Prolonged overload of cognitive mechanisms contributes to the progressive depletion of cognitive reserves, which can accelerate the formation of cognitive deficits and psychosocial disorders.

This creates a pathological circle: difficulties in processing auditory perception cause excessive cognitive load, which, in turn, exacerbates the development of neurodegenerative processes (i.e., exacerbates existing impaired auditory neurosensory function) and causes structural changes in the brain, further impairing cognitive processes. In addition, hypothetically, such excessive load can lead to cognitive decline due to the fact that in such conditions there is a redistribution of cognitive resources towards the processing of auditory information, "robbing" other mental processes, such as working memory [23]. The forced need to perceive and analyse overly quiet sound signals increases the load not only on cognitive resources. The attention resources involved in controlling posture and balance are also overloaded. B.S. Tsai Do *et al.* [21] presented the results of a cross-sectional study that showed a positive correlation between an increased probability of social isolation and the degree of hearing loss in elderly Americans. Moreover, the desire for solitude does not depend on whether such individuals receive correction for audiological disorders or not. Under such conditions, the risk of cognitive decline increases: brain stimulation is limited, and the mechanisms involved in overcoming not only mental but also physical difficulties are reduced. In other words, communication disorders associated with presbycusis have a direct impact not only on social activity but also on the overall quality of life, including physical health. In other words, communication problems associated with presbycusis have a direct impact not only on social activity but also on overall quality of life, including physical activity.

Hearing loss is just one of the symptoms of age-related deprivation, which has several common pathogenetic links with cardiovascular and metabolic diseases. Improving hearing function contributes to increased social activity, optimisation of cognitive resources and a reduction in hearing-related fatigue, which has a positive overall effect on the quality of life of older people. Timely audiological rehabilitation indirectly improves physical functioning, psycho-emotional state, and vascular-metabolic indicators. Thus, correction of hearing dysfunction is a substantial component of strategies for maintaining functional independence and preserving a high quality of life in the ageing process.

★ CONCLUSIONS

An analysis of scientific data has revealed that age-related hearing loss is becoming a global medical and social issue. The analysis showed that disabling hearing loss is one of the key problems in geriatrics, requiring improved approaches to early diagnosis and comprehensive correction. The study proved that the leading link in the pathogenesis of presbycusis is degenerative changes in the neurons of the auditory pathways from peripheral receptor structures to cortical centres, the development of which is exacerbated by age-related microvascular disorders, hypoperfusion and hypoxia of the cells of the auditory and vestibular apparatus. Genetically determined alteration is a consequence of changes in the expression of *Atoh1*, *Neurog1*, *Neurod1*, deficiency of transcription factors and their regulatory disorders, which lead to disruption of intracellular biochemical and electrophysiological processes, mitochondrial dysfunction, excessive oxidative activity, etc. The study

established that similar pathophysiological mechanisms underlie age-related cognitive disorders, which often develop in the context of hearing loss or in parallel with it, demonstrating a mutually reinforcing negative effect. Study determined that auditory deprivation causes excessive cognitive load, leading to depletion of cognitive reserve, decreased physical activity, and limited social engagement. The analysis showed that the multi-organ nature of age-related changes determines the need for a multidisciplinary approach to the prevention and treatment of hearing disorders and associated diseases to preserve the functional independence and quality of life of older people. Prospects for further research lie in an in-depth study of the causal

relationships between hearing dysfunction and cognitive decline, as well as in the development of integrated models for the early diagnosis and rehabilitation of age-related sensory and cognitive disorders.

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Нейробіологічні аспекти слухової депривації та її вплив на якість життя у похилому віці

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Анотація. Вікові зміни в організмі можуть призводити до функціональних обмежень, які ускладнюють старшим людям підтримку способу життя та виконання соціальних та особистісних ролей, що впливає на здатність жити повноцінно. Стаття присвячена з'ясуванню основних механізмів впливу зниження слуху на якість життя у осіб похилого віку. Було опрацьовано наукові публікації за 2016-2025 роки у електронній базі даних біомедичних досліджень MEDLINE/PubMed. Аналіз показав, що вікова втрата слуху передусім зумовлена нейродегенеративними процесами. Було з'ясовано, що дегенерація нейронів слухового шляху – від волоскових клітин кохлеї до нейронів неокортексу – проявляється редукцією клітинної популяції, морфологічною альтерацією нейронів і зменшенням кількості синаптичних контактів. Ці зміни супроводжуються порушенням біохімічного та електрофізіологічного гомеостазу, дисрегуляцією внутрішньоклітинної кальцієвої сигналізації та зниженням рівнів ключових нейромедіаторів, зокрема глутамату, гліцину та γ -аміномасляної кислоти. Подальший аналіз засвідчив, що зазначені нейробіологічні порушення призводять до зниження імпульсної активності та ослаблення гальмівних процесів, що клінічно проявляється слуховою дисфункцією, погіршенням сприйняття акустичних сигналів і зниженням здатності до просторової локалізації звуку. Було встановлено, що супутня мікроангіопатія характеризується пригніченням ангиогенезу, зменшенням щільності функціонуючих капілярів, потовщенням базальної мембрани та ендотеліальною дисфункцією, що зумовлює зниження тканинної перфузії. Було з'ясовано, що мікроциркуляторна недостатність сприяє вторинному ішемічному ушкодженню клітин через активацію оксидативного стресу та запальних каскадів. Генералізована вікова дегенерація нейронів і мікросудинного русла виявляється також у структурах мозку, відповідальних за когнітивні функції. У результаті формується рекурентний патофізіологічний механізм: слухова депривація підвищує когнітивне навантаження та прискорює виснаження нейронних ресурсів, що, своєю чергою, посилює нейродегенеративні процеси й структурні зміни мозку. Аналіз показав, що ці процеси взаємно потенціюють одне одного, спричиняючи прогресивне погіршення когнітивних функцій і зниження фізичної та соціальної активності у осіб похилого віку

Ключові слова: пресбіакузис; сенсоневральна приглухуватість; деменція; когнітивна функція; нейродегенерація; ангіопатія



The role of catestatin in left ventricular myocardial remodelling in patients with combined cardiometabolic pathology

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Abstract. The study is necessitated by the need to investigate the effect of catestatin on the structural and functional myocardial state in patients with chronic heart failure under conditions of cardiometabolic polymorbidity (type 2 diabetes mellitus and obesity). The aim was to evaluate the role of catestatin in the formation of structural and functional changes in the myocardium in patients with chronic heart failure in coronary artery disease with concomitant type 2 diabetes mellitus and obesity. The study involved 225 patients who were divided into four groups depending on the presence of metabolic disorders. A transthoracic echocardiographic examination was performed to assess the morphofunctional state of the myocardium. The level of catestatin in blood serum was determined by immunoenzymatic method. Spearman's correlation coefficient was used to assess the degree of correlation. The results showed that the most unfavourable indicators of left ventricular remodelling, including the maximum increase in end-systolic volume (101.57 mL) and end-diastolic volume (192.16 mL), as well as the lowest ejection fraction (42.67%), were recorded in patients with a combination of chronic heart failure, coronary artery disease, type 2 diabetes mellitus and obesity. This group had the lowest level of catestatin (1.53 ng/mL), which was 78.0% lower than in patients without metabolic disorders. Correlation analysis confirmed a strong direct relationship between catestatin levels and left ventricular ejection fraction ($r = 0.68$), as well as strong inverse correlations with end-diastolic volume ($r = -0.69$) and end-systolic volume ($r = -0.67$). A decrease in catestatin concentration is closely associated with an increase in left ventricular volume, its pathological remodelling, and a decrease in pumping function. The presence of polymorbid pathology leads to the most pronounced dilated type of left ventricular remodelling, and low catestatin levels are not only a marker but also a probable participant in the pathogenesis of adverse structural and functional changes in the myocardium

Keywords: chronic heart failure; coronary artery disease; type 2 diabetes mellitus; obesity; morpho-functional state of the myocardium

✦ INTRODUCTION

Chronic heart failure (CHF) remains a global challenge for modern medicine, due to high mortality and disability rates among populations around the world. The problem becomes particularly acute in cases of ischaemic origin, when the pathological process is aggravated by comorbid conditions. The combination of myocardial ischaemia with metabolic disorders, in particular type 2 diabetes mellitus (T2DM) and obesity, creates a complex pathogenetic knot that accelerates the degradation of cardiac function. The search for new biological markers capable of reflecting the depth of structural changes in the myocardium under such

conditions is critically important for improving the diagnosis and prognosis of the disease.

An analysis of scientific literature indicated that researchers were paying close attention to the problem of polymorbidity in cardiovascular pathology. In a large-scale review, B. Shahim *et al.* [1] emphasised that despite advances in therapy, the global burden of heart failure continues to grow, requiring an update of strategies for monitoring high-risk patients. Supplementing these data, A.D. Sotomayor-Julio *et al.* [2], based on the AMERICCAASS registry, analysed the clinical characteristics of more than 2,500

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patients, proving that the presence of concomitant metabolic disorders significantly complicates the achievement of target indicators with standard drug therapy. The state of renal and metabolic functions plays a special role in the progression of ischaemic heart damage. Ukrainian scientists H.B. Mankovsky *et al.* [3] studied in detail the mechanisms of development of coronary artery disease (CAD) disease in patients with T2DM through the prism of renal filtration, demonstrating that insulin resistance is a trigger for microvascular complications that directly affect myocardial viability. In parallel with this, M. Mazurkiewicz *et al.* [4] investigated the role of adipokines and adipose tissue in patients with heart failure (HF), emphasising that obesity creates a specific pro-inflammatory environment that stimulates pathological remodelling of the left ventricle (LV).

The issue of structural remodelling of the heart in the context of hypertension, diabetes and obesity remains the focus of attention of both Ukrainian and foreign specialists. B.O. Shelest *et al.* [5] demonstrated in their study that the combined effect of T2DM and obesity in patients with hypertension leads to the most pronounced types of LV remodelling, in particular eccentric hypertrophy. These findings correlate with the results of the Framingham Heart Study presented by B. von Jeinsen *et al.* [6], where a large population sample confirmed the independent contribution of each metabolic factor to changes in heart geometry and volume parameters. Modern molecular cardiology is actively seeking explanations for these processes at the cellular level. S. Appunni *et al.* [7] presented the concept of molecular remodelling in comorbid conditions in their report, pointing to the activation of specific signalling pathways leading to myocardial fibrosis and a decrease in its contractile capacity under the influence of systemic inflammation. In this context, catestatin, a peptide derived from chromogranin A, is of particular interest. The role of catestatin as a multifunctional regulator was described in detail by E. Zalewska *et al.* [8], who characterised it as an endogenous negative regulator of the sympathoadrenal system (SAS) with cardioprotective and metabolic effects. This topic was further developed in the work of J. Kulpa *et al.* [9], where it was shown that this peptide not only inhibits the secretion of catecholamines, but also actively influences the oxidation of fatty acids and insulin sensitivity, which is critical for patients with T2DM. A study by Z. Qiu *et al.* [10] found that catestatin can protect the heart from diastolic dysfunction by reducing the generation of mitochondrial reactive oxygen species. This opens up new prospects for the use of the peptide as a marker of early stages of HF. On the other hand, the clinical significance of plasma catestatin levels was confirmed by S. Izci *et al.* [11], who demonstrated its prognostic value for mortality and severity of cardiovascular events, although their study focused on the acute phase of pulmonary embolism, highlighting the versatility of this biomarker.

Despite such a wide range of studies, it remains unclear how exactly catestatin levels correlate with specific morphofunctional parameters of the heart in patients who have concomitant CAD, T2DM and obesity. Most of the available studies focused on individual nosologies, while polymorbidity creates a unique metabolic profile that

requires separate study. Thus, the aim of this study was to determine the role of catestatin in the mechanisms of structural and functional changes in the myocardium in patients with CHF of ischaemic origin with concomitant T2DM and obesity.

✦ MATERIALS AND METHODS

The present clinical study was carried out during the period from 2022 to 2025 and involved a cohort of 225 individuals diagnosed with CHF of ischemic etiology who received specialised care at the cardiology unit of the Municipal Clinical Hospital No. 27 of the Kharkiv City Council. To allow for a comparative analysis of the disease course, participants were categorised into four distinct groups based on their metabolic status, where Group 1 comprised 75 patients with CHF arising from CAD with coexisting T2DM and obesity, Group 2 included 50 individuals with CHF and CAD accompanied by T2DM, Group 3 consisted of 50 patients with ischemic CHF and concomitant obesity and Group 4 served as a comparison group consisting of 50 patients presenting with signs of ischemic-origin CHF without any associated metabolic pathologies.

The criteria for inclusion of patients in the analysis were: age over 18 years; verified diagnosis of CAD with clinical and instrumental signs of CHF; presence or absence of concomitant metabolic disorders, namely: overweight, obesity of I-III degree (according to the World Health Organization [12] classification by body mass index) and T2DM in the stage of compensation or subcompensation; the presence of the patient's voluntary written consent to participate in the study and to the processing of personal data. The study protocols excluded pregnant women along with individuals suffering from acute infections, autoimmune disorders, or diffuse connective tissue pathologies. Potential participants were also ineligible if they presented with oncological conditions, disorders of the pituitary and hypothalamic axis, or chronic kidney disease characterised by a Glomerular Filtration Rate below 35 mL/min/1.73 m². Additional exclusion factors comprised symptomatic hypertension, a history of acute coronary syndrome, or cerebrovascular accidents occurring within the previous six months. Furthermore, the study did not enroll patients experiencing exacerbations of chronic inflammation, those with documented alcohol misuse or psychiatric illnesses, and individuals deemed unlikely to adhere to the research procedures. Finally, non-citizens of Ukraine were not considered for inclusion in this clinical investigation.

The studies were approved by the Ethics and Bioethics Committee of the Kharkiv National Medical University (Protocol No. 2 dated 12 October 2022) and conducted with the written consent of the participants and in accordance with the principles of bioethics set out in The Helsinki Declaration [13] and The UNESCO Universal Declaration on Bioethics and Human Rights [14]. All patients underwent transthoracic echocardiography using standard methodology on a RADMIR (Ultima PRO 30) ultrasound machine (Kharkiv, Ukraine). To assess cardiovascular coupling (CVC), the ratio of effective elasticity (Ea) to end-systolic elasticity of the LV (Es) was calculated using the LV volume-pressure curve: $CVC = Ea/Es$. Ea and Es were calculated non-invasively using echocardiographic parameters:

$$Ea = \frac{ESP}{SV}, \quad (1)$$

where ESP – the end-systolic pressure, SV – the stroke volume.

ESP was calculated using the formula:

$$ESP = 0.9 \times SBP, \quad (2)$$

where SBP – systolic blood pressure.

$$Es = \frac{ESP}{ESV}, \quad (3)$$

where ESV – the end-systolic volume.

The Ea/Es ratio within the range of 0.6 to 1.2 under physiological conditions was taken as an indicator reflecting the optimal interaction between the arterial system and the LV. The serum concentration of catestatin (ng/mL) was quantified via enzyme-linked immunosorbent assay (ELISA) utilising the CUSABIO Human Catestatin-1 ELISA Kit. The procedure strictly followed the manufacturer's protocol and was executed on a Labline-90 automated microplate analyser (Austria). All laboratory measurements were conducted at the Biochemical Department of the Central Research Laboratory within Kharkiv National Medical University (Ministry of Health of Ukraine). The primary data management, including the systematisation and

visualisation of findings, was performed using Microsoft Office Excel. Comprehensive statistical processing was carried out using the Statistica 14.0 (TIBCO Software Inc., USA) software package. The normality of data distribution was verified through the Kolmogorov-Smirnov test. Quantitative variables following a normal distribution are expressed as the arithmetic mean (M) and standard deviation (SD). Inter-group differences for continuous variables were evaluated using Fisher's F-test (ANOVA). The strength and direction of associations between the studied myocardial parameters and catestatin levels were determined using Spearman's rank correlation coefficient (r). For all statistical tests, a p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS AND DISCUSSION

The initial stage of the study involved a meticulous analysis of the age and gender distribution among the surveyed groups to ensure the validity of subsequent comparisons. Analysis of demographic indicators confirmed the homogeneity of the formed groups. No statistically significant differences were found between patients in terms of gender composition ($\chi^2 = 1.844$; $p = 0.606$) and average age ($F = 0.57$; $p = 0.636$), which allowed to conclude that the samples are comparable. A comparison of the study groups was presented in Table 1.

Table 1. Clinical characteristics of the examined groups

Indicator, units	Observation groups			
	Patients with CHF against a background of CAD, T2DM and obesity (n = 75)	Patients with CHF, CAD and concomitant T2DM (n = 50)	Patients with CHF, CAD and concomitant obesity (n = 50)	Patients with ischaemic CHF without metabolic disorders (n = 50)
Male, abs (%)	42 (56%)	27 (54%)	22 (44%)	26 (52%)
Female, abs (%)	33 (44%)	23 (46%)	28 (56%)	24 (48%)
Age, years	63.44 ± 2.06	64.47 ± 1.88	60.59 ± 2.43	63.27 ± 1.72

Source: compiled by the author

The study revealed deep structural and functional transformations of the LV myocardium in patients with ischaemic CHF, particularly when complicated by metabolic disorders. The cumulative effect of T2DM and obesity significantly exacerbated the processes of pathological remodelling. As indicated in Table 2, patients in Group 1 exhibited the most severe deviations in all echocardiographic parameters. The LV end-systolic dimension (ESD) reached 4.86 ± 0.18 cm and the end-diastolic dimension (EDD) reached 6.56 ± 0.28 cm. When compared to Group 4, where ESD and EDD were 3.06 ± 0.17 cm and 4.08 ± 0.11 cm respectively, it becomes evident that the presence of T2DM and obesity promotes significant chamber dilatation ($p < 0.05$). The volumetric indicators showed even more alarming trends. The LVESV in Group 1 was 101.57 ± 4.16 mL, which is 117.6% higher than in Group 4. LV end-diastolic volume (EDV) was 192.16 ± 3.57 mL, a 76.9% increase compared to the group without metabolic disorders. Such dramatic expansion of the LV cavity in polymorbid patients suggests a severe loss of myocardial elasticity and a shift towards eccentric remodelling. The Left Ventricular Myocardium Mass Index (LVMMI) and Left Ventricular Myocardium Mass (LVMM) were highest in patients of Group 1 (171.64 ± 12.34 g/m² and 313.87 ± 17.34 g respectively). This indicated that the combination

of ischemic damage and hyperinsulinemia, as a characteristic of T2DM, triggers robust hypertrophic signals. Interestingly, while Left Ventricular Posterior Wall (LVPW) and Interventricular Septum (IVS) thickness were slightly thinner in Group 1 compared to Group 4, this does not signify a lack of hypertrophy, but rather the transition to eccentric hypertrophy, where the wall thickness is insufficient for the vastly increased chamber volume. This is confirmed by the Relative Wall Thickness (RWT) value of 0.48 ± 0.02 in Group 1, which is significantly lower than the 0.67 ± 0.03 found in Group 4. Systolic function, measured by the Ejection Fraction (EF), was most compromised in the polymorbid group ($42.67 \pm 2.32\%$), representing a significant drop from the $54.43 \pm 1.45\%$ seen in Group 4. This drop below the 45-50% threshold in Group 1 highlighted the transition from CHF with preserved or mildly reduced EF to a more severe clinical phenotype. The serum concentration of catestatin varied dramatically between groups. The lowest level of catestatin (1.53 ± 0.21 ng/mL) was found in Group 1, which was statistically significantly lower than in Group 4 (6.96 ± 0.17 ng/mL). This 78% reduction in polymorbid patients indicated a massive exhaustion of the body's cardioprotective resources. Catestatin inhibits the release of catecholamines from chromaffin cells. Therefore, its critical deficiency in patients with

CAD, T2DM, and obesity likely results in “unchecked” sympathetic activity. This, in turn, accelerates heart rate, promotes arrhythmias, and worsens the ischemic state of the myocardium, creating a vicious cycle of damage.

Table 2. Myocardial morphofunctional parameters and catestatin levels

Indicator, units	Observation groups				p
	Patients with CHF against a background of CAD, T2DM and obesity (n = 75)	Patients with CHF, CAD and concomitant T2DM (n = 50)	Patients with CHF, CAD and concomitant obesity (n = 50)	Patients with ischaemic CHF without metabolic disorders (n = 50)	
	1	2	3	4	
ESD, cm	4.86 ± 0.18	4.09 ± 0.13	4.44 ± 0.12	3.06 ± 0.17	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
EDD, cm	6.56 ± 0.28	5.48 ± 0.14	6.23 ± 0.16	4.08 ± 0.11	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ < 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
LVPW, cm	1.29 ± 0.02	1.31 ± 0.01	1.30 ± 0.03	1.44 ± 0.04	p ₁₋₂ > 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
IVS, cm	1.25 ± 0.02	1.29 ± 0.03	1.27 ± 0.04	1.36 ± 0.03	p ₁₋₂ > 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
RWT	0.48 ± 0.02	0.51 ± 0.02	0.54 ± 0.01	0.67 ± 0.03	p ₁₋₂ > 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
LVMMI, g/cm ²	171.64 ± 12.34	156.78 ± 8.67	169.31 ± 11.26	123.72 ± 9.78	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
LVMM, g	313.87 ± 17.34	258.76 ± 9.78	265.38 ± 11.76	203.51 ± 11.48	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
ESV, mL	101.57 ± 4.16	78.89 ± 3.56	94.12 ± 5.23	46.67 ± 3.12	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ < 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
EDV, mL	192.16 ± 3.57	139.25 ± 3.66	176.93 ± 4.28	108.64 ± 2.39	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ < 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
EF, %	42.67 ± 2.32	51.48 ± 2.71	49.34 ± 1.86	54.43 ± 1.45	p ₁₋₂ < 0.05 p ₁₋₃ < 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ > 0.05 p ₃₋₄ < 0.05

Table 2. Continued

Indicator, units	Observation groups				p
	Patients with CHF against a background of CAD, T2DM and obesity (n = 75)	Patients with CHF, CAD and concomitant T2DM (n = 50)	Patients with CHF, CAD and concomitant obesity (n = 50)	Patients with ischaemic CHF without metabolic disorders (n = 50)	
	1	2	3	4	
LAD, cm	4.93 ± 0.09	4.38 ± 0.06	4.78 ± 0.11	4.04 ± 0.05	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ < 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
RAD, cm	4.00 ± 0.08	3.52 ± 0.05	3.89 ± 0.07	3.44 ± 0.04	p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ < 0.05 p ₂₋₄ > 0.05 p ₃₋₄ < 0.05
Ea/Es	2.01 ± 0.06	1.89 ± 0.03	1.99 ± 0.02	1.78 ± 0.04	p ₁₋₂ > 0.05 p ₁₋₃ > 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05
Catestatin, ng/mL	1.53 ± 0.21	4.86 ± 0.19	4.99 ± 0.20	6.96 ± 0.17	p ₁₋₂ < 0.05 p ₁₋₃ < 0.05 p ₁₋₄ < 0.05 p ₂₋₃ > 0.05 p ₂₋₄ < 0.05 p ₃₋₄ < 0.05

Source: compiled by the author

The correlation analysis of catestatin with indicators of the morpho-functional state of the myocardium is shown in Table 3. A strong inverse correlation was found between the level of catestatin and EDV ($r = -0.69$, $p < 0.001$), ESV ($r = -0.67$, $p < 0.001$); inverse correlations of moderate strength were found with ESD ($r = -0.61$, $p < 0.001$), EDD ($r = -0.56$, $p < 0.001$), LVMM ($r = -0.56$, $p < 0.001$), left atrium

dimension (LAD) ($r = -0.55$, $p < 0.001$), right atrium dimension (RAD) ($r = -0.49$, $p < 0.001$), Ea/Es ($r = -0.49$, $p < 0.001$), left ventricular posterior wall (LVPW) ($r = -0.44$, $p < 0.001$) and LVMMI ($r = -0.43$, $p < 0.001$). Most importantly, the strong direct correlation with EF ($r = 0.68$, $p < 0.001$) provides evidence that maintaining catestatin levels may be essential for preserving the systolic pump function of the heart.

Table 3. Correlations between catestatin levels and parameters of the morphofunctional state of the myocardium ($r_{crit} = 0.41$)

Indicator, units	r	p
ESD, cm	-0.61	<0.001
EDD, cm	-0.56	<0.001
LVPW, cm	-0.44	<0.001
IVS, cm	-0.36	0.074
RWT	-0.33	0.065
LVMI, g/cm ²	-0.43	<0.001
LVMM, g	-0.56	<0.001
ESV, mL	-0.67	<0.001
EDV, mL	-0.69	<0.001
EF, %	0.68	<0.001
LAD, cm	-0.55	<0.001
RAD, cm	-0.49	<0.001
Ea/Es	-0.49	<0.001

Source: compiled by the author

The correlations found showed that a decrease in catestatin concentration is closely associated with an increase in LV volume, its pathological remodelling, and a decrease in pumping function. This confirms the hypothesis that low catestatin levels are not only a marker but also, probably, a

participant in the pathogenesis of adverse structural and functional changes in the myocardium in patients with CHF complicated by metabolic disorders. The results obtained in this study provided compelling evidence that serum catestatin levels serve as a critically important biomarker

for assessing the severity of ischemic CHF, particularly in the complex setting of comorbid metabolic disorders. The synthesis of authors' findings with existing international data allows for a deeper understanding of the pathogenetic role of this peptide.

According to the comprehensive clinical and experimental studies conducted by S.K. Mahata *et al.* [15] and E. Zalewska *et al.* [16], catestatin functions as a pleiotropic cardioprotective peptide. Its primary mechanism involves counteracting the deleterious effects of catecholamine excess by inhibiting their secretion from chromaffin cells and adrenergic nerve endings. In this study, the lowest levels of catestatin (1.53 ng/mL) were recorded in Group 1 (CHF + T2DM + Obesity). This significant decline, when viewed alongside the most unfavorable LV parameters, reflects a state of "exhaustion" or decompensation of this endogenous protective mechanism. This aligns with the findings of J.S. Rathee *et al.* [17], who recently emphasised that catestatin and its variants play a pivotal role in physiological cardiovascular regulation, and its deficiency leads to an inability to suppress the SAS effectively. Consequently, low catestatin levels fail to mitigate the proarrhythmic, vasoconstrictive, and remodelling effects of chronic SAS hyperactivation.

The relationship between catestatin and myocardial structure is a central theme in modern cardiology. Research by Z. Qiu *et al.* [10] indicated that catestatin is not merely a marker but an active protector against diastolic dysfunction. In their experimental models, catestatin was shown to attenuate mitochondrial reactive oxygen species generation, thereby reducing myocardial hypertrophy and fibrosis. Authors' clinical data strongly correlate with these experimental findings: the high inverse correlations found between catestatin and LV volumes (EDV $r = -0.69$; ESV $r = -0.67$) suggest that in patients with low catestatin, the heart lacks a critical defense against oxidative stress. This is further supported by Q. Yan *et al.* [18], who highlighted targeting oxidative stress as a vital preventive approach for cardiovascular disease, identifying peptides like catestatin as key components of this strategy.

A significant contribution to the understanding of post-infarction remodelling was made by D. Zhu *et al.* [19], who identified catestatin as a novel predictor of LV remodelling after acute myocardial infarction. While their study focused on the acute phase, authors' results extend this observation to CHF, showing that persistent catestatin deficiency in polymorbid patients is associated with the most pronounced dilated remodelling (ESV increase of 117.6%). The prognostic value of this biomarker deserves special attention. Ł. Wołowicz *et al.* [20] established that a decrease in catestatin is associated with a worsening two-year prognosis for patients with heart failure and reduced ejection fraction. Conversely, S.Y. Chu *et al.* [21] found that elevated catestatin might be a more sensitive predictor of cardiac death in patients with mildly reduced or preserved ejection fraction compared to those with severely reduced EF. Authors' findings bridge these perspectives: the lowest catestatin levels in this study were associated with the lowest ejection fraction ($42.67 \pm 2.32\%$), reinforcing the hypothesis that catestatin deficiency is a marker of severe systolic dysfunction and heightened cardiovascular risk in polymorbid states.

Metabolic integration is another facet of catestatin's action. M.P. Gallo *et al.* [22] demonstrated that catestatin induces glucose uptake and GLUT₄ translocation in cardiomyocytes, playing a role in metabolic homeostasis. This is particularly relevant to authors' results in Group 1. The presence of T2DM and obesity likely creates a state of "metabolic exhaustion". As I. Dunaeva & O. Bilovol [23] observed in their research on comorbid hypertension, catestatin levels are significantly altered in patients with combined cardiovascular and metabolic disorders, serving as a sensitive indicator of metabolic syndrome-related sympathetic overactivation. Authors' study confirmed this, showing that the combination of T2DM and obesity leads to a much steeper decline in catestatin (1.53 ng/mL) than either condition alone (Groups 2 and 3). Furthermore, the work of J.A. Borovac *et al.* [24] noted that catestatin levels are dynamic in acutely decompensated HF. Authors' data suggested that in chronic stable patients with polymorbidity, catestatin levels do not "recover" but remain low, contributing to the persistent progression of LV dilatation.

In conclusion, this data demonstrated that catestatin is a critically important biomarker. The results of the study, supported by the findings of international scientific community, suggest that low catestatin levels in this cohort not only reflect but may also exacerbate the degree of pathological LV remodelling. This emphasised the urgent need for clinical strategies aimed at correcting SAS hyperactivation. Moreover, the strong correlations with contractile function observed in research highlighted the potential prospect of catestatin-based replacement therapy or pharmacological stabilisation as a future therapeutic avenue for patients with ischemic HF and metabolic syndrome.

★ CONCLUSIONS

The combination of metabolic disorders in the form of T2DM and obesity critically worsens the structural and functional state of the myocardium and leads to a maximum deficiency of catestatin. Patients with CHF of ischaemic origin against a background of concomitant T2DM and obesity had the worst indicators, which included the maximum increase in end-systolic volume (101.57 ± 4.16 mL) and end-diastolic volume (192.16 ± 3.57 mL), the highest left ventricular myocardial mass (313.87 ± 17.34 g) and the lowest left ventricular ejection fraction ($42.67 \pm 2.32\%$) compared to all other groups. At the same time, this group had the lowest level of catestatin (1.53 ± 0.21 ng/mL), which was significantly lower than in all other groups. This indicates that the presence of polymorbid pathology leads to the most pronounced dilated type of left ventricular remodelling.

Correlation analysis confirmed a strong direct correlation between the level of catestatin and left ventricular ejection fraction ($r = 0.68$, $p < 0.001$), and also revealed strong inverse correlations between catestatin and left ventricular volume parameters: end-diastolic ($r = -0.69$, $p < 0.001$) and end-systolic volumes ($r = -0.67$, $p < 0.001$). This demonstrates that a decrease in catestatin concentration is closely associated with an increase in left ventricular volumes, its pathological remodelling, and a decrease in pumping function. The data obtained confirm the hypothesis that low catestatin levels are not only a marker but also a probable participant in the pathogenesis of adverse

structural and functional changes in the myocardium. Further study of the relationship between low catestatin levels and systemic markers will help confirm the hypothesis that catestatin deficiency leads to a lack of myocardial protection against oxidative stress and fibrosis, as well as to establish optimal catestatin threshold values that can be used for risk stratification and identification of patients with polymorbid pathology at high risk of decompensation and rapid progression of left ventricular remodelling.

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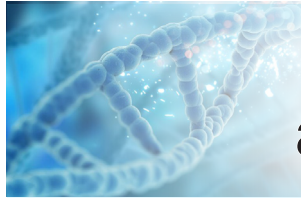
Роль катестатину в ремоделюванні міокарда лівого шлуночка у хворих із поєднаною кардіометаболічною патологією

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Анотація. Актуальність роботи зумовлена необхідністю вивчення впливу катестатину на структурно-функціональний стан міокарда у пацієнтів із хронічною серцевою недостатністю за умови кардіометаболічної поліморбідності (цукрового діабету 2 типу та ожиріння). Мета полягала в оцінці ролі катестатину у формуванні структурно-функціональних змін міокарда у хворих з хронічною серцевою недостатністю, що виникла на тлі ішемічної хвороби серця з супутнім цукровим діабетом 2 типу та ожирінням. Дослідження залучило 225 пацієнтів, які були розподілені на чотири групи залежно від наявності метаболічних порушень. Для оцінки морфо-функціонального стану міокарда проводилось трансторакальне ехокардіографічне дослідження. Рівень катестатину в сироватці крові визначали імуноферментним методом. Для оцінки ступеня взаємозв'язку використовували коефіцієнт кореляції Спірмена. Результати продемонстрували, що найбільш несприятливі показники ремоделювання лівого шлуночка, включаючи максимальне зростання кінцево-систоличного об'єму (101,57 мл) та кінцево-діастолічного об'єму (192,16 мл), а також найнижчу фракцію викиду (42,67 %), були зафіксовані у пацієнтів із поєднанням хронічної серцевої недостатності, ішемічної хвороби серця, цукрового діабету 2 типу та ожиріння. У цій групі виявлено найнижчий рівень катестатину (1,53 нг/мл), знижений на 78,0 % порівняно з пацієнтами без метаболічних порушень. Кореляційний аналіз підтвердив сильний прямий зв'язок між рівнем катестатину та фракцією викиду лівого шлуночка ($r = 0,68$), а також сильні зворотні зв'язки з кінцево-діастолічним об'ємом ($r = -0,69$) та кінцево-систолическим об'ємом ($r = -0,67$). Зниження концентрації катестатину тісно асоційоване зі збільшенням об'ємів лівого шлуночка, його патологічним ремоделюванням та зниженням насосної функції. Наявність поліморбідної патології призводить до найбільш вираженого дилатаційного типу ремоделювання лівого шлуночка, а низький рівень катестатину є не лише маркером, а й вірогідним учасником патогенезу несприятливих структурно-функціональних змін міокарда

Ключові слова: хронічна серцева недостатність; ішемічна хвороба серця; цукровий діабет 2 типу; ожиріння; морфо-функціональний стан міокарда



Microbial community state type stratification and quantitative culture-based assessment of vaginal microbiota in reproductive-age women

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Abstract. The vaginal microbiota plays a crucial role in maintaining female reproductive health; however, subclinical forms of dysbiosis remain insufficiently characterised, particularly regarding the integration of molecular, culture-based, and morphological assessment methods. The purpose of the study was to evaluate the structural, quantitative, and morphological characteristics of the vaginal microbiota in reproductive-age women and to determine the correspondence between molecular microbiome stratification and culture-based morphological findings. Thirty reproductive-age women were selected from 1,000 initially screened participants. Quantitative culture analysis with determination of CFU/mL was performed, along with Gram-stained smear microscopy using digital image documentation and molecular classification of the vaginal microbiota based on 16S ribosomal ribonucleic acid gene sequencing. Microbial concentrations ranged from 10^2 to 10^7 CFU/mL. The lactobacillary population showed the greatest variability, with a mean value of $(1.6 \pm 1.1) \times 10^6$ CFU/mL. Samples were classified into three microbial community types: type I accounted for 30%, type III for 13.3%, and type IV for 56.7%. Type I was characterised by dominance of *Lactobacillus crispatus* at $(3.8 \pm 1.7) \times 10^6$ CFU/mL and a mean acidity of 3.6 ± 0.3 . Type III was associated with *Lactobacillus iners* at $(1.5 \pm 0.8) \times 10^6$ CFU/mL and a moderate increase in acidity to 4.5 ± 0.3 . Type IV demonstrated reduced lactobacilli at $(4.9 \pm 3.2) \times 10^2$ CFU/mL, increased anaerobic bacteria to 10^3 - 10^4 CFU/mL, and elevated acidity to 5.6 ± 0.4 . The morphological patterns of Gram-stained smears corresponded closely to the molecularly defined microbial types. The integration of quantitative culture analysis with standardised smear microscopy represents an informative tool for stratifying vaginal microbiota states in settings where molecular diagnostics are limited

Keywords: pathogenic flora; *Lactobacillus* dominance; anaerobic bacterial communities; microbiology of the reproductive system; culture-based microbiology; Gram-stained smear analysis

★ INTRODUCTION

The vaginal microbiota represents a specialised microbial ecosystem of the female reproductive tract and plays a central role in maintaining reproductive health. The stability of this microbial ecosystem contributes to the barrier function of the mucosal surface, maintenance of optimal acidity, and colonisation resistance against pathogenic and opportunistic microorganisms. Disturbances

in the balance of vaginal microbial communities may result in dysbiotic states that alter the protective functions of the mucosal environment. Despite significant advances in microbiome research, the mechanisms underlying the development and dynamics of different ecological states of the vaginal microbiota remain insufficiently understood.

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Studies indicated that the vaginal microbiota is characterised by relatively low taxonomic diversity and predominance of bacteria belonging to the genus *Lactobacillus*, which maintain acidic vaginal pH and suppress the growth of opportunistic microorganisms. The study by R. Mirzaei *et al.* [1] demonstrated that the microbiota of different compartments of the female reproductive tract forms a continuous microbial ecosystem, and alterations in vaginal microbiota composition may be associated with inflammatory and neoplastic conditions. The researchers emphasised the importance of analysing the structural organisation of the microbiome for understanding mechanisms underlying pathological processes. M.J. Kim *et al.* [2] reported that recurrent vaginitis is associated with a significant decrease in the proportion of *Lactobacillus* spp. and an increase in bacterial diversity. In their study, more than half of the examined patients demonstrated a microbiota profile corresponding to the dysbiotic community state type (CST) IV, suggesting that structural changes within the microbial community play an important role in the development of chronic inflammatory processes.

In another study, J. Novak *et al.* [3] investigated vaginal microbiota dominated by *Lactobacillus iners*. The researchers found that this microbiota profile is characterised by relative instability and an increased tendency to shift toward dysbiosis. This phenomenon is associated with the fact that *L. iners* produces lower amounts of lactic acid and exhibits reduced antagonistic activity against anaerobic bacteria. Further studies have highlighted the complex interactions between bacterial and fungal components of the vaginal microbiome. C. Zhao *et al.* [4] demonstrated that different forms of vulvovaginal candidiasis are associated with specific alterations in bacterial microbiota composition. Their findings suggested that fungal infections may modify the structure of bacterial communities by altering the balance of dominant microorganisms. An important area in microbiome research is the application of molecular methods for microbiota analysis. H.N. Brochu *et al.* [5] performed molecular profiling of the vaginal microbiome in patients with bacterial vaginosis and identified clear differences in the structure of bacterial communities. The researchers noted that sequencing of the 16S ribosomal ribonucleic acid (rRNA) gene provides a more accurate characterisation of microbiota taxonomic composition compared with conventional culture-based methods.

However, several studies also highlighted methodological limitations of molecular approaches. C.A. Broedlow *et al.* [6] demonstrated that the use of different sequencing protocols may result in discrepancies in the molecular diagnosis of bacterial vaginosis. Such variability may arise from both technical differences in analytical methods and significant strain-level diversity within certain bacterial species, particularly *Gardnerella vaginalis*. Other studies emphasised the importance of integrating different microbiological approaches for a comprehensive evaluation of vaginal microbiota. L. Mancabelli *et al.* [7] showed that the combination of molecular and culture-based techniques allows a more accurate assessment of the functional characteristics of the vaginal microbiome. Culture-based methods remain essential for determining the absolute abundance of microorganisms and evaluating their functional potential.

Thus, contemporary research confirmed that the vaginal microbiota represents a complex and dynamic

ecosystem whose structure may vary under the influence of numerous biological and environmental factors. Despite significant progress in molecular microbiome profiling, there remains a clear need for integrated analytical approaches combining molecular, culture-based, and morphological methods. Such approaches enable not only identification of the taxonomic composition of microbial communities but also evaluation of their quantitative and functional characteristics. The purpose of this study was to investigate quantitative culture-based characteristics of vaginal microbiota across different CST and to assess the agreement between molecular microbiome classification and classical microbiological diagnostic methods.

✦ MATERIALS AND METHODS

The study was conducted between 2023 and 2025 at medical institutions in Uzhhorod and Odesa, Ukraine. The study design was observational and cross-sectional. A total of 1,000 reproductive-age women underwent initial clinical examination. The participants sought gynaecological consultation for preventive purposes or routine medical evaluation. Women were included in the study if they met the following criteria: age 18–45 years; absence of clinical signs of acute infectious diseases; no antibacterial therapy during the previous 4 weeks; no antifungal therapy during the previous 2 weeks; provision of written informed consent. The exclusion criteria were: pregnancy or postpartum period; clinically confirmed sexually transmitted infections; systemic inflammatory or autoimmune diseases; hormonal therapy or use of hormonal intrauterine devices; incomplete clinical or laboratory data. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki [8]. The study protocol was approved by the Local Ethics Committee of Uzhhorod National University (Protocol No. 11, December 30, 2022). All participants provided written informed consent prior to enrolment in the study.

Vaginal samples were collected using sterile swabs from the posterior vaginal fornix during gynaecological examination. All specimens were transported to the laboratory within 2 hours at a temperature of +4 to +8°C. Quantitative determination of microorganisms was performed using serial tenfold dilutions, followed by inoculation of 100 µL aliquots of the appropriate dilutions onto universal, selective, and anaerobic culture media. Incubation was carried out at 37°C under aerobic, microaerophilic, or anaerobic conditions depending on the microbial group. De Man-Rogosa-Sharpe agar was used for isolation of *Lactobacillus* spp.; blood agar for Gram-positive cocci; mannitol salt agar for staphylococci; selective anaerobic media for bacterial vaginosis-associated anaerobes; and Sabouraud dextrose agar and chromogenic media for yeast-like fungi. Identification of isolates was performed based on morphological characteristics and standard biochemical test systems (PLIVA-Lachema, Czech Republic) in accordance with the manufacturer's instructions. Colony-forming units per millilitre were calculated with consideration of the dilution factor, and the results were expressed in logarithmic format (log CFU/mL). Smears were prepared from vaginal secretion, stained using the standard Gram staining procedure, and examined under oil immersion at ×1,000 magnification. For each specimen, at least 10 randomly selected fields of view were analysed with digital

image documentation. Bacterial morphotypes, their relative abundance, spatial density, and the presence of mixed microbial consortia were assessed.

Classification of samples into community state types was performed based on previously obtained 16S rRNA gene sequencing results of the vaginal microbiota, as described in detail by S.Y. Borshosh & N.V. Boyko [9]. Sequencing of the vaginal microbiota was performed through amplification of variable regions of the 16S rRNA gene, followed by bioinformatic processing and taxonomic assignment of the obtained sequences. The resulting microbial profiles were classified according to the CST concept originally described by A. Gerede *et al.* [10]. Based on the taxonomic composition of the microbiota, the samples were assigned to three microbial community types: CST I – microbiota dominated by *Lactobacillus crispatus*; CST III – microbiota dominated by *Lactobacillus iners*; CST IV – polymicrobial anaerobic microbiota characterised by a reduced abundance of lactobacilli. The molecularly defined community state type profile was used as a reference standard for subsequent comparison with culture-based and microscopic characteristics.

Statistical analysis was performed using SPSS Statistics software. The normality of data distribution was evaluated using the Shapiro-Wilk test. For comparison of quantitative variables between the three CST groups, one-way analysis of variance (ANOVA) was applied for normally distributed data, whereas the Kruskal-Wallis test was used for non-parametric variables. Post hoc pairwise comparisons were performed using the Tukey test or Dunn's test where appropriate. Agreement between morphological assessment and molecular classification was evaluated using Cohen's kappa coefficient. Differences were considered

statistically significant at $p < 0.05$. The main limitation of the study is the relatively small final sample size resulting from the application of strict selection criteria. In addition, the composition of the vaginal microbiota may change under the influence of individual hormonal, behavioural, and environmental factors that cannot always be fully standardised in a clinical research setting.

RESULTS AND DISCUSSION

The mean age of the examined women was 29.8 ± 6.4 years (range 19–44). Most participants were sexually active and had no clinical signs of acute vaginal infection at the time of examination. No statistically significant differences in age distribution were observed between CST groups ($p > 0.05$). The lactobacillary population demonstrated the greatest variability among the detected microbial groups. Its concentration ranged from $(5.1 \pm 3.4) \times 10^2$ to $(3.4 \pm 2.1) \times 10^6$ CFU/mL, reaching 10^7 CFU/mL in individual samples, with a mean value of $(1.6 \pm 1.1) \times 10^6$ CFU/mL. In contrast, other representatives of the vaginal microbiota showed relatively stable concentrations (Table 1). These findings indicate that variation in *Lactobacillus* density represents the principal axis of microbiota shifts, whereas facultative bacteria reflect the degree of reduction in colonisation resistance.

According to 16S rRNA gene sequencing, samples were classified into three community state types: CST I – 9 cases (30%), CST III – 4 cases (13.3%), and CST IV – 17 cases (56.7%). Comparative analysis of microbiological indicators across CST groups revealed significant differences in the concentration of *Lactobacillus* spp., levels of anaerobic bacteria, and vaginal pH values (Table 2).

Table 1. Mean concentration of representatives of the vaginal microbiota

Microorganism	Mean concentration \pm SD (CFU/mL)
<i>Lactobacillus</i> spp.	$(1.6 \pm 1.1) \times 10^6$
<i>Corynebacterium</i> spp.	$(3.9 \pm 1.6) \times 10^5$
<i>Enterococcus faecalis</i>	$(1.3 \pm 0.5) \times 10^5$
<i>Escherichia coli</i>	$(6.8 \pm 2.9) \times 10^2$
<i>Streptococcus</i> spp.	$(9.8 \pm 3.6) \times 10^2$

Source: compiled by the authors based on research

Table 2. Comparative characteristics of quantitative indicators of vaginal microbiota according to CST

Parameter	CST I (n = 9)	CST III (n = 4)	CST IV (n = 17)	p-value	Statistical test
<i>Lactobacillus</i> spp., CFU/mL	$(3.8 \pm 1.7) \times 10^6$	$(1.5 \pm 0.8) \times 10^6$	$(4.9 \pm 3.2) \times 10^2$	<0.001	Kruskal-Wallis
BV-associated anaerobes, CFU/mL	$\leq 1.0 \times 10^2$	$\leq 1.0 \times 10^5$	$1.0 \times 10^5 - 1.0 \times 10^4$	<0.001	Kruskal-Wallis
<i>Escherichia coli</i> / <i>Klebsiella</i> spp., CFU/mL	$(3.8 \pm 1.6) \times 10^2$	$(7.8 \pm 3.2) \times 10^2$	$(9.1 \pm 3.7) \times 10^2$	0.04	Kruskal-Wallis
<i>Enterococcus faecalis</i> , CFU/mL	$(7.4 \pm 2.6) \times 10^2$	$(1.2 \pm 0.5) \times 10^5$	$(2.4 \pm 0.9) \times 10^5$	0.02	Kruskal-Wallis
<i>Candida</i> spp., CFU/mL	$\leq 1.0 \times 10^2$	$(3.6 \pm 1.4) \times 10^2$	$\leq 1.0 \times 10^5$	0.05	Kruskal-Wallis
Vaginal pH	3.6 ± 0.3	4.5 ± 0.3	5.6 ± 0.4	<0.001	One-way ANOVA

Source: compiled by the authors based on research

The predominance of CST IV is noteworthy. In population-based studies of apparently healthy women, including those by A. Gerede *et al.* [10], lactobacillus-dominated profiles usually prevail, whereas CST IV is observed less frequently. In contrast, in the present study CST IV constituted more than half of all samples, suggesting the presence of subclinical dysbiotic states in a predominantly asymptomatic cohort. In the CST I group, the microbiota

was dominated by *Lactobacillus crispatus*. This type was characterised by high concentrations of lactobacilli, low levels of facultative microorganisms, and a mean vaginal pH of 3.6 ± 0.3 . Morphologically, Gram-stained smears demonstrated a homogeneous pattern with predominance of long Gram-positive rods. Bacterial vaginosis-associated anaerobes were either absent or detected only in trace amounts, which corresponds to a classical eubiotic microbiota profile.

CST III represented a transitional microbiota state dominated by *Lactobacillus iners*. This group demonstrated moderate concentrations of lactobacilli, accompanied by a gradual increase in facultative microorganisms such as *Escherichia coli* and *Enterococcus* spp. The mean vaginal pH reached 4.5 ± 0.3 . Morphologically, Gram-stained smears showed thinner and more variable rods, reflecting the ecological instability of this microbiota type. The CST IV group showed the most substantial shifts in microbial composition. This type was characterised by a marked reduction in *Lactobacillus* spp., increased concentrations of facultative Gram-negative bacteria, and a high prevalence of anaerobic microorganisms associated with bacterial vaginosis, including *Gardnerella vaginalis*, *Prevotella* spp., and

Atopobium vaginae. Vaginal pH increased to 5.6 ± 0.4 , reflecting the loss of colonisation resistance and the development of a dysbiotic microbial community.

Microscopic analysis of digitised Gram-stained smears confirmed the correspondence between morphological patterns and molecularly defined community state types. CST I demonstrated predominance of long Gram-positive rods with minimal diversity, CST III showed greater morphological variability, whereas CST IV was characterised by a dense polymicrobial pattern dominated by small Gram-negative rods and cocci. The agreement between morphological assessment and molecular CST classification was high ($\kappa = 0.87$), confirming the diagnostic value of integrated microbiological analysis (Table 3).

Table 3. Agreement between morphological assessment and molecular classification of vaginal microbiota

Assessment method	CST I	CST III	CST IV
Molecular classification (16S rRNA sequencing)	9	4	17
Morphological assessment (Gram-stained microscopy)	8	4	16

Note: Cohen's kappa coefficient: 0.87, p-value: <0.001

Source: compiled by the authors based on research

Overall, the obtained results demonstrated a clearly structured spectrum of vaginal microbiota states ranging from stable lactobacillus-dominated eubiosis to polymicrobial anaerobic dysbiosis. The key quantitative marker of this transition is a reduction in *Lactobacillus* spp., particularly *Lactobacillus crispatus*, accompanied by increased vaginal pH and progressive expansion of anaerobic microbial consortia. The results of the present study demonstrated a clear stratification of vaginal microbiota states corresponding to different CST. In the examined cohort, CST IV represented the most prevalent microbiota profile. This finding differs from the observations reported by M.J. Kim *et al.* [2], who showed that the stability of the vaginal microbiome is associated with a high abundance of lactobacilli and relatively low microbial diversity. In addition, the conceptual model of bacterial vaginosis proposed by Y. Zhang *et al.* [11] indicated that lactobacillus-dominated microbiota usually represents the physiological state of the vaginal ecosystem. The predominance of CST IV in the present study therefore suggests that subclinical dysbiotic states may occur more frequently in apparently asymptomatic populations than previously assumed.

In the present study, CST I was characterised by the dominance of *Lactobacillus crispatus*, high concentrations of lactobacilli, and low vaginal pH values. Similar microbiota profiles have been described in several microbiome studies. For example, W. Dong *et al.* [12] reported that lactobacillus-dominated microbiota represents the most stable and protective microbial state of the vaginal ecosystem. Likewise, H. Xu *et al.* [13] emphasised that high concentrations of lactobacilli play a crucial role in maintaining vaginal microbial homeostasis and colonisation resistance against opportunistic microorganisms. These observations are also supported by the findings of A. Borrego-Ruiz & J.J. Borrego [14], who highlighted the important role of lactobacilli in maintaining vaginal acidity and suppressing the growth of anaerobic bacteria. Therefore, the CST I microbiota profile identified in the present study corresponds to a classical eubiotic vaginal microbiota state.

The CST III microbiota type observed in this study was dominated by *Lactobacillus iners*. Previous studies have shown that *L. iners* – dominated microbial communities often represent a transitional ecological state between eubiosis and dysbiosis. Similar observations were reported in clinical microbiological studies of vaginal microbiota in women with intermediate Nugent scores, where *L. iners* frequently predominated in microbiota profiles demonstrating ecological instability [9]. In particular, J. Novak *et al.* [3] demonstrated that *Lactobacillus iners* produces smaller amounts of lactic acid and exhibits reduced antagonistic activity against anaerobic microorganisms compared with other lactobacillus species. Similar conclusions were reported by C. Zhao *et al.* [4], who found that microbiota dominated by *L. iners* frequently displays increased ecological variability and may transition toward dysbiotic microbial states under certain conditions. The moderate concentrations of lactobacilli and increased variability of microbial composition observed in the CST III group of the present study therefore correspond well with previously described characteristics of this microbiota type.

The most pronounced microbiological alterations in the present study were observed in CST IV, which accounted for more than half of the analysed samples. This microbiota type was characterised by a substantial reduction in *Lactobacillus* spp. and an increased prevalence of facultative and obligate anaerobic microorganisms associated with bacterial vaginosis. Similar microbial patterns have been reported by C.A. Broedlow *et al.* [6] who demonstrated that dysbiotic vaginal microbiota is frequently associated with anaerobic taxa such as *Gardnerella vaginalis*, *Prevotella* spp., and *Atopobium vaginae*. Comparable findings were also described by L. Mancabelli *et al.* [7], who identified polymicrobial anaerobic communities as a characteristic feature of CST IV microbiota and reported that these communities are associated with increased microbial diversity and reduced abundance of lactobacilli. Furthermore, the influence of behavioural and environmental factors on

the structure of vaginal microbial communities has been described S. Ottinger *et al.* [15], who demonstrated that sexual behaviour and other host-related factors may significantly affect microbiota composition and contribute to dysbiotic microbial states.

An important observation of this study was the relatively high prevalence of CST IV among women who did not present with pronounced clinical symptoms. This finding supports the concept of subclinical vaginal dysbiosis. For example, C. Adapen *et al.* [16] reported that dysbiotic microbial communities may persist in the vaginal environment without clear clinical manifestations for extended periods. In addition, epidemiological studies conducted by M. Gholiou *et al.* [17] demonstrated that alterations in vaginal microbiota composition may increase susceptibility to sexually transmitted infections and inflammatory conditions of the reproductive tract. These observations suggest that subclinical microbiota instability may represent an important factor in reproductive health.

Another important finding of the present study is the high level of concordance observed between molecular sequencing results, quantitative culture-based microbiological analysis, and morphological smear assessment. Similar conclusions were reported by M.J. Kim *et al.* [2], who emphasised that the integration of molecular microbiome profiling with classical microbiological methods allows a more comprehensive characterisation of vaginal microbial communities. Moreover, experimental studies conducted by J.B. Holm *et al.* [18] demonstrated that lactobacillus species may serve not only as key biomarkers of vaginal health but also as functional agents that regulate microbial interactions within the vaginal ecosystem. These findings support the diagnostic value of combining molecular and classical microbiological approaches.

The classification of microbial communities into CST profiles in the present study was based on previously established microbiome concepts. The CST classification system originally described by A. Gerede *et al.* [10] has become one of the most widely used frameworks for describing vaginal microbial community structure. Further refinement of CST classification methods was proposed by B. Oliva-Arancibia *et al.* [19], who confirmed the reproducibility of these microbial community profiles across different populations. More recently, M.T. France *et al.* [20] developed the VALENCIA classification approach for improved identification of vaginal microbial community types using molecular sequencing data. In addition, experimental studies by P.B. Heczko *et al.* [21] highlighted the important functional role of lactobacillus species in maintaining microbial stability within the vaginal ecosystem.

Overall, the findings of the present study confirmed that the reduction of *Lactobacillus* spp., particularly *Lactobacillus crispatus*, represents a key microbiological marker of the transition from stable eubiosis to dysbiosis. Increased vaginal pH, expansion of anaerobic microbial communities, and morphological polymorphism observed in Gram-stained smears reflect progressive disruption of vaginal microbial homeostasis. The integration of molecular microbiome profiling with quantitative culture-based and morphotypic microbiological approaches may therefore improve the diagnostic stratification of vaginal microbiota states and contribute to more accurate detection of

dysbiotic conditions in reproductive health research and clinical practice.

✦ CONCLUSIONS

The analysis of vaginal microbiota in reproductive-age women demonstrated the presence of clearly differentiated microbial community states corresponding to distinct community state types. Molecular classification based on 16S rRNA gene sequencing identified three microbiota profiles within the examined cohort: CST I, CST III, and CST IV. It was found that CST I accounted for 30% of samples, CST III for 13.3%, and CST IV for 56.7% of cases, indicating a predominance of dysbiotic microbiota patterns among the studied participants. The results indicated that the transition from eubiotic to dysbiotic microbiota states is primarily associated with a pronounced reduction in the concentration of *Lactobacillus* spp., particularly *Lactobacillus crispatus*. In the CST I group, the mean concentration of lactobacilli reached $(3.8 \pm 1.7) \times 10^6$ CFU/mL and was accompanied by a low vaginal pH of 3.6 ± 0.3 , reflecting a stable lactobacillus-dominated microbial environment. In contrast, CST IV was characterised by a marked decrease in *Lactobacillus* spp. to $(4.9 \pm 3.2) \times 10^2$ CFU/mL, combined with an increase in anaerobic microorganisms associated with bacterial vaginosis and an elevation of vaginal pH to 5.6 ± 0.4 . These findings demonstrated that a quantitative decline of lactobacilli represents a key microbiological marker of vaginal dysbiosis.

A high level of concordance between molecular microbiota classification, quantitative culture-based microbiological analysis, and morphological evaluation of Gram-stained smears was observed. The calculated Cohen's kappa coefficient ($\kappa = 0.87$, $p < 0.001$) confirmed strong agreement between these diagnostic approaches, indicating that standardised culture-based and microscopic methods can reliably reflect structural changes in vaginal microbial communities. The predominance of CST IV detected in a largely asymptomatic cohort suggests that dysbiotic microbiota states may persist in a subclinical form and remain undetected during routine clinical examination. From a clinical perspective, early identification of such microbial shifts may be important for the prevention of infectious and inflammatory disorders of the female reproductive tract. Further studies involving larger cohorts are required to clarify the influence of hormonal, behavioural, and environmental factors on the distribution of vaginal microbial community state types. Integrating molecular microbiome profiling with quantitative microbiological and morphotypic approaches may improve diagnostic strategies for assessing vaginal microbiota stability and contribute to more effective prevention and management of dysbiotic conditions in reproductive health.

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✦ CONFLICT OF INTEREST

None.

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Стратифікація станів мікробної спільноти та кількісна культуральна оцінка вагінальної мікробіоти у жінок репродуктивного віку

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Анотація. Вагінальна мікробіота є ключовим фактором підтримання репродуктивного здоров'я жінки, однак субклінічні форми дисбіозу залишаються недостатньо вивченими, особливо в аспекті поєднання молекулярних, культуральних і морфологічних методів оцінки. Метою було оцінити структурні, кількісні та морфологічні характеристики вагінальної мікробіоти жінок репродуктивного віку та встановити відповідність між молекулярною стратифікацією мікробіому і культурально-морфологічними показниками. Обстежено 30 жінок репродуктивного віку, відібраних із 1 000 первинно оглянутих пацієнток. Проведено кількісний культуральний аналіз із визначенням КУО/мл, мікроскопію мазків, забарвлених за Грамом із цифровою фіксацією зображень, а також молекулярну класифікацію вагінальної мікробіоти на підставі секвенування гена 16S рибосомної рибонуклеїнової кислоти. Концентрації мікроорганізмів варіювали від 10^2 до 10^7 КУО/мл. Найбільш варіабельною була лактобацилярна популяція із середнім значенням $(1,6 \pm 1,1) \times 10^6$ КУО/мл. Зразки було розподілено на три типи мікробної організації: перший тип становив 30 %, третій – 13,3 %, четвертий – 56,7 %. Перший тип характеризувався домінуванням *Lactobacillus crispatus* у концентрації $(3,8 \pm 1,7) \times 10^6$ КУО/мл та кислотністю $3,6 \pm 0,3$. Третій тип асоціювався з *Lactobacillus iners* у концентрації $(1,5 \pm 0,8) \times 10^6$ КУО/мл і помірним підвищенням кислотності до $4,5 \pm 0,3$. Четвертий тип характеризувався зниженням лактобацил до $(4,9 \pm 3,2) \times 10^2$ КУО/мл, зростанням анаеробних бактерій до $10^3 - 10^4$ КУО/мл і підвищенням кислотності до $5,6 \pm 0,4$. Морфологічна картина мазків повністю відповідала молекулярно визначеним типам мікробіоти. Поєднання кількісного культурального аналізу та стандартизованої мікроскопії може слугувати інформативним інструментом стратифікації стану вагінальної мікробіоти у випадках обмеженого доступу до молекулярних методів

Ключові слова: патогенна флора; домінування *Lactobacillus*; анаеробні бактеріальні спільноти; мікробіологія статевої системи; культуральна мікробіологія; аналіз забарвлених за Грамом мазків



Mechanisms of influence of Tok Sen Massage techniques on chronic muscle pain in the back

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Abstract. Chronic non-specific low back pain is maintained by a combination of peripheral mechanical hyperalgesia and changes in central pain modulation; therefore, comparing standardised mechanical interventions is of practical value. The study aimed to compare the clinical and sensory effects of three mechanical intervention models over the same treatment duration. A prospective, randomised, controlled, assessor-blinded study was conducted in 96 patients who received 10 sessions of 30 minutes each over 4 weeks using the percussive-vibration (PV), classical manual (CM) or myofascial (MF) model. Baseline pain intensity on a numerical rating scale was 5.9 ± 1.3 points. Two weeks after completion of the course, pain intensity decreased in all groups, with the greatest reduction observed in the SV group, an intermediate reduction in the MF group, and the smallest in the CM group. The proportion of participants who achieved a clinically significant reduction in pain of at least 2 points was 81.3% in the PV group, 75.0% in the MF group and 62.5% in the CM group, reflecting differences not only in mean values but also in the probability of achieving noticeable relief at the individual patient level. The pressure pain threshold increased by 0.95, 0.72 and 0.61 kg/cm², respectively. Functional limitations, as measured by the disability index, decreased by 8.4, 11.6 and 7.5 percentage points, with the greatest functional improvement recorded in the MF group, indicating differences in the response profile between the mechanical intervention models. The practical significance of the study is determined by the fact that, given the same treatment duration and standardised treatment areas, mechanical models demonstrate different advantages; therefore, the choice of intervention can be guided by the dominant clinical need: increasing the probability of a rapid, clinically significant reduction in pain, or prioritising the improvement of daily function, incorporating tolerability profile

Keywords: mechanical hyperalgesia; central pain modulation; percussive-vibrational therapy; myofascial release; manual therapy

★ INTRODUCTION

Chronic non-specific lower back pain remains one of the leading factors contributing to reduced work capacity and quality of life, characterised by a prolonged course, a tendency to relapse, and significant clinical heterogeneity. In the works of Ukrainian authors D. Chopovskyi [1] and M. Oros & N. Fister [2] emphasised that for a significant proportion of patients, there are no specific structural causes of pain; instead, myofascial and functional mechanisms predominate, requiring rational physical therapy and standardised approaches to the management of such patients, particularly in primary care settings and outpatient rehabilitation programmes. Neurophysiologically, chronic pain differs from acute pain not only in duration

but also in qualitative changes in nociceptive systems: phenomena of peripheral and central sensitisation develop, the balance between excitatory and inhibitory processes shifts, and the role of affective-cognitive modulatory circuits is enhanced, which is reflected in the intensity of symptoms and response to treatment, as demonstrated by P. Poisbeau & E. Salvat [3]. In this context, approaches that combine targeting tissue-based sources of pain with interventions capable of modifying the central mechanisms underlying symptom maintenance are becoming increasingly relevant. J. Song *et al.* [4] demonstrated that, in cases of chronic non-specific low back pain with signs of central sensitisation, protocols combining soft tissue mobilisation

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with pain neuroscience education show promise, demonstrating clinically significant improvements in pain and function in a controlled trial.

One of the key scientific challenges remains explaining how mechanical stimulation of soft tissues translates into changes in pain perception and function. Mechanical stimulation can activate various types of mechanoreceptors in the skin, muscles and fascia, alter local microcirculation and tissue compliance, and influence segmental spinal gate control mechanisms and descending antinociceptive systems. At the same time, the biological plausibility of the therapeutic effect is strengthened when mechanical interventions are considered within the broader paradigm of neuromodulation. A review of electrical neuromodulation in chronic pain by G. Guzzi *et al.* [5] systematised the anatomical and physiological foundations of nociception modulation and emphasised the role of afferent stimulation and central circuits in the formation of the clinical effect, which is conceptually relevant for mechanical stimuli as well. Similarly, in the field of more invasive methods (spinal stimulation), G. Guzzi *et al.* [6] described in detail the mechanisms of pain signal modulation and the clinical outcomes, which further emphasised the universality of neuromodulatory logic regardless of the nature of the stimulus.

In addition, manual approaches have also proposed pathophysiological explanations. A review of the mechanisms of spinal manipulative therapy for chronic musculoskeletal pain by O. Vazic *et al.* [7] included hypotheses regarding the influence on afferent input, segmental reflexes, descending inhibition and changes in the Pressure Pain Threshold (PPT), which makes the use of PPT as an objective marker of mechanical hyperalgesia appropriate. In the publication by I.A. Sasko *et al.* [8], dedicated to physical therapy for chronic vertebrogenic lumbosacral pain, the need for individualisation and the combination of methods was emphasised; however, the lack of well-standardised comparative protocols that distinguish the effect of mechanical action from the overall dose of interventions was highlighted. Furthermore, the role of massage in physical therapy was considered by V.I. Bondarchuk *et al.* [9] as a component of comprehensive programmes, but the level of evidence regarding specific mechanistic components remains limited.

Of particular interest are impact-vibration (IV) or percussive stimuli as a form of short-pulse mechanical stimulation. Data from a randomised, parallel-group clinical trial by M. Hartard *et al.* [10], which assessed the effect of vibration and/or heat on non-specific back pain, confirmed the potential of the vibration model to reduce symptoms, but at the same time highlighted the need for a clearer comparison of vibrational effects with other standardised manual models and the use of validated indicators of sensitisation and function. For this reason, within the context of scientific analysis, the Tok Sen technique should be regarded not as a culture-specific practice, but as a model of a percussive mechanical stimulus with definable parameters of frequency, duration and areas of influence, which can be compared with CM and MF approaches.

Despite the accumulation of data on the efficacy of physical and manual therapy for chronic non-specific low back pain, the empirical evidence directly comparing different types of mechanical stimulation at the same “dose”

of intervention remains limited. In studies from 2020-2025, chronic non-specific low back pain was viewed as a condition with a multi-component pathophysiology, in which peripheral nociceptive sources (muscle overload, trigger points, soft tissue dysfunction) interacted with neuroplastic changes in the central nervous system, sustaining the persistence of pain afferentation and impaired motor control. Within this paradigm, it became fundamental not only to apply physical interventions in general, but also to consider the specific type of mechanical stimulus and its parameters as determinants of afferent input and mechanical hyperalgesia, and thus of the potential modification of segmental and descending pain modulation. However, there remains a lack of empirical comparative studies which, using the same dose of procedures and standardised areas of application, would distinguish effect of short-pulse HF stimulation from the effects of CM and MF techniques, whilst simultaneously assessing both clinical and sensory indicators. For this reason, the PV stimulus in this study was considered as a reproducible model of mechanical soft tissue stimulation, within which Tok Sen was used exclusively as a conceptual prototype of percussive-vibrational stimulation for mechanistic comparison with other standardised approaches.

The study aimed to compare the clinical and sensory effects of PV, CM and MF treatment modalities in patients with chronic non-specific lower back pain. The objectives of the study were to assess changes in pain intensity and functional limitations at time points before treatment, following the course of treatment, and during short-term follow-up; to determine changes in indicators of central sensitisation and cognitive-affective factors of pain using validated scales; to compare changes in mechanical sensitivity above the pain sensitivity threshold to pressure and to correlate these with clinical outcomes.

✦ MATERIALS AND METHODS

The study was conducted as a prospective, randomised, controlled trial with parallel groups and blinded outcome assessors. The study was conducted at the “New World” International Massage Institute [11]. Recruitment and follow-up took place from September 2024 to March 2025. Participants were divided into three groups receiving mechanical therapy with the same “dose” of treatment: PV (Tok Sen model), CM, and MF. The sample was formed as a sequential sample with subsequent randomisation of all patients with chronic lower back pain; they were screened for eligibility, and after signing the informed consent form, they were included in the randomisation. Physical activity levels were assessed at the baseline examination through self-reporting of average weekly physical activity and the nature of the exertion; based on these data, participants were classified as predominantly sedentary, moderately active, or highly active. During the intervention period, participants were required to maintain their usual activity patterns.

A total of $n = 96$ individuals were included, with 32 participants in each group. The mean age was 42.1 ± 10.3 years; 56.3% ($n = 54$) were women and 43.7% ($n = 42$) were men. According to self-reports, the nature of work was distributed as follows: predominantly sedentary office/remote work – 61%, physically active occupation – 24%, mixed pro- work – 15%. The median duration of pain was 18 months [IQR

9-36], and the mean baseline pain over the previous 7 days was 5.9 ± 1.3 points on a 0-10 numerical scale. The sample size was determined based on a priori power calculation for the primary endpoint (Visual Analogue Scale (VAS) in a repeated-measures model with the “group×time” factor. The minimum clinically meaningful difference was set at 2 VAS points, the expected mean effect between groups at $d \approx 0.5$, the significance level at 0.05, and the statistical power at 0.8.

The study included individuals with non-specific low back pain lasting at least 12 weeks and pain intensity of ≥ 4 points on an 11-point numerical rating scale (0-10). Pain was assessed using the VAS (0 – “no pain”, 10 – “the worst pain imaginable”) [12]. Any analgesic regimen (if present) had been stabilised for at least 2 weeks before randomisation and remained unchanged throughout the course of the intervention. Exclusion criteria included specific causes of back pain (neoplastic, infectious, inflammatory systemic conditions), signs of progressive neurological deficit or severe radiculopathy, invasive spinal procedures within the previous 3 months, pregnancy, active skin lesions in the treatment areas, clinically significant coagulopathies/high risk of bleeding, and other conditions that precluded the safe performance of mechanical procedures.

Randomisation was performed in a 1:1:1 ratio using a computer-generated sequence with blocks of variable length, stratified by sex and duration of pain (among the included chronic patients: 12-24 months versus >24 months). Baseline pain intensity was not used as a separate stratification factor during randomisation; its balance between groups was checked at the baseline assessment stage, and the groups were comparable in terms of baseline pain ($p=0.79$). All participants underwent 10 sessions, each lasting 30 minutes, three times a week for four weeks (with an interval of at least 48 hours between sessions). The treatment areas were standardised identically for all groups: the paravertebral muscles of the lumbar region (L1-S1), the quadratus lumborum, and the muscles of the pelvic girdle (primarily the gluteal muscles). Direct mechanical contact with the spinous processes was not used; treatment in the renal region and on areas of skin lesions was prohibited.

The PV group underwent a standardised protocol of manual percussive-vibrational therapy as a model of short-pulse mechanical stimulation of soft tissues. The Tok Sen technique was performed using a classic professional set of four wooden instruments: a mallet and three blades (with wide, rounded, flat and thin pointed ends). A certified Tok Sen set (Lanna Wellness, Thailand) was used. The total “active time” was 30 minutes per session: 3 minutes – preparatory stage (gentle application of the mallet and the blade with a wide rounded tip to warm up the back tissues), 25 minutes – main stage (treatment with a hammer, a blade with a flat narrow tip and a blade with a round thin tip), 2 minutes – final stage (gentle treatment with a hammer and a blade with a round wide tip).

The CM group underwent a standardised soft tissue massage protocol without high-speed manoeuvres. The sequence included stroking, kneading and controlled friction, focusing on the paravertebral and pelvic regions. The intensity was maintained within the range of 3-5/10; the total duration of active treatment was comparable to that of the PV group.

The MF group received standardised MF techniques: slow fascial gliding (speed <2 cm/s) and static holds in areas of MF restriction. The duration of each hold was 60-90 seconds, the intensity was 3-5/10, and the total duration of active treatment was comparable to that of the PV group. To ensure consistency in the performance of interventions, a standardised session checklist was used, which included a list of treatment areas, actual duration, subjective intensity (0-10), presence/absence of post-procedure exacerbation, and any adverse events.

No additional interventions (physiotherapy, new courses of manual or mechanical therapy outside the protocol) were prescribed during the 4-week course. The primary endpoint was the change in pain intensity on the VAS (mean value over the previous 7 days) at three time points: before the start of the course (T0), after completion of the 10th procedure (T1) and 2 weeks after completion of the course (T2). Functional limitations were assessed using the Oswestry Disability Index (ODI) in the form of the Oswestry Low Back Pain Disability Questionnaire, with the total score and percentage index calculated in accordance with the instructions [13]. Signs of central sensitisation were assessed using the Central Sensitisation Inventory (CSI), Part A (25 items, 0-4 points) [14]. Pain catastrophising was assessed using the Pain Catastrophising Scale (PCS), 13 items (0-4) [15]. Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) via a standardised form [16].

The PPT threshold was determined using a digital handheld algometer of the FPX series (Wagner Instruments, USA) with a 1 cm² tip and standard accessories. Measurements were taken at standardised points: paravertebrally (L3-L5) on the right and left, and in the projection of the gluteus medius muscle on the right and left. PPT algometry was performed according to a standardised protocol: the participant lay prone with the lumbar region relaxed; a 10-minute rest period was provided before measurement. Pressure was applied perpendicular to the tissue surface at a constant rate of approximately 1 kg/cm²/s; the point of fixation was defined as the first sensation of pain reported verbally by the participant (“stop”). Each point was tested three times at 45-60-second intervals, and the mean value was used for analysis; the order of the points was the same for all participants and was repeated at T0, T1 and T2.

At the T0 visit, the following procedures were performed sequentially: collection of demographic and clinical data; administration of the VAS/ODI/CSI/PCS/HADS questionnaires; PPT algometry; recording of concomitant therapy; and instruction regarding the need to maintain treatment as usual outside the protocol. At T1 and T2, the same sequence of measurements was repeated, with additional recording of adverse events and the use of “rescue” analgesia (if required). Adverse events were recorded as any new or exacerbated symptoms occurring during the session or within 48 hours thereafter and potentially related to the intervention. They were classified by type (local tenderness/increased pain, bruising or petechiae, paraesthesia, autonomic reactions), by severity (mild – requiring no additional measures; moderate – requiring temporary modification of the workload or occasional analgesia) and by duration (≤ 24 hours or >24 hours). All measurements were taken in the morning, in the same room; the assessor

was not present during therapeutic procedures and did not have access to the session logs.

Statistical analysis was performed on an intention-to-treat basis using the R software environment (version 4.3.x) with packages for mixed-effects modelling and multiple comparisons. The normality of the distribution was tested using the Shapiro-Wilk test. To compare baseline indicators between groups, Student's t-test (for normal distributions) or the Mann-Whitney U-test (for non-normal distributions) was used; for within-group comparisons of T0-T1 and T0-T2, paired t-test or the Wilcoxon test was used. For categorical variables, the χ^2 test or Fisher's exact test was applied.

The main effect of interventions over time was assessed using a Group \times Time model (a linear mixed model or RM-ANOVA, depending on the data structure and missing values) with correction for multiple comparisons (Holm-Bonferroni). In the presence of missing values, linear mixed models with REML parameter estimation were used to cover participants with incomplete repeated measurements to be included without exclusion from the analysis. A sensitivity analysis was performed comparing the results of the complete data set and the set with missing values to verify the robustness of the conclusions. For regression models (e.g., logistic regression for the proportion of "responders" with a pain reduction of ≥ 2 points; additionally, the proportion of participants with a VAS reduction of ≥ 3 was assessed as a more stringent threshold), the significance of the coefficients was assessed using the Wald test. Additionally, a covariate analysis was performed, including baseline PCS and HADS as covariates to assess their contribution to changes in VAS and to verify the robustness of the Group \times Time effect. The level of statistical significance was set at $p < 0.05$. Adverse events were documented at each session (worsening of pain > 2 VAS points over 24 hours, haematomas, paraesthesia, autonomic reactions). The criteria for discontinuation of participation were the onset or progression of neurological deficit or any reactions requiring off-protocol medical intervention. Ethical requirements were adhered to in accordance with the principles of the Declaration of Helsinki [17]. The study's limitations include the short follow-up period (only 2 weeks after the end of the treatment course), which did not include an assessment of the medium- and long-term

stability of the effects. Therapists were not blinded due to the nature of the interventions; consequently, there remained a possibility that non-specific factors (expectations, interaction context) could influence the subjective endpoints.

RESULTS

Baseline comparability of groups, course completion and completeness of follow-up. All 96 randomised participants were included in the analysis on an intention-to-treat basis. At baseline (T0), the PV, CM and MF groups demonstrated comparable demographic and clinical characteristics, indicating the absence of systematic bias before the start of the interventions. Baseline pain intensity on the VAS, the degree of functional limitations on the ODI, the severity of sensitisation symptoms on the CSI, catastrophising on the PCS, and levels of anxiety/depressive symptoms on the HADS did not differ significantly between groups ($p > 0.05$), which enhanced the interpretative reliability of intergroup comparisons of subsequent changes in these indicators.

Following completion of the 10-session course (T1), follow-up assessments were available for most participants, and the two-week post-treatment follow-up (T2) was also characterised by high data completeness. The loss to follow-up among some participants did not result in a marked imbalance between groups on key baseline measures and was therefore unlikely to significantly bias the results. Overall course completion was high, which indirectly reflected the acceptability and tolerability of standardised mechanical interventions in an outpatient setting. In the context of a short course (4 weeks) and three weekly visits, such completion rates are relevant as they reduce the risk of systematic error associated with incomplete delivery of the intervention dose.

Baseline pain intensity scores on the VAS generally corresponded to a clinically significant level of symptoms (mean approximately 6/10), whilst the ODI fell within the range of moderate functional limitations. The CSI and PCS demonstrated mean values characteristic of a subset of patients with chronic pain in whom, alongside nociceptive components, sensitisation and cognitive-affective mechanisms may be present (Table 1). This provided an adequate basis for testing the divergent effects of mechanical stimulation models on pain intensity, function and PPT.

Table 1. Baseline values (T0) in the PV, CM and MF groups

Indicator	PV (n = 32)	CM (n = 32)	MF (n = 32)	Intergroup (p)
Age, years (M \pm SD)	41.6 \pm 10	42.8 \pm 10.7	41.9 \pm 10.3	0.86
Females, n (%)	18 (56.3)	19 (59.4)	17 (53.1)	0.88
Duration of pain, months (Me [IQR])	18 [9-30]	18 [9-36]	18 [12-36]	0.77
VAS, 0-10 (M \pm SD)	6 \pm 1.2	5.8 \pm 1.3	5.9 \pm 1.4	0.79
ODI, % (M \pm SD)	36.8 \pm 10.4	35.9 \pm 11.1	36.3 \pm 10.8	0.94
CSI, 0-100 (M \pm SD)	41.2 \pm 11.7	40.5 \pm 12.1	42.1 \pm 12.5	0.83
PCS, 0-52 (M \pm SD)	19.4 \pm 8.2	18.8 \pm 8.5	19.9 \pm 8.7	0.86
HADS-A, 0-21 (M \pm SD)	8.2 \pm 3.1	8 \pm 3.2	8.4 \pm 3	0.84
HADS-D, 0-21 (M \pm SD)	20.9 \pm 2.5	6.7 \pm 2.8	7.1 \pm 2.7	0.81

Source: compiled by the author

The absence of significant differences at T0 made it possible to interpret subsequent intergroup differences as being more likely to be associated with the type of mechanical intervention rather than with baseline imbalances in

symptoms or psychometric characteristics. In particular, the comparability of the groups on the VAS, ODI and CSI indicated comparable baseline levels of pain burden, functional limitations and sensitisation profile, which is critical

for interpreting the dynamics of the primary and key secondary endpoints. The similarity of PCS and HADS scores reduced the likelihood that different response trajectories could be attributed to differences in catastrophising or affective symptoms at baseline. Thus, baseline equivalence strengthened the internal validity of the comparison and the validity of conclusions regarding the specific effects of mechanical intervention models within the same “dose” of procedures.

Pain intensity on the VAS at the primary endpoint T0-T2. Following a 4-week course of standardised procedures, a reduction in pain intensity was observed in all groups, which persisted for 2 weeks after the interventions had ended, indicating short-term maintenance of the

effect. At the same time, the trajectories of change differed between groups: the greatest reduction and the lowest pain scores at the follow-up stage were characteristic of the PV model. The MF model demonstrated intermediate results, whilst the CM model showed the smallest reduction (Table 2). The clinical significance of the effects was confirmed by the fact that the mean changes in all groups exceeded the minimum clinically significant difference of 2 points; however, the advantage of the PV model was evident both in the magnitude of reduction and in the stability of the indicators between T1 and T2. The overall picture was consistent with the responder analysis, where the proportion of participants with clinically significant improvement was highest for PV, intermediate for MF, and lowest for CM.

Table 2. VAS dynamics (0-10) in T0-T2

Indicator	PV (n = 32)	CM (n = 32)	MF (n = 32)
VAS T0, M±SD	6±1.2	5.8±1.3	5.9±1.4
VAS T1, M±SD	3.2±1.3	3.8±1.4	3.5±1.4
VAS T2, M±SD	2.5±1.4	3.6±1.5	3.3±1.5
Δ(T1-T0), M±SD	-2.8±1.4	-2±1.3	-2.4±1.4
Δ(T2-T0), M±SD	-3±1.5	-2.2±1.4	-2.6±1.5

Source: compiled by the author

Linear mixed-effects modelling (Time factor and Group × Time interaction) revealed a statistically significant effect of time ($p < 0.001$), reflecting the overall efficacy of mechanical interventions in reducing pain. The Group×Time interaction was also statistically significant ($p = 0.012$), indicating differences in pain reduction trajectories depending on the group. After correction for multiple comparisons (Holm-Bonferroni), the most consistent between-group difference in VAS change was observed between the UB and CM groups (T1: $p = 0.018$; T2: $p = 0.026$). The comparison of MF versus CM demonstrated a smaller but consistent advantage for MF in terms of the magnitude of VAS reduction, which, however, did not always remain statistically significant after correction (tendency). The difference between PV and MF was small and mostly insignificant after adjustment, which was consistent with the similar mean VAS scores at the follow-up stage.

From the perspective of clinical relevance, the mean VAS reduction in all groups exceeded the threshold for a minimally clinically significant change (≥ 2 points) as early as T1, and at T2, the effect either persisted or increased. The greatest difference between the groups was observed when comparing PV versus CM, which may indicate a potentially stronger influence of the PV model on the rate of pain reduction and on the mechanisms of nociceptive modulation, which are more readily realised with short-pulse mechanical stimulation. The smallest reduction in pain in the CM group, despite the same intervention dose, may suggest that purely CM techniques involving controlled friction and kneading, at the proposed standardised intensity

(3-5/10), may have had a lesser effect on the rapid mechanisms of sensory pain modulation compared to short-pulse or prolonged fascial interventions. At the same time, the clinically significant effect in CM confirmed that even the basic manual model remained therapeutically beneficial.

Secondary endpoints: Function, sensitisation, catastrophising. The ODI decreased in all groups following treatment, reflecting an improvement in daily activities and a reduction in disability. Notably, the pattern of changes in the ODI differed somewhat from that of the VAS: the greatest improvement in function was observed in the MF group, whereas the PV group more frequently showed an advantage in terms of reduced pain intensity and increased PPT. All groups showed a reduction in disability following the treatment course, with the effect persisting during the follow-up period (Table 3). The MF model demonstrated the greatest functional improvement, whilst the PV and CM models showed a smaller but clinically significant reduction. Two weeks after the completion of interventions, ODI scores remained lowest in the MF group ($23.8 \pm 9.6\%$), which was consistent with the greatest reduction relative to baseline and confirmed the superiority of this model specifically regarding the functional component of the outcome. The time effect was significant ($p < 0.001$), and the Group×Time interaction was also significant ($p = 0.021$). After adjustment for multiple comparisons, the MF demonstrated a statistically significantly greater reduction in ODI compared with the CM at T1 and T2 ($p \approx < 0.02$), whilst the PV showed a moderate advantage over the CM, which was more pronounced at T2.

Table 3. Secondary outcomes (M±SD) at T0-T2

Indicator	Time	PV	CM	MF
ODI, %	T0	36.8±10.4	35.9±11.1	36.3±10.8
	T1	26.1±9.6	28.8±10.2	24.6±9.4
	T2	24.9±9.8	27.9±10.5	23.8±9.6

Table 3. Continued

Indicator	Time	PV	CM	MF
CSI, 0-100	T0	41.2 ± 11.7	40.5 ± 12.1	42.1 ± 12.5
	T1	34.3 ± 11.2	36.7 ± 11.8	33.2 ± 11.4
	T2	33.1 ± 11.5	35.9 ± 12	31.9 ± 11.6
PCS, 0-52	T0	19.4 ± 8.2	18.8 ± 8.5	19.9 ± 8.7
	T1	14.2 ± 7.6	15.9 ± 8	13.8 ± 7.4
	T2	13.5 ± 7.8	15.3 ± 8.2	12.9 ± 7.6
HADS-A, 0-21	T0	8.2 ± 3.1	8 ± 3.2	8.4 ± 3
	T1	7.4 ± 3	7.6 ± 3.1	7.2 ± 2.9
	T2	7.2 ± 3	7.4 ± 3	7 ± 2.9
HADS-D, 0-21	T0	20.9 ± 2.5	6.7 ± 2.8	7.1 ± 2.7
	T1	6.3 ± 2.8	6.4 ± 2.8	6.2 ± 2.6
	T2	6.1 ± 2.8	6.3 ± 2.7	6 ± 2.6
PPT (average), kPa	T0	286 ± 72	291 ± 75	284 ± 74
	T1	364 ± 80	336 ± 78	354 ± 79
	T2	372 ± 83	342 ± 79	360 ± 81

Source: compiled by the author

The more pronounced effect of MF on the ODI may indicate that fascial techniques involving slow, low-speed stimulation and static holds were more effective in influencing movement strategies, feelings of stiffness and movement confidence, which are directly reflected in the functional domains of the ODI. Thus, pain reduction and functional recovery are not always strictly parallel: in some patients, functional limitations may depend more on fascial restrictions, fear of movement and disrupted motor patterns than on current pain intensity. The CSI decreased in all groups, most consistently in the MF group and least markedly in the CM group. The time effect was significant ($p < 0.001$), and the Group×Time interaction was significant ($p = 0.034$). After adjusting for multiple comparisons, the MF group showed a statistically significant advantage over the CM group, particularly at T2. PCS also decreased in all groups. The time effect was significant ($p < 0.001$), whilst between-group differences in PCS were less consistent. This suggested that the cognitive components of pain might have changed as a secondary response to general clinical improvement, rather than as a specific consequence of a particular type of mechanical stimulation. The combination of a more pronounced reduction in CSI in the MF group and moderate changes in PCS across all groups was consistent with the hypothesis that slow fascial influences more strongly modify somatosensory integration, tension perception and bodily vigilance, whereas catastrophising, being a cognitive construct, responds less specifically to the type of mechanical stimulus in the absence of a specific psychoeducational intervention.

The HADS-A and HADS-D showed a small but statistically significant improvement over time, with no marked differences between groups. This suggested that the positive changes in affective symptoms were likely mediated by a reduction in pain and improved function, rather than a unique psychotropic effect of a specific mechanical technique. PPT increased on average following the course, which was interpreted as a reduction in mechanical pain/hyperalgesia at the tested points. The greatest increase in PPT was observed in the PV group, which was consistent with the most pronounced reduction in VAS in this group. The mean PPT value across four standardised points

was used for analysis. The time effect was significant ($p < 0.001$), and the Group×Time interaction was significant ($p = 0.018$). Paired comparisons showed an advantage of PV over CM (most consistently after correction at T2), whilst MF demonstrated an intermediate position. The advantage of PV in terms of PPT reflected stronger stimulation of fast mechanoreceptor afferents and more pronounced involvement of segmental inhibitory mechanisms, which reduce pressure sensitivity in the test area. At the same time, similar PPT values between PV and MF at T1-T2 indicated that both models could influence mechanical sensitivity, but potentially via different pathways: PV – via short-pulse, more intense sensory modulation; MF – via slower changes in tissue/fascial compliance and proprioceptive processing.

From a practical perspective, the changes observed were reflected not only as statistical improvements on the scales but also as a measurable shift in everyday functionality and the ability to cope with physical demands. A reduction in disability as measured by the ODI of 7.5-11.6 percentage points meant that some participants moved to a less restrictive level of daily activity: domains that are usually the most problematic in chronic low back pain (sitting/standing positions, walking, lifting objects, self-care and social and domestic participation) were performed more easily. A parallel decrease in the CSI and an increase in the PPT were consistent with reduced bodily vigilance and reactivity to mechanical stimuli, clinically manifested by less stiffness, better tolerance of movement, and greater confidence in resuming activity without fear of exacerbation. A moderate improvement in affective symptoms as measured by the HADS further indicated that the reduction in pain and restoration of function were accompanied by a subjective alleviation of the emotional burden of the condition; that is, the changes showed signs of a genuine improvement in quality of life, rather than merely a redistribution of scores on the questionnaires.

Additional clinical indicators and verification of the stability of results. Incorporating the threshold for a clinically significant reduction in pain (VAS ≥ 2 points), the proportion of responders at T1 and T2 was assessed. PV showed the highest proportion of responders both immediately after the course and after 2 weeks. MF occupied an

intermediate position, whilst CM had the lowest values. This distribution was consistent with the mean changes in VAS and the significant Group×Time interaction in the main model. Additionally, the proportion of participants

with a more pronounced response (VAS ≥ 3 points) was assessed, which is a stricter criterion and better reflects a strong clinical response. A gradation was observed in favour of PV, followed by MF, followed by CM (Table 4).

Table 4. Responder analysis and safety (n, %)

Indicator	PV (n = 32)	CM (n = 32)	MF (n = 32)
VAS responders ≥ 2 , T1	25 (78.1)	18 (56.3)	22 (68.8)
VAS responders ≥ 2 , T2	26 (81.3)	20 (62.5)	24 (75)
VAS responders ≥ 3 , T2	18 (56.3)	11 (34.4)	15 (46.9)
Early withdrawal	1 (3.1)	2 (6.3)	1 (3.1)
Increased pain lasting more than 24 hours (as a safety criterion)	1 (3.1)	2 (6.3)	1 (3.1)

Source: compiled by the author

Increase in pain > 2 . The responder analysis added a practical dimension to the mean values: specifically, when the mean VAS scores at T2 were relatively close, the difference in the proportion of participants who achieved a clearly perceptible reduction in pain was most pronounced between PV and CM. This is relevant for the clinical choice of the type of mechanical intervention when the priority is to increase the likelihood of achieving a minimally meaningful reduction in pain. As therapists were not blinded due to the nature of the interventions, there remained a possibility that non-specific contextual factors could influence subjective endpoints (primarily pain intensity as measured by VAS and, to some extent, psychometric indicators). In this context, the consistent trend of the more objective PPT marker with the direction of VAS changes across groups was considered as further evidence that between-group differences were not solely attributable to placebo effects. At the same time, the interpretation of between-group differences on self-report scales was conducted, covering potential limitations.

The diary data indicated an overall trend towards a reduction in the frequency of rescue analgesia use over the course of treatment, which was consistent with the VAS trends. Although between-group differences in analgesic consumption did not demonstrate consistent statistical significance after adjustment for multiple comparisons, the direction of the changes was logically consistent: in groups with a more pronounced reduction in pain, a greater reduction in the need for episodic analgesic use was observed. From a practical point of view, this reinforced the clinical interpretation: the reduction in VAS was not a questionnaire-based phenomenon, but was accompanied by behavioural markers of a reduction in symptom burden.

All reported adverse events were mild or moderate in nature and were predominantly limited to local reactions at the treatment sites. The most common were transient local tenderness/hypersensitivity of soft tissues in the first 24 hours after the procedure and episodic temporary exacerbation of pain (according to the safety criterion > 24 hours – isolated cases in all groups, Table 4). Reactions classified as moderate usually manifested as the need for a temporary reduction in the subjective intensity of the treatment during the next session or the occasional use of rescue analgesia; no prolonged or systemic reactions were recorded.

A comparison of the results across the full dataset (incorporating missing values in the LMM/REML models) and

in the complete-case subsample did not alter the overall picture: the order of effects between the groups remained unchanged. PV retained its advantage in terms of VAS reduction and PPT improvement, whilst MF demonstrated the greatest gain in ODI and a more pronounced reduction in CSI. This indicated that the main findings were not an artefact of missing data or the selective “dropout” of participants with poorer/better prognoses. Additional covariate models (including baseline PCS and HADS) showed that a higher level of catastrophising at baseline was associated with a smaller reduction in VAS, whilst affective symptoms (HADS-A/HADS-D) had less robust associations. However, the inclusion of these covariates did not negate the Group×Time interaction effect for VAS and PPT, confirming that intergroup differences were not explained solely by the psychological profile at T0, but were consistent with physiologically oriented indicators (PPT) and functional outcomes (ODI).

The results demonstrated that all three standardised mechanical intervention models produced a statistically significant and clinically relevant reduction in pain as measured by the VAS and an improvement in function as measured by the ODI, with the effect persisting at the 2-week follow-up. The PV model exhibited the most pronounced profile of pain reduction and PPT increase, consistent with potentially stronger sensory modulation of mechanical sensitivity. The MF model demonstrated the greatest improvement in functional status and a more pronounced reduction in CSI, which may reflect the specific contribution of slow fascial influences to the reduction of sensitisation manifestations and improvement in motor adaptation. The CM model was also effective, but on average was inferior in terms of the magnitude of changes, whilst maintaining a favourable safety profile.

DISCUSSION

The results demonstrated that three standardised mechanical stimulation models (PV, CM and MF) produced clinically significant reductions in pain intensity and improvements in function in patients with chronic non-specific low back pain, when administered at the same intervention dose. At the same time, intergroup differences were evident in the profile of effects: the PV model was associated with greater pain reduction and a larger increase in PPT, whilst the MF model demonstrated a more pronounced improvement in ODI and a more consistent reduction in CSI-related

indicators. This differentiation in response was consistent with the notion that mechanical interventions may exert their effect through various components of the nociceptive system (peripheral mechanical hyperalgesia, segmental modulation, descending inhibition), and that clinical symptoms in chronic pain reflect the heterogeneous interplay of these mechanisms across different patients.

The advantage of the PV model in terms of pain reduction and increased PPT could indicate more intense sensory modulation of mechanical sensitivity, in particular through the activation of fast-conducting mechanoreceptor afferents and competitive inhibition of the nociceptive stream at the spinal cord level, as well as through the involvement of descending antinociceptive systems. This reasoning was consistent with the findings of L. Dueñas *et al.* [18] regarding the effect of vibratory stimuli on myofascial trigger points: in a pilot RCT for the cervical region, local vibratory therapy reduced symptoms and was associated with changes in local pain, which indirectly supported the concept of modulation of mechanical hyperalgesia by mechanical stimulation. Similarly, in myofascial pain, local vibratory stimulation in a double-blind, placebo-controlled design by E. Serritella *et al.* [19] demonstrated the potential to reduce pain manifestations, suggesting the transferability of this neurosensory intervention to other anatomical regions. Although these studies did not address the lower back, they support the notion that vibratory stimuli can modify peripheral pain and sensory input in myofascial syndromes.

The results are also consistent with broader data on percussion therapy: a systematic review by L. Sams *et al.* [20] showed that percussion therapy can influence pain perception and functional parameters, although the evidence base was heterogeneous and protocols varied significantly in terms of stimulus frequency and duration. In a clinical RCT by B. Menek *et al.* [21] for cervical disc pathology, the combination of instrument-assisted soft tissue mobilisation and percussion massage demonstrated benefits in terms of symptoms and function, indicating the clinical relevance of percussion techniques as a form of mechanical stimulation. Although these data cannot be directly extrapolated to chronic non-specific low back pain, they support the general conclusion that short-pulse mechanical stimuli may be clinically significant and potentially differ from CM models in their mechanisms of action.

The MF model in the study demonstrated more pronounced changes in the ODI and more stable trends in CSI-related indicators. This is consistent with the empirical RCT by K. Iranpour *et al.* [22], in which MF interventions for chronic non-specific low back pain reduced pain and the disability index: specifically, MF release of the iliopsoas muscle was associated with a reduction in pain and an improvement in disability indicators. In a randomised controlled trial by M.D. Arguisuelas *et al.* [23] assessed the effect of MF release on the myoelectric activity of the erector spinae muscles and lumbar kinematics in patients with chronic non-specific low back pain. The authors recorded changes in electromyographic activity parameters and lumbar motion characteristics following the intervention, supporting the hypothesis of a neuromuscular component to the action of MF techniques. This effect may explain the more pronounced improvement in

functional domains in the MF group due to modifications in motor control, a reduction in protective co-contraction, and increased movement confidence. Furthermore, L.R. Paulo *et al.* [24] noted that even a single session of thoracolumbar myofascial release could induce short-term pain reduction and functional improvement in a balanced crossover design, highlighting the rapidity of neuromuscular and sensory changes following fascial stimulation. Meta-analyses and systematic reviews by Z. Chen *et al.* [25] and Z. Wu *et al.* [26] confirmed the efficacy of myofascial release for low back pain, although they highlighted the heterogeneity of the protocols and the moderate quality of some of the included studies. Following this logic, the more pronounced effect of the MF model on the ODI in the presented protocol could reflect a greater impact on the functional component of chronic pain (stiffness, movement restrictions, adaptive movement strategies), whereas the PV model had a stronger effect on the sensory component (pain intensity and mechanical hyperalgesia).

The significance of changes in the CSI and the differences between groups are relevant given that central sensitisation is regarded as a key modifier of the response to treatment in chronic low back pain. Systematic manual therapy in the approach by A. Aponte & A. Halili [27], which targeted the central sensitisation component, demonstrated efficacy in reducing symptoms, supporting the validity of assessing sensitisation markers alongside pain and function. A meta-analysis by A. Tabatabaei *et al.* [28] on the efficacy of manual therapy specifically regarding central sensitisation also confirmed that manual interventions can alter sensitisation manifestations, although the clinical effect depends on patient characteristics and protocols. In the present study, the more pronounced reduction in CSI in the MF group may reflect the specific nature of slow fascial stimuli (low sliding speed and static holds), which potentially have a stronger influence on interoceptive processing and on the sensory discrimination of tension/pain, thereby reducing the central amplifying component of symptoms in some patients. However, the interpretation of the CSI should remain cautious, as the instrument assesses a complex of symptoms that is not a direct neurophysiological measure of central sensitisation, but rather a clinical indicator of a sensitisation phenotype.

The validity of the PPT as a key mechanistic marker required particular attention. The reliability of PPT measurements in lower back/neck pain is supported by a systematic review by A. Bhattacharyya *et al.* [29], which highlighted generally acceptable reproducibility but also emphasises the dependence of results on the device, protocol and researcher's experience. The study by C.A. Zicarelli *et al.* [30], which examined the ability of PPT to distinguish between individuals with low back and neck pain, also indicated the usefulness of the method provided that the test sites and the rate of pressure increase are standardised. Regarding the issue of intra-rater reliability for different algometers, A. Nunes & V. Leite [31] confirmed that instrumental differences may affect absolute values, but relative changes within a single protocol are informative. Thus, the observed increase in PPT across all groups could be interpreted as a reduction in mechanical hyperalgesia, whilst the more pronounced dynamics in the PV group may reflect greater

sensory modulation. The consistency of this conclusion is reinforced by data from the RCT by B.M. Bond *et al.* [32], where spinal manipulative therapy altered mechanical pain sensitivity in patients with chronic non-specific low back pain; that is, mechanical interventions can indeed “switch” mechanical sensory sensitivity. Vibration interventions, in a broader sense, have also demonstrated clinical efficacy when combined with exercise in other musculoskeletal conditions. In an RCT, the combination of vibration exercises in patients with patellofemoral pain syndrome led to better outcomes compared with the control group, which indirectly supports the concept of synergy between mechanical stimulation and functional activity, as proposed by A. Yañez-Álvarez *et al.* [33]. In the context of chronic back pain, this highlights the promise of combining mechanical protocols with active approaches (exercise, motor control, pain neuroscience education) in future studies, although in the present design, co-interventions were deliberately restricted to ensure the purity of the comparison of mechanical models.

The findings also had practical implications. With the same treatment duration and standardised treatment areas, different models of mechanical stimulation demonstrated different predominant effects: the PV model had a greater impact on pain and PPT, whilst the MF model had a greater impact on function and CSI. This could support a stratified approach: where mechanical hyperalgesia and high pain intensity predominate, a short-pulse sensory-modulating stimulus might be more appropriate; where there are marked functional limitations and a sensitisation profile, slow fascial techniques. At the same time, the CM model was also effective and could be considered a baseline strategy, although the average effects were less pronounced. The safety profile remained favourable in all groups, and adverse events were rare and predominantly mild; the higher incidence of bruising in the CM group may reflect a greater proportion of prolonged local compression and friction, necessitating attention to the dosage of mechanical load.

◆ CONCLUSIONS

A study involving 96 patients with chronic non-specific low back pain found that all three standardised mechanical intervention models provided clinically significant pain relief and functional improvement; however, the profile of

effects differed between the groups. The greatest reduction in pain intensity (VAS) was demonstrated by the PV model: the mean reduction was approximately -3.2 points at T1 and remained at approximately -3.4 points at T2 compared with the baseline value (baseline 5.9 ± 1.3). In the MF group, the reduction in pain was moderate (approximately -2.9 at T1 and -3.1 at T2), whilst in the CM group it was less pronounced (approximately -2.4 at T1 and -2.6 at T2). Clinical significance was confirmed by a responder analysis: the proportion of participants with a VAS reduction of ≥ 2 points at T2 was 81.3% in the PV group, 75% in the MF group and 62.5% in the CM group.

In terms of mechanical sensitivity (PPT), the greatest improvement was also associated with PV (approximately +0.8-1 kg/cm² at standardised points), which was consistent with better pain dynamics. In contrast, MF demonstrated a more pronounced improvement in function as measured by the ODI (approximately -10-12 percentage points versus -7-9 in the other groups) and a more consistent reduction in the CSI (approximately -7-9 points), indicating a potentially better effect on the sensitisation-functional component of the condition. The interventions were well tolerated: early withdrawal was rare (1-2 cases per group), and no serious adverse events were reported. The data obtained support a differentiated choice of mechanical intervention model depending on the dominance of the pain, mechanosensory or functional-sensitisation components in a particular patient. Promising areas for further research include expansion of follow-up to 3-6 months; testing of combined protocols (mechanical stimulation + therapeutic exercise/education), based on the potential synergistic effects demonstrated for vibration-based approaches in other clinical contexts; stratifying patients according to sensitisation phenotype and mechanical hyperalgesia to identify predictors of response, consistent with role of central sensitisation in chronic pain.

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None.

◆ REFERENCES

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Механізми впливу техніки масажу Ток Сен на хронічний м'язовий біль у спині

Дмитро Чоповський

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Анотація. Хронічний неспецифічний біль у попереку підтримується поєднанням периферичної механічної гіпералгезії та змін центральної модуляції болю, тому зіставлення стандартизованих механічних впливів має практичну цінність. Мета роботи – порівняти клінічні та сенсорні ефекти трьох механічних моделей впливу за однакової тривалості курсу. Проведено проспективне рандомізоване контрольоване дослідження із засліпленням оцінювача в 96 пацієнтів, які отримали 10 процедур по 30 хвилин протягом 4 тижнів за ударно-вібраційною (УВ), класичною мануальною (КМ) або міофасціальною (МФ) моделлю. Вихідна інтенсивність болю за числовою рейтинговою шкалою становила $5,9 \pm 1,3$ бала. Через 2 тижні після завершення курсу інтенсивність болю знижувалася в усіх групах, причому найбільша редукція спостерігалася в УВ групі, проміжна – у МФ, найменша – у КМ. Частка учасників, які досягли клінічно значущого зменшення болю щонайменше на 2 бали, становила 81,3 % в УВ групі, 75,0 % у МФ та 62,5 % у КМ, що відображало відмінності не лише в середніх значеннях, а й у ймовірності досягнення відчутного полегшення на рівні окремого пацієнта. Поріг больової чутливості до тиску зростав відповідно на 0,95; 0,72 і 0,61 кг/см². Функціональні обмеження за індексом інвалідизації зменшувалися на 8,4, 11,6 і 7,5 відсоткового пункту, при цьому найбільший функціональний виграш реєструвався в МФ групі, що вказувало на відмінності профілю відповіді між моделями механічного впливу. Практична значущість полягає в тому, що за однакової тривалості курсу та стандартизованих зон впливу механічні моделі демонструють різні переваги, тому вибір втручання може орієнтуватися на домінуючий клінічний запит: підвищення ймовірності швидкого клінічно значущого зниження болю, або пріоритетне покращення повсякденної функції, з урахуванням профілю переносимості

Ключові слова: механічна гіпералгезія; центральна модуляція болю; ударно-вібраційний вплив; міофасціальний реліз; мануальна терапія

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