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Научно-практический
журнал для работников
здравоохранения

Включён в Перечень
ведущих рецензируемых
периодических изданий
ВАК Минобрнауки РФ

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Подписано в печать 20.07.2026 года

Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору
в сфере связи, информационных технологий и массовых
коммуникаций (Роскомнадзор).

Свидетельство о регистрации

ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)

ISSN 2411-6564 (Online)

Отпечатано в типографии «Onebook.ru»

ООО «Сам Полиграфист»

г. Москва, Волгоградский проспект, д. 42, корп. 5

www.onebook.ru

Контент доступен под лицензией

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Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной
электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Урал-Пресс Округ» 87732

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Signed for printing on 20.07.2026
Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961,
26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Printed «Onebook.ru»

«Sam Poligrafist»
Moscow, Volgograd Prospect, 42-5
www.onebook.ru

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The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific
Electronic Library www.elibrary.ru

Subscription index in the catalogue «Ural-Press Okrug» 87732

DOI: 10.20514/2226-6704-2026-4

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DOI: 10.20514/2226-6704-2026-16-2068

УДК 616.72–002.77–074:577.27:543.544

EDN: BJEEZR



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Modern Immunoassay Methods for The Detection of Rheumatoid Arthritis Biomarkers

Резюме

Ревматоидный артрит (РА) является хроническим аутоиммунным заболеванием с высокой инвалидизирующей способностью, ранняя диагностика которого имеет ключевое значение для своевременного назначения базисных противоревматических препаратов и улучшения прогноза. В последние десятилетия особое внимание уделяется серологическим биомаркерам, среди которых ведущую роль играют ревматоидный фактор (РФ) и антитела к цитруллинированным белкам (АЦБ), включая анти-CCP (англ. anti-cyclic citrullinated peptide antibodies, антитела к циклическому цитруллинированному пептиду) и анти-MCV (англ. anti-mutated citrullinated vimentin antibodies, антитела

к мутантному цитруллинированному виментину). Эти маркеры позволяют не только подтвердить диагноз, но и прогнозировать риск агрессивного течения и эрозивных изменений суставов. Современные методы иммуноанализа существенно расширили диагностические возможности. Наряду с традиционными подходами (латекс-агглютинация, иммуноферментный анализ (ИФА), турбидиметрия) активно внедряются инновационные технологии: электрохимическая импедансная спектроскопия, спектроскопия комбинационного рассеяния с усилением поверхности (SERS), фотоэлектрические сенсоры и микрожидкостные платформы. Особое значение имеют мультиплексные иммуноанализы, обеспечивающие одновременное выявление нескольких биомаркеров в одном образце, что повышает точность диагностики, облегчает стратификацию пациентов и способствует реализации принципов персонализированной медицины. Несмотря на очевидные преимущества, мультиплексные методы сталкиваются с рядом ограничений: необходимостью использования высокоспецифичных антител, риском перекрёстной реактивности, отсутствием унифицированных эталонных стандартов для АЦБ, а также сложностями в обеспечении контроля качества. Дальнейшее развитие технологий связано с стандартизацией анализов, внедрением международных контрольных материалов и оптимизацией диагностических порогов. Таким образом, интеграция современных методов иммуноанализа и мультиплексных платформ в клиническую практику открывает новые возможности для ранней диагностики и прогнозирования РА, что в конечном итоге может снизить частоту инвалидизации и улучшить качество жизни пациентов.

Ключевые слова: ревматоидный артрит, серологические биомаркеры, ревматоидный фактор, антитела к цитруллинированным белкам, анти-CCP, анти-MCV, иммуноанализ, мультиплексные технологии, ранняя диагностика, персонализированная медицина

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 14.09.2025 г.

Одобрена рецензентом 28.10.2025 г.

Принята к публикации 28.11.2025 г.

Для цитирования: Семченко Д.А., Смирнова К.С., Низамова Л.А. и др. СОВРЕМЕННЫЕ МЕТОДЫ ИММУНОАНАЛИЗА ДЛЯ ВЫЯВЛЕНИЯ БИОМАРКЕРОВ РЕВМАТОИДНОГО АРТРИТА. Архивъ внутренней медицины. 2026; 16(4): 245-259. DOI: 10.20514/2226-6704-2026-16-2068. EDN: BJEEZR

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a high potential for disability, where early diagnosis is crucial for timely initiation of disease-modifying antirheumatic drugs (DMARDs) and for improving long-term outcomes. In recent decades, particular attention has been paid to serological biomarkers, among which rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), including anti-CCP and anti-MCV, play a leading role. These markers not only confirm the diagnosis but also help predict the risk of aggressive disease course and joint erosions. Modern immunoassay methods have significantly expanded diagnostic opportunities. Along with traditional approaches such as latex agglutination, enzyme-linked immunosorbent assay (ELISA), and turbidimetry, innovative technologies are actively being implemented, including electrochemical impedance spectroscopy (EIS), surface-enhanced Raman spectroscopy (SERS), photoelectrochemical biosensors, and microfluidic platforms. Multiplex immunoassays are of particular importance, as they allow the simultaneous detection of multiple biomarkers in a single sample, thereby increasing diagnostic accuracy, facilitating patient stratification, and promoting the principles of personalized medicine. Despite their advantages, multiplex methods face several limitations: the need for highly specific antibody pairs, the risk of cross-reactivity, the lack of standardized reference materials for ACPA, and challenges in quality control. Future development of these technologies depends on assay standardization, implementation of international reference standards, and optimization of diagnostic thresholds. In conclusion, the integration of modern immunoassay techniques and multiplex platforms into clinical practice provides new opportunities for early diagnosis and prognosis of RA, ultimately reducing disability rates and improving patients' quality of life.

Key words: rheumatoid arthritis, serological biomarkers, rheumatoid factor, anti-citrullinated protein antibodies, anti-CCP, anti-MCV, immunoassay, multiplex technologies, early diagnosis, personalized medicine

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 14.09.2025

Reviewer approved 28.10.2025

Accepted for publication on 28.11.2025

For citation: Semchenko D.A., Smirnova K.S., Nizamova L.A. et al. Modern Immunoassay Methods for The Detection of Rheumatoid Arthritis Biomarkers. The Russian Archives of Internal Medicine. 2026; 16(4): 245-259. DOI: 10.20514/2226-6704-2026-16-2068. EDN: BJEEZR

ACPA — anti-citrullinated protein antibodies, anti-CCP — anti-cyclic citrullinated peptide, anti-MCV — Antibodies to mutated citrullinated vimentin, CDC — Centers for Disease Control and Prevention, ДМARDs — disease-modifying antirheumatic drugs, ECL —electrochemiluminescence, EIS — electrochemical impedance spectroscopy, ELISA —enzyme-linked immunosorbent assay, EULAR — European Alliance of Associations for Rheumatology, LFIA —lateral flow immunoassay, MRI —magnetic resonance imaging, NIBSC — National Institute for Biological Standards and Control, PAD4 — Peptidylarginine deiminase type 4, ПOC — point-of-care, РА — Rheumatoid arthritis, RF — rheumatoid factor, SERS — surface-enhanced Raman spectroscopy, WHO —World Health Organization, ,

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, which involves inflammatory damage to the joints and their destruction, as well as various extraarticular manifestations and associated complications of various degree of intensity [1]. The disease can occur at any age; however, it is more common in women, and its prevalence varies depending on the region, generally being higher in industrialised countries [2]. Despite significant advances in basic science, the etiology of RA has not yet been fully established. It is believed that the pathogenesis is based on an interaction between genetic predisposition, environmental factors, and characteristics of the microbiome [1, 3].

Over the past two decades, the management of patients with RA has changed significantly due to the introduction of new medications and a deeper understanding of the mechanisms underlying the development of the disease [4]. At present, the key principle of treatment is the earliest possible diagnosis of RA and the prompt initiation of disease-modifying antirheumatic drugs (DMARDs). It has been demonstrated that timely treatment can prevent significant structural joint damage in 90% of patients and substantially improve prognosis [5]. At the same time, early diagnosis remains challenging because the clinical manifestations at disease onset are often nonspecific. Imaging techniques, such as ultrasonography and magnetic resonance imaging, are used to clarify the diagnosis; however, their effectiveness is limited, and they are primarily indicated for patients with pronounced clinical symptoms [6].

Serological markers are of particular importance in the early diagnosis of RA. The most valuable markers are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). These autoantibodies can be detected several years before the onset of clinical manifestations, making them important not only for diagnosis but also for predicting disease course, assessing the risk of developing erosive arthritis, and evaluating response to therapy [7, 8]. Accordingly, RF and ACPA were incorporated into the 2010 classification criteria developed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) [9]. They are also included in the Russian Ministry of Health's Clinical Guidelines "Rheumatoid Arthritis" (approved by the Ministry of Health of the Russian Federation in 2021), which recommend their determination as mandatory laboratory criteria for the diagnosis and monitoring of the disease [10].

Modern approaches to the laboratory diagnosis of RA involve the implementation of multiplex immunoassay methods, which enable the simultaneous detection of multiple biomarkers. This creates opportunities for more accurate patient stratification, optimisation of treatment

selection, and the implementation of personalised disease management strategies [11].

This article aims to analyse the clinical and prognostic significance of RF and ACPA in RA, evaluate current methods for their detection, and discuss the potential of multiplex technologies to enhance the effectiveness of early diagnosis and improve patient outcomes.

Biomarkers for Early Diagnosis of Rheumatoid Arthritis

Rheumatoid Factor

Rheumatoid factor was the first autoantibody identified in patients with RA; it recognises antigenic determinants in the Fc region of immunoglobulin G (IgG) [12]. RF was first described by Erik Waaler in 1940 as a factor exhibiting hemagglutinating activity in the sera of patients with RA [13]. In 1949, H. M. Rose confirmed this observation and, together with Waaler, developed a test based on the agglutination of sensitised sheep erythrocytes, which became known as the Waaler-Rose test [14].

In the following decades, the determination of RF became an integral part of the classification criteria for RA in 1956, 1958, and 1987. Initially, antibodies were detected using manual methods; however, with the advancement of laboratory diagnostics, automated approaches, including turbidimetry and enzyme-linked immunosorbent assay (ELISA), were introduced, improving both the sensitivity and specificity of testing. Modern methods enable the quantitative assessment of different RF isotypes, including IgM, IgA, and IgG [15].

A systematic analysis by Motta et al. showed that RF IgA has the highest specificity, but lower sensitivity as compared to RF IgM, whereas RF IgG has limited diagnostic value [16]. In a study by Sieghart et al., in which RF, anti-citrullinated protein antibodies (ACPA), and RA33 were assessed in parallel, RF IgM demonstrated the highest sensitivity among the nine antibody isotypes tested [17]. At the same time, in patients with undifferentiated inflammatory arthralgia, the combined assessment of different RF isotypes did not demonstrate any advantage over the isolated measurement of RF IgM and, in some cases, even increased the risk of false-positive results [18]. Therefore, RF IgM remains the most popular marker in routine clinical settings.

According to meta-analyses, the specificity of RF in RA patients is approximately 85%, while sensitivity varies between 60% and 90% [19]. High RF titres are associated with a more severe disease and unfavourable prognosis, especially at early stages [8].

Of particular interest are the interactions between RF and ACPA. It has been shown that the presence of

RF IgM enhances the ability of immune complexes containing ACPA to activate macrophages, stimulating the production of pro-inflammatory cytokines and thereby accelerating disease progression [20, 21]. Moreover, the simultaneous presence of RF and ACPA in serum is associated with more pronounced systemic inflammation and a shorter preclinical phase of RA [22].

Anti-citrullinated Protein Antibodies

Anti-citrullinated protein antibodies are a large group of autoantibodies directed against citrullinated epitopes of native proteins or synthetic peptides. These antibodies are detected both in the serum and in the synovial fluid of patients with RA and are characterised by high specificity and sensitivity, making them among the most important serological markers for the early detection and prognostic assessment of the disease [23].

Under conditions of chronic inflammation, enzymes of the peptidyl arginine deiminase (PAD) family catalyse the conversion of arginine residues into citrulline, generating new antigenic determinants. Targets of ACPA include fibronectin, vimentin, keratin, α -enolase, type II collagen, and histones, which are expressed in various tissues throughout the body [24]. Citrullinated proteins can be incorporated into major histocompatibility complex (MHC) structures, activate T lymphocytes, and stimulate B cells to produce additional autoantibodies. These processes contribute to increased inflammation, bone resorption, and pain in RA [25].

Although rheumatoid factor was the first serological marker used in the diagnosis of RA, ACPA have demonstrated significantly higher specificity and comparable, and in some cases even superior, sensitivity. This makes them a valuable tool for the early detection of the disease, prediction of its course, and timely initiation of targeted therapy, ultimately helping to slow disease progression and reduce the risk of disability [26].

Antibodies to Citrullinated Filamentous Protein

The first RA-specific autoantibodies from the ACPA group to be described were the anti-perinuclear factor (APF) and anti-keratin antibodies (AKA). In 1964, Nienhuis et al. reported the presence of antibodies against perinuclear factor in the serum of patients with RA, which demonstrated high specificity [27]. Later, in 1979, Young et al. identified AKA, which also demonstrated a strong association with RA [28]. Initially, keratin was thought to be the target of these antibodies; however, in 1995, Sebbag et al. established that, for both APF and AKA, the target antigens are citrullinated intermediate filament proteins of epidermal cells. This led to the

introduction of the general term “antibodies to citrullinated filamentous protein” [29].

APF is found in rheumatoid nodules and synovial fluid and is often found together with RF. This marker can be used for the differential diagnosis of RA and other inflammatory arthropathies, with its specificity estimated at approximately 94.3 % [30]. AKA, in turn, can be detected even before the clinical manifestations of RA become apparent. Moreover, they have been shown to be strongly associated with erosive bone changes, making them important prognostic markers [31]. According to a meta-analysis, the specificity of AKA reaches 94 %, whereas their sensitivity remains relatively low (approximately 46 %) [32].

Thus, despite their high specificity, the limited sensitivity of APF and AKA reduces their value in routine clinical settings. Nevertheless, these antibodies played a key role in shaping our understanding of the pathogenesis and serological diagnosis of RA, serving as precursors to more modern markers, such as anti-CCP antibodies and other ACPA tests.

In 2000, Schellekens et al. were the first to propose the use of a synthetic cyclic peptide containing a citrulline residue as an antigenic substrate for the detection of anti-cyclic citrullinated peptide (anti-CCP) antibodies using an enzyme-linked immunosorbent assay (ELISA). The test was shown to have high specificity (up to 96 %) for RA and to be of significant value for the early diagnosis of the disease [33]. Several studies have confirmed that anti-CCP antibodies outperform RF in terms of specificity and diagnostic accuracy, particularly in the evaluation of patients with early undifferentiated arthralgia and in predicting a more aggressive comcurses of the arthropathy [34].

Currently, second-generation (anti-CCP2) and third-generation (anti-CCP3) tests are available, based on the use of synthetic mixtures of cyclic citrullinated peptides. These tests provide substantially higher sensitivity while maintaining high specificity compared with first-generation assays [35]. According to prospective studies, anti-CCP3 plays an important role in predicting the development of inflammatory arthritis in high-risk individuals who are already positive for anti-CCP2 [36]. Vos et al. showed that the results of anti-CCP2 and anti-CCP3 tests are generally comparable; however, the risk of developing RA was significantly higher among patients who tested positive on both assays [37].

It is worth mentioning that some patients with RA have negative serological markers, both RF and ACPA. Moreover, these patients are not only unprotected against severe disease but also face an increased risk of disability and premature mortality, underscoring the need to identify more sensitive biomarkers for seronegative forms of RA [38].

In recent years, a test has been developed to detect both IgG and IgA isotypes of anti-CCP antibodies (anti-CCP3.1). It was hypothesised that this assay might offer higher sensitivity than standard anti-CCP3 tests, which predominantly detect IgG antibodies [39]. However, subsequent studies showed that after adjusting the cutoff values to maintain high specificity, the differences in diagnostic accuracy between anti-CCP3.1 and anti-CCP3 were no longer significant [40]. Thus, the inclusion of IgA isotypes in test systems did not demonstrate a meaningful improvement in the diagnostic value of anti-CCP antibodies [41].

Vimentin belongs to the class of intermediate filaments of the cytoskeleton, which are located in the cytoplasm of various cells, including macrophages. During activation of the inflammatory process, an increase in intracellular Ca^{2+} concentration leads to the activation of peptidyl arginine deiminase (PAD) enzymes, which catalyse the citrullination of vimentin. The modified protein acquires new antigenic properties, contributing to the activation of the immune response, persistence of chronic inflammation, synovial hyperplasia, and destruction of joint structures in patients with RA [42].

Antibodies to mutated citrullinated vimentin (anti-MCV) are considered a promising marker within the ACPA group. According to clinical studies, the sensitivity of anti-MCV is approximately 77 %, while specificity reaches 89 % [43,44]. The diagnostic value of this test is comparable to that of anti-CCP and RF; however, there are several distinctive features. Anti-MCV is more frequently associated with a more aggressive course of RA and pronounced changes in the peripheral joints. Moreover, the combined assessment of anti-MCV, anti-CCP, and RF increases the likelihood of detecting the disease in patients who are seronegative on standard anti-CCP and RF testing [45, 46].

Thus, anti-MCV antibodies expand the possibilities of laboratory diagnosis of RA, particularly in challenging diagnostic cases, and may be used as an additional prognostic marker for risk stratification of an aggressive disease course.

In addition to the well-studied markers, patients with RA may also have other antibodies directed against citrullinated autoantigens. These include autoantibodies against fibrinogen, α -enolase, and type II collagen. These antibodies can also be detected at early stages of the disease and are characterised by high specificity for RA [47].

Their formation is thought to be associated with both genetic predisposition and environmental factors; however, the mechanisms underlying the involvement of these antibodies in the pathogenesis of RA, as well as their clinical significance, remain insufficiently

understood. At present, there is no convincing evidence of their independent diagnostic or prognostic value. Further research is needed to assess their role in risk stratification and their potential application in the comprehensive diagnosis of RA.

Combined Analysis of Rheumatoid Factor and Anti-Citrullinated Protein Antibodies

The diagnosis of RA is based on a combination of criteria, including the pattern of joint involvement, serological biomarkers, acute-phase inflammatory markers, and symptom duration [9]. Among the serological markers, RF and ACPA are of particular importance, as they can predict the development of the disease in individuals at high risk of disease onset. However, the results of RF and ACPA testing may vary depending on the methodology used, which affects sensitivity and specificity, particularly for RF [48, 49]. This variability complicates the standardisation of diagnostic criteria and may reduce the accuracy of RA classification.

It should be noted that RF is detected not only in RA but also in other autoimmune diseases, chronic infections, and in some clinically healthy individuals. Furthermore, RF is absent in 30–45 % of patients with RA, which limits its diagnostic value [50]. Recently, Oskam et al. described a novel RF variant targeting the T3-17 epitope, which demonstrated high specificity for RA and was not detected in patients with Sjögren's syndrome or healthy donors. This marker may potentially have greater prognostic value than conventional IgM RF; however, the available data are currently limited to seropositive patients, and further studies in other populations are required [51].

To date, there are no serological assays with absolute specificity for RA alone, highlighting the need to develop new strategies to improve the sensitivity and accuracy of diagnosis. One such approach is the combined assessment of RF and ACPA. It has been shown that combining anti-CCP and RF testing significantly improves diagnostic and prognostic value compared with the use of either marker alone [52]. In a study by Martinez-Prat et al., the likelihood of RA development and progression was shown to increase in patients with double or triple serological positivity [53].

In the context of precision medicine, the integration of biomarkers, particularly the simultaneous testing of RF and ACPA, may improve the accuracy of RA diagnosis and classification, as well as reduce the number of seronegative cases [54]. Table 1 presents a comparison of the main characteristics and clinical significance of RF and ACPA.

Table 1. Comparative Characteristics of Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA)

Parameter	Rheumatoid Factor (RF)	Anti-Citrullinated Protein Antibodies (ACPA)
Sensitivity	60–90 % [19, 50]	65–85 % [23, 26]
Specificity	≈85 % [19, 50]	90–98 % [23, 26]
Time of appearance	Usually at the onset of clinical symptoms [19]	May be detected years before RA manifestation [23, 26]
Prognostic value	Associated with severe disease course and extra-articular manifestations [8, 50]	Predicts erosive arthritis and rapid disease progression [23, 26]
Limitations	Detected in other autoimmune and infectious diseases, as well as in healthy individuals [50]	Absent in some patients (seronegative RA forms) [26]

Note. RF — rheumatoid factor; ACPA — anti-citrullinated protein antibodies; RA — rheumatoid arthritis

Immunoassay Methods for the Detection of Biomarkers in RA

Immunoassay Methods for the Detection of Rheumatoid Factor

Accurate and sensitive detection of IgM RF is of critical importance for the early diagnosis of RA. In clinical practice, latex agglutination, enzyme-linked immunosorbent assay (ELISA), and immunoturbidimetry are traditionally used [48]. Latex agglutination is simple to perform and provides rapid results; however, it offers only qualitative or semi-quantitative assessment, which limits its value in early diagnosis. ELISA enables the detection of individual RF isotypes and has prognostic value, but it remains a relatively labor-intensive method requiring several sequential steps. Therefore, the development of faster and more reliable methods with high sensitivity, a broad linear range, and accurate quantitative determination of IgM RF remains an important objective.

In recent years, innovative rapid diagnostic technologies, including nanomaterial-based biosensors, have been actively developed. These technologies show promise due to their high sensitivity and reliability, as well as their potential applicability to the clinical diagnosis of RA. For example, Chinnadayala et al. proposed an electrochemical immunosensor based on impedance measurements. In this system, RF antigen was immobilised on a thiocyanic acid-functionalised self-assembled monolayer (TA-SAM) deposited on an interdigitated wave-shaped microelectrode (IDWμE). The resulting system provided a low detection limit and good selectivity, although its storage stability remained limited [55].

Veigas et al. developed a colorimetric immunosensor based on gold nanoparticles. The presence of RF IgM in the sample induced aggregation of the nanoprobe and a colour change in the solution from red to purple, allowing the result to be detected visually without the use of additional antibodies or complex washing steps.

This approach provides a rapid and simple assay, offering advantages over traditional methods [56].

Schmidt et al. proposed a lateral flow immunoassay (LFIA) using fluorescent dye-labeled polymethyl methacrylate (PMMA) nanoparticles as indicators. For the detection of RF IgM, the assay employed the following binding scheme: anti-human IgM antibodies were immobilised on the nanoparticles, while the Fc fragment of IgG was immobilised on the test line and protein G on the control line. This system enabled specific binding of the labelled nanoparticles only in the presence of RF IgM in the sample. Compared with commercial ELISA, this method required a smaller serum volume and substantially reduced the assay time, making it a promising tool for point-of-care diagnostics [57].

Immunological Methods for the Detection of Anti-Citrullinated Protein Antibodies

Modern approaches to the detection of ACPA include enzyme-linked immunosorbent assay (ELISA), surface-enhanced Raman spectroscopy (SERS), and electrochemical methods. In recent years, a number of novel immunosensors with improved analytical performance and greater ease of use compared with conventional ELISA have been developed, although ELISA remains labour-intensive and time-consuming [58].

Particular attention is being paid to label-free electrochemical impedance spectroscopy (EIS). Miniaturised systems based on microelectrode arrays can achieve high sensitivity while offering the advantages of miniaturisation and rapid analysis. Chinnadayala et al. developed a sensor based on interdigitated microelectrodes using a simple biotin-based affinity-binding system. This sensor demonstrated high selectivity for the detection of anti-CCP antibodies and was suitable for early screening [59]. The same group developed screen-printed electrodes modified with polyaniline (PANI)/MoS₂, which enhanced the signal and improved sensitivity [60]. Wu et al. employed interdigitated electrodes modified with gold nanoparticles (AuNPs) and demonstrated that the

Table 2. Modern Rapid Immunoassay Methods for the Detection of RF and ACPA

Method	Principle	Advantages	References
Latex agglutination	Agglutination of latex particles with immobilized antigen	Simplicity and rapid performance, low cost	[48]
Enzyme-linked immunosorbent assay (ELISA)	Detection of antibodies using conjugates and enzymatic reaction	Quantitative analysis capability, determination of antibody isotypes	[48]
Electrochemical impedance spectroscopy (EIS)	Measurement of impedance changes on modified electrodes	High sensitivity, miniaturization, label-free detection	[59–60]
Colorimetric immunosensor based on gold nanoparticles	Color change of the solution due to nanoparticle aggregation	Simplicity, rapid visual result without complex reagents	[56]
Lateral flow immunoassay (LFIA)	Binding of antibodies on the test line using fluorescently labeled nanoparticles	Rapid testing, small sample volume, suitable for point-of-care diagnostics	[57]
Photoelectrochemical biosensor	Use of bacteriorhodopsin or nanomaterials to register photocurrent	High specificity, innovative signal detection principles	[63]
SERS immunosensor	Surface-enhanced Raman spectroscopy using nanoparticles	Extremely low detection limits, high selectivity	[64,67]

Note. RF — rheumatoid factor; ACPA — anti-citrullinated protein antibodies; POC — point-of-care; SERS — surface-enhanced Raman spectroscopy; LFIA — lateral flow immunoassay; EIS — electrochemical impedance spectroscopy.

density and distribution of the nanoparticles influence anti-CCP binding, enabling high sensitivity with a short response time [61].

New peptide-based sensors are also being developed. Lin et al. developed a label-free electrochemical sensor using a guanine-modified peptide capable of self-assembly on the surface of a gold electrode, thereby increasing the binding area and sensitivity [62]. Chen et al. proposed a photoelectric sensor based on bacteriorhodopsin, in which a decrease in photocurrent was used as a quantitative parameter [63]. Szarka et al. synthesised a multi-epitope peptide and incorporated it into a surface plasmon resonance sensor, achieving high sensitivity and detecting antibodies in 90 % of patients with RA [64].

Nanomaterials significantly expand the capabilities of biosensors due to their high specific surface area and unique electronic properties. Zhao et al. synthesised asymmetric polyaniline-gold (PANI–Au) nanohybrids, which were used to develop an electrochemiluminescence (ECL) sensor with high specificity and stability [65, 66]. Hwang et al. proposed a surface-enhanced Raman spectroscopy (SERS) method using anisotropic bimetallic core-satellite nanohybrids, which demonstrated excellent optical properties and enabled accurate quantitative determination of anti-CCP antibodies [67].

Efforts are also underway to improve ELISA and turbidimetric methods. Ramos et al. developed a microfluidic ELISA-based sensor using magnetic nanoparticles, which reduced the sample volume and shortened the analysis time [68]. Deng et al. proposed a turbidimetric method using latex particles immobilised with cyclic

citrullinated peptide, enabling rapid diagnosis [69]. Sheng et al. developed a time-resolved immunofluorescence assay based on lanthanides and chelating agents, which demonstrated high stability and good correlation with commercial assay kits [70]. Tai et al. presented a microfluidic platform integrating a reaction chip with a microspectrometer, opening up opportunities for the early diagnosis and monitoring of RA in both laboratory and clinical settings [71].

To date, numerous biosensor platforms have been developed, including peptide-based optical and electrochemical sensors. These technologies have demonstrated promise for clinical applications due to their relative stability, high affinity for target molecules, and ease of use [72]. Nanomaterials play an important role in the development of this field, as their unique physicochemical properties enable the detection of biomarkers at extremely low concentrations with high sensitivity and selectivity. However, the diagnostic accuracy of such systems largely depends on the appropriate selection of biomarkers. In the near future, a key objective will be to integrate additional serological and molecular markers associated with RA into unified multiplex platforms. This will enable comprehensive analysis and improve diagnostic accuracy [73].

Multiplex Immunoassay Methods for the Detection of RA Biomarkers

Combined assessment of RF and ACPA has demonstrated that the prognostic value of multimarker testing exceeds that of either marker alone. Simultaneous

detection of RF and ACPA improves the accuracy of early diagnosis, facilitates patient stratification, and enables prediction of the response to disease-modifying antirheumatic drugs (DMARDs). Therefore, multiplex immunoassay methods, which allow the simultaneous determination of multiple biomarkers in a single sample, are considered a promising tool for personalised management of patients with RA.

Multiplex Immunoassay Methods for the Detection of RF and ACPA

Immunosensors offer a number of advantages, including high sensitivity, selectivity, rapid response, and the potential for portable use. At the same time, systems designed for the simultaneous detection of multiple markers provide greater diagnostic value than single-channel biosensors [74].

Guerrero et al. developed a dual electrochemical biosensor based on functionalised magnetic microparticles and dual screen-printed carbon electrodes. This approach enabled the simultaneous detection of RF and anti-CCP antibodies while reducing the required serum volume fourfold compared to conventional ELISA, without compromising sensitivity [75]. Subsequently, the same research group introduced a quadruplex electrochemical immunosensor capable of simultaneously detecting RF, anti-PAD4, anti-MCV, and anti-CCP antibodies. The device demonstrated high sensitivity and specificity, along with a broad linear range [76].

Hwang et al. proposed a novel SERS biosensing method using hybrid bimetallic nanostructures (CBCPHNs) and magnetic beads (MBs). The resulting sandwich-type immune complexes enabled the simultaneous detection of anti-CCP and RF with high

sensitivity [77]. In another study, the same group synthesised anisotropic bimetallic nanoparticles (ABPNs), which were used as SERS probes for multiplex analysis. This technology provided strong signals and good reproducibility [78].

Wu et al. developed a dual-purpose microfluidic chip with a symmetrical architecture that enabled the simultaneous and automated detection of RF and anti-CCP. The system demonstrated high sensitivity and specificity, as well as suitability for clinical diagnostic applications [79].

García-Moreno et al. developed a multiplex assay based on eight chimeric citrullinated peptides identified from the synovial fluid of patients with RA. This approach enabled high specificity in the detection of ACPA while simultaneously reducing the required serum volume [80]. Chen et al. proposed a miniaturised optical sensor using light-emitting diodes (LEDs) and silicon photomultipliers, enabling rapid detection of RF and anti-CCP with a minimal sample volume [81].

Renger et al. developed an LFIA test for the simultaneous detection of anti-MCV and RF. The assay was based on the capillary migration of the sample across a nitrocellulose membrane, resulting in the formation of a visible line. This method demonstrated high sensitivity and ease of use in clinical settings [82]. In a subsequent study, Zandman-Goddard et al. showed that the diagnostic accuracy of LFIA was comparable to that of conventional ELISA, with positive agreement reaching 97 % and negative agreement 98 %. These findings support the potential use of such kits in outpatient settings for the rapid diagnosis of RA [83].

Table 3 presents various multiplex immunoassay methods for the simultaneous detection of RF and ACPA.

Table 3. Multiplex Immunoassay Methods for the Simultaneous Detection of RF and ACPA

Method	Detected Markers	Advantages	References
Dual electrochemical biosensor (magnetic microbeads + screen-printed carbon electrodes)	RF, anti-CCP	Fourfold reduction in sample volume, high sensitivity	[75]
Quadruplex electrochemical immunosensor	RF, anti-PAD4, anti-MCV, anti-CCP	High sensitivity and specificity, wide linear range	[76]
SERS biosensor with hybrid nanostructures (CBCPHNs + MBs)	RF, anti-CCP	High selectivity and sensitivity, multiplex detection	[77]
SERS biosensor with anisotropic bimetallic nanoparticles (ABPN)	RF, anti-CCP	Strong signal, good reproducibility	[78]
Dual-purpose microfluidic chip	RF, anti-CCP	Automated analysis, high accuracy, clinical applicability	[79]
LFIA test for simultaneous detection of anti-MCV and RF	RF, anti-MCV	Simplicity, rapid results, accuracy comparable to ELISA	[82–83]

Note. RF — rheumatoid factor; ACPA — anti-citrullinated protein antibodies; PAD4 — peptidylarginine deiminase 4; MCV — mutated citrullinated vimentin; CCP — cyclic citrullinated peptide; LFIA — lateral flow immunoassay; SERS — surface-enhanced Raman spectroscopy.

Limitations of Multiplex Immunoassay Methods in Clinical Practice

The simultaneous detection of RA-associated auto-antibodies using clinically validated multiplex plat-forms can significantly simplify the diagnosis of the disease in routine laboratory practice. However, several major challenges remain in the implementation of this technology.

A key obstacle is the need to select highly specific antibody pairs to minimise cross-reactivity, as well as to effectively block interfering substances that may dis-tort assay results [84]. Todd et al. demonstrated that the presence of RF can substantially affect the mea-sured concentrations of cytokines and chemokines in patients with RA, with the risk of nonspecific binding being higher in multiplex systems than in single-ana-lyte assays [85].

Additional challenges are associated with differ-ences in protein immobilisation strategies, which reduce reproducibility and lead to signal variabil-ity. Conformational changes in antigens on the solid phase may increase the frequency of false-positive results [86].

Difficulties also arise in quality control: multiplex assays require the simultaneous assessment of mul-tiple biomarkers, making test validation more labour-intensive compared with single-analyte methods [87]. The lack of standardised control samples remains one of the major unresolved issues. While serum samples with high levels of antibodies against a single auto-antigen may serve as adequate controls for that par-ticular marker, obtaining serum samples containing reproducible concentrations of multiple antibodies simultaneously is extremely challenging [88].

Thus, despite methodological and organisational limitations, multiplex immunoassays represent a prom-ising tool for the comprehensive monitoring of autoan-tibodies in RA patients. Their further development and standardisation will be of critical importance for opti-mising diagnosis and improving the accuracy of patient stratification.

Recommendations for Improving the Diagnostic Performance of Combined RF and ACPA Testing

Acceleration of early RA diagnosis is possible through the standardised determination of key biomarkers and the selection of optimal autoantibody combinations. For example, parallel or sequential measurement of anti-CCP and IgM RF can improve diagnostic sensitivity. However, autoantibodies are complex analytes whose levels vary both between patients and within the same patient over time, making complete standardisation of testing methods challenging. Nevertheless, further improvement of combined RF and ACPA assays remains an important objective for enhancing the quality of early diagnosis [89].

The majority of commercial assay systems for detect-ing autoantibodies in RA lack unified international ref-erence standards, resulting in variability in results and assay heterogeneity [90]. For RF, calibration is typi-cally performed using standards from the World Health Organisation (WHO) or the UK National Institute for Biological Standards and Control (NIBSC). In con-trast, the ACPA standard developed by the U.S. Centers for Disease Control and Prevention (CDC) is based on serum from a single donor and has not been endorsed by the WHO [91]. Recently, the NIBSC reference mate-rial 18/204 was recognised as suitable for standardising ACPA assays, helping to improve result comparability and clinical interpretation [92]. Thus, the use of certi-fied international standards for RF and ACPA facilitates comparison across different methods; however, it does not resolve all issues, as differences in antigen sources and analytical principles persist [93].

For practical application, it is important to establish diagnostically optimal cutoff values for RF and anti-CCP within a range that provides high specificity and allows RA to be differentiated from other rheumatic diseases [94]. Several researchers emphasise the need to estab-lish these cutoff values based on population data from healthy individuals, which requires large-scale con-trol studies [90]. The use of likelihood ratios (LRs) and

Table 4. Limitations of Multiplex Immunoassay Methods and Possible Solutions

Limitation	Consequence	Possible Solutions
Cross-reactivity of antibodies	False-positive results, decreased assay specificity	Use of highly specific antibody pairs, optimization of blocking conditions [84]
RF interference	Distortion of cytokine and chemokine concentrations, risk of misinterpretation	Implementation of RF-blocking algorithms, adjustment of multiplex assay protocols [85]
Variability of protein immobilization	Reduced reproducibility and accuracy, false-positive signals	Standardization of immobilization methods, control of antigen conformation [86]
Quality control challenges	Difficulties in test validation, absence of universal reference materials	Development of multi-analyte standards, creation of combined serum panels [87–88]

ROC analysis enables objective assessment of test performance and determination of optimal diagnostic cutoff points [95, 96].

The probability of developing RA can also be refined by taking into account other laboratory and clinical parameters, including C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), clinical presentation (pattern of joint involvement, morning stiffness, and systemic manifestations), and characteristics of the local population. Several studies have calculated LR_s for RF, ACPA, and their combination, making it possible to estimate post-test probabilities based on pre-test probabilities and thereby confirm or exclude the diagnosis more accurately [97].

Additional opportunities to improve diagnostic accuracy are associated with adjusting the weighting coefficients of serological criteria. Given the higher specificity and diagnostic value of anti-CCP compared with RF, greater weight should be assigned to these antibodies in the classification criteria. Priority should be given to the following criteria:

- Dual seropositivity (RF + ACPA) compared with isolated seropositivity
- Anti-CCP compared with RF
- High antibody titres compared with low titres [98–102].

Numerous studies have shown that high anti-CCP levels are associated with a greater likelihood of disease and a poorer prognosis [53, 101]. Therefore, incorporating serological stratification (based on the presence and levels of antibodies) into the classification criteria for RA may increase their specificity while maintaining high sensitivity, thereby improving diagnostic accuracy at the early stages of the disease.

According to clinical guidelines [10], determination of rheumatoid factor (RF) and anti-CCP is included among the mandatory laboratory tests in patients with suspected RA. The guidelines emphasise that the detection of these serological markers is of key importance for establishing the diagnosis, assessing disease prognosis, and selecting the appropriate treatment strategy. The presence of anti-CCP and/or high RF levels is regarded as a supportive diagnostic criterion and a factor associated with an unfavorable prognosis in RA.

A promising area is the adaptation and implementation of multiplex immunoassays capable of simultaneously detecting multiple autoantibodies (RF, anti-CCP, anti-MCV, and anti-PAD4). Such systems are already being evaluated at leading federal rheumatology centers in Moscow, St. Petersburg, and Kazan and are regarded as a step toward personalised diagnosis and risk stratification for aggressive disease. In the long term, the localisation of manufacturing and standardisation of

multiplex platforms could substantially improve access to high-precision RA diagnostics across Russian regions while also reducing dependence on imported reagents.

Conclusion

Over the past several decades, the serological diagnosis of rheumatoid arthritis has undergone significant evolution. The determination of rheumatoid factor and anti-citrullinated protein antibodies has become an essential component of the diagnostic algorithm, enabling not only confirmation of the diagnosis but also prediction of disease course, the likelihood of erosive joint damage, and treatment response. The introduction of anti-CCP and anti-MCV assays has substantially increased diagnostic specificity, while the combined assessment of RF and ACPA has significantly improved the accuracy of early RA detection.

Modern immunological assay methods, including electrochemical, optical, and nanotechnology-based platforms, have enabled more sensitive and rapid detection of autoantibodies. The development of multiplex systems has opened up opportunities for the simultaneous determination of multiple biomarkers, thereby increasing the informativeness of testing, facilitating patient stratification, and supporting the implementation of personalised medicine.

Nevertheless, several challenges remain unresolved, including variability in results among commercial assay systems, the lack of standardised reference materials for ACPA, difficulties in quality control of multiplex systems, and interference caused by RF. Improving the reliability of test results will require further standardisation of analytical methods, the implementation of international reference materials, and the establishment of optimal cutoff values based on population-based studies.

In modern rheumatology, particular importance is placed on integrating serological data with the clinical presentation, acute-phase reactants, and imaging methods. The combined use of RF and ACPA, along with the implementation of multiplex technologies, can substantially improve the accuracy and reproducibility of RA diagnosis, ultimately facilitating earlier initiation of therapy, reducing the incidence of disability, and improving patients' quality of life.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Семченко Д.А.: концепция и дизайн исследования, редактирование статьи

Смирнова К.С.: научная редакция рукописи, сбор и анализ литературных источников, подготовка и написание текста статьи

Низамова Л.А.: сбор и анализ литературных источников, подготовка и написание текста статьи

Назаренко П.Е.: обзор литературы, сбор и анализ литературных источников, написание текста и редактирование статьи
 Мартянова Е.В.: поиск и анализ литературы, написание текста статьи
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All authors made a significant contribution to the preparation of the paper, read, and approved the final version of the article before publication
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DOI: 10.20514/2226-6704-2026-16-4-260-266

УДК 616.379-008.64-03-06-085

EDN: CLNSLH

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КЛАССИФИКАЦИЯ ДИАБЕТА И ПЕРСониФИЦИРОВАННАЯ ТЕРАПИЯ

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Clustering of Diabetes: Implications for Personalized Treatment

Резюме

Предпосылки. Исторически сахарный диабет подразделяют на следующие группы: сахарный диабет 1-го типа (СД1), сахарный диабет 2-го типа (СД2), гестационный диабет и другие специфические типы сахарного диабета. Новая модель классификации включает 5 групп: тяжелый аутоиммунный диабет (SAID), тяжелый инсулин-дефицитный диабет (SIDD), тяжелый инсулинорезистентный диабет (SIRD), связанный с ожирением диабет средней степени тяжести (MOD) и возрастной диабет средней степени тяжести (MARD). В основе новой классификации лежат 6 клинических переменных: возраст, индекс массы тела при постановке диагноза, показатели гликированного гемоглобина, антитела к декарбоксилазе глутаминовой кислоты, оценка гомеостатической модели функции бета-клеток 2 и резистентность к инсулину. Модель способствует назначению персонифицированной терапии и позволяет прогнозировать осложнения. **Цель.** В этом обзоре проводится оценка клинических и терапевтических аспектов применения классификации, основанной на 5 группах, с использованием данных, полученных в 2010–2023 годах, и анализируется влияние на эффективность терапии и персонифицированную помощь. **Методы.** Обзор ограничивался последними 15 годами и проводился с применением баз данных и платформ PubMed, Web of Science и Google Scholar. Использовались следующие термины: прецизионная терапия, подгруппы диабета, SAID, SIDD, SIRD, MOD и MIRD. В обзор включены доклинические и клинические данные исключительно на английском языке. **Результаты.** Основанная на 5 группах модель выявляет специфические клинические векторы: SIRD связан с нефропатией, SAID и SIDD вызывают большее количество осложнений (например, нейропатию, кетоацидоз) и имеют тяжелое течение. Метаболические расстройства и дисфункция органов (MARD и MOD), которые чаще встречаются у пациентов с ожирением, протекают в более легкой форме. Валидационные исследования выявили региональные и этнические различия в распространенности SIRD и MOD. В частности, представляется, что у жителей Южной Азии SIRD встречается чаще, чем у африканского населения, и MOD превалирует. **В заключение,** учитывая метаболический профиль при определении терапевтического подхода, основанный на 5 группах, метод способствует внедрению прецизионной медицины; терапия должна основываться на биологии.

Ключевые слова: резистентность к инсулину, осложнения диабета, прецизионная медицина, персонифицированная терапия, группы диабета, SAID, SIDD, SIRD, MOD, MIRD

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 12.02.2025 г.

Одобрена рецензентом 25.08.2025 г.

Принята к публикации 15.01.2026 г.

Для цитирования: Абдел-Сатер Х.А. КЛАССИФИКАЦИЯ ДИАБЕТА И ПЕРСониФИЦИРОВАННАЯ ТЕРАПИЯ. Архив внутренней медицины. 2026; 16(4): 260-266. DOI: 10.20514/2226-6704-2026-16-4-260-266. EDN: CLNSLH

Abstract

Background: Diabetes mellitus traditionally classified into type 1 (T1D), type 2 (T2D), gestational, and other specific types. A novel five-cluster model severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD). This new classification was based on six clinical variants: age, body-mass index at diagnosis,

glycosylated hemoglobin, glutamic acid decarboxylase antibodies, homeostasis model assessment 2 beta and insulin resistance. This model enhances personalized treatment and complication prediction. **Objective:** This review evaluates the clinical and therapeutic implications of the five-cluster classification, synthesizing evidence from 2010–2023 to assess its impact on treatment efficacy and personalized care. **Methods:** This review was limited to the last 15-years and was done using PubMed, Web of Science and Google Scholar. Terms used included “precision therapy,” “diabetes sub-categories,” “SAID,” “SIDD,” “SIRD,” “MOD” and “MIRD.” Only preclinical and clinical data in English were used. **Results:** The five-cluster model highlights specific clinical trajectories: SIRD is associated with nephropathy, while SAID and SIDD clusters have more complications (e.g., neuropathy, ketoacidosis) severity. The metabolic and organ dysfunction (MARD and MOD) that is more common in obesity, is less severe. Validation studies have brought attention to regional and ethnic disparities in the distribution of SIRD and MOD; specifically, it seems that South Asians have a higher incidence of SIRD than African cohorts, where MOD is more prevalent. **In conclusion,** by customizing therapeutic applications to metabolic profiles, the five-cluster method promotes precision medicine; therapy ought to be in line with biology.

Key words: *insulin resistance, diabetic complications, precision medicine, individualized therapy, diabetes clusters, SAID, SIDD, SIRD, MOD and MIRD*

Conflict of interest

There are no competing interests.

Funding Sources

No specific funding agency grant was provided for this research. The authors did not receive any funding to assist in this work. No funding was received for this study.

Article received on 12.02.2025

Reviewer approved 25.08.2025

Accepted for publication on 15.01.2026

For citation: Abdel-Sater Kh.A. Clustering of Diabetes: Implications for Personalized Treatment. The Russian Archives of Internal Medicine. 2026; 16(4): 260-266. DOI: 10.20514/2226-6704-2026-16-4-260-266. EDN: CLNSLH

BMI — body mass index; CKD — chronic kidney disease; GADA — glutamic acid decarboxylase antibodies; LADA — late autoimmune diabetes in adults; MARD — mild age-related diabetes; MOD — moderate obesity-related diabetes; SAID — severe autoimmune diabetes; SIDD — severe insulin-deficient diabetes; SIRD — severe insulin-resistant diabetes; T1D — type 1 diabetes; T2D — type 2 diabetes



1. Introduction

Diabetes impacts 537 million adults all over the world with estimates expecting this number to reach 783 million by 2045. They remain, however, overly simplified with their T1D and T2D diabetes classification systems because their categorization strategies are holistic and address the complexities of the disease heterogeneity poorly [1].

Ahlqvist et al. [2] performed a cluster analysis and was able to categorize subjects into five discrete clusters using age at diagnosis, BMI, HbA1c, GADA, HOMA2- β , and HOMA2-IR as six variables. While T1D and T2D classifications remain foundational, their inability to capture diabetes heterogeneity often leads to suboptimal treatment [3]. The five-cluster model (SAID, SIDD, SIRD, MOD, MARD) addresses this gap by stratifying patients based on pathophysiology, enabling targeted therapies [4].

This review examines the clinical implications of a model paradigm for diabetes classification, based on previous studies. The model aims to reduce complications and improve treatment outcomes by combining clinical data from different geographic locations.

2. Methodology

This review has been conducted through the last 15 years utilizing PubMed, Google Scholar, and Web of Science. “Diabetes Clusters,” “SAID,” “SIDD,” “SIRD,”

“MOD,” “MARD,” and “personalized treatment” were the search phrases used. The criteria for inclusion aimed at concentrating on the classification of diabetes and its traditional models versus the newly proposed classification system based on five groups. Exclusion criteria were applied to remove studies with small sample sizes, non-randomized designs, or those lacking clarity in the categorization of diabetes subtypes. Studies from Scandinavian, Asian, and African cohorts were prioritized to evaluate the model’s applicability across ethnicities, addressing potential biases in cluster prevalence.

3. Old Classification of Diabetes

Diabetes mellitus is traditionally divided into a number of types according to insulin dependency and etiology. These include insulin-dependent diabetes (type 1 diabetes, or T1D), “non-insulin dependent” diabetes (type 2 diabetes, or T2D), gestational diabetes mellitus, and other forms [5]. The forms that stem from secondary diabetes, such as those caused by pancreatic disorders, medication and chemical disorders, or hormonal imbalances, and monogenic diabetic syndromes like neonatal diabetes as well as maturity-onset diabetes of the young (MODY) are included [6].

The old classification of diabetes has weaknesses in pathogenesis, treatment, and diagnosis. The heterogeneity of patient responses to treatment makes this

classification insufficient. So, this review argues for further classification steps by providing examples of situations that do not conform to traditional classification.

4. Characteristics of New Diabetes Clusters (Table 1)

Measuring fasting C-peptide and glutamic acid decarboxylase antibodies (GADA) is the initial step in classifying diabetes. In step two, HOMA2-IR and HOMA2-β are calculated using the following formulas:

HOMA2-IR=fasting insulin×fasting glucose22.5

HOMA2-IR=22.5fasting insulin×fasting glucose

HOMA2-β=20×fasting insulinfasting glucose–3.5

HOMA2-β=fasting glucose–3.520×fasting insulin

Finding the patient’s age and body mass index (BMI) upon diagnosis is the third stage [4]. According to Ahlqvist et al. [2], there are five subgroups or clusters of diabetes: moderate obesity-related diabetes (MOD), mild age-related diabetes (MARD), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), and severe autoimmune diabetes (SAID).

Cluster 1: Severe Autoimmune Diabetes (SAID)

This kind of diabetes is marked by being diagnosed at a young age (early-onset diabetes), having a low BMI, very high HbA1c (indicating poor metabolic control),

high insulin resistance (high HOMA-IR), high β-cell dysfunction (low HOMA-2-β), and positive glutamate decarboxylase antibodies (GADA positive) [2,4].

Approximately 6% of adults belong to this cluster. Studies have indicated that up to 7% of patients in GADA-negative clusters have antibodies against islet cells and/or insulin, suggesting that testing for additional autoantibodies may increase the prevalence of this Cluster [7].

Both T1D and LADA have certain characteristics in common with SAID. The existence of blood autoantibodies against pancreatic tissues, which can be utilized as a diagnostic marker, is a characteristic shared by T1D and LADA. The patient will eventually need insulin therapy to control blood glucose levels if these antibodies are detected [8].

Cluster 2: Severe Insulin-Deficient Diabetes (SIDD)

This form of diabetes is identified by low age at diagnosis (early-onset diabetes), low BMI, very high HbA1c, high insulin resistance (HOMA-IR is high but lower than in SIRD), high β-cell dysfunction (low HOMA-2-β), and no glutamate decarboxylase antibodies (GADA negative). Around 18% of adult individuals fall into this Cluster, sharing similar characteristics with SAID but without the involvement of the immune system as the underlying cause of their condition [2,4].

Because of their extremely high HbA1c levels at diagnosis, SAID and SIDD are more directly linked to the risk

Table 1. New diabetes Cluster Profiles

CLUSTER	%	Age at diagnosis	BMI	HbA1c	HOMA-IR	HOMA-2-β	GADA	COMPLICATIONS
SAID	6%	Low age	Low	Very high	High	Low	Positive	Ketoacidosis Retinopathy Kidney diseases
SIDD*	18%	Low age	Low	Very high	High but lower than SIRD	Low	Negative	Ketoacidosis Retinopathy Neuropathy CV diseases Erectile dysfunction
SIRD	15%	High age	High	Normal	Very high	Low (but higher than SAID & SIDD)	Negative	Neuropathy Fatty liver Nephropathy CV diseases Erectile dysfunction
MOD	22%	High age	Very high	Normal	High but lower than SIRD	Normal	Negative	Retinopathy
MARD**	39%	Very high age	Normal	Normal	Normal	Normal	Negative	Low risk of complication but kidney and CV diseases may occur

* SIDD is similar to SAID but without GADA. ** MARD is similar to MOD, but the MOD is characterized by a high BMI (obesity), while MARD has a higher age at diagnosis. CV= cardiovascular; SAID = severe autoimmune diabetes; SIDD = severe insulin-deficient diabetes; SIRD = severe insulin-resistant diabetes; MOD = mild obesity-related diabetes; MARD = mild age-related diabetes.

of ketoacidosis [2]. Diabetic sensorimotor polyneuropathy and cardiac autonomic neuropathy were also more common in SIDD patients upon diagnosis. According to these results, early, intense therapy, regular monitoring for complications, and sensitive diagnostic techniques for early diagnosis would all be beneficial for people with SIDD [7].

The greatest levels of liver fat and NAFLD-related markers, such as the fatty liver index, AST-to-platelet ratio index, and NAFLD fibrosis scores, were also found in SIRD patients [7]. Also, people with SIDD and SIRD are known to have a high prevalence of erectile dysfunction [9].

Cluster 3: Severe Insulin-Resistant Diabetes (SIRD)

This type of diabetes is marked by high age at diagnosis (late-onset diabetes), a high BMI (overweight to obese), normal HbA1c, very high insulin resistance (very high HOMA-IR), high β -cell dysfunction (low HOMA-2- β , but higher than SAID & SIDD), and no glutamate decarboxylase antibodies (GADA negative) [2,4]. In SIRD, β -cell function is less impaired, and HbA1c levels are lower compared to SAID and SIDD. This Cluster represents about 15 % of adult individuals [10].

According to studies, between 10 % and 20 % of diabetics exhibit objective neuropathy symptoms, and the prevalence rises as the condition worsens. In comparison to other diabetes clusters, diabetes-related neuropathy was most prevalent in the SIRD subgroup with short-term diabetes (N=3455) and was comparable across all subgroups with long-term diabetes (N=5580) [11]. According to Ahlqvist et al. [2], diabetes-related nephropathy was more common in the SIRD subgroup with short-term diabetes than in other diabetes clusters, although it was more common in the long-term diabetes SAID, MARD, and MOD subgroups than in SIDD and SIRD. Among participants with both short-term (N=3418) and long-term (N=5502) diabetes, CKD was most common in the SAID, SIRD, and MARD subgroups [11]. SIRD had a significantly increased risk of kidney complications, emphasizing the link between insulin resistance and kidney disease. Insulin resistance has been associated with higher salt sensitivity, glomerular hypertension, hyperfiltration, and declining kidney function, all of which are hallmarks of diabetes-related nephropathy [12].

Cluster 4: Mild Obesity-Related Diabetes (MOD)

This kind of diabetes is associated with high age at diagnosis (late-onset diabetes), high BMI (obesity), normal HbA1c, high insulin resistance (high HOMA-IR but lower than SIRD), normal β -cell dysfunction (normal HOMA-Beta), and no glutamate decarboxylase

antibodies (GADA negative). About 22 % of cases fall into this category, and it is thought to be linked to obesity [2,4].

Cluster 5: Mild Age-Related Diabetes (MARD)

This type of diabetes is characterized by a very high age at diagnosis (late-onset diabetes), normal insulin resistance (normal HOMA-IR), normal β -cell function (normal HOMA-Beta), normal BMI, normal HbA1c, and no glutamate decarboxylase antibodies (GADA negative). The difference between MOD and MARD is primarily based on the age at diagnosis and BMI; MOD is characterized by a high BMI (obesity), while MARD is diagnosed at a later age [2,4]. This Cluster is the most common form of diabetes, accounting for 39 % of cases, and carries the lowest risk of diabetic complications [10].

The Ahlqvist et al. [2] research (Scandinavian cohorts) found that those with high BMIs were more likely to have SIRD. According to further research in Asian populations [6], South Asians had a greater prevalence of SIRD, which was linked to an increased risk of NAFLD. The increased frequency of MOD in African cohorts is probably caused by inequalities in adiposity. While the Scandinavian clusters were replicated in some populations [13,14] in others they could not be fully replicated [15,6]. Depending on age and sex, SIDD, SIRD, and MARD were associated with a higher risk of cardiovascular events, coronary events, and stroke [16].

5. Clinical Advantages of Clustering of Diabetes

While Scandinavian cohorts validated the original clusters, Asian studies [6] identified higher SIRD prevalence linked to NAFLD, underscoring the need for region-specific adaptations. Understanding diabetes's various forms and Clusters is a crucial first step in understanding its causes. This new classification helps i) Improved reclassification based on clinical and metabolic profiles [2], ii) Enhanced understanding of Cluster-specific pathophysiology [4], iii) Better prediction of complications (e.g., nephropathy, cardiovascular disease) [17], and iv) Personalized treatment strategies aligned with Cluster characteristics [6].

Clustering can help predict complications from diabetes and inform treatment decisions, ultimately lessening the impact of the disease. To implement this approach, we need standardized diagnostic tests and effective treatment algorithms, which calls for a well-defined plan [6]. The five-cluster diabetes model encounters several challenges in practical use, such as technical and infrastructure issues, necessitating specialized diagnostic tools,

uniform protocols, and extensive training [4]. The cost and availability of diagnostic procedures and treatments may limit the application of this paradigm, which might strain healthcare organizations' finances [6]. Therefore, a comprehensive assessment of cost-effectiveness is essential to provide fair access to treatment and successful integration.

6. Treatment Strategies

The first-line treatment for regulating blood glucose levels in people with SIRD, MARD, and MOD is metformin. Metformin is a biguanide, an oral drug that helps stop the liver from producing too much glucose, decreases intestinal absorption of glucose, and improves the body's reaction to insulin [18].

Metformin is favored as the initial treatment option due to its effectiveness and strong supporting evidence, including a reduced risk of major cardiovascular events as demonstrated in the United Kingdom Prospective Diabetes Study [19].

If metformin alone doesn't sufficiently manage a patient's blood sugar, if metformin isn't suitable due to contraindications or if specific patient characteristics necessitate additional treatment, several non-insulin second-line medications are available. These include sodium-glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase-4 inhibitors (DPP-4is), and sulfonylureas [10].

SGLT2is directly targets SGLT2, a protein responsible for absorbing filtered glucose in the kidney's proximal convoluted tubules. Inhibiting SGLT2 leads to glucosuria, resulting in reduced HbA1c levels by 0.6-0.9% and fasting glucose by 1.1-1.9 mmol/L compared to a placebo. SGLT2 is also associated with weight loss and lower blood pressure [20]. Moreover, they have positive effects on cardiovascular death, heart failure, and the progression of chronic kidney disease [21]. Several studies indicate that treatment with SGLT2is improves the sensitivity of β -cells to glucose. For instance, Ferrannini et al. [22] reported a 25% increase in β -cell glucose sensitivity after just 48 hours of SGLT2is treatment in patients with T2D who were either treatment-naïve or on metformin. Additionally, SGLT2is can enhance insulin sensitivity by reducing plasma glucose levels and body weight [20].

GLP-1 is a hormone produced by the intestine's L-cells in response to food intake, particularly meals rich in fat and carbohydrates. This hormone aids in regulating glucose levels through various mechanisms, including glucose-dependent insulin secretion, reduced food intake, weight loss, and lowered glucagon levels. Anholm et al. [23] found that a 12-week regimen

of metformin combined with GLP-1RA significantly improved β -cell function, as measured by the disposition index, compared to a metformin-only or placebo group in a randomized, double-blind crossover trial. Furthermore, the impact of GLP-1RAs on body weight may explain their positive effects on hepatic and peripheral insulin sensitivity, as observed in other studies [24].

DPP-4is belongs to a class of glucose-lowering drugs that inhibit the enzyme DPP-4, which is found on the surface of various cells, including adipocytes, kidneys, the liver, and the small intestine. DPP-4is increases insulin secretion and decreases glucagon secretion [25].

Due to their overlapping mechanisms of action, it is not advisable to use GLP-1RAs and DPP-4is in combination, as both medications increase circulating GLP-1 levels and they are unlikely to exhibit greater efficacy when used together [10]. However, the final choice of treatment for T2D patients should also consider other diabetes-related factors. For instance, in the presence of cardiovascular disease, GLP-1RAs or SGLT2is are preferred options without regard to specific subgroups. Other factors such as the presence of kidney disease, the importance of weight loss alongside lifestyle changes, patient age, preferences, and potential side effects should also be taken into account [26].

Treatment of SAID is similar to those with T1D and LADA requires early introduction of insulin supplementation. SIDD Cluster requires early introduction of insulin supplementation, but they also take oral medications [27]. They could benefit from most of the current second-line anti-diabetic treatments. Since the SIDD group is associated with a lower BMI, there is also no preferred type of medication for those patients to correct body weight. SIDD may also benefit from DPP4is or, when cost is a major issue, a sulfonylurea [10].

Patients with SIRD may benefit most from treatments that promote weight loss and improve insulin sensitivity, such as SGLT2is or GLP-1RAs. These treatments may help enhance insulin sensitivity and lead to significant reductions in body weight, while also addressing the risk of cardiovascular disease or nephropathy. If safety and efficacy are established, new insulin sensitizers (e.g., peroxisome proliferator-activated receptor agonists) or anti-inflammatory drugs could also provide targeted treatment for SIRD [27]. Pioglitazone treatment is effective in improving insulin sensitivity and reducing NAFLD but should be considered only when no other treatment options are available due to the well-known side effects of weight gain and other adverse effects associated with pioglitazone use. DPP-4is do not seem to play a therapeutic role in this group as they have no established effects on insulin sensitivity, weight reduction, or NAFLD [10].

Lifestyle modifications, weight loss, increased physical activity, and metformin may suffice as the sole therapy for individuals with mild cases of MARD and MOD [28]. MOD patients might benefit most from GLP-1RAs and SGLT2is because both medications substantially reduce body weight. The use of pioglitazone should be avoided in this group due to its association with weight gain [29].

For patients with MARD, sulfonylureas and DPP-4is could be viable additional therapies if metformin alone cannot adequately control blood sugar levels. While sulfonylureas do not impact insulin sensitivity, they can initially enhance β -cell function [29]. However, SGLT2is and GLP-1RAs may also be options for patients with established end-organ diseases such as cardiovascular disease and reduced kidney function. Since this population tends to be older, decisions regarding additional treatment should be made thoughtfully, taking into consideration the potential side effects associated with each medication type [10]. On the other hand, individuals with MARD should receive treatments that do not lead to weight loss and sarcopenia, such as protein-balanced diets and moderate resistance training [27].

Lastly, each subtype requires a different course of treatment due to its unique pathophysiology. The broad use of this new classification system in diabetes care will depend on pragmatic factors like customized treatment plans and suitable diagnostic equipment. The implementation of cluster-specific therapies is limited by the high cost of diagnostic tools (such GADA testing) and the need for clinical training, even when there are promising therapy alternatives. Ensuring that policy efforts may be implemented globally requires equitable access [4,6].

7. Conclusion and Future Directio

The five-Cluster model is a precision medicine framework that helps physicians choose diabetic treatments and anticipate problems. It advocates for health policies incorporating cluster-based diabetes treatment into standard care. However, more study is needed to validate this strategy across age and ethnic groups and assess its long-term impacts on reducing diabetes-related complications.

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DOI: 10.20514/2226-6704-2026-16-4-267-277
УДК [616.233-002.2-06:616.399-008.9]-053.81-07
EDN: DBWLNN



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АССОЦИАЦИИ АДИПОКИНОВОГО ПРОФИЛЯ КРОВИ И НАЛИЧИЯ ХРОНИЧЕСКОГО БРОНХИТА У МОЛОДЫХ ЛИЦ

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Associations Of Blood Adipokine Profile and The Presence of Chronic Bronchitis in Young Individuals

Резюме

Целью данного исследования является поиск ассоциации наличия хронического бронхита (ХБ) и уровня адипокинов крови у лиц 25-44 лет с абдоминальным ожирением (АО) и без него. Исследование выполнено на популяционной выборке жителей города Новосибирска (1415 человек). После исключения лиц с зафиксированной бронхообструкцией и с отсутствием данных спирометрии для анализа была сформирована подвыборка в размере 1086 человека, возраст обследованных составил 37,8 [32,0;41,9] года. Всем лицам произведена антропометрия, сбор анамнеза и забрана кровь из локтевой вены для определения показателей липидного профиля, уровня глюкозы и адипокинов. Диагноз ХБ выставлялся на основании стандартного эпидемиологического опросника при наличии кашля с мокротой не менее 3 месяцев в году или при наличии медицинской истории заболевания. Результаты. У лиц с ХБ и АО регистрировались более высокие значения систолического артериального давления (САД) ($p=0,001$) и диастолического артериального давления (ДАД) ($p=0,003$), наблюдались атерогенные изменения в липидном профиле (более высокие показатели холестерина липопротеинов низкой плотности (ХС-ЛНП), триглицеридов (ТГ), низкие холестерина липопротеинов высокой плотности (ХС-ЛВП)) и более высокие показатели глюкозы по сравнению с лицами без АО. Шанс наличия ХБ был ассоциирован с курением, АО и увеличением САД. При изучении концентрации адипокинов крови у лиц с ХБ и без него получено, что у лиц с ХБ и АО регистрировались более высокие уровни резистина ($p=0,023$), амилина ($p=0,041$), интерлейкина 6 (IL-6) ($p=0,002$), С-пептида ($0,0001$), инсулина ($p=0,035$), лептина ($p=0,0001$), фактора некроза опухоли альфа (TNF α) ($p=0,003$) и глюкагон-подобного пептида 1 (GLP-1) ($p=0,001$) по сравнению с лицами с ХБ и без АО. При проведении однофакторного логистического регрессионного анализа получено, что шанс наличия ХБ обратно ассоциирован с уровнем резистина (ОШ 0,998 ДИ 0,997-0,999) и пептида YY (РYY) (ОШ 0,994 ДИ 0,989-0,999), модели стандартизованы по полу, возрасту, окружности талии (ОТ) и статусу курения. При включении обеих молекул в модель многофакторного логистического регрессионного анализа вместе с АО, САД, курением, полом и возрастом ассоциации были получены только для резистина (ОШ 0,998 ДИ 0,997-0,999) и курения (ОШ 4,656 ДИ 2,802-7,738). Заключение. У лиц 25-44 лет шанс наличия ХБ прямо ассоциирован с курением и АО, обратно ассоциирован с концентрацией в крови резистина, независимо от пола и возраста.

Ключевые слова: хронический бронхит, абдоминальное ожирение, молодые лица, адипокины, резистин, РYY, курение

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Исследование выполнено в рамках бюджетной темы № FWNR-2024-0002

Соответствие принципам этики

Исследование одобрено локальным этическим комитетом НИИТПМ — филиал ИЦиГ СО РАН (Протокол № 71 от 27.02.2024). Исследование выполнено в соответствии с принципами Хельсинской декларации. Все лица, включенные в исследование лица, подписывали информированное согласие, одобренное локальным этическим комитетом.

Статья получена 18.12.2025 г.

Одобрена рецензентом 21.02.2026 г.

Принята к публикации 24.03.2026 г.

Для цитирования: Афанасьева А.Д., Щербакowa Л.В., Полонская Я.В. и др. АССОЦИИИ АДИПОКИНОВОГО ПРОФИЛЯ КРОВИ И НАЛИЧИЯ ХРОНИЧЕСКОГО БРОНХИТА У МОЛОДЫХ ЛИЦ. Архивъ внутренней медицины. 2026; 16(4): 267-277. DOI: 10.20514/2226-6704-2026-16-4-267-277. EDN: DBWLNN

Abstract

The aim of this study was to investigate the association between the presence of chronic bronchitis (CB) and blood adipokine levels in individuals aged 25-44 years with and without abdominal obesity (AO). The study was conducted on a population-based sample of 1,415 residents of Novosibirsk. After excluding individuals with documented broncho-obstruction and missing spirometry data, a subsample of 1,086 individuals aged 37.8 [32.0; 41.9] years was formed for analysis. All individuals underwent anthropometry, anamnesis collection, and blood collection from the cubital vein to determine lipid profile, glucose, and adipokine levels. CB was diagnosed based on a standard epidemiological questionnaire in the presence of a cough with sputum for at least 3 months per year or with a medical history of the disease. Results. Individuals with chronic bronchitis and oxidative stress had higher systolic blood pressure (SBP) ($p=0.001$) and diastolic blood pressure (DBP) ($p=0.003$), atherogenic changes in the lipid profile (higher levels of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDL-C)) and higher glucose levels compared to individuals without oxidative stress. The likelihood of having chronic bronchitis was associated with smoking, oxidative stress, and increased SBP. When studying the concentration of blood adipokines in individuals with and without CB, it was found that individuals with CB and AO had higher levels of resistin ($p=0.023$), amylin ($p=0.041$), interleukin 6 (IL-6) ($p=0.002$), C-peptide (0.0001), insulin ($p=0.035$), leptin ($p=0.0001$), tumor necrosis factor alpha (TNF α) ($p=0.003$) and glucagon-like peptide 1 (GLP-1) ($p=0.001$) compared to individuals with CB and without AO. Univariate logistic regression analysis revealed that the odds of having CB were inversely associated with the levels of resistin (OR 0.998 CI 0.997-0.999) and peptide YY (PYY) (OR 0.994 CI 0.989-0.999); the models were adjusted for gender, age, waist circumference (WC), and smoking status. When both molecules were included in the multivariate logistic regression analysis model along with AO, SBP, smoking, gender, and age, associations were obtained only for resistin (OR 0.998 CI 0.997-0.999) and smoking (OR 4.656 CI 2.802-7.738). Conclusion. In individuals aged 25-44 years, the odds of having chronic kidney disease are directly associated with smoking and AO, and inversely associated with the blood concentration of resistin, regardless of gender and age.

Key words: chronic bronchitis, abdominal obesity, young people, adipokines, resistin, PYY, smoking

Conflict of Interest

The authors declare that this work, its topic, subject matter, and content do not affect any competing interests.

Funding Sources

The study was carried out within the framework of budget topic No. FWNR-2024-0002.

Compliance with the principles of ethics

The study was approved by the local ethics committee of the Research Institute of Therapeutic and Preventive Medicine, a branch of the Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences (Protocol No. 71, dated February 27, 2024). The study was conducted in accordance with the principles of the Declaration of Helsinki. All individuals included in the study signed informed consent, approved by the local ethics committee.

Article received on 18.12.2025

Reviewer approved 21.02.2026

Accepted for publication on 24.03.2026

For citation: Afanasyeva A.D., Shcherbakova L.V., Polonskaya Ya.V. et al Associations Of Blood Adipokine Profile and The Presence of Chronic Bronchitis in Young Individuals. The Russian Archives of Internal Medicine. 2026; 16(4): 267-277. DOI: 10.20514/2226-6704-2026-16-4-267-277. EDN: DBWLNN

ECRHS — European Community Respiratory Health Survey, EMD Millipore Corporation — diagnostic kit manufacturer (Germany), GIP — glucose-dependent insulinotropic polypeptide, GLP-1 — glucagon-like peptide-1, GOLD — Global Initiative for Chronic Obstructive Lung Disease, IL-6 — interleukin-6, MCP-1 — monocyte chemoattractant protein-1, PAI-1 — plasminogen activator inhibitor-1, PYY — peptide YY, BP — blood pressure, AO — abdominal obesity, WHO — World Health Organisation, BMI — body mass index, WC — waist circumference, TC — total cholesterol, TG — triglycerides, TNF- α — tumour necrosis factor alpha, CB — chronic bronchitis, COPD — chronic obstructive pulmonary disease, HDL cholesterol — high-density lipoprotein cholesterol, LDL cholesterol — low-density lipoprotein cholesterol, non-HDL cholesterol — non-high-density lipoprotein cholesterol

Introduction

The classical definition of chronic bronchitis (CB), i.e. wet cough for at least three months a year for at least two consecutive years in the absence of other causes, is used worldwide. However, recently the validity of CB as a separate diagnosis has been questioned. This is caused by a number of factors, the main one of which is the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (global guidelines for chronic obstructive pulmonary disease (COPD)), where chronic bronchitis as a separate disease has been removed altogether; it is defined rather as a phenotype or COPD manifestation. This is because

the majority of patients with classical CB develop a form of obstruction, since the mechanisms of inflammation and bronchi remodelling are very similar to those in COPD patients (GOLD 2025) [1]. In Russia, the clinical guidelines for chronic bronchitis (2024) specify the classical criteria and describe algorithms for diagnosing and differential diagnosis [2]: US authors stick to the same concept; they rely on the classical clinical definition (wet cough for at least three times a year for at least two years), emphasising assessment of risk factors (smoking, occupational hazards) and identification of other causes of chronic cough [3]. However, it is hardly possible to

rule out all causes of bronchial inflammation; that is why numerous experts believe that the “pure” CB hardly exists, it is usually a part of another respiratory condition. The criteria of “three months and two years” have mostly historical meaning; however, they are useful for epidemiological studies [4].

Over the years, obesity has been studied as a contributing factor of chronic respiratory conditions, including CB. Higher body weight and excessive fat deposits are associated with systemic low-grade inflammation, which can facilitate inflammatory responses in bronchi and boost sputum production, creating conditions for CB [5].

A large population-based study reported an association between abdominal and general obesity and a high risk of chronic respiratory inflammation (including clinical manifestations resembling chronic bronchitis) and poorer outcomes. A prospective study of obese individuals showed a higher incidence of COPD, including manifestations resembling chronic bronchitis [6]. Besides, in patients with COPD, overweight modifies the clinical presentation: obesity affects symptom intensity, exacerbation frequency and overall disease severity, indirectly evidencing the role of adipose tissue and metabolic disorders in pathogenesis of chronic bronchopulmonary findings [7]. However, another large-scale cohort study demonstrates a dubious association between body mass index (BMI) and the risk of COPD: in some study arms, excessive body weight is associated with a higher risk of symptoms, while other subjects demonstrate protective effects, underlining the heterogeneity of effects from adipose tissue and its products on the respiratory system [8].

The objective of this study is to search for an association between presence of CB and blood adipokines in patients with AO.

Materials and methods

In 2013–2016, the Research Institute of Internal and Preventive Medicine, a branch of the Federal Research Centre at the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, hosted a population-based study among the citizens of Novosibirsk aged 25 to 44 years. The study was performed under state-finance topic No. FWNr-2024-0002.

For population sampling, the database of the Territorial Federal Compulsory Medical Insurance Fund was used, which included subjects of 25 to 44 years of age in one district of Novosibirsk with the typical industrial, social, populational, demographic, and transport structures, as well as population migration levels. A random number generator was applied to form a random representative sample of 2,500 individuals. Younger age groups are known to be more reluctant to respond, that is why staggered epidemiological incentives were used: post

invitations, phone calls, mass media ads. 1,512 individuals were screened; the response rate was 60.5 %. After the exclusion of pregnant women and women on maternity leave, the study included 1,415 subjects (670 men, 47.3 %, and 745 women, 52.7 %). The mean age was 37.3 [31.8; 42.0] years. All subjects signed an informed consent form for personal data processing.

Respiratory symptoms were identified using the WHO respiratory disease detection tool and ECRHS (European Community Respiratory Health Survey) questionnaire [9]. The epidemiologic diagnosis of CB was made in the presence of wet cough for at least three months a year or a history of the disease. Besides, respiratory function was tested using spirometry under the spirometry guidelines with the use of Spiro USB Micro Medical Limited (UK) in order to rule out bronchial obstruction.

Exclusion criteria were: recorded bronchial obstruction and lack of spirometry results for the analysis.

Eventually, the sample comprised 1,086 subjects (517 men (45.4 %), and 569 women (54.6 %); the mean age was 37.8 [32.0; 41.9] years old).

Subjects receiving drug treatment accounted for under 1 % and did not affect the final results.

All patients had their height, weights, waist circumference, and blood pressure (BP) measured. Subjects' height was measured using a vertical height meter in the upright position without shoes, with the accuracy of 0.5 cm. For weighing, calibrated electronic hospital scales were used; and the measurement accuracy was 100 grams. BMI was calculated as follows: $BMI = \text{body weight (kg)} / \text{height (m)}^2$. Overweight was reported as $BMI \geq 25 \text{ kg/m}^2$, obesity was diagnosed at $BMI \geq 30 \text{ kg/m}^2$ [10].

Waist circumference (WC) was measured using a measuring tape, placed horizontally strictly between the lower costal arch and sacral section of the iliac bone. Abdominal obesity (AO) was reported as waist circumference of $\geq 94 \text{ cm}$ in men and $\geq 80 \text{ cm}$ in women [10].

BP was measured three times at a 2-minute interval on both arms seated after 5-minute rest, using Omron M5-I (Japan) blood pressure sensor; the mean of the three measurements was recorded. AH was reported using the epidemiological criteria, where SBP was $\geq 140 \text{ mm Hg}$ and/or DBP was $\geq 90 \text{ mm Hg}$ [11].

All subjects underwent a one-off fasting blood draw from their ulnar vein (12 hours after meal). Lipid profile, i.e. triglycerides (TG), high-density lipoprotein cholesterol (HDL cholesterol) and total cholesterol (TC), as well as serum glucose levels, were measured using enzymic methods with standard Termofisher reagents (Finland) and Konelab 30i analyser (Finland).

Serum glucose was converted into plasma glucose using the following formula: $\text{Plasma Glucose (mmol/L)} = -0.137 + 1.047 \times \text{serum glucose (mmol/L)}$. An elevated fasting plasma glucose level was reported at $\geq 7 \text{ mmol/L}$ [12].

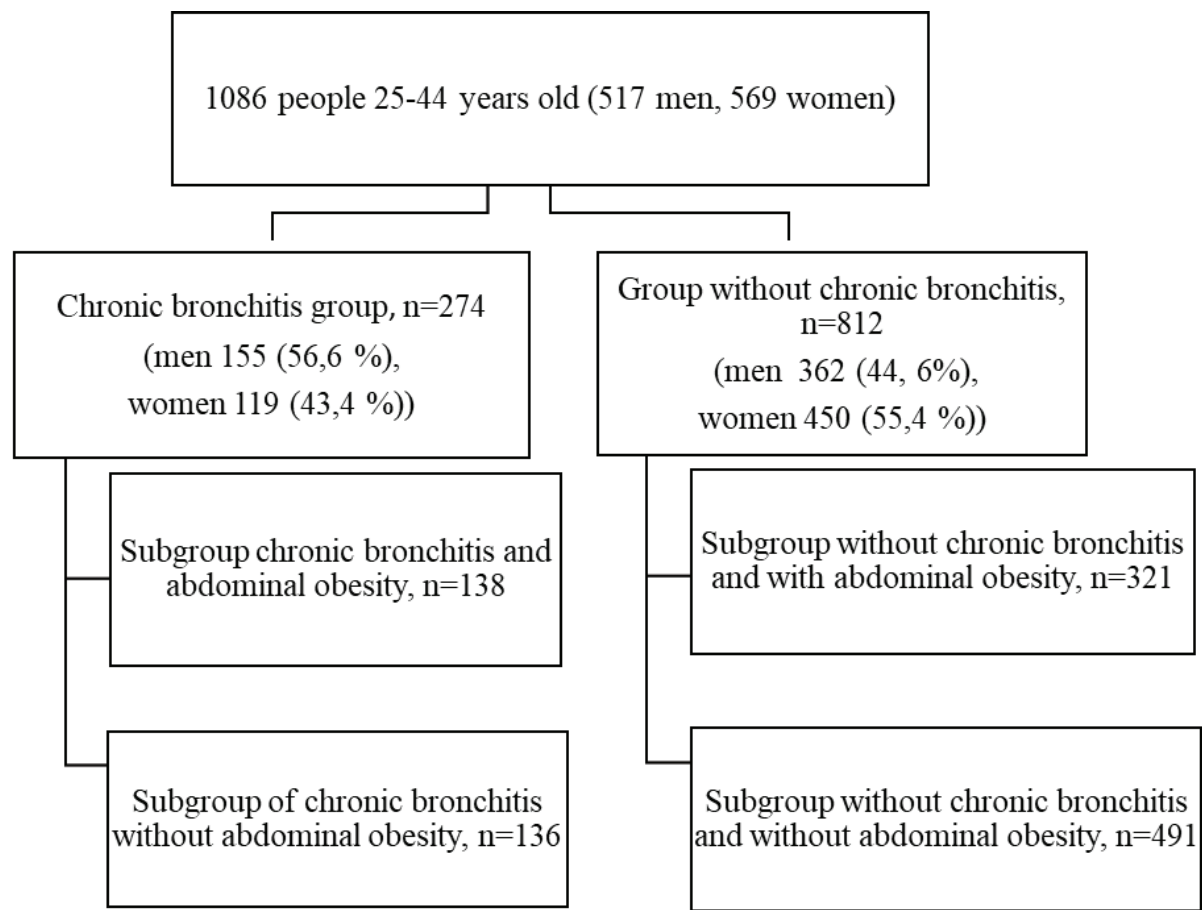


Figure 1. Study design

Low-density lipoprotein cholesterol (LDL cholesterol) was calculated using Friedewald formula: $\text{LDL cholesterol} = \text{TC} - (\text{TG} / 2.2) - \text{HDL cholesterol}$. According to epidemiological criteria, elevated blood LDL cholesterol levels were reported at LDL cholesterol and TG of ≥ 3.0 mmol/L and ≥ 1.7 mmol/L, respectively [13].

Non-high-density lipoprotein cholesterol (non-HDL cholesterol) values were calculated as follows: $\text{non-HDL cholesterol (mmol/L)} = \text{TC (mmol/L)} - \text{HDL cholesterol (mmol/L)}$.

Characteristics of the subjects with and without CB are presented in Table 1.

A multiplex assay using Luminex 20 MAGPIX flow cytometer was utilised to measure the blood levels of biomolecules associated with secretory activity of visceral fat cells:

- a) using Human Adipokine Magnetic Bead Panel 1 kit (EMDMillipore Corporation, Germany): adiponectin, adipisin, lipocalin-2, resistin, plasminogen activator inhibitor 1 (PAI-1);
- b) using Human Metabolic Hormone V3 kit (EMD-Millipore Corporation, Germany): amylin, C-peptide, ghrelin, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1

(GLP-1), glucagon, insulin, pancreatic polypeptide (PP), peptide YY (PYY), interleukin 6 (IL-6), leptin, monocyte chemoattractant protein 1 (MCP-1), tumour necrosis factor alpha (TNF- α), secretin.

SPSS package (version 13.0) was used for statistical processing of results. The normality of distribution was tested using the Kolmogorov-Smirnov test. Since the distribution of the majority of tested parameters was not normal, the data for continuous variables are presented as Me [25%; 75%], where Me is the median, 25% and 75% are the 1st and 3rd quartiles; categorical variables are presented as absolute and relative values — n (%). Two independent samples were compared using the Mann-Whitney U test. For ratio comparison, the Pearson's chi-square test was utilised. Associations were evaluated with the help of the multivariate logistic regression analysis under the following conditions: a dependent variable, dichotomic: presence/absence of CB; independent observations; absence of multicollinearity; linear dependance between each independent variable and log odds (logarithm factors); tail independence. Results of the multivariate logistic regression analysis are presented as odds ratio (OR) and 95% confidence interval (CI) for OR. The zero hypothesis significance level (p) was set at 0.05.

Table 1. Clinical and anamnestic data of individuals with and without CB

Indicators		CB group (+), n=274	CB group (-), n=812	p
Age, years				
Me [25 %;75 %]		38.5 [32.6;42.0]	37.2 [31.8;41.9]	0.057
Sex, n %	Men	155 (56.6 %)	362 (44.6 %)	0.001
	Women	119 (43.4 %)	450 (55.4 %)	
BMI, kg/m ²				
Me [25 %;75 %]		26.2 [22.6;29.9]	24.8 [21.9;28.5]	0.002
WC, cm				
Me [25 %;75 %]		89.0 [80.0;98.1]	84.0 [74.0;94.2]	<0.001
AO, n %		138 (50.4 %)	321 (39.5 %)	0.002
SBP, mmHg				
Me [25 %;75 %]		123.0 [113.4;132.1]	118.5 [109.5;129,0]	<0.001
DBP, mmHg				
Me [25 %;75 %]		80.5 [74.0;89.5]	78.0 [71.0;85.6]	<0.001
HR, beats/min				
Me [25 %;75 %]		74.0 [67.0;80.0]	72.0 [66.0;79.0]	0.102
TCH, mmol/l				
Me [25 %;75 %]		5.2 [4.5;5.8]	4.9 [4.2;5.6]	0.004
LDL-C, mmol/L				
Me [25 %;75 %]		3.3 [2.7;3.9]	3.1 [2.5;3.7]	0.002
HDL-C, mmol/L				
Me [25 %;75 %]		12 [11;15]	13 [11;15]	0.009
NonHDL-C, mmol/L				
Me [25 %;75 %]		38 [32;46]	36 [29;42]	<0.001
TG, mmol/L				
Me [25 %;75 %]		1.0 [0.7;1.6]	0.9 [0.7;1.4]	0.006
Glucose, mmol/l				
Me [25 %;75 %]		5.8 [5.4;6.2]	5.6 [5.3;6.0]	0.001
Smoking, n (%)	Never smoked	56 (20.4 %)	356 (43.8 %)	0.0001
	Smokes	173 (63.1 %)	207 (25.5 %)	
	Smoked, but quit	45 (16.4 %)	249 (30.7 %)	
Hypertension, n (%)		70 (25.5 %)	143 (17.7 %)	0.004
TG≥1,7 mmol/L, n (%)		60 (21.9 %)	128 (15.8 %)	0.020
LDL-C≥3,0 mmol/L, n (%)		172 (62.8 %)	429 (52.9 %)	0.004
Glucose ≥7 mmol/l, n (%)		13 (4.7 %)	16 (2.0 %)	0.014

Note: CB — chronic bronchitis, SBP — systolic blood pressure, DBP — diastolic blood pressure, AG — arterial hypertension, HR — heart rate, BMI — body mass index, WC — waist circumference, TC — cholesterol, LDL-C — low-density lipoprotein cholesterol, HDL-C — high-density lipoprotein cholesterol, non-HDL-C — non-high-density lipoprotein cholesterol, TG — triglycerides, Me — median, 25 % and 75 % — 1st and 3rd quartiles

Study results

The study group included subjects with CB: 274 patients (25.2 %).

Individuals with CB and AO had higher systolic blood pressure (SPB) (p=0.001) and diastolic blood pressure (DBP) (p=0.003) vs. individuals without AO. Besides, subjects with CB and AO demonstrated atherogenic changes in their lipid profile (higher LDL cholesterol, TGs and lower HDL cholesterol values) as well as higher glucose levels vs. subjects without AO (Table 2).

Subjects with CB and AO more frequently had a history of smoking, but currently smoked less (p=0.001) than patients with CB who did not have AO. They also

had a higher incidence of AH (p=0.007) and hypertriglyceridemia (p=0.002). Of note, despite the fact that subjects with CB and AO had higher absolute values of LDL cholesterol vs. subjects without AO, there were no differences between the incidence of hyper-LDL cholesterol values between these arms (p=0.278) (Figure 2).

Male subjects with CB and AO had more differences in their smoking status (p=0.023): used to smoke (15 (20.0 %) vs. 5 (6.3 %)), smoked less at present (50 (66.7 %) vs. 67 (83.8 %)); approximately the equal number of men mentioned that they had never smoked (10 (13.3 %) vs. 8 (10.0 %)) vs. subjects with CB and AO. Men with AO also had higher incidences of AH

($p=0.007$) and hypertriglyceridemia ($p=0.0001$) vs. men without AO (Figure 3).

Female subjects with CB and AO also differed in their smoking status ($p=0.017$): used to smoke more (19 (30.2 %) vs. 6 (10.7 %)) and mentioned that they had never smoked before (15 (20.0 %) vs. 5 (6.3 %)); approximately the equal number of women shared that they currently were smokers (29 (46.0 %) vs. 27 (48.2 %)) vs. individuals with CB without AO. Women with AO had a high rate of AH ($p=0.007$) vs. women without AO. Hyperglycaemia was reported more often in women with CB who also had AO (2 (3.2 %)) (Figure 4).

The logistic regression analysis showed that the odds of CB increases more than 5-fold in smokers, 1.5-fold in the presence of AO, and is associated with higher SBP values (Table 3).

Blood adipokine tests showed that individuals with CB had higher values of adipsin (1.1 times higher), IL-6 (1.4 times higher), C-peptide (1.1 times higher), GIP (1.1 times higher), PP (1.2 times higher), PYY was 1.2 times lower than in subjects without CB (Table 4).

Patients with CB and AO had higher levels of resistin, amylin, IL-6, C-peptide, insulin, leptin, TNF α , and GLP-1 vs. patients with CB, but without AO (Table 5).

Table 2. Quantitative indicators of metabolic risk factors in individuals with CB in subgroups with and without AO

Subgroups Indicator	CB /AO (-), n=136		CB /AO (+), n=138		P
	Me	[25 %;75 %]	Me	[25 %;75 %]	
Age, years	37.9	31.8;41.4	39.8	33.9;42.5	0.019
BMI, kg/m ²	22.6	20.7;25.1	29.8	27.3;32.9	0.0001
WC, cm	80.0	74.1;87.9	98.0	90.8;105.9	0.0001
SBP, mmHg	120.0	110.1;128.9	125.0	115.4;137.0	0.001
DBP, mmHg	78.5	71.6;86.8	83.0	75.4;91.5	0.003
HR, beats/min	73.0	66.0;79.0	74.0	67.3;82.8	0.110
TCH, mmol/l	5.0	4.3;5.7	5.2	4.6;5.9	0.141
HDL-C, mmol/L	1.3	1.1;1.5	1.2	1.0;1.4	0.0001
LDL-C, mmol/L	3.2	2.6;3.8	3.4	2.7;4.0	0.315
NonHDL-C, mmol/L	3.6	3.0;4.4	4.1	3.3;4.8	0.018
TG, mmol/L	0.8	0.6;1.4	1.3	0.9;1.9	0.0001
Glucose, mmol/L	5.7	5.3;6.1	5.9	5.5;6.2	0.027

Note: CB — chronic bronchitis, AO — abdominal obesity, SBP — systolic blood pressure, DBP — diastolic blood pressure, AG — arterial hypertension, HR — heart rate, BMI — body mass index, WC — waist circumference, TC — cholesterol, LDL-C — low-density lipoprotein cholesterol, HDL-C — high-density lipoprotein cholesterol, non-HDL-C — non-high-density lipoprotein cholesterol, TG — triglycerides, Me — median, 25 % and 75 % — 1st and 3rd quartiles

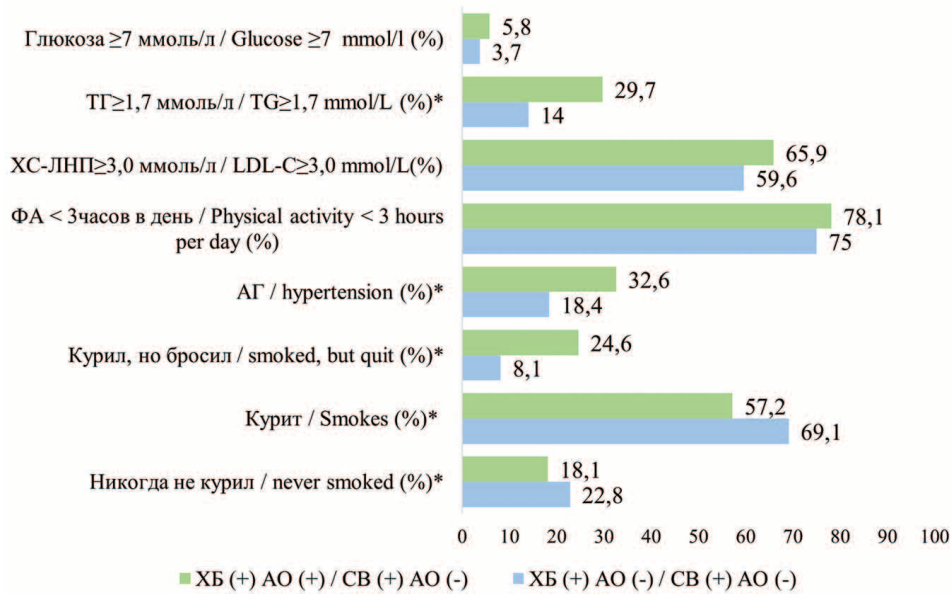


Figure 2. Frequency of metabolic risk factors in individuals with CB depending on the presence of AO

Note: CB — chronic bronchitis, AO — abdominal obesity, TG — triglycerides, LDL-C — low-density lipoprotein cholesterol, PA — physical activity, AG — arterial hypertension.

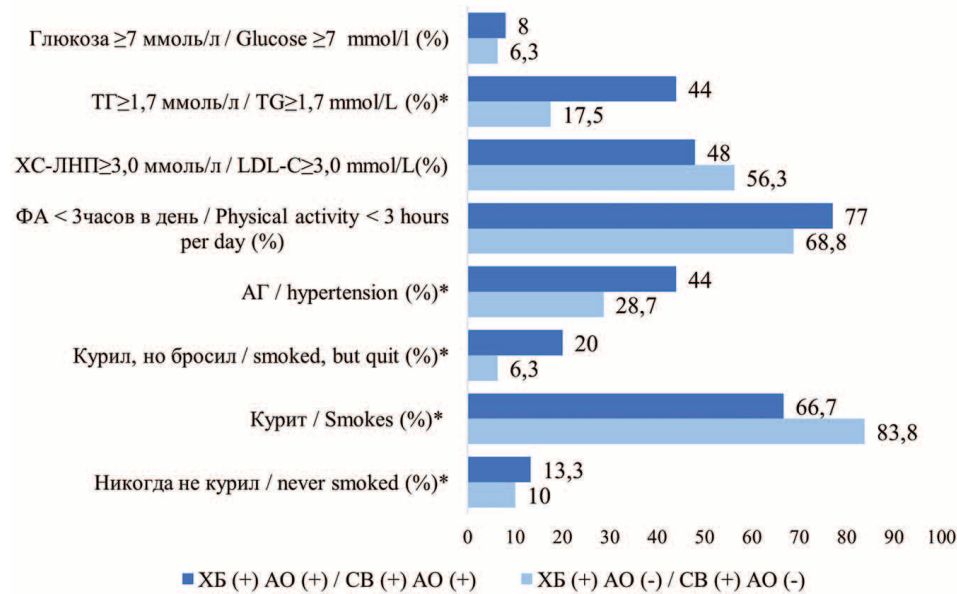


Figure 3. Frequency of metabolic risk factors in men with CB depending on the presence of AO
Note: CB — chronic bronchitis, AO — abdominal obesity, TG — triglycerides, LDL-C — low-density lipoprotein cholesterol, PA — physical activity, AG — arterial hypertension

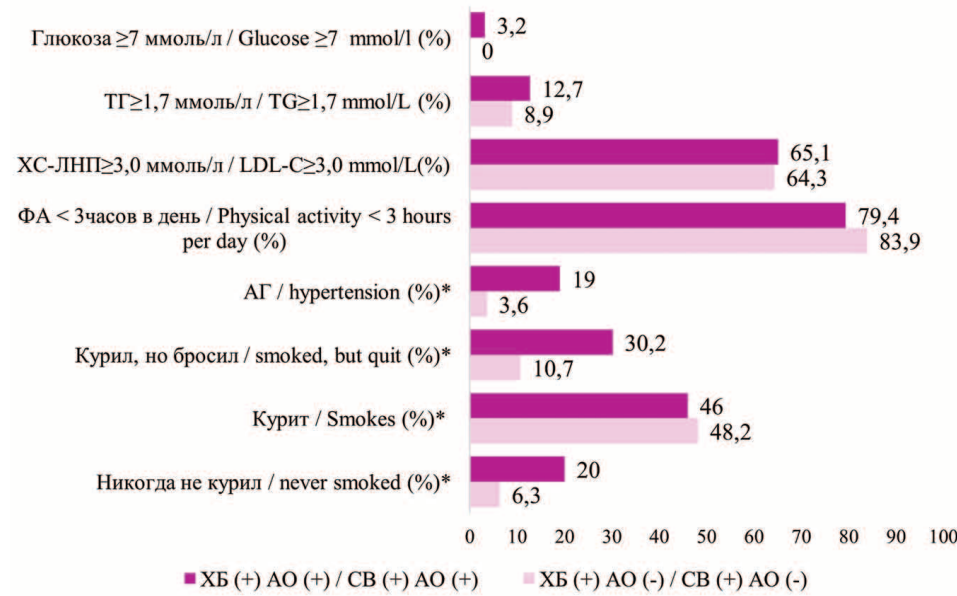


Figure 4. Frequency of metabolic risk factors in women with CB depending on the presence of AO
Note: CB — chronic bronchitis, AO — abdominal obesity, TG — triglycerides, LDL-C — low-density lipoprotein cholesterol, PA — physical activity, AG — arterial hypertension

Table 3. Univariate logistic regression analysis of the odds of having CB depending on metabolic risk factors (standardized by gender, age)

Indicator	OR	95 % confidence interval (CI)		P
		Lower limit	Upper limit	
Smoking,				
Smokes vs never smoked	5.187	3.629	7.415	0.0001
Smoked but quit vs never smoked	1.084	0.705	1.667	0.712
AO, yes vs no	1.480	1.117	1.962	0.006
SBP, per 1 mm Hg.	1.013	1.003	1.022	0.010
TG per 1 mmol/l	1.148	0.981	1.342	0.085
Glucose, per 1 mmol/l	1.144	0.983	1.331	0.083

Note: AO — abdominal obesity, AG — arterial hypertension, PA — physical activity, LDL-C — low-density lipoprotein cholesterol, Non-HDL-C — non-high-density lipoprotein cholesterol, TG — triglycerides, OR — odds ratio.

Table 4. Levels of the studied human adipokines (Me [25 %;75 %])

Adipokines	Group CB (+), n=274	Group CB (-), n=812	P
Adiponectin, µg/ml	42.3 [28.1;115.2]	37.2 [23.9;120.1]	0.233
Adipsin, µg/ml	12.5 [9.0;14.9]	11.0 [6.9;13.9]	0.001
Lipoclin-2, ng/ml	458.7 [274.0;945.3]	378.1 [190.0;1214.7]	0.304
Resistin, ng/ml	22.6 [12.6;31.6]	21.2 [13.4;31.5]	0.902
Amylin, pg/ml	170.8 [38.3;536.2]	132.2 [22.3;619.3]	0.954
IL-6, pg/ml	6.2 [3.5;13.9]	6.3 [5.0;14.2]	0.741
PAI-1, ng/ml	1.4 [0.7;3.8]	1.0 [0.6;2.0]	0.001
C-peptide, ng/ml	0.8 [0.4;1.4]	0.7 [0.2;1.2]	0.027
Insulin, pmol/L	438.6 [277.6;646.6]	463.9 [277.6;675.4]	0.749
Leptin, ng/ml	4.3 [1.5;8.5]	4.1 [1.6;7.8]	0.770
MCP-1, pg/ml	243.7 [144.9;328.0]	230.6 [158.2;313.2]	0.440
Ghrelin, pg/ml	29.3 [18.6;56.2]	36.4 [18.1;95.4]	0.258
TNFa, pg/ml	4.6 [2.9;7.4]	4.5 [2.9;7.0]	0.294
GIP, pg/ml	27.9 [169.8;448.7]	25.2 [15.7;50.5]	0.032
Glucagon, pg/ml	266.9 [169.8;448.7]	267.8 [169.3;492.2]	0.495
PP, pg/ml	11.1 [6.0;23.8]	12.4 [8.3;23.4]	0.178
GLP1, pg/ml	43.2 [26.5;85.8]	37.0 [20.5;74.5]	0.001
PYY, pg/ml	48.2 [36.0;66.2]	58.0 [37.8;79.2]	0.008
Secretin, pg/ml	22.4 [14.1;68.3]	22.5 [15.6;69.0]	0.831

Note: CB — chronic bronchitis, PAI-1 — plasminogen activator inhibitor type 1, IL-6 — interleukin 6, MCP-1 — monocyte chemoattractant protein-1, TNFα — tumor necrosis factor-α, GIP — glucose-dependent insulintropic polypeptide, PP — pancreatic polypeptide, GLP1 — glucagon-like peptide type 1, PYY — peptide YY, Me — median, 25 % and 75 % — 1st and 3rd quartiles

Table 5. Levels of the studied blood adipokines in individuals with CB with AO and without it (Me [25 %; 75 %])

Adipokines	People with CB (n=274)		P
	No AO (n=136)	Yes AO (n=138)	
Adipokines	40.5 [30.0;101.1]	47.9 [27.1;121.7]	0.682
Adiponectin, µg/ml	12.1 [8.2;14.6]	12.7 [9.7;15.4]	0.079
Adipsin, µg/ml	407.6 [227.6;781.9]	484.8 [328.8;1066.0]	0.065
Lipoclin-2, ng/ml	21.5 [10.7;30.1]	24.2 [16.0;32.0]	0.092
Resistin, ng/ml	130.7 [23.5;502.8]	189.8 [103.4;547.5]	0.023
Amylin, pg/ml	6.0 [1.4;10.4]	6.5 [4.0;14.2]	0.041
IL-6, pg/ml	1.2 [0.6;1.9]	1.7 [0.8;5.7]	0.002
PAI-1, ng/ml	0.6 [0.2;0.9]	1.2 [0.5;1.7]	0.0001
C-peptide, ng/ml	404.4 [277.4;549.7]	483.2 [322.9;719.1]	0.035
Insulin, pmol/L	1.8 [0.7;4.5]	6.8 [4.0;11.8]	0.0001
Leptin, ng/ml	232.0 [141.0;322.9]	256.6 [145.4;331.6]	0.652
MCP-1, pg/ml	29.3 [17.9;61.0]	29.3 [18.8;50.3]	0.656
Ghrelin, pg/ml	4.1 [2.7;6.5]	5.6 [3.4;7.8]	0.003
TNFa, pg/ml	27.5 [16.9;49.5]	29.5 [20.2;55.7]	0.225
GIP, pg/ml	228.2 [155.4;413.3]	323.1 [206.2;506.4]	0.001
Glucagon, pg/ml	11.1 [6.7;23.3]	11.1 [5.5;25.9]	0.912
PP, pg/ml	41.8 [25.1;80.6]	52.1 [31.7;89.0]	0.072
GLP1, pg/ml	48.2 [36.0;67.7]	48.2 [35.3;65.5]	0.886
PYY, pg/ml	20.3 [11.9;36.5]	23.5 [17.4;80.4]	0.169

Note: CB — chronic bronchitis, AO — PAI-1 — plasminogen activator inhibitor type 1, IL-6 — interleukin 6, MCP-1 — monocyte chemoattractant protein-1, TNFα — tumor necrosis factor-α, GIP — glucose-dependent insulintropic polypeptide, PP — pancreatic polypeptide, GLP1 — glucagon-like peptide type 1, PYY — peptide YY, Me — median, 25 % and 75 % — 1st and 3rd quartiles.

Table 6. Logistic regression analysis of associations of adipokines with the odds of having chronic kidney disease, standardized for gender, age, smoking status, and WC

Indicators	Univariate regression analysis			
	OR	95 % confidence interval (CI)		p
		Lower limit	Upper limit	
Adipsin at 1 µg/ml	1.008	0.995	1.021	0.227
IL-6 at 1 pg/ml	0.997	0.983	1.011	0.664
C-peptide at 1 pg/ml	1.121	0.901	1.396	0.306
GIP at 1 pg/ml	1.000	0.997	1.004	0.914
PP at 1 pg/ml	1.002	0.998	1.005	0.310
PYY at 1 pg/ml	0.994	0.989	0.999	0.030
GLP-1 at 1 pg/ml	0.999	0.999	1.000	0.082
Resistin at 1 mcg/ml	0.998	0.997	0.999	0.020
Amylin at 1 pg/ml	0.989	0.972	1.007	0.218
Insulin at 1 pg/ml	1.0001	1.000	1.0002	0.285
Leptin at 1 ng/ml	1.0001	1.000	1.0002	0.537
TNFα at 1 pg/ml	1.009	0.963	1.056	0.714

Note: PAI-1 — plasminogen activator inhibitor type 1, IL-6 — interleukin 6, MCP-1 — monocyte chemoattractant protein-1, TNFα — tumor necrosis factor-alpha, GIP — glucose-dependent insulintropic polypeptide, PP — pancreatic polypeptide, GLP1 — glucagon-like peptide type 1, PYY — peptide YY, OR — odds ratio.

Table 7. Results of multivariate logistic regression analysis of the relationship between adipokines and the chance of having CB

Indicators	Multivariate regression analysis			
	OR	95 % confidence interval (CI)		p
		Lower limit	Upper limit	
Age by 1 year	1.043	0.998	1.090	0.062
Sex, men vs women	1.268	0.764	2.107	0.358
Smokes vs. doesn't smoke	4.656	2.802	7.738	0.0001
AO, yes vs no	2.300	1.402	3.774	0.001
PYY at 1 pg/ml	0.998	0.992	1.004	0.420
Resistin 1 mcg/ml	0.998	0.997	0.999	0.0001

Note: AO — abdominal obesity, PYY — peptide YY, OR — odds ratio

When the logistic regression analysis included adipokines, which demonstrated significant differences at previous stages of the study, it was established that the odds of CH were directly correlated with resistin levels and had inverse relationship with PYY levels (Table 6). Where the model included both molecules, which demonstrated associations with the odds of CB in the univariate regression analysis (resistin and PYY), age, gender, smoking status, and presence/absence of AO, it was found out that the odds of CB in younger population is over 4.5-times higher in smokers and is 2.3 higher with AO; it is directly associated with age and has inverse relationship with resistin levels, irrespective of gender (Table 6).

Discussion

We have demonstrated in a group of subjects of 25 to 44 years of age that the presence of CB is associated with active smoking status, higher SBP values and AO. These

results confirm and supplement the existing knowledge about the multi-factor nature of early manifestations of chronic respiratory diseases and are of practical significance for early prevention and screening. The leading role of smoking in forecasting CB development is in line with the extensive epidemiological data on tobacco smoking as the main risk factor of bronchitis and COPD. Current reviews and guidelines emphasise that, even in young people, prolonged smoking significantly increases the odds of chronical bronchi inflammation and subsequent progression of obstructive changes [14]. Association between CB and AO in young people correlates with recent studies, which show that abdominal obesity is associated with a higher risk of chronic inflammatory respiratory conditions and reduced pulmonary function irrespective of BMI. Mechanisms trigger impairment of respiratory function (diaphragm limitations, reduced lung capacity), as well as metabolic inflammatory changes linked to the biochemical activity

of adipose tissue, which worsen cough and facilitate chronic inflammation in bronchi [15].

Resistin activates transcription factor NF- κ B and signal cascades via TLR4/CAP1 receptors in monocytes and macrophages, inducing production of pro-inflammatory cytokines (TNF- α , IL-6, etc.). In such settings, higher resistin levels correlate with systemic and local inflammation in lungs, and a number of studies demonstrated an association with impaired pulmonary function and COPD severity [16]. At the same time, despite the fact that the majority of studies report direct association between blood resistin levels and development of bronchopulmonary diseases [17], Wang et al. demonstrated reduced serum resistin and leptin levels in COPD patients, which was most prominent in patients with cachexia [18]. In this study, we have also observed inverse association between resistin levels and CB; in subjects with CB and AO, its levels were higher than in subjects without AO. It can evidence that resistin can be a marker of chronic inflammation in bronchi also in individuals with normal BMI levels.

PYY is an intestinal peptide (it is mostly secreted by L-cells of distal segment of the bowels); it is primarily known as a regulator of appetite and energy exchange (through Y-receptors, including Y2). Nevertheless, PYY can also modify systemic metabolic and inflammation responses, and can affect respiratory system via the intestine — lungs axis [19]. Another possible association of PYY — bronchopulmonary system can be the fact that PYY suppresses appetite and impacts energy distribution, while changes in PYY levels are associated with changes in the body fat mass. Since AO impairs respiratory function and worsens systemic inflammation, changes in PYY concentrations can indirectly alter the risk of respiratory symptoms. In other words, a higher PYY level is associated with lower fat tissue deposits; therefore, the load on the bronchopulmonary system drops [20]. We have observed the inverse association between the PYY level and CB, and there was no correlation when resistin was included in the model.

Conclusion

In individuals of 25 to 44 years of age, the odds of CB are associated with active smoking status, SBP and AO. The odds of CB in individuals of 25 to 44 years old have inverse association with blood PYY and resistin levels; however, when age, gender, smoking status, AO status, PYY, and resistin were included in the model, the association remained only with smoking status, AO, and blood resistin. The results confirm the available data on the presence of cause-effect relation between development of CB and AO; they also add to the understanding of the pathogenetic patterns of bronchopulmonary inflammations.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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DOI: 10.20514/2226-6704-2026-16-4-278-283

УДК 618.3-06:616.379-008.64-07

EDN: DOMKQD

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РАННИЕ ПРЕДИКТОРЫ ГЕСТАЦИОННОГО САХАРНОГО ДИАБЕТА И ПРЕЭКЛАМПСИИ: ОБОСНОВАНИЕ ПЕРСОНАЛИЗИРОВАННОЙ СТРАТЕГИИ СКРИНИНГА В I ТРИМЕСТРЕ

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Early Predictors of Gestational Diabetes Mellitus and Preeclampsia: Rationale for A Personalized Screening Strategy in The First Trimester

Резюме

Цель исследования: выявить ранние клиничко-метаболические предикторы гестационного сахарного диабета (ГСД) и преэклампсии в I триместре беременности и обосновать необходимость персонализированной стратегии скрининга. **Материалы и методы:** Проведено ретроспективное когортное исследование типа «случай-контроль» на базе Многопрофильной городской больницы № 2 г. Астаны (n=600). Основную группу составили 300 беременных с ГСД, контрольную — 300 женщин с физиологической беременностью. Проанализированы антропометрические данные (ИМТ), анамнез и лабораторные показатели (глюкоза натощак, HbA1c) при постановке на учет до 12 недель. Статистический анализ включал U-критерий Манна-Уитни, расчет отношения шансов (OR) и ROC-анализ. **Результаты:** пациентки с ГСД имели достоверно более высокий ИМТ (ожирение у 31,0 % против 9,0 %, $p < 0,001$) и возраст. Частота преэклампсии в группе ГСД составила 7,3 % против 3,3 % в контроле; установлено, что наличие ГСД повышает риск развития преэклампсии более чем в два раза ($OR=2,295$; 95 % CI: 1,067–4,934). ROC-анализ выявил высокую диагностическую ценность отдельных маркеров в I триместре. Глюкоза натощак при пороговом значении $>4,49$ ммоль/л показала чувствительность 71,6 % и специфичность 76,6 % ($AUC=0,787$; 95 % ДИ: 0,745–0,825). Гликированный гемоглобин (HbA1c) при уровне $>5,27$ % продемонстрировал чувствительность 63,8 % и высокую специфичность 85,7 % ($AUC=0,792$; 95 % ДИ: 0,653–0,894). Разработанная комбинированная прогностическая модель (HbA1c + глюкоза натощак) показала наивысшую предсказательную ценность с площадью под ROC-кривой (AUC) 0,849, обеспечивая чувствительность 90,0 % и специфичность 78,2 %. **Заключение:** Гликированный гемоглобин и тощачовая гликемия в I триместре являются независимыми предикторами ГСД и ассоциированной преэклампсии. Внедрение балльной оценки риска при первой явке позволяет выделить группу для раннего начала персонализированной профилактики, не дожидаясь стандартных сроков перорального глюкозотолерантного теста (24–28 недель), что может снизить частоту акушерских осложнений.

Ключевые слова: гестационный сахарный диабет, преэклампсия, ранний скрининг, HbA1c, прогнозирование, первый триместр

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Исследование одобрено Локальным этическим комитетом НАО «Медицинский университет Астана» (Протокол № 7 от 16.01.2026 г.). Исследование проведено в соответствии с Хельсинкской декларацией Всемирной медицинской ассоциации.

Статья получена 21.01.2026 г.

Одобрена рецензентом 23.03.2026 г.

Принята к публикации 21.04.2026 г.

Для цитирования: Есжанова А.А., Бекетова М.А. РАННИЕ ПРЕДИКТОРЫ ГЕСТАЦИОННОГО САХАРНОГО ДИАБЕТА И ПРЕЭКЛАМПСИИ: ОБОСНОВАНИЕ ПЕРСОНАЛИЗИРОВАННОЙ СТРАТЕГИИ СКРИНИНГА В I ТРИМЕСТРЕ. Архивъ внутренней медицины. 2026; 16(4): 278-283. DOI: 10.20514/2226-6704-2026-16-4-278-283. EDN: DOMKQD

Abstract

Aim: To identify early clinical and metabolic predictors of gestational diabetes mellitus (GDM) and preeclampsia in the first trimester of pregnancy and to justify the need for a personalized screening strategy. **Materials and Methods:** A retrospective case-control cohort study was conducted at the Multidisciplinary City Hospital No. 2 in Astana (n=600). The main group consisted of 300 pregnant women with GDM, and the control group comprised 300 women with physiological pregnancy. Anthropometric data (BMI), medical history, and laboratory indicators (fasting glucose, HbA1c) recorded at registration (up to 12 weeks) were analyzed. Statistical analysis included the Mann-Whitney U-test, odds ratio (OR) calculation, and ROC analysis. **Results:** Patients with GDM had significantly higher BMI (obesity in 31.0 % vs. 9.0 %, $p<0.001$) and age. The incidence of preeclampsia in the GDM group was 7.3 % vs. 3.3 % in the control group; it was established that GDM increases the risk of preeclampsia by more than two times (OR=2.295; 95 % CI: 1.067–4.934). ROC analysis revealed high diagnostic value of individual markers in the first trimester. Fasting glucose at a threshold of >4.49 mmol/L showed a sensitivity of 71.6 % and specificity of 76.6 % (AUC=0.787; 95 % CI: 0.745–0.825). Glycated hemoglobin (HbA1c) at a level >5.27 % demonstrated a sensitivity of 63.9 % and high specificity of 85.7 % (AUC=0.792; 95 % CI: 0.653–0.894). The developed combined prognostic model (HbA1c + fasting glucose) showed the highest predictive value with an area under the ROC curve (AUC) of 0.849, providing a sensitivity of 90.0 % and specificity of 78.2 %. **Conclusion:** Glycated hemoglobin and fasting glycemia in the first trimester are independent predictors of GDM and associated preeclampsia. Implementing a risk score assessment at the first antenatal visit allows for the identification of a group for early initiation of personalized prevention, without waiting for the standard OGTT timing (24–28 weeks), which may reduce the incidence of obstetric complications.

Key words: *gestational diabetes mellitus, preeclampsia, early screening, HbA1c, prediction, first trimester*

Conflict of Interest

The authors declare that this work, its topic, subject matter, and content do not affect any competing interests

Funding Sources

The study was performed without external funding

Compliance with the principles of ethics

The study was approved by the Local Ethics Committee of the NJSC "Astana Medical University" (Protocol No. 7 dated January 16, 2026). The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association

Article received on 21.01.2026

Reviewer approved 23.03.2026

Accepted for publication on 21.04.2026

For citation: Yeszhanova A.A., Beketova M.A. Early Predictors of Gestational Diabetes Mellitus and Preeclampsia: Rationale for A Personalized Screening Strategy in The First Trimester. The Russian Archives of Internal Medicine. 2026; 16(4): 278–283. DOI: 10.20514/2226-6704-2026-16-4-278-283. EDN: DOMKQD

GDM — gestational diabetes mellitus, BMI — body mass index, OGTT — oral glucose tolerance test, HbA1c — glycated haemoglobin, CI — confidence interval, OR — odds ratio, AUC — area under the ROC curve

Introduction

At the present stage of obstetrics development, metabolic disorders during pregnancy are not an isolated endocrinological problem, but a fundamental risk factor of severe obstetrical and perinatal complications. There is a persistent global trend of a higher rate of hyperglycaemia: global studies show that carbohydrate metabolism disorders are reported in 7.5 % to 27 % depending on the area and diagnostic criteria [1, 2]. A meta-analysis of the data in the USA and Canada for 2023 shows 6.9 % to 13.7 %, which confirms the immensity of the problem [2].

Of special concern is the close pathogenetic association between gestational diabetes mellitus (GDM) and hypertensive disorders, particularly preeclampsia [3]. Both conditions share the common origin, that is endothelial dysfunction, chronic systemic inflammation, and insulin resistance [4]. Maternal hyperglycaemia, which affects the foetus, not only causes gigantism and birth traumas, but also programs long-term vascular health of descendants [5].

However, despite the proven risks, the currently used screening approaches need reviewing. According to the current Clinical Protocol of the Ministry of Health of the Republic of Kazakhstan, all pregnant women, who

come for their first visit, undergo mandatory glucose level measurement (fasting venous plasma) to rule out manifestations of diabetes mellitus. A traditional algorithm for GDM diagnosis includes an oral glucose tolerance test (OGTT) at week 24–28 for all pregnant women having risk factors [6, 7]. Clinically, this timing is rather late: by the end of the second trimester, placentation is complete, and the main vascular modifications are over. The therapeutic window, i.e. first trimester, when angiogenesis can be most successfully corrected, is lost [7–9].

The objective of the study is to use a retrospective analysis to identify statistically significant clinical and laboratory parameters of GDM and preeclampsia during the first trimester and to justify the early risk stratification.

Materials and methods

Study design. A retrospective cohort (case-control) study was conducted in the obstetrics unit of Multidisciplinary Hospital No. 2 (Astana). Study duration: 2024–2025. The study was approved by the Local Ethics Committee (Minutes No. 7 dated 16.01.2026).

Sample description. The study included 600 pregnant women.

- **Main group (n=300):** patients with GDM confirmed with laboratory test results.
- **Control group (n=300):** patients with uncomplicated pregnancy, similar age and parity.
- **Exclusion criteria:** symptomatic type 1 or type 2 diabetes mellitus, multiple pregnancy, severe comatic pathology.

Methods of analysis. Since the study was retrospective, informed consent was not required; patient data were anonymised. Data were collected from forms 077/y, 096/y, and 097/y. Body mass index (BMI) was calculated using anthropometric data (height and weight) recorded at the first visit to register as pregnant during the first trimester. SPSS Statistics 26.0 package was used for statistical processing. Mann-Whitney U test, Pearson’s

chi-square test (χ^2), and ROC analysis with AUC calculation were used.

Results

A comparative analysis showed statistically significant intergroup differences (Table 1). Patients with GDM were significantly older (34.51 ± 4.69 vs. 32.93 ± 5.21 years old, $p=0.0002$). A pivotal factor was obesity: BMI ≥ 30.0 kg/m² was reported three times more frequently in the main group (31.0 % vs. 9.0 %, $p < 0.0001$).

The analysis of laboratory parameters during the first trimester demonstrated that the mean fasting glucose levels in the main group were 4.81 ± 0.62 mmol/L (controls: 4.25 ± 0.49 mmol/L, $p < 0.001$). HbA1c values were also significantly higher: 5.57 ± 0.46 % vs. 4.32 ± 1.63 % ($p < 0.003$).

Table 1. Clinical and Anamnestic Characteristics of the Groups

Indicator	Group with GDM (n = 300)	Control group (n = 300)	P-level
Age, years (M $\pm$ SD)	34.51 $\pm$ 4.69	32.93 $\pm$ 5.21	0.0002
BMI, obesity (≥ 30 kg/m ²), n (%)	93 (31.0 %)	27 (9.0 %)	<0.0001
BMI, normal (18.5–24.9 kg/m ²), n (%)	105 (35.0 %)	201 (67.0 %)	<0.0001
Inheritance of diabetes, n (%)	47 (15.7 %)	15 (5.0 %)	0.00002
HSD in the anamnesis, n (%)	57 (19.0 %)	7 (2.3 %)	<0.0001

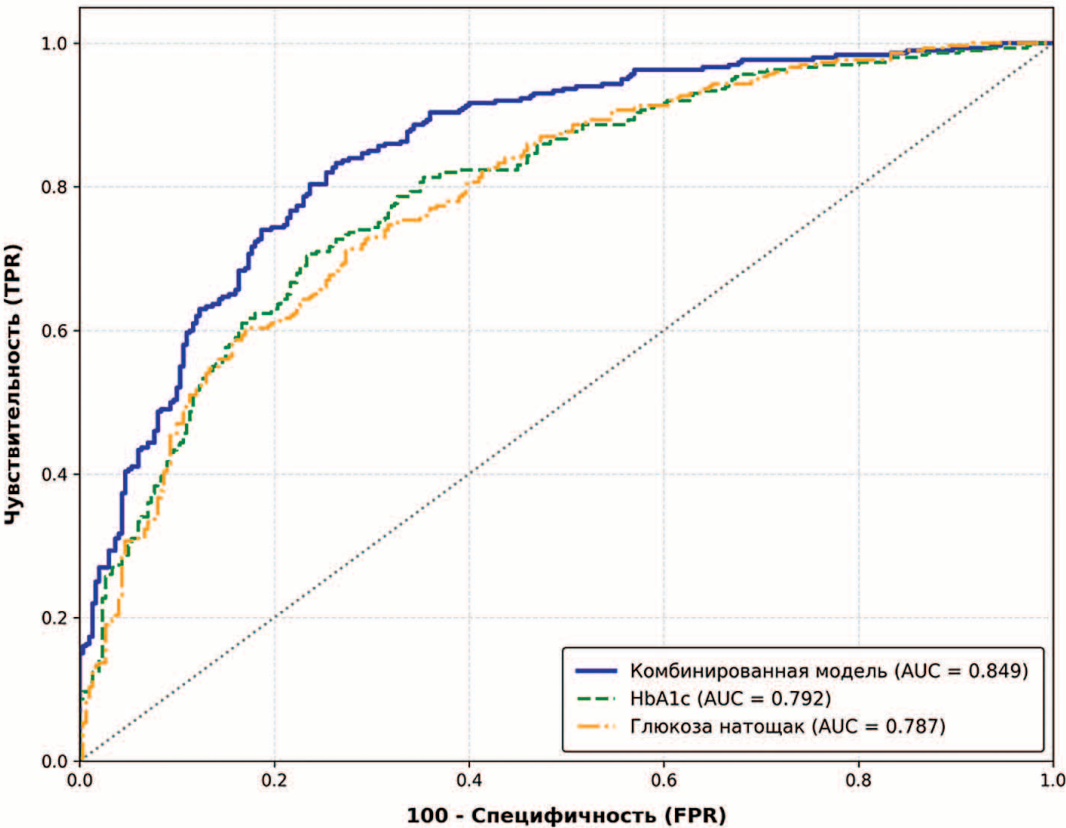


Figure 1. Comparison of the predictive value of monomarkers and the combined model (ROC analysis)

Association with preeclampsia. The rate of pre-eclampsia in the main group was 7.3 % (n=22); it is more than twice as high as in controls (3.3 % (n=10)). GDM increases the risk of preeclampsia by 2.29 times (OR=2.295; 95 % CI: 1.067–4.934).

ROC analysis. In order to evaluate the prognostic value, the following cut-off values were recorded:

- **HbA1c:** > 5.27 % (AUC=0.792; p < 0.0001).
- **Fasting glucose:** > 4.49 mmol/L (AUC=0.787; p < 0.0001).

Combined model (HbA1c + glucose): the best result was demonstrated, with AUC=0.849, sensitivity of 90.0 %, and specificity of 78.2 %.

The analysis of significant predictors and ROC analysis (Figure 1) were used to develop a patient-specific prognostic model. For the practical use, a scoring (Table 2) was suggested, which allows stratifying patients at their first visit before week 12 of pregnancy.

The identified pathogenetic association between GDM and preeclampsia necessitates some changes in the screening paradigm. The scale will allow routing patients into two groups (Figure 2).

The low-risk group (less than three points) will follow the standard protocol. Patients scoring **three and more points** will be routed along the “red corridor”, requiring patient-specific preventive measures.

Table 2. Scoring of Risk Factors

Risk Factor	Criteria	Points
Chronic arterial hypertension (CAH)	Presence	3
Obesity (BMI)	≥30 кг/м²	3
History of gestational diabetes (GDM)	Past occurrence	3
Glycated hemoglobin (HbA1c)	≥5,51 %	2
Fasting glucose	≥4,81 ммоль/л	2
Family history of diabetes mellitus (DM)	Presence	2
Age	≥30	1

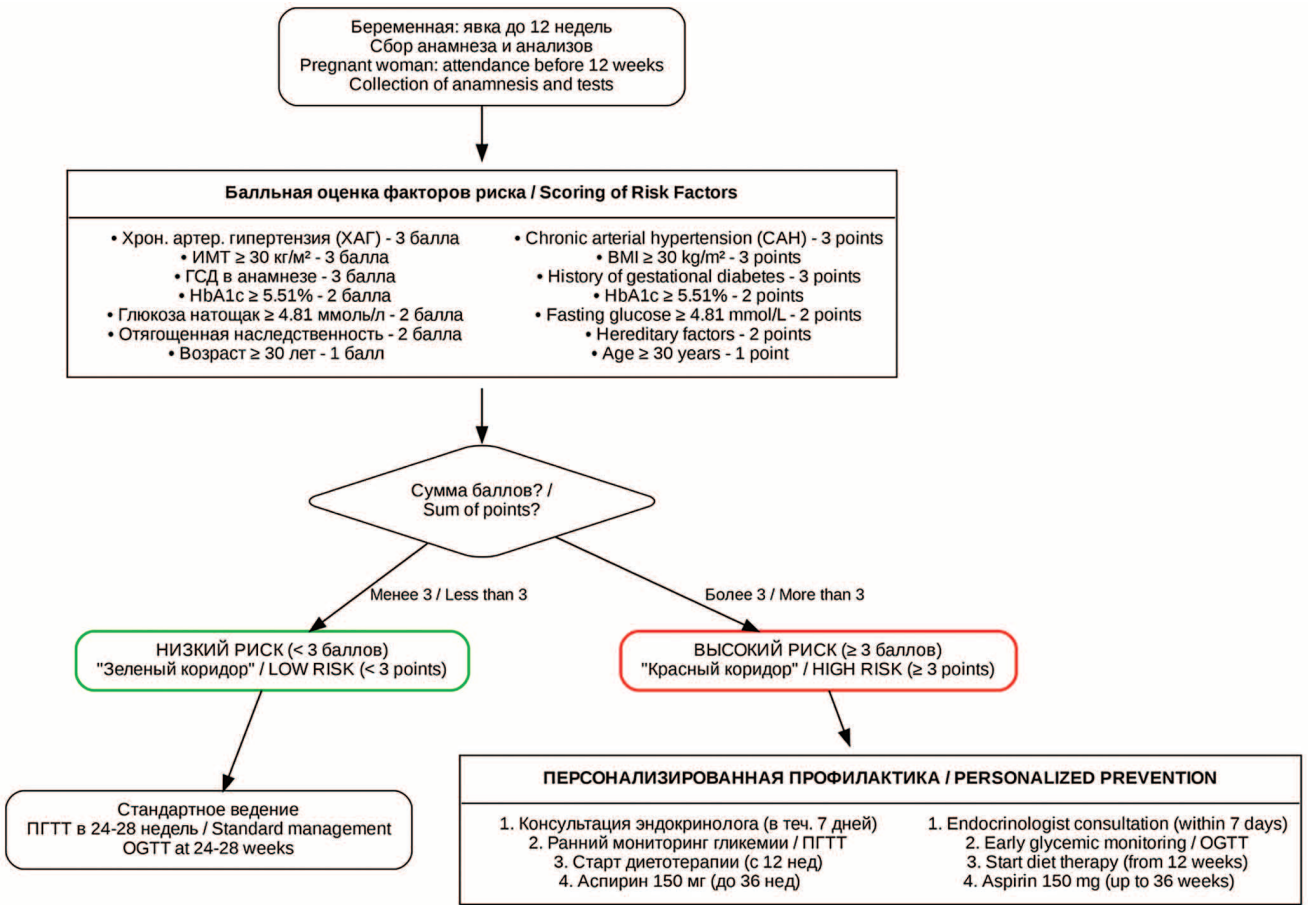


Figure 2. Algorithm for risk-oriented two-level routing of pregnant women at the primary healthcare stage

Discussion

Our thesis about the required start of the therapy at 10–12 weeks of pregnancy corresponds to the data reported by McIntyre et al. (2018) and Benhalima et al. (2024) [8, 9]. Early intervention allows targeting angiogenesis prior to placentation completion, which is essential for hypertension prevention. Thus, early diagnosis of metabolic predictors makes it possible to achieve the preventative potential, which is usually lost by 24–28 weeks of pregnancy.

Management depending on the risk group

A key tool of the proposed strategy is dividing patients into risk groups when they come for their pregnancy registration visit. Patients scoring **under three points** are in the low-risk group (“green corridor”); their management falls under the standard procedure, and they undergo OGTT at 24–28 weeks of pregnancy.

A high-risk group (**three and more points**, “red corridor”) requires immediate start of patient-specific prevention. The following measures are proposed for this group of patients (Figure 2):

- Consultation by an endocrinologist within 7 days.
- Early glycaemia monitoring or early OGTT.
- Diet therapy starting from week 12 of pregnancy.
- Low-dose acetylsalicylic acid (Aspirin) (150 mg/day, up to 36 weeks of pregnancy) in the high-risk group (pregnant women with metabolic disorders, obesity and chronic arterial hypertension) to prevent associated preeclampsia is clinically justified and is strictly regulated by the current Clinical Protocol of the Ministry of Health of the Republic of Kazakhstan, as well as by the current international guidelines, particularly by the recommendations of the International Federation of Gynaecology and Obstetrics (FIGO, 2019) and the United States Preventive Services Task Force (USPSTF, 2021) [8, 10].
- The proposed approach makes it possible to use the therapeutic window of the first trimester, which is pathogenetically justified to lower the rate of obstetrical complications.

Study limitations: retrospective single-centre design, requiring cautious data extrapolation.

Conclusion

1. Glycated haemoglobin ($\geq 5.51\%$) and fasting glycaemia (≥ 4.81 mmol/L) in the first trimester are the most significant independent predictors of GDM and preeclampsia.
2. Introduction of the scoring allows objectifying the risk of GDM and preeclampsia as early as at the first pregnancy visit.

3. Use of the «Red corridor» strategy (sum of points) ensures early start of the patient-specific prevention and interdisciplinary monitoring, which is a must for better perinatal outcomes.

The results confirm the hypothesis of the pathogenic association between early carbohydrate metabolism disorders and obstetric complications. The risk of preeclampsia (OR=2.295) established in this study is in line with the global data [3,4]. The key observation is that metabolic predictors (glucose > 4.8 mmol/L, HbA1c $> 5.51\%$) are diagnosed at the very first visit.

The current use of OGTT at 24–28 weeks of pregnancy is the golden standard of diagnostics; however, it is too late for prevention. High rates of C-section in the main group (69.3%) is a result of delayed diagnosis. Given the high accuracy of the combined model (AUC=0.849), we propose to introduce risk scoring. Patients with a combination of factors (age > 30 , BMI > 25 , glucose > 4.5) should have patient-specific prevention, and therapy should be initiated as early as 10–12 weeks of pregnancy.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Есжанова А.А.: концепция, сбор данных, статистика, написание статьи

Бекетова М.А.: научное консультирование, статистика, написание статьи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Yeszhanova A.A.: concept and design development, data collection and processing, statistical analysis, writing the manuscript

Beketova M.A.: scientific consulting, critical review of intellectual content, approval of the manuscript for publication.

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DOI: 10.20514/2226-6704-2026-16-4-284-291

УДК 616.721-002.77-053.8(470.56)

EDN: NNARGO



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ОБЩАЯ И ПЕРВИЧНАЯ ЗАБОЛЕВАЕМОСТЬ СПОНДИЛОАРТРИТАМИ СРЕДИ ВЗРОСЛОГО НАСЕЛЕНИЯ ОРЕНБУРГСКОЙ ОБЛАСТИ В 2019-2023 ГГ.

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General And Primary Incidence of Spondyloarthritis Among the Adult Population of The Orenburg Region in 2019-2023

Резюме

Целью исследования явилось изучение показателей общей и первичной заболеваемости спондилоартритами, включая анкилозирующий спондилит (АС) и псориатический артрит (ПсА), среди взрослого населения Оренбургской области в период с 2019 по 2023 гг. **Материалы и методы.** Проанализированы отчётные формы федерального статистического наблюдения № 12 «Сведения о числе заболеваний, зарегистрированных у пациентов, проживающих в районе обслуживания медицинской организации» в период с 2019 по 2023 годы среди взрослого населения Оренбургской области, с оценкой общей и первичной заболеваемости всей группы болезней костно-мышечной системы и соединительной ткани, в том числе спондилопатий, включающих анкилозирующий спондилит, и болезней кожи и подкожной клетчатки, в том числе псориатический артрит. **Результаты.** За исследуемый период среди взрослого населения Оренбургской области установлена тенденция к повышению как общей, так и первичной заболеваемости болезнями костно-мышечной системы и соединительной ткани и спондилопатиями в 2023 году по сравнению с 2019 годом. В период с 2020 по 2022 гг. зафиксировано снижение этих показателей. Динамика общей заболеваемости АС была неоднозначной: в 2019 году она была выше, чем в 2023 году. Первичная заболеваемость АС нарастала к 2023 году. Отмечена тенденция к увеличению общей и первичной заболеваемости болезнями кожи и подкожной клетчатки и ПсА в 2023 году в сравнении с 2019 г., при снижении данного показателя в период пандемии с 2020 по 2022 годы. Выявлен ряд особенностей при сравнении показателей общей и первичной заболеваемости болезнями костно-мышечной системы и соединительной ткани, спондилопатиями, АС, болезнями кожи и подкожной клетчатки, ПсА в Оренбургской области и в Российской Федерации (РФ). **Заключение.** Полученные данные определяют необходимость проведения дальнейших эпидемиологических исследований в отношении аксиальных спондилоартритов, оптимизации диагностики, мониторингования и течения этих заболеваний.

Ключевые слова: анкилозирующий спондилит, псориатический артрит, общая и первичная заболеваемость, болезни костно-мышечной системы и соединительной ткани, болезней кожи и подкожной клетчатки

Конфликт интересов

Соавтор статьи Сайфутдинов Р.И. является членом редакционной коллегии журнала «Архивъ внутренней медицины». Статья прошла принятую в журнале процедуру рецензирования. Сайфутдинов Р.И. не участвовал в принятии решения о публикации этой статьи. Об иных конфликтах интересов авторы не заявляли

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Исследование представляет собой анализ отчётных форм федерального статистического наблюдения № 12 «Сведения о числе заболеваний, зарегистрированных у пациентов, проживающих в районе обслуживания медицинской организации». В рамках данного исследования медицинское вмешательство участникам не проводилось, поэтому работа не считается исследованием на человеке и не требует заключения этического комитета

Статья получена 13.10.2025 г.

Одобрена рецензентом 28.11.2025 г.

Принята к публикации 16.01.2026 г.

Для цитирования: Сагитова Э.Р., Бугрова О.В., Сайфутдинов Р.И. и др. ОБЩАЯ И ПЕРВИЧНАЯ ЗАБОЛЕВАЕМОСТЬ СПОНДИЛОАРТРИТАМИ СРЕДИ ВЗРОСЛОГО НАСЕЛЕНИЯ ОРЕНБУРГСКОЙ ОБЛАСТИ В 2019-2023 ГГ. Архивъ внутренней медицины. 2026; 16(4): 284-291. DOI: 10.20514/2226-6704-2026-16-4-284-291. EDN: NNARGO

Abstract

The **purpose of the study** was to investigate the indicators of general and primary incidence of spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, among the adult population of the Orenburg region during the period from 2019 to 2023. **Materials and Methods.** The reporting forms of federal statistical monitoring No. 12 "Information on the number of diseases registered in patients residing in the service area of the healthcare organization" were analyzed for the period from 2019 to 2023 among the adult population of the Orenburg region. This analysis assessed the general and primary incidence of the entire group of diseases of the musculoskeletal system and connective tissue, including spondyloarthropathies, such as ankylosing spondylitis, as well as skin and subcutaneous tissue diseases, including psoriatic arthritis. **Results.** During the study period, a trend was established among the adult population of the Orenburg region for an increase in both the general and primary incidence of musculoskeletal system and connective tissue diseases, as well as spondyloarthropathies, in 2023 compared to 2019. From 2020 to 2022, a decrease in these indicators was recorded. The dynamics of the general incidence of ankylosing spondylitis (AS) were ambiguous: it was higher in 2019 than in 2023. The primary incidence of AS increased by 2023. There was a noted trend toward an increase in the overall and primary incidence of skin and subcutaneous tissue diseases and psoriatic arthritis (PsA) in 2023 compared to 2019, with a decrease in this indicator during the pandemic from 2020 to 2022. Several differences were identified when comparing the indicators of overall and primary incidence of musculoskeletal system and connective tissue diseases, spondyloarthropathies, AS, skin and subcutaneous tissue diseases, and PsA between the Orenburg region and the Russian Federation. **Conclusion.** The obtained data underscore the necessity for further epidemiological studies concerning axial spondyloarthritis, as well as the optimization of diagnosis, monitoring, and the progression of these diseases.

Key words: *ankylosing spondylitis, psoriatic arthritis, general and primary incidence, musculoskeletal system and connective tissue diseases, skin and subcutaneous tissue diseases*

Conflict of interests

Co-author of the article Sayfutdinov R.I. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Sayfutdinov R.I. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The study represents an analysis of the reporting forms of federal statistical monitoring No. 12 "Information on the number of diseases registered in patients residing in the service area of the healthcare organization." There were no medical interventions performed on participants in this study, so the work is not considered human research and does not require an ethics review

Article received on 13.10.2025

Reviewer approved 28.11.2025

Accepted for publication on 16.01.2026

For citation: Sagitova E.R., Bugrova O.V., Sayfutdinov R.I. et al. General And Primary Incidence of Spondyloarthritis Among the Adult Population of The Orenburg Region in 2019-2023. The Russian Archives of Internal Medicine. 2026; 16(4): 284-291. DOI: 10.20514/2226-6704-2026-16-4-284-291. EDN: NNARGO

Background

Currently, diseases of the musculoskeletal system and connective tissue (MSCD) are one of the most significant social and economic problems, ranking highly

among other chronic diseases [1, 2]. First and foremost, these are chronic inflammatory pathologies involving the spine, peripheral joints, entheses, and extraskelatal manifestations associated with axial spondylarthritis [3].

Given that this pathology is typical for young and active working age and is often the main cause of temporary and permanent disability [4], and in the majority of cases it requires expensive drug therapies [5], the study of the incidence and incidence is one of the most important problems in the modern rheumatology.

Recently, general rise in the incidence of the main types of axial spondylarthritides, i.e. ankylosing spondylitis and psoriatic arthritis, has been observed [6]. AS is included in category XIII “Diseases of the musculoskeletal system and connective tissue”, section “Spondylopathies”; PsA — category XII “Diseases of the skin and subcutaneous tissue” (S&STD), section “Psoriasis”.

The data on the incidence of this pathology are ambiguous: in 2019, the global incidence of MSCD was 18,407.49 per 100 000 people [7]; in Russia in 2019–2023, this figure was 13,068.6 per 100 000 people [8]. The total incidence of individual disease entities of axial spondylarthritis also varies and is not always presented under the widely recognised statistical methods.

For example, AS incidence in Europe was 23.8 per 100,000 people, in Asia — 167 per 100,000 people [9, 10, 11]. Statistical reports issued by the Ministry of Health of Russia do not present any data on the total and primary incidence of AS in Russia since it is included into the subsection “Spondylopathies”, the total incidence in which in 2019–2023 was 93.2 per 100,000 people [8]. As far as PsA is concerned, the systematic review and meta-analysis by Stephanie Lembke et al. (2024) reported the total global PsA incidence to be 112 per 100,000 adults: in Europe — 188, Asia — 48, North America — 133, and South America — 17 per 100,000 people [12]. According to the data from the Russian authors, the total incidence of diseases of the skin and subcutaneous tissue, including PsA, was 5,287.7 per 100,000 people, while the total incidence of PsA is 14.3 per 100,000 people [13], which is significantly lower than the global data.

Without doubt, available statistical data on the incidence of such a significant pathology in Russia cannot fully present the social scope of the problem, since there are almost no data on individual regions, particularly the Orenburg Region. According to the data from the only study conducted by Begun D.N. in 2015, the total incidence of MSCD in the Orenburg Region in 2000–2013 was 15,024.4 per 100,000 people, while the average incidence of AS was 35.5 cases per 100,000 people. There are no data on the number of PsA cases [14]. The author mentioned the rise in the incidence of MSCD and AS in general. It was typical of the total incidence of AS with a drop in primary cases. The author drew a conclusion on the effect of chronic patient accumulation, their longer life expectancy with the prevention of new cases, which can be an explanation to the results. Unfortunately, there

are no other data on the incidence of axial spondylarthritides, including AS, in the Orenburg Region.

Therefore, **the objective of the study** was to review the total and primary incidence of spondylarthritis, including ankylosing spondylitis and psoriatic arthritis, among the adult population in the Orenburg Region in 2019 to 2023.

Materials and methods

We analysed report forms No. 12 of the federal statistical monitoring “Information on the number of cases registered for the patients in the area of the medical organisation’s location” for the period from 2019 to 2023 among the adult population of the Orenburg Region, and review the total and primary incidence of all diseases of the musculoskeletal system and connective tissue, including spondylopathies, which include AS; and diseases of the skin and subcutaneous tissue, as well as PsA among adults. According to the annual statistical reports under form No. 12 of the Ministry of Health of the Orenburg Region, the information on PsA related to PsA together with skin psoriasis; therefore, an assessment of the incidence of psoriatic arthritis included only the mentioned cases. The data were compared to the Russia-wide results taken from similar statistical sources of the Ministry of Health of the Russian Federation on the total and primary incidence among the adult population in Russia in 2019 to 2023.

The absolute values in report form No. 12 were used to calculate the total and primary incidence per 100,000 adults in the Orenburg Region; and the common formulae were used [15]. The total and primary incidence per 100,000 adults were taken into account. The rate of increase and reduction of the values were reviewed. The non-parametric Wilcoxon test was used to evaluate the differences (*p*) between the total and primary incidence values. Differences were considered statistically significant at *p* < 0.05. IBM SPSS Statistics V27 package was used for statistical data processing.

Results

According to the results (Table 1), the total incidence of diseases of the musculoskeletal system and connective tissue among the adult population of the Orenburg Region tended to rise: in 2019 — 20,974.1, in 2020 — 15,754.9, in 2021 — 15,904.1, in 2022 — 18,097.5, and in 2023 — 33,128.5 per 100,000 adults; the rate of increase vs. 2019 was 57.9 % (*p*=0.3).

The total incidence of spondylopathies was: in 2019 — 101.7, in 2020 — 99.8, in 2021 — 102.6, in 2022 — 104.4, in 2023 — 166.3 per 100,000 adults, and the rate of increase was 63.5 % vs. 2019 (*p*=0.29) (Table 1).

Changes in the total incidence of AS was ambiguous (Table 1). In 2019, it was 51.02, in 2020 — 52.3, in 2021 — 53.02, in 2022 — 44.3, in 2023 — 50.9 per 100,000 adults, meaning a reduction of –0.2 % in 2023 vs. 2019 (p=0.4).

The primary incidence of MSCD also clearly tended to rise within the group: in 2019 — 5,365.7, in 2020 — 3,084.3, in 2021 — 4,091.6, in 2022 — 4,737.9, in 2023 — 8,538.6, with the rate of increase being 59.1 % vs. 2019 (p=0.28) (Table 2).

However, the trends of statistical data on spondylopathies varied: in 2019, the primary incidence was 28.6 per 100,000 people; in 2020, it dropped to 19.3; then

it increased annually, and in 2023 it was 36.9, with the rate of increase being 29.1 % vs. 2019 (p=0.4) (Table 2).

A similar trend was observed for the primary incidence of AS: in 2019 — 5.5, in 2020 — 3.3, in 2021 — 3.8, in 2022 — 4.6, in 2023 — 7.2 per 100,000 people; while the rate of increase was 30.9 % vs. 2019 (p=0.3) (Table 2).

As far as the total incidence of S&STD is concerned, in 2019, it was 4,380.1, in 2020 — 3,207.1, in 2021 — 3,529.6, in 2022 — 3,427.7, in 2023 — 5,087.6 per 100,000 people. The rate of increase in the total incidence in 2023 was 16.2 % vs. 2019, while of the primary incidence — 23.9 % (p=0.25) (Table 3).

Table 1. The total incidence of diseases of the musculoskeletal system, spondylopathies and AS among the adult population of the Orenburg region for 2019-2023 (the number of patients per 100 thousand population)

Years/Nosology	MSD		Spondylopathies		AS	
	Absolute values	per 100 thousand	Absolute values	per 100 thousand	Absolute values	per 100 thousand
2019	222367	20974,1	1078	101,7	541	51,02
2020	169460	15754,9	1074	99,8	563	52,3
2021	168864	15904,1	1090	102,6	563	53,02
2022	194556	18097,5	1122	104,4	476	44,3
2023	338397	33128,5	1699	166,3	520	50,9

Notes: MSD — Musculoskeletal and connective tissue diseases, AS — ankylosing spondylitis

Table 2. The primary incidence of diseases of the musculoskeletal system, spondylopathies and AS among the adult population of the Orenburg region for 2019-2023 (the number of patients per 100 thousand population)

Years/Nosology	MSD		Spondylopathies		AS	
	Absolute values	per 100 thousand	Absolute values	per 100 thousand	Absolute values	per 100 thousand
2019	56887	5365,7	303	28,6	58	5,5
2020	33174	3084,3	208	19,3	36	3,3
2021	43444	4091,6	247	23,3	41	3,8
2022	50935	4737,9	301	27,9	50	4,6
2023	87219	8538,6	377	36,9	73	7,2

Notes: MSD — Musculoskeletal and connective tissue diseases, AS — ankylosing spondylitis

Table 3. The total incidence of diseases of the skin and subcutaneous tissue and PsA among the adult population of the Orenburg region for 2019-2023. (the number of patients per 100 thousand population)

Years/Nosology	DSST		PsA	
	Absolute values	per 100 thousand	Absolute values	per 100 thousand
2019	46437	4380,1	264	24,9
2020	34496	3207,1	265	24,6
2021	37477	3529,6	215	20,2
2022	36849	3427,7	212	19,7
2023	51968	5087,6	327	32,1

Notes: DSST — diseases of the skin and subcutaneous tissue, PsA — psoriatic arthritis

Table 4. The primary incidence of skin and subcutaneous tissue diseases and PsA among the adult population of the Orenburg region for 2019-2023. (the number of patients per 100 thousand population)

Years/Nosology	DSST		PsA	
	Absolute values	per 100 thousand	Absolute values	per 100 thousand
2019	31134	2936,6	51	4,8
2020	23735	2206,7	41	3,8
2021	25825	2432,3	21	1,9
2022	28000	2604,5	10	0,9
2023	37187	3640,5	63	6,6

Notes: DSST — diseases of the skin and subcutaneous tissue, PsA — psoriatic arthritis

The total incidence of psoriatic arthritis in the Orenburg Region gradually decreased from 2019 (24.9) to 2022 (19.7), with the rate of decrease of 20.8 %. However, in 2023, the figure reached 32.1 per 100,000 people; this is 28.9 % higher than in 2019 ($p=0.37$) (Table 3).

The primary incidence of diseases of the skin and subcutaneous tissue (Table 4) in 2019 was 2,936.6, in 2020 — 2,206.7, in 2021 — 2,432.3, in 2022 — 2,604.5, in 2023 — 3,640.5 per 100,000 people. The rate of increase in the primary incidence in 2023 was 23.9 % ($p=0.4$) vs. 2019.

An analysis of the primary incidence of PsA in the Orenburg Region also showed decrease in the figures from 4.8 in 2019 to 0.9 in 2022, i.e. by 81.3 %, with a sharp increase of 6.6 per 100,000 adults in 2023. The rate of increase in 2023 was 37.5 % vs. 2019 ($p=0.2$) (Table 4).

Discussion

The objective of this study was to review the total and primary incidence of spondylarthritides, including AS and PsA, among the adult population of the Orenburg Region in 2019–2023. The objective is of interest due to the potential severity and debilitating effect of this pathology and the need to plan both diagnostic measures and monitoring of the disease, and therapy with expensive antiinflammatory drugs, including genetically engineered biologic drugs and target basic agents, in accordance with the available clinical guidelines [16].

The results of this study were based on the analysis of statistical reports of the Ministry of Health of the Orenburg Region and the calculation of the absolute values for the total and primary incidence of MSCD, taking into account spondylopathies, particularly AS, as well as S&STD and PsA together with psoriasis.

In general, over the period of the study, there was a trend towards higher incidence of MSCD and spondylopathies among the adult population of the Orenburg Region in 2023 vs. 2019.

In 2020–2022, the total incidence of MSCD and spondylopathies dropped, reflecting a clear impact of the COVID pandemic [17]; therefore, it is not possible to have an accurate estimate of the total incidence of MSCD and spondylopathies.

Of note, the total incidence of ankylosing spondylitis remained approximately the same in 2019–2023. Apparently, it was caused by the need in medical care due to AS severity as a result of chronic persistent immune inflammation [18].

The primary incidence of MSCD and spondylopathies was similar to their total incidence. Unlike the total incidence, the primary incidence of AS was lower during the COVID-19 pandemic, and increased by 2023. Despite the fact that the data on the rates of increase (decrease) over the period in question were unreliable, it is worth mentioning a relatively high rate of the increase both in the total and primary incidence of MSCD, spondylopathies and AS in 2023.

The most probable cause of this trend is an increased need in therapeutic and diagnostic measures for these patients after the COVID-19 pandemic, as well as accumulation of chronic patients and longer life expectancy [14]. An increase in the primary incidence of AS may show the higher efficiency of diagnostic measures. Therefore, the data on the primary incidence of ankylosing spondylitis in 2019–2023 differ from the data for 2000–2013 [14], where the incidence dropped.

When discussing the incidence of diseases of the skin and subcutaneous tissue as well as psoriatic arthritis, a similar trend should be mentioned in the primary incidence of S&STD and PsA in 2023 vs. 2019, with a decrease in the figures during the pandemic (2020–2022). It may correspond to the mentioned assumptions on seeking medical care and peculiar compliance of patients with PsA [19, 20].

A comparison of the data on the total incidence of MSCD in Russia and the Orenburg Region shows significantly higher figures in the Orenburg Region:

in Russia — 14,696.8 and 14,934.0 per 100,000 adults in 2019 and 2023, respectively; in the Orenburg Region — 20,974.1 and 33,128.5 per 100,000 adults in 2019 and 2023, respectively. Similar data were reported on the primary incidence of spondylopathies: in Russia — 102.5 and 92.2 per 100,000 adults in 2019 and 2023, respectively; in the Orenburg Region — 101.7 and 166.3 per 100,000 adults in 2019 and 2023, respectively.

It is not possible to compare the incidence of AS in the Orenburg Region and Russia due to unavailability of the data in statistical reports of the Ministry of Health of Russia.

Similar data were observed for the total incidence of PsA: in Russia — 14.2 and 14.7 per 100,000 people in 2019 and 2023, respectively; in the Orenburg Region — 24.9 and 32.1 per 100,000 people in 2019 and 2023, respectively.

An increase in the primary incidence of MSCD and AS was reported both in Russia and the Orenburg Region. Interestingly, the primary incidence of PsA in Russia tended to decrease, making 2.4 in 2019 and 2.06 in 2023, unlike the Orenburg Region, where it increased significantly (Table 4).

These observations might have been a result of the rigorous work of the rheumatological service regarding the awareness and understanding the pathogenesis of spondylarthritis, facilitated by the regular educational initiatives in the region, as well as availability of genetically engineered biologic drugs.

Conclusion

The total incidence of diseases of musculoskeletal system, spondylopathies and PsA among the adult population of the Orenburg Region tended to increase over the period from 2019 to 2023. There was also a trend towards decrease in the total incidence and increase in the primary incidence of AS. In general, the dropping incidence of MSCD and spondylopathies in 2020–2021 was reported during the COVID-19 pandemic. Comparison of the analysed parameters of the incidence of MSCD, spondylopathies, AS, and PsA with the corresponding figures for Russia shows their significant increase in the Orenburg Region. The reported data necessitate further epidemiological studies of axial spondylarthritis as a burning interdisciplinary issue (rheumatology and internal medicine); optimisation of diagnosis, monitoring and management of these conditions.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Sagitova E.R.: research concept and design, obtaining data, analyzing and interpreting data, writing articles, review of scientific literature, approving the final version of the publication.

Bugrova O.V.: research concept and design, verification of critical intellectual content; final approval of the manuscript for publication.

Sayfutdinov R.I.: research concept and design, interpreting data, approving the final version of the publication.

Seleva S.S.: analyzing and interpreting data, review of scientific literature, editing the manuscript.

Kadyrmaeva D.R.: scientific consultation, analyzing and interpreting data, editing the manuscript, approving the final version of the publication.

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DOI: 10.20514/2226-6704-2026-16-4-292-304
УДК 575.174.015.3:[616.12-008.331.1-06:616.711-002]
EDN: OYYRMK



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ОЦЕНКА ВЛИЯНИЯ ПОЛИМОРФИЗМА A1166C ГЕНА *AGTR1* НА ФОРМИРОВАНИЕ КОМОРБИДНОЙ ПАТОЛОГИИ, АССОЦИИРОВАННОЙ С КАРДИОВАСКУЛЯРНЫМ РИСКОМ, У ПАЦИЕНТОВ С АНКИЛОЗИРУЮЩИМ СПОНДИЛИТОМ

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Assessment of The Effect of The A1166C Polymorphism of The *AGTR1* Gene on The Formation of Comorbidity Associated with Cardiovascular Risk in patients with ankylosing spondylitis

Резюме

Анкилозирующий спондилит (АС) — это хроническое воспалительное заболевание, характеризующееся поражением аксиального скелета, периферических суставов и околосуставного аппарата, манифестацией системных проявлений с преимущественным вовлечением сосудистой оболочки глаза, кожи с развитием псориаза и кишечника. Для АС характерен более ранний дебют артериальной гипертензии (АГ), а также ассоциированный с АГ более высокий уровень кардиоваскулярного риска (КВР). Эндотелиальная дисфункция как начальный этап развития сердечно-сосудистых заболеваний (ССЗ) может возникать вследствие активации прогормона ренина и высокой активности ангиотензина (Ang) II. Ang II участвует не только в регуляции артериального давления, но и выполняет гемопозитические функции, в основном эритропоз и миелопоэз. Несколько исследований показали связь полиморфизма гена рецептора к ангиотензину II 1-го типа *AGTR1* (1166A>C) с АГ, вазоконстрикцией и задержкой натрия в организме. Следовательно, потенциально важно оценить роль олигонуклеотидного полиморфизма (ОНП) A1166C гена *AGTR1* в клинической манифестации АС, а также его значение в развитии коморбидной патологии и формировании КВР, включая АГ. **Цель исследования:** оценить влияние полиморфизма A1166C гена *AGTR1* на развитие коморбидной патологии и формирование КВР, включая АГ. **Материалы и методы:** В исследование было включено 176 пациентов с диагнозом АС. Проводилось генотипирование полиморфизма A1166C гена *AGTR1* методом полимеразной цепной реакции. Статистический анализ проводился с использованием критерия Краскела-Уоллиса. **Результаты.** У пациентов с генотипом AA выявлен более высокий индекс BASMI (Bath Ankylosing Spondylitis Metrology Index) ($p=0,024$, $p_{1,3}=0,023$). У гомозигот CC фиксировались более низкие уровни эритроцитов ($p=0,025$, $p_{2,3}=0,02$) и гемоглобина ($p=0,031$, $p_{2,3}=0,042$), при генотипе AA — меньшее количество тромбоцитов ($p=0,0001$, $p_{1,3}=0,001$). Больше содержание глюкозы зарегистрировано у гомозигот CC ($p=0,0001$, $p_{1,3}=0,001$, $p_{1,2}=0,025$), триглицеридов — у гетерозигот АС ($p=0,038$). Наибольшая частота энтезитов зарегистрирована для пациентов с генотипом CC ($p_{2,3}=0,006$, $p=0,015$). У гетерозигот АС выявлена большая встречаемость АГ ($p_{1,2}=0,05$, $p=0,025$), дислипидемии ($p_{1,2}=0,012$, $p_{2,3}=0,006$, $p=0,031$). Сахарный диабет был выявлен только среди пациентов с генотипом CC ($p_{1,3}=0,007$, $p=0,017$). Поражение почек чаще определялось у носителей аллеля А ($p_{1,3}=0,015$, $p_{2,3}=0,004$, $p=0,023$). Выявлены статистические различия в отношении частоты выявления отдельных степеней АГ ($p=0,0001$): у гетерозигот АС — 2 (AA 26 (27,1%); АС 4 (33,3%); CC 14 (24,1%)) и 3 степени (AA 0 (0,0%) против АС 2 (16,7%) CC 0 (0,0%), $p_{1,2}<0,001$, $p_{2,3}=0,004$). **Заключение.** Продemonстрировано влияние ОНП

1166A>C гена *AGTR1* на формирование АГ, регуляцию гемопоэза, уровни метаболических показателей, глюкозы и липидов и ассоциированных метаболических заболеваний в виде сахарного диабета, дислипидемии, патологии почек у пациентов с АС.

Ключевые слова: анкилозирующий спондилит, артериальная гипертензия, дислипидемия, метаболический синдром, ангиотензин-превращающий фермент (АПФ), *AGTR1*, полиморфизм генов, A1166C

Конфликт интересов

Авторы заявляют, что данная работа, ее тема, предмет и содержание не затрагивают конкурирующих интересов

Источник финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Исследование соответствовало этическим нормам Хельсинкской декларации (2013 г.). Обследование пациентов с применением генотипирования было одобрено локально-этическим комитетом ФГАОУ ВО «КФУ им. В.И. Вернадского» (Протокол № 8 заседания «Комитета по биомедицинской этике» от 27.11.2025 г.), проведено с соблюдением этических принципов и наличием информированного согласия на обследование. Все участники подписали письменное информированное согласие на участие в исследовании.

Статья получена 25.01.2026 г.

Одобрена рецензентом 27.02.2026 г.

Принята к публикации 27.03.2026 г.

Для цитирования: Гаффарова А.С., Белоглазов В.А., Яцков И.А. и др. ОЦЕНКА ВЛИЯНИЯ ПОЛИМОРФИЗМА A1166C ГЕНА *AGTR1* НА ФОРМИРОВАНИЕ КОМОРБИДНОЙ ПАТОЛОГИИ, АССОЦИИРОВАННОЙ С КАРДИОВАСКУЛЯРНЫМ РИСКОМ, У ПАЦИЕНТОВ С АНКИЛОЗИРУЮЩИМ СПОНИДИЛИТОМ. Архив внутренней медицины. 2026; 16(4): 292-304. DOI: 10.20514/2226-6704-2026-16-4-292-304. EDN: OYYRMK

Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by damage to the axial skeleton, peripheral joints and periarticular apparatus, manifestation of systemic manifestations with predominant involvement of the vascular membrane of the eye, skin with the development of psoriasis and intestines. AU is characterized by an earlier onset of arterial hypertension (AH), as well as a higher level of cardiovascular risk (CVR) associated with AH. Endothelial dysfunction as the initial stage of the development of cardiovascular diseases (CVD) can occur due to the activation of the prohormone renin and high activity of angiotensin (Ang) II. Ang II is involved not only in the regulation of blood pressure, but also performs hematopoietic functions, mainly erythropoiesis and myelopoiesis. Several studies have shown the association of *AGTR1* (1166A>C) angiotensin II type 1 receptor polymorphism with hypertension, vasoconstriction, and sodium retention in the body. Therefore, it is potentially important to evaluate the role of oligonucleotide polymorphism (SNP) A1166C of the *AGTR1* gene in the clinical manifestation of AS, as well as its significance in the development of comorbid pathology and the formation of CVR, including hypertension. **Aim:** to evaluate the effect of the A1166C polymorphism of the *AGTR1* gene on the development of comorbid pathology and the formation of CFS, including AH. **Materials and methods:** The study included 176 patients diagnosed with AS. Genotyping was carried out according to the A1166C polymorphism of the *AGTR1* gene by the polymerase chain reaction method (PCR). The statistical analysis was carried out using the Kruskal-Wallis criterion. **Results:** Patients with the AA genotype had a higher BASMI (Bath Ankylosing Spondylitis Metrology Index) ($p=0.024$, $p_{1,3}=0.023$). CC homozygotes had lower levels of red blood cells ($p=0.025$, $p_{2,3}=0.02$) and hemoglobin ($p=0.031$, $p_{2,3}=0.042$), while AA genotypes had lower platelet counts ($p=0.0001$, $p_{1,3}=0.001$). Higher glucose levels were recorded in CC homozygotes ($p=0.0001$, $p_{1,3}=0.001$, $p_{1,2}=0.025$), triglycerides — in heterozygotes AC ($p=0.038$). The highest incidence of enthesitis was recorded for patients with the CC genotype ($p_{2,3}=0.006$, $p=0.015$). High incidence of hypertension ($p_{1,2}=0.05$, $p=0.025$), dyslipidemia ($p_{1,2}=0.012$, $p_{2,3}=0.006$, $p=0.031$) was found in heterozygotes of AC. Diabetes mellitus was detected only among patients with the CC genotype ($p_{1,3}=0.007$, $p=0.017$). Kidney damage was more often detected in carriers of the A allele ($p_{1,3}=0.015$, $p_{2,3}=0.004$, $p=0.023$). Statistical differences were found in the frequency of detection of individual degrees of hypertension ($p=0.0001$): in heterozygotes of AC — 2 (AA 26 (27.1%); AC 4 (33.3%); CC 14 (24.1%)) and grade 3 (AA 0 (0.0%) versus AC 2 (16.7%) CC 0 (0.0%), $p_{1,2}<0.001$, $p_{2,3}=0.004$). **Conclusion:** The obtained results reveal a wide range of functions of the SNP 1166A>C of the *AGTR1* gene, extending beyond participation in the formation of hypertension, and include the regulation of hematopoiesis, metabolic parameters, glucose and lipids in particular, and the formation of comorbid pathology in the form of diabetes mellitus, dyslipidemia, kidney pathology in patients with AS, which determines the potential and feasibility of genotyping patients with AS with the identification of SNPs in order to personalize approaches to pharmacotherapy of AS and monitoring these indicators in the presence of a risk of developing conditions associated with this SNP.

Key words: ankylosing spondylitis, arterial hypertension, dyslipidemia, metabolic syndrome, angiotensin converting enzyme (ACE), *AGTR1*, gene polymorphism, A1166C (rs5186)

Conflict of interests

The authors declare that this work, its topic, subject matter, and content do not affect any competing interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The study corresponded to the ethical standards of the Helsinki Declaration (2013). The examination of patients using genotyping was approved by the local Ethics committee of the V.I. Vernadsky CFU (Protocol No. 8 of the meeting of the Committee on Biomedical Ethics dated 11/27/2025), conducted in compliance with ethical principles and informed consent to the examination. All participants signed a written informed consent to participate in the study

Article received on 25.01.2026

Reviewer approved 27.02.2026

Accepted for publication on 27.03.2026

For citation: Gaffarova A.S., Beloglazov V.A., Yatskov I.A. et al. Assessment of The Effect of The A1166C Polymorphism of The *AGTR1* Gene on The Formation of Comorbidity Associated with Cardiovascular Risk in patients with ankylosing spondylitis. The Russian Archives of Internal Medicine. 2026; 16(4): 292-304. DOI: 10.20514/2226-6704-2026-16-4-292-304. EDN: OYYRMK

AH — arterial hypertension, AxSpA — axial spondylarthritis, ACE — angiotensin converting enzyme, AS — ankylosing spondylitis, IBD — inflammatory bowel disease, HSC — haematopoietic stem cells, DNA — deoxyribonucleic acid, IHD — ischaemic heart disease, CVR — cardiovascular risk, BMI — body mass index, HDL — high-density lipoproteins, LDL — low-density lipoproteins, NSAIDs — non-steroidal anti-inflammatory drugs, NSAID gastropathy — NSAID-associated gastropathy, KSD — kidney stone disease, SNP — single nucleotide polymorphism, PCR — polymerase chain reaction, RAAS — rennin-angiotensin-aldosterone system, CRP — C-reactive protein, DM2 — type 2 diabetes mellitus, ESD — erythrocyte sedimentation rate, CVD — coronary vascular diseases, SpA — spondylarthritis, ED — endothelial dysfunction, *AGTR1* — type 1 angiotensin II receptor, Ang II — angiotensin II, ASAS — Assessment of SpondyloArthritis International Society, ASDAS-CRP — Ankylosing Spondylitis Disease Activity Score, BASDAI — Bath AS Disease Activity Index, BASMI — Bath AS Metrology Index, HLA B27 — human leucocyte antigen B27, MAPK — mitogenic-activated protein kinase, VEGF — vascular endothelial growth factor, VEGFR2 — VEGF receptor

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disorder, associated with the development of an inflammatory process in axial and peripheral joints and in peri-axial structures, with systemic manifestations, related to uvea involvement, such as uveitis and iridocyclitis, skin conditions (psoriasis), and bowel inflammations. [1, 2]. Clinically, AS manifests as inflammatory back pain and gradual progression of irreversibly restricted mobility in the spine caused by ankylosis [3].

Patients with AS have earlier onset of arterial hypertension (AH), as well as a higher cardiovascular risk (CVR) resulting from AH [2, 3]. AH is a multigenic condition and is triggered by an interaction of environmental and genetic predictors together with epigenetic factors. Renin-angiotensin-aldosterone system (RAAS) is a complex multiple-level mechanism, regulating vascular tone, metabolic homeostasis, and water-electrolytic balance [4].

Endothelial dysfunction (ED) is associated with vasoconstrictive, pro-adhesive, pro-thrombotic, proliferative, and pro-inflammatory processes, which potentiate atherosclerotic lesions and are an initial stage in the development of cardiovascular diseases (CVDs) [5]. In individuals with AH, ED, which causes reduced NO availability, impairs endothelium-dependent vasodilation [6].

ED can be a result of (pro)renin receptor (PRR) activation and high angiotensin (Ang) II activity [7]. Renin can interact with PRR, stimulating RAAS, catalysing Ang I production [8], thus triggering activation of mitogenic-activated protein kinase (MARK) pathways [9] in the presence of V-ATPase, as well as Wnt/ β -catenin pathway regulation [10].

Studies of vascular reconstruction demonstrated that Ang II intensifies angiogenic functions of progenitor cells, which is mainly a result of elevated levels of vascular endothelial growth factor (VEGF) and its receptor VEGFR2. Excessive vascular permeability in the presence of Ang II and VEGF can stimulate progenitor cell transmigration to damaged areas and facilitate vascular repair [11].

Simultaneously intensified activity of the ACE/Ang II/AGT1R pathway slows down cardiovascular reconstruction and postnatal vasculogenesis, at least partially

due to inhibition of the reparative functions of progenitor cells. AGT1P activation by hypertensive concentrations of Ang II reduced the number of circulating progenitor cells in the experimental mice model and inhibited their functions involved in vascular restoration, leading to endothelial damage and impaired vascular regeneration [12].

Of note, Ang II is involved not only in blood pressure regulation, but it also has hematopoietic functions, mostly erythropoiesis and myelopoiesis, which was demonstrated with the help of angiotensin receptor blockers in vitro or in the mice model of genetic deficit of angiotensin converting enzyme (ACE) [13, 14, 15]. ACE is essential for normal hematopoiesis, while ACE inhibitors increase the risk of anaemia [16].

Therefore, the study of type 1 angiotensin II receptor (*AGTR1*) gene is very important for the evaluation of the risk of AH in patients with AS, including its participation in vasculogenesis and hematopoiesis. A number of studies demonstrated the association between polymorphism of *AGTR1* (1166A>C, rs5186) with AH, vasoconstriction and sodium retention in the body [17, 18].

Therefore, it is potentially essential to assess the role of polymorphism A1166C of the *AGTR1* gene in clinical presentation of AS, as well as its significance for the development of comorbidity and CVR, including AH.

Objective of the study: to assess the implications of polymorphism A1166C of the *AGTR1* gene for the development of comorbidity and CVR, including AH.

Materials and methods

The study enrolled 176 patients with confirmed AS, who were admitted to the rheumatology ward of N. A. Semashko Republican Clinical Hospital, Simferopol, Crimea. Biological material (whole blood) was taken from all patients upon admission. Patients were included into the study group provided they had confirmed AS. Inclusion criteria were: age of 18 to 55 years old; inpatient and outpatient patients with verified AS, meeting the modified 1984 New York criteria and classification of the ASAS (Assessment of SpondyloArthritis International Society) experts issued in 2009; symptom duration of under 20 years; informed consent; positive result for

human leucocyte antigen (HLA) B27. Exclusion criteria: lack of informed consent; age under 18 years old and over 55 years old; symptom duration of over 20 years; chronic grade III pulmonary heart disease; chronic stage V kidney disease; hepatic failure; acute or chronic infections; cancer; negative HLA-B27.

Information on comorbidities was retrieved from medical records of previously hospitalised patients.

Over a half of all subjects were men (115 (65.3 %)); mean age was 44 [38; 49] years old; AS duration upon enrollment was 11 [8; 20] years. Body weight index corresponded to overweight (26.1 [24; 30] kg/m²). Patients had high AS activity (BASDAI: 7.4 [6.8; 7.9],

ASDAS-CRP: 4.2 [3.8; 4.5]) and moderate dysfunction (BASMI: 4.0 [3.0; 6.0]). Clinical blood count results (Hb (141.0 [128.0; 151.0] g/L), WBC (7.1 [5.45; 8.82] ×10⁹/L), RBC (4.7 [4.3; 5.1] ×10¹²/L), and platelets (273.0 [231.5; 312.0] ×10⁹/L) were normal, while ESR (20.5 [10.0; 29.5] mm/h) and CRP (6.65 [2.85; 14.65] mL/L) were over the reference range. As for metabolic parameters, cholesterol (5.6 [4.6; 6.3] mmol/L) and LDL (3.4 [2.7; 4.0] mmol/L) levels were higher than normal. HDL, triglycerides, glucose, uric acid, creatinine, urea, and iron were within the reference range. Clinical and laboratory characteristics of patients enrolled into the study are presented in Table 1.

Table 1. Clinical and laboratory characteristics of patients with ankylosing spondylitis

Characteristics		Patients with ankylosing spondylitis (n=176)
Gender	Male. abs. (%)	115 (65.3)
	Female. abs. (%)	61 (34.7)
Age, full years		44 [38; 49]
Duration of the disease, full years		11 [8; 20]
BMI, kg/m ²		26.1 [24; 30]
BASDAI		7.4 [6.8; 7.9]
ASDAS-CRP		4.2 [3.8; 4.465]
BASMI		4.0 [3.0; 6.0]
Haemoglobin, g/l		141.0 [128.0; 151.0]
White blood cells, ×10 ⁹ /l		7.1 [5.45; 8.82]
Red blood cells, ×10 ¹² /l		4.655 [4.3; 5.1]
Platelets, ×10 ⁹ /l		273.0 [231.5; 312.0]
ESR, mm/h		20.5 [10.0; 29.5]
CRP, mg/l		6.65 [2.85; 14.65]
Cholesterol, mmol/l		5.6 [4.6; 6.32]
LDL, mmol/l		3.425 [2.67; 3.995]
HDL, mmol/l		1.5 [1.28; 1.8]
Triglycerides, mmol/l		1.24 [0.89; 1.715]
Glucose, mmol/l		5.1 [4.5; 5.68]
Uric acid, mcmol/l		307.0 [242.0; 422.5]
Creatinine, mcmol/l		81.0 [70.4; 91.5]
Urea, mmol/l		5.01 [4.2; 5.94]
Iron, mmol/l		14.9 [11.3; 20.5]

Notes: Ankylosing spondylitis — AS, Body Mass Index — BMI, Bath AS Disease Activity Index — BASDAI, Ankylosing Spondylitis Disease Activity Score with calculation of CRP — ASDAS-CRP, Bath AS Metrology Index — BASMI, erythrocyte sedimentation Rate — ESR, C-reactive protein — CRP, low-density lipoproteins — LDL, high-density lipoproteins — HDL

The majority of patients had X-ray stage II AS (108 (61.4%)), while stage III and stage IV was diagnosed in 30 (17.0%) and 34 (19.3%) patients, respectively. X-ray changes in hip joints were absent in 30 (17.0%) patients; X-ray stage I, II, III, and IV was reported in 44 (25.0%), 74 (42.1%), 26 (14.8%), and 2 (1.1%) patients, respectively. Extraaxial manifestations were arthritis (156 (88.6%)), enthesitis (100 (56.8%)), and dactylitis (4 (2.3%)). Spondylitis as a manifestation of the late clinical stage of AS was reported in 54 (30.7%) patients. Extraaxial manifestations were observed in 40 (22.7%) patients; eye disorders prevailed (30 (17.0%)), mostly in the form of uveitis (20 (11.4%)); psoriasis (18 (10.2%)) and inflammatory bowel disease (6 (3.4%)) were less common.

Clinical characteristics of patients depending on manifestations and progression of ankylosing spondylitis are presented in Table 2.

The most common CVR-associated comorbidities were dyslipidemia (90 (51.1%) patients); AH (60 (34.1%)), where stage II (34 (19.3%)), grade 2 (44 (25.0%)), risk 3 (44 (25.0%)) prevailed; obesity (38 (21.6%)), and

hyperuricemia (20 (11.4%)). GI disorders were reported in 30 (17.0%) patients, and NSAID-associated gastropathy prevailed (18 patients (10.2%)).

The clinical characteristics of patients with ankylosing spondylitis with and without comorbidities are presented in Table 3.

The study was conducted at the Molecular Biology Centre for the Shared Use of Scientific Equipment, Vernadsky Crimean Federal University. Whole blood of patients with AS was used to extract deoxyribonucleic acid (DNA) with the help of DNA Express Blood kit (Litekh, Russia) in accordance with the manufacturer's instructions. Polymorphism A1166C of the *AGTR1* gene was analysed using allele-specific PCR kits (Litekh, Russia). Amplification products were detected using horizontal electrophoresis with 3% agarose gel.

The study complied with the ethical principles of the Declaration of Helsinki (2013). Patient genetic typing was approved by the Local Ethics Committee at the Vernadsky Crimean Federal University (Meeting Minutes No. 8 of the Biomedical Committee dated 27.11.2025).

Table 2. Clinical characteristics of patients with ankylosing spondylitis

Characteristics	AS (n=176)
Sacroiliitis, the X-ray stage	
– I	0
– II	108 (61.4%)
– III	30 (17.0%)
– IV	34 (19.3%)
Coxitis, the X-ray stage	
– 0	30 (17.0%)
– I	44 (25.0%)
– II	74 (42.1%)
– III	26 (14.8%)
– IV	2 (1.1%)
Arthritis	156 (88.6%)
Enthesitis	100 (56.8%)
Dactylitis	4 (2.3%)
Spondylitis	54 (30.7%)
Extraskkeletal manifestations	40 (22.7%)
Eye lesions	30 (17.0%)
– uveitis	20 (11.4%)
– iridocyclitis	6 (3.4%)
– episcleritis	4 (2.3%)
Psoriasis	18 (10.2%)
Inflammatory bowel disease	6 (3.4%)

Table 3. Comorbidities in patients with ankylosing spondylitis

Comorbidities	Patients with ankylosing spondylitis (n=176)
Arterial hypertension, abs. (%)	n=60 (34.1 %)
– stage	
– 1, abs. (%)	16 (10.8 %)
– 2, abs. (%)	34 (19.3 %)
– 3, abs. (%)	10 (5.7 %)
– degree	
– 1, abs. (%)	14 (8.0 %)
– 2, abs. (%)	44 (25.0 %)
– 3, abs. (%)	2 (1.1 %)
– risk	
– 1, abs. (%)	0 (0.0 %)
– 2, abs. (%)	8 (4.5 %)
– 3, abs. (%)	44 (25.0 %)
– 4, abs. (%)	8 (4.5 %)
Dyslipidemia, abs. (%)	90 (51.1 %)
Diabetes mellitus, abs. (%)	4 (2.3 %)
Coronary heart disease, abs. (%)	6 (3.4 %)
Hyperuricemia, abs. (%)	20 (11.4 %)
Gout, abs. (%)	6 (3.4 %)
Gastrointestinal diseases, abs. (%)	n=30 (17.0 %)
– NSAID-gastropathy, abs. (%)	18 (10.2 %)
– Erosive gastropathy, abs. (%)	12 (6.8 %)
– GOUT/GOUT, abs. (%)	2 (1.1 %)
– Gastroesophageal reflux disease, abs. (%)	2 (1.1 %)
Kidney diseases, abs. (%)	n=12 (6.8 %)
– Chronic pyelonephritis, abs. (%)	6 (3.4 %)
– Urolithiasis, abs. (%)	6 (3.4 %)
Osteoporosis, abs. (%)	6 (3.4 %)
Obesity, abs. (%)	n=38 (21.6 %)
– 1st degree, abs. (%)	26 (14.8 %)
– 2nd degree, abs. (%)	12 (6.8 %)
– 3rd degree, abs. (%)	0 (0.0 %)
Overweight, abs. (%)	44 (25.0 %)
Body weight deficiency, abs. (%)	2 (1.1 %)
Smoking, abs. (%)	18 (10.2 %)

The study was conducted in accordance with the ethical principles. All subjects signed the informed consent forms for the participation in the study.

The data were analysed using IBM SPSS Statistics 27 package. The Shapiro-Wilk test was used to check the normality of quantitative indicator distribution. Groups were compared with the Kruskal-Wallis test. Results were statistically significant at 0.05. The rate of qualitative attributes was tested using the Pearson’s chi-square test or Fisher’s test. Distribution was normal at $p \geq 0.1$ if the Kolmogorov-Smirnov test was used.

Study results

Patients with genotype AA had higher BASMI values vs. allele C carriers (AA 5.0 [4.0; 6.0]; AC 3.0 [3.0; 7.0]; CC 4.0 [3.0; 5.0], $p=0.024$, $p_{1,3}=0.023$). At the same time, homozygote of allele CC carriers showed significantly lower RBC (AA 4.7 [4.3; 5.12] $\times 10^{12}/L$; AC 5.29 [4.63; 5.6] $\times 10^{12}/L$; CC 4.57 [4.38; 4.93] $\times 10^{12}/L$, $p=0.025$, $p_{2,3}=0.02$) and Hb levels (AA 143 [128; 152] g/L; AC 150 [141; 153] g/L; CC 140 [126; 143] g/L, $p=0.031$, $p_{2,3}=0.042$); while AA homozygotes had lower platelet counts (AA 252 [223; 297] $\times 10^9/L$; AC 282 [236; 338]

Table 4. Comparison of clinical and laboratory parameters in patients with ankylosing spondylitis and various variants of single nucleotid polymorphism (SNP) A1166C AGTR1 gene

Signs	AGTR1 A-1166C			p
	AA (n=104)	AC (n=14)	CC (n=58)	
Age, full years	43.0 [39.0-49.0]	46.0 [36.0-50.0]	44.0 [37.0-48.0]	>0.05
Gender	8 (57.1 %)	56 (63.6 %)	>0.05	>0,05
	6 (42.9 %)	32 (36.4 %)		
Duration of the disease, full years	11.0 [8.5; 18.0]	10.0 [5.0; 30.0]	13 [8.0;20.0]	>0.05
BASDAI	7.4 [6.8; 7.8]	7.7 [7.4; 8.0]	7.4 [6.8; 7.8]	>0.05
ASDAS-CRP	4.2 [3.8; 4.5]	3.9 [3.47; 4.6]	4.08 [3.8; 4.4]	>0.05
BASMI	5.0 [4.0; 6.0]	3.0 [3.0; 7.0]	4.0 [3.0; 5.0]	0.024 p _{1,3} =0.023
BMI, kg/m², Me (Q1-Q3)	26.8 [24.0; 31.6]	29.0 [25.25; 31.7]	25.7 [24.0; 28.1]	>0.05
White blood cells, ×10 ⁹ /l	6.86 [5.5; 8.81]	7.62 [6.49; 9.6]	7.6 [5.3; 8.69]	>0.05
Red blood cells, ×10 ¹² /l	4.7 [4.3; 5.12]	5.29 [4.63; 5.6]	4.57 [4.38; 4.93]	P=0.025 p _{2,3} =0.02
Platelets, ×10 ⁹ /l	252 [223; 297]	282 [236; 338]	283 [254; 333]	p=0.0001 p _{1,3} =0.001
Haemoglobin, g/l	143 [128; 152]	150 [141; 153]	140 [126; 143]	p=0.031 p _{2,3} =0.042
ESR, mm/h	20 [10; 29]	27 [4; 36]	20 [10; 30]	>0.05
CRP, mg/l	8.0 [2.7; 16.0]	8.6 [6.1; 18.5]	5.2 [4.3; 6.1]	>0.05
Glucose, mmol/l	4.8 [4.36; 5.4]	5.4 [5.1; 5.95]	5.4 [4.9; 5.8]	p=0.0001 p _{1,3} =0.001 p _{1,2} =0.025
Cholesterol, mmol/l	5.6 [4.6; 6.5]	6.3 [4.8; 6.7]	5.3 [4.3; 6.1]	>0.05
LDL, mmol/l	3.5 [2.9; 4.2]	3.7 [3.0; 4.8]	3.2 [2.6; 3.8]	>0.05
HDL, mmol/l	1.5 [1.3; 2.1]	1.3 [1.0; 1.5]	1.6 [1.5; 1.8]	>0.05
Triglycerids, mmol/l	1.3 [0.9. 1.7]	1.5 [1.0; 4.1]	0.9 [0.8; 1.2]	0.038
Creatinine, mcmol/l	80.7 [70.3; 100.0]	80.0 [64.7; 88.0]	81.3 [74.0; 87.1]	>0.05
Urea, mmol/l	4.9 [4.2; 6.1]	5.4 [4.9; 5.9]	5.0 [4.0; 5.9]	>0.05
Urea acid, mcmol/l	331.0 [262.0; 446.0]	311.8 [277.0; 346.0]	262.0 [217.0; 356.0]	>0.05
Iron, mcmol/l	13.9 [11.7; 20.6]	16.4 [14.0; 29.5]	15.0 [10.7; 20.4]	>0.05

Notes:
p_{1,2} — differences identified between AA and AC genotypes
p_{1,3} — differences identified between AA and CC genotypes
p_{2,3} — differences identified between AC and CC genotypes
Ankylosing spondylitis — AS, Body Mass Index — BMI, Bath AS Disease Activity Index — BASDAI, Ankylosing Spondylitis Disease Activity Score with calculation of CRP — ASDAS-CRP, Bath AS Metrology Index — BASMI, erythrocyte sedimentation Rate — ESR, C-reactive protein — CRP, low-density lipoproteins — LDL, high-density lipoproteins — HDL.

$\times 10^9/L$; CC 283 [254; 333] $\times 10^9/L$, $p=0.0001$, $p_{1,3}=0.001$). As far as metabolic parameters are concerned, allele C carriers demonstrated higher glucose concentration (AA 4.8 [4.36; 5.4] mmol/L; AC 5.4 [5.1; 5.95] mmol/L; CC 5.4 [4.9; 5.8] mmol/L, $p=0.0001$, $p_{1,3}=0.001$, $p_{1,2}=0.025$); while AC homozygotes had lower triglycerides values (AA 1.3 [0.9, 1.7] mmol/L; AC 1.5 [1.0; 4.1] mmol/L; CC 0.9 [0.8; 1.2] mmol/L, $p=0.038$). There were no statistically significant differences in other clinical and laboratory results (Table 4).

Patients with genotype AC had the lowest rate of enthesitis, while the highest enthesitis rate was reported in patients with genotype CC (AA 56 (53.8 %); AC 4 (28.6 %); CC 40 (69.0 %), $p_{2,3}=0.006$, $p=0.015$). There were no statistically significant differences in extraaxial manifestations when genotypes were compared (Table 5). Also, there were no statistically significant difference in comparison groups as regards X-ray stages of sacroilitis and coxitis and extraaxial manifestations of AS (Table 5).

Table 5. Comparison of clinical manifestations of ankylosing spondylitis depending on different variants of the A1166C polymorphism of the AGTR1 gene

	AA (n=104)	AC (n=14)	CC (n=58)	p	p (total)
Clinical manifestations					
Arthritis	94 (90.4 %)	12 (85.7 %)	50 (86.2 %)	-	>0.05
Enthesite	56 (53.8 %)	4 (28.6 %)	40 (69.0 %)	p _{2,3} =0.006	=0.015
Dactylitis	4 (3.9 %)	0 (0.0 %)	0 (0.0 %)		-
Spondylitis	28 (28.0 %)	4 (28.6 %)	22 (37.9 %)	-	>0.05
Radiographic stage of sacroiliitis					
II	62 (62.0 %)	8 (57.1 %)	38 (65.5 %)	-	p>0.05
III	18 (18,0 %)	4 (28,6 %)	8 (13,8 %)	-	
IV	20 (20,0 %)	2 (14,3 %)	12 (20,7 %)	-	
Radiographic stage of coxitis					
0	18 (17,3 %)	2 (14,3 %)	10 (17,2 %)	-	p>0,05
I	22 (21.2 %)	4 (28.6 %)	18 (31.0 %)	-	
II	46 (44.2 %)	6 (42.9 %)	22 (37.9 %)	-	
III	16 (15.4 %)	2 (14.3 %)	8 (13.8 %)	-	
IV	2 (1.9 %)	0 (0.0 %)	0 (0.0 %)	-	
Extraskeletal manifestations					
Extraskeletal manifestations	0 (0.0 %)	28 (21.5 %)	6 (23.1 %)	-	p>0.05
Eye lesions	26 (25.0 %)	4 (28.6 %)	10 (17.2 %)	-	p>0.05
– uveit	22 (22.5 %)	4 (28.6 %)	4 (7.1 %)	-	p>0.05
– iridocyclitis	14 (14.3 %)	2 (14.3 %)	4 (7.1 %)	-	p>0.05
– episclerite	4 (4.1 %)	2 (14.3 %)	(0.0 %)	-	p>0.05
Psoriasis	4 (4.1 %)	0 (0.0 %)	(0.0 %)	-	p>0.05
IBD	10 (10.0 %)	2 (14.3 %)	6 (10.7 %)	-	p>0.05

Notes
* $p_{1,2}$ — differences identified between AA and AC genotypes
** $p_{1,3}$ — differences identified between AA and CC genotypes
*** $p_{2,3}$ — differences identified between AC and CC genotypes
Inflammatory bowel disease — IBD.

Table 6. Comparison of comorbid pathology depending on SNP A1166C of the AGTR1 gene in patients with ankylosing spondylitis

Comorbid pathology	AA (n=104)	AC (n=14)	CC (n=58)	p	P (total)
AH	32 (37.2 %)	8 (80.0 %)	20 (35.7 %)	$p_{1,2}=0.05$	$=0.025$
Dyslipidemia	52 (53.1 %)	12 (85.7 %)	26 (46.4 %)	$p_{1,2}=0.012$ $p_{2,3}=0.006$	$=0.031$
CHD	4 (4.2 %)	0 (0.0 %)	2 (3.6 %)	-	$p>0.05$
DM 2	0 (0.0 %)	0 (0.0 %)	4 (7.1 %)	$p_{1,3}=0.007$	$=0.017$
Hyperuricemia	16 (16.7 %)	0 (0.0 %)	4 (7.4 %)	-	$p>0.05$
Gout	6 (6.3 %)	0 (0.0 %)	0 (0.0 %)	-	$p>0.05$
Renal lesions	10 (10.5 %)	2 (14.3 %)	0 (0.0 %)	$p_{1,3}=0.015$ $p_{2,3}=0.004$	$=0.023$
– Chronic pyelonephritis	6 (6.3 %)	0 (0.0 %)	0 (0.0 %)	-	
– Urolithiasis	4 (4.2 %)	2 (14.3 %)	0 (0.0 %)	-	
Osteoporosis	2 (2.1 %)	0 (0.0 %)	4 (7.1 %)	-	$p>0.05$
Smoking	10 (10.4 %)	4 (28.6 %)	4 (7.4 %)	-	$p>0.05$

Notes
 $p_{1,2}$ — differences identified between AA and AC genotypes
 $p_{1,3}$ — differences identified between AA and CC genotypes
 $p_{2,3}$ — differences identified between AC and CC genotypes
Arterial hypertension — AH, coronary heart disease — CHD, type 2 diabetes mellitus — DM2.

Table 7. Comparison of the stage, degree and risk of arterial hypertension in patients with ankylosing spondylitis depending on the SNP A1166C of the AGTR1 gene

	AA (n=104)	AC (n=14)	CC (n=58)	p	p (общее)
Stage					
I	8 (8.3 %)	2 (16.7 %)	6 (10.7 %)	-	p>0.05
II	16 (16.7 %)	6 (50.0 %)	12 (21.4 %)	-	
III	8 (8.3 %)	0 (0.0 %)	2 (3.6 %)	-	
Degree					
1	6 (6.3 %)	2 (16.7 %)	6 (10.3 %)	-	=0.0001 p _{1,2} <0.001 p _{2,3} =0.004
2	26 (27.1 %)	4 (33.3 %)	14 (24.1 %)	-	
3	0 (0.0 %)	2 (16.7 %)	0 (0.0 %)		
Risk					
1	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-	p>0.05
2	4 (4.0 %)	0 (0.0 %)	4 (7.1 %)	-	
3	24 (24.0 %)	6 (42.9 %)	14 (25.0 %)	-	
4	4 (4.0 %)	2 (14.3 %)	2 (3.6 %)	-	

Notes
 $p_{1,2}$ — differences identified between AA and AC genotypes
 $p_{1,3}$ — differences identified between AA and CC genotypes
 $p_{2,3}$ — differences identified between AC and CC genotypes
Arterial hypertension — AH

AC heterozygote demonstrated the highest rate of AH cases (AA 32 (37.2%); AC 8 (80.0%); CC 20 (35.7%), $p_{1,2}=0.05$, $p=0.025$). In addition, this patient group had the highest number of dyslipidemia cases (AA 52 (53.1%); AC 12 (85.7%); CC 26 (46.4%), $p_{1,2}=0.012$, $p_{2,3}=0.006$, $p=0.031$). Diabetes mellitus was reported only in patients with genotype CC (AA 0 (0.0%); AC 0 (0.0%); CC 4 (7.1%), $p_{1,3}=0.007$, $p=0.017$). Kidney damage as a comorbidity was recorded in allele A carriers (AA 10 (10.5%); AC 2 (14.3%); CC 0 (0.0%), $p_{1,3}=0.015$, $p_{2,3}=0.004$, $p=0.023$). Also, homozygote of AA carriers demonstrated higher rates of chronic pyelonephritis (AA 6 (6.3%); AC 0 (0.0%); CC 0 (0.0%)) and KSD (AA 4 (4.2%); AC 2 (14.3%); CC 0 (0.0%)). There were no statistically significant differences regarding other comorbidities (Table 6).

AC carriers demonstrated higher rates of grade 2 (AA 26 (27.1%) vs. AC 4 (33.3%); CC 14 (24.1%)) and grade 3 AH (AA 0 (0.0%); AC 2 (16.7%); CC 0 (0.0%), $p_{1,2}<0.001$, $p_{2,3}=0.004$). In general, intergroup differences were statistically significant ($p=0.0001$). There were no statistically significant differences in the rates of individual AH grades and risks between groups (Table 7).

Discussion

Currently, literature references do not report studies of the clinical parameters of AS and the association with SNP A1166C of the *AGTR1* gene. As for the clinical parameters, this study was the first to demonstrate higher BASMI values in AA homozygote. Moreover, analysis of clinical manifestations of the disease showed that CC genotype carriers had the highest rate of enthesitis.

Assessment of laboratory parameters and comorbidity manifestations yielded some interesting results.

ACE and RAAS are known to have an essential role in blood pressure regulation. However, not less interesting is the presence of ACE and local RAAS in bone marrow, which impact the peptide chain contributing to haematopoiesis regulation. ACE is expressed over the entire duration of hematopoietic tissue development [19]. Even at the early stages of fetation, before blood circulation has been established, local ACE production can be observed. Local ACE is likely to facilitate the development of haematopoietic stem cells (HSCs) and other haematopoietic cells in the adult bone marrow.

AT1-mediated Ang II signalling is essential for myeloid differentiation and functional maturation. Pilot studies show that enzymatic activity of ACE can be required to sustain haematopoietic homeostasis. For example, ACE inhibition blocked haemangioblast expansion and differentiation as endothelium or multipotent haematopoietic precursors. In turn, ACE inhibition

significantly reduced the ability of the embryoid body to produce haematopoietic colony-forming cells.

This study of patients with AS demonstrated for the first time that SNP A1166C genotype CC of the *AGTR1* gene caused lower RBC count and Hb and higher platelet levels. Therefore, our study was the first to show the differences in RBC and platelets production depending on genetic variants of SNP A1166C of the *AGTR1* gene, confirming genetic predisposition to lower RBC and Hb levels and higher platelet values in patients with genotype CC.

Ang II-triggered increase in oxidative stress, inflammation and free fatty acid levels promotes β -cell dysfunction in patients with diabetes [20]. Various organs have a role to play in regulation of glucose homeostasis, including pancreas, adipose tissue, skeletal muscles, and liver. It is worth noting that these organs have their own local RAAS, the activation of which is associated with diabetic pathology. It appears that RAAS activation boosts effects of other pathogenic pathways, including glucotoxicity, lipotoxicity and increased glycation, thus leading to hyperglycaemia and insulin resistance [21, 22]. On the contrary, hyperglycaemia, hypercholesterolemia and insulin resistance can increase the activity of RAAS components [23, 24].

In this study, allele C carriers had higher glucose levels vs. homozygotes AA, while AA and AC genotype carriers had higher triglyceride levels, again confirming the role of RAAS in glucose and Hb regulation, having the same genetics with SNP A1166C of the *AGTR1* gene.

When comorbidity of patients with AS was analysed, the role of SNP A1166C of the *AGTR1* gene in the metabolic syndrome was demonstrated by a higher rate of dyslipidemias in allele A carriers, particularly in heterozygote AC carriers, while type 2 diabetes mellitus (DM2) was reported only in genotype CC carriers.

During nephrogenesis, RAAS components demonstrate high expression and play a vital role in the regular structure of kidneys and their physiological function [25]. In kidneys, Ang II is expressed in significantly higher concentrations in the interstitial space. Local Ang II production can significantly affect kidney function by changing glomerule haemodynamics, inhibiting sodium excretion, and narrowing small arterioles [26]. Moreover, excessive RAAS activity directs pro-inflammatory and profibrotic factors to damage kidneys [27], while RAAS inhibition demonstrated efficiency in reducing renal fibrosis.

According to available data [28, 29], it has been demonstrated that the *AGTR1* gene contributes to chronic kidney damage. This study also demonstrated higher rates of renal pathologies in allele A carriers.

AGT1R activation by Ang II causes vasoconstriction and boosts the activity of the sympathetic nervous

system. It results in elevation in BP and aldosterone secretion, as well as heart hypertrophy and fibrosis. Numerous studies report the association between polymorphism 1166A>C (rs5186) of the *AGTR1* gene and arterial hypertension, vasoconstriction, and sodium retention [30]. The study by Semianiv et al. identified the association between allele C of the *AGTR1* gene (rs5186) and AH severity. This study demonstrated a higher rate of AH and more cases of grade 2 and 3 AH in genotype AC carriers, underlining a higher probability of AH development and higher severity of AH in genotype AC carriers with AS.

Conclusion

The results do not suggest any significant impact of SNP 1166A>C of the *AGTR1* gene on clinical manifestations of AS, except for BASMI and the rate of enthesitis. However, the results of the study demonstrated intriguing data on the role of SNP 1166A>C of the *AGTR1* gene in the hemopoiesis, namely reduced RBC and Hb levels, and higher platelet counts in genotype CC carriers.

Of special interest are the metabolic parameters: high glucose values in allele C carriers and DM2 only in homozygote CC. In turn, allele A was associated with higher blood triglyceride concentrations and dyslipidemia, especially in heterozygote AC. It is worth noting that allele A carriage was also associated with higher rates of renal pathologies and AH, and their severity.

The results of the study uncover the vast spectrum of functions of SNP 1166A>C of the *AGTR1* gene beyond contribution to AH. The results include regulation of hemopoiesis, metabolic mechanisms and comorbidities in patients with AS. It shows the significance and viability of genetic typing of patients with AS and identifying SNP 1166A>C of the *AGTR1* gene in order to provide patient-specific drug therapy of AS and monitor these parameters in the presence of a risk of SNP-associated conditions.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Гаффарова А.С.: существенный вклад в замысел и дизайн исследования, сбор данных, анализ и интерпретация данных, подготовка статьи, критический пересмотр в части значимого интеллектуального содержания

Белоглазов В.А.: существенный вклад в замысел и дизайн исследования, анализ и интерпретация данных, критический пересмотр в части значимого интеллектуального содержания

Яцков И.А.: существенный вклад в замысел и дизайн исследования, анализ и интерпретация данных, критический пересмотр в части значимого интеллектуального содержания

Ареева Е.С.: сбор данных, анализ и интерпретация данных, подготовка статьи, критический пересмотр в части значимого интеллектуального содержания

Петров А.В.: подготовка статьи, критический пересмотр в части значимого интеллектуального содержания

Contribution of Authors

All the authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication

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DOI: 10.20514/2226-6704-2026-16-4-305-311
УДК [616.832-004.2+616-097]-06:616-006.442
EDN: RQFQUL



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БОЛЕЗНЬ КИКУЧИ-ФУДЖИМОТО НА ФОНЕ ПЕРВИЧНОГО ИММУНОДЕФИЦИТА И РАССЕЯННОГО СКЛЕРОЗА: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Kikuchi-Fujimoto's Disease on The Background of Primary Immunodeficiency and Multiple Sclerosis: A Clinical Case

Резюме

Впервые описано сочетание болезни Кикучи-Фуджимото с общей вариабельной иммунной недостаточностью и рассеянным склерозом. Наличие у пациентки первичного иммунодефицита, сопровождающегося частыми и тяжелыми обострениями хронических заболеваний, привело к затяжному диагностическому поиску. Случай подчеркивает важность своевременного морфологического исследования при стойкой лимфаденопатии, даже у пациентов с известными иммунными нарушениями.

Ключевые слова: Болезнь Кикучи-Фуджимото, гистиоцитарный некротизирующий лимфаденит, первичный иммунодефицит, общая вариабельная иммунная недостаточность, рассеянный склероз

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «БОЛЕЗНЬ КИКУЧИ-ФУДЖИМОТО НА ФОНЕ ПЕРВИЧНОГО ИММУНОДЕФИЦИТА И РАССЕЯННОГО СКЛЕРОЗА: КЛИНИЧЕСКИЙ СЛУЧАЙ» для журнала «Архивъ внутренней медицины», подписав информированное согласие

Статья получена 20.01.2026 г.

Одобрена рецензентом 10.03.2026 г.

Принята к публикации 01.04.2026 г.

Для цитирования: Аранович Э.В., Лисовой В.А., Фефелова В.А. БОЛЕЗНЬ КИКУЧИ-ФУДЖИМОТО НА ФОНЕ ПЕРВИЧНОГО ИММУНОДЕФИЦИТА И РАССЕЯННОГО СКЛЕРОЗА: КЛИНИЧЕСКИЙ СЛУЧАЙ. Архивъ внутренней медицины. 2026; 16(4): 305-311. DOI: 10.20514/2226-6704-2026-16-4-305-311. EDN: RQFQUL

Abstract

For the first time, a combination of Kikuchi-Fujimoto's disease with general variable immune deficiency and multiple sclerosis has been described. The patient's primary immunodeficiency, accompanied by frequent and severe exacerbations of chronic diseases, led to a protracted diagnostic search. The case highlights the importance of timely morphological examination in persistent lymphadenopathy, even in patients with known immune disorders.

Key words: Kikuchi-Fujimoto's disease, histiocytic necrotizing lymphadenitis, primary immunodeficiency, general variable immune deficiency; multiple sclerosis

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Kikuchi-Fujimoto's Disease on The Background of Primary Immunodeficiency and Multiple Sclerosis: A Clinical Case» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

Article received on 20.01.2026

Reviewer approved 10.03.2026

Accepted for publication on 01.04.2026

For citation: Aranovich E.V., Lisovoy V.A., Fefelova V.A. Kikuchi-Fujimoto's Disease on The Background of Primary Immunodeficiency and Multiple Sclerosis: A Clinical Case. The Russian Archives of Internal Medicine. 2026; 16(4): 305-311. DOI: 10.20514/2226-6704-2026-16-4-305-311. EDN: RQFQUL

KFD — Kikuchi-Fujimoto disease, LN — lymph nodes, SLE — systemic lupus erythematosus, PID GVID — primary immunodeficiency: general variable immunodeficiency, MRI — magnetic resonance imaging, MS — multiple sclerosis, aHSCT — autologous haematopoietic stem cell transplantation, Ig — immunoglobulin

Introduction

Kikuchi-Fujimoto disease (KFD) is a benign self-limiting inflammatory disease characterised by histiocytic necrotising lymphadenitis. The condition affects primarily cervical lymph nodes (LNs); however, the pathologic process can also involve axillary and inguinal LNs. Due to the similarity of the clinical and anatomico-pathological presentation with lymphoproliferative disorders, the primary diagnoses is often wrong; therefore, it is important to raise awareness of this disorder among clinicians and pathologists [1, 2].

Clinically, KFD manifests as painful lymphadenopathy (the main criterion for the diagnosis, which is observed in all reported cases), fever and marked weakness. The clinical presentation can include diarrhea, weight loss, dyspepsia, arthralgia, skin rashes, and enlarged liver and spleen. In individual cases, the disease is aggravated by aseptic meningitis or optic neuritis. Skin manifestations can vary from simple papules to necrosis of individual keratinocytes, and are reported in 30 % of cases. Histologic examination of affected skin of KFD patients shows lymphohistiocytic infiltration of the derma, nuclear disruption, mucin deposits, panniculitis, and disrupted dermoepidermal junction. Clinical blood analysis comes back normal; however, anemia, leukopenia, leukocytosis, lymphocytosis, and slightly elevated erythrocyte sedimentation rate can be reported [3–5].

The cause of the disease remains unclear. There is no connection with the race; and the condition usually manifests in individuals of 30 to 40 years of age. It is assumed that the disease is triggered by Epstein-Barr virus, human herpes virus 6 and 8, parvovirus B19, cytomegalovirus, *Yersinia enterocolitica*, *Toxoplasma gondii*, and *Brucella*. An infectious or non-infectious trigger causes an immune reaction mediated by T-cells and histiocytes. The viral origin is supported by elevated levels of alpha-interferon and its stimulating agents, as

well as tubuloreticular structures in the cytoplasm of stimulated lymphocytes, histiocytes, and vascular endothelium. A favourable therapeutic response to tominocycline, ciprofloxacin and ofloxacin in several clinical cases proposes the possible pathogenic role of other non-viral microorganisms, which are sensitive to antimicrobial agents. There is a theory about an autoimmune mechanism, since there are numerous patients with autoimmune pathologies before, during, and after the diagnosis of KFD is confirmed. Systemic lupus erythematosus (SLE) is most common, assuming the existence of common pathogenic links. The histological pattern of lymphadenitis in SLE patients can resemble that of KFD; however, the key distinguishing characteristic in SLE is the presence of hematoxylin bodies. Moreover, KFD is a self-limiting condition and is not a chronic pathology. KFD can be associated with other autoimmune conditions, e.g. primary Sjögren's syndrome, Hashimoto's thyroiditis, antiphospholipid syndrome, and hypersensitivity vasculitis [1–4, 6].

KFD is diagnosed on the basis of histological and immunohistochemical examinations of a removed LN.

There are three stages of the disease:

1. Early (proliferative) stage: the paracortical layer of histiocytes and plasmacytoid dendritic cells is widened; the infiltrate incorporates lymphocytes and karyorrhectic nuclear debris.
2. Intermediate (necrotic) stage: areas of necrosis start appearing in the paracortex.
3. Late (xanthomatous) stage: foamy histiocytes prevail, irrespective of the presence or absence of necrosis [3, 6].

The complex histological pattern, which depends on the stage of the disease, can make the diagnosis even more challenging.

KFD regresses spontaneously within several months and is associated with a favourable prognosis. Patients

should be followed up for several years after recovery, since 5 % of cases relapse or show signs of an autoimmune pathology. There is no KFD-specific therapy, since the evidence base is limited to the data from observational studies. In severe cases, symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) with glucocorticosteroids is used [3, 6, 7].

A PubMed analysis as of 20.10.2025 using “Kikuchi-Fujimoto disease” search returned 397 publications from 1996 to 2025, including 267 clinical cases; the rest are literature reviews. It confirms that this pathology is quite rare.

Clinical Case Report

Patient A., 42 years of age, has primary immunodeficiency: general variable immunodeficiency (PID GVID), and receives life-long therapy with human immunoglobulin once a month. PID is caused by heterozygous mutation in exon 6 chr4:102567013 c.285G>T, p.Lys95Asn (NM_003998.4) of gene *NFKB1*. Immunodeficiency resulted in frequent episodes of chronic tonsillitis; acute respiratory viral infections were associated with lingering cough.

The family history shows rheumatoid arthritis in her mother and confirmed alopecia localis in her younger daughter.

When she was 20 years of age, the patient complained of facial numbness, headaches, and double vision. NSAIDs had a short positive effect. Three years later, magnetic resonance imaging (MRI) showed areas of demyelination in the brain. The patient was later diagnosed with multiple sclerosis (MS). She was treated with interferon-beta-1b and vascular therapy, and also attended exercise therapy sessions. Six years later, MS progression was confirmed: she had lurching walk; brain and cervical spine contrast-enhanced MRI showed multiple areas of demyelination of up to 11 mm in periventricular and supraventricular regions and cerebellum. There was also a 9x4 mm area at the C3-4 level in the spine. In order to manage the aggressive progression of MS, autologous haematopoietic stem cell transplantation (aHSCT) was performed with BEAM modified immunosuppression therapy. The therapy was associated with grade IV neutropenia (max. 0.2 ths/ μ L), grade IV thrombocytopenia (max. 18 ths/ μ L), grade 2 hepatotoxicity (ALT 198 U/L, AST 62 U/L, total bilirubin 30.8 μ mol/L).

Long after the transplantation, the patient had lingering catarrhal diseases, which required regular antibacterial therapy. She had frequent episodes of chronic bronchitis, tonsillitis, sinusitis, otitis, and maxillitis.

A follow-up MRI performed three years after the aHSCT showed supraventricular areas of inactive demye-

linating disease. Blood immunoglobulin lab results demonstrated lower immunoglobulin G (IgG) (291 mg/dL; reference range: 900–1800 mg/dL); IgM values were normal (226 mg/dL; reference range: 80–250 mg/dL); IgA levels dropped to 5 mg/dL (reference range: 100–350 mg/dL). An extended lymphocyte immunophenotyping with T-cell subpopulation identification returned the following results: CD switch 0.9–2.7 %, CD4 1190, CD8 810, CD19 430, NK 300, CD21low 5,3, CD transient 1.5–1.2. A comprehensive immunoassay aimed at the restoration of the humoral and cellular components of the immune system; facilitation of the decision whether a replacement immunoglobulin therapy was required; assessment the risks of infectious complications of PID GVID; and MS therapy correction. These assays were performed for the first time, since the initial levels of blood immunoglobulins and lymphocyte subpopulations were unknown.

From February 2023 to November 2024, the patient had to interrupt her therapy with human immunoglobulin. During this period, she had monthly penicillin antimicrobials for frequent respiratory diseases. In November 2024, immunoglobulin therapy was resumed.

Due to regular catarrhal diseases and episodes of chronic conditions, the patient was repeatedly admitted to the allergology and immunology ward. During one of the admissions in April 2024, polymerase chain reactions for cytomegalovirus, Epstein-Barr virus, and human herpes virus 6 returned negative results. Helminthic involvement was excluded when negative anti-parasite antibodies results were received. Immunoblotting for a wide range of antinuclear antibodies was performed, which allowed excluding SLE, Sjögren's syndrome, systemic scleroderma, and other diffuse connective tissue disorders. Besides, C3-complement component levels dropped to 0.84 g/L with normal C4-complement component values (0.178 g/L), which is a sign of the classical complement pathway activation and can evidence the presence of an immunoinflammatory process of any other nature. A sputum sample was tested for *M. tuberculosis*, the result was negative. Peripheral LN ultrasound showed peripheral lymphadenopathy.

In April 2025, when the patient was 42 years of age, she noticed sudden marked enlargement of cervical LNs on the left; fever of up to 38.5 degrees Celcius in the evening, difficulty in swallowing, and sore throat with prodromes. Her GP prescribed levofloxacin; the therapy was ineffective. Several days later, her LNs got enlarged on the right side of the neck, these were painful to the touch; and diarrhea appeared. The patient started amoxicillin with clavulanic acid, with no effect.

Three months later, the patient started feeling very poorly; she developed extreme weakness, haze, excessive

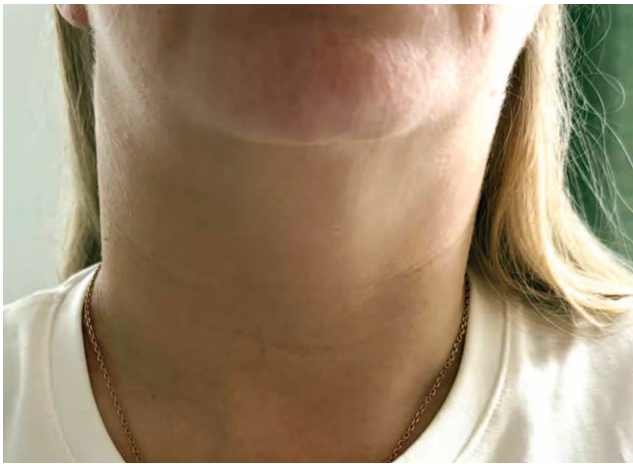


Figure 1. Enlarged lymph nodes of the neck

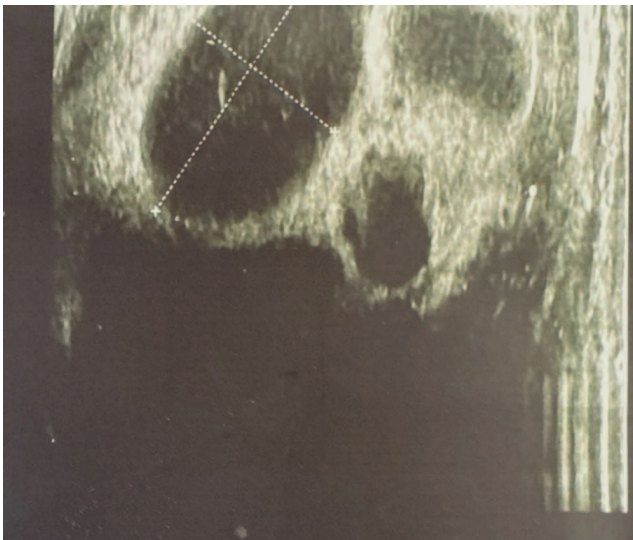


Figure 2. Ultrasound examination of the lymph nodes of the neck

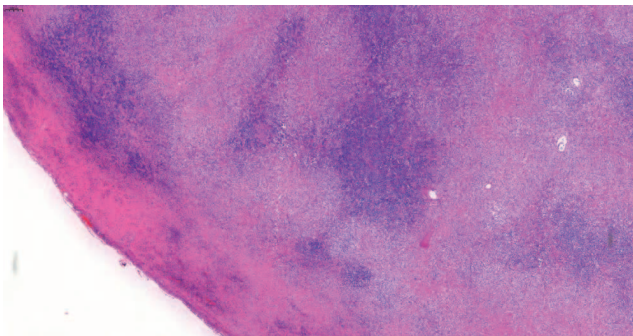


Figure 3a. Hematoxylin and eosin staining $\times 400$. Expansion of the paracortical zone with the formation of foci of necrosis. The cellular infiltrate includes a mixed cell population, including histiocytes with a virtually complete absence of neutrophils and eosinophils.

sweat, dry mouth, polydipsia, and loss of appetite, where she lost 10 kg of her weight. Over time, the LNs enlarged even more and the patient started feeling as if her neck skin was stretched. Severe headaches appeared, with NSAIDs therapy being of little to no use.

By September, the elevated body temperature was observed immediately after awakening, with the highest values reaching 38.7°C with NSAIDs therapy. Since the symptoms progressed and the patient's condition was resistant to the antibiotic treatment, the patient was admitted to the allergology and immunology ward. Stool test results: *Escherichia coli* 10^5 CFU/mL, *Klebsiella oxytoca* 10^4 CFU/mL, *Candida albicans* 10^5 CFU/mL. Tests for acute enteric infection pathogens (*Shigella spp*, *Salmonella*, *Campylobacter spp*, *Adenovirus F*, *Enterovirus*, *Rotavirus grA*, *Norovirus G2*, *Astrovirus*) came back negative. Blood draw results showed an inflammatory response; however, imaging examinations did not find the focus of inflammation.

Since a malignancy was suspected, the patient was consulted by a cancer specialist. On palpation, left and right cervical LNs, left axillary LNs were enlarged up to 3 cm, moderately painful and soft (Fig. 1). During the consultation, another LN ultrasound was performed, which showed the following results: cervical LNs: multiple on both sides, not tending to fuse, impaired corticomedullary differentiation, ovoid, with even contours, without hypervascularisation, up to 26×21 mm on the right and up to 24×18 mm on the left. Axillary LNs: individual on both sides, not tending to fuse, preserved corticomedullary differentiation, ovoid, with uneven contours, without hypervascularisation, up to 25×14 mm on the right and up to 21×15 mm on the left. Inguinal LNs: individual on both sides, not tending to fuse, preserved corticomedullary differentiation, ovoid, with even contours, without hypervascularisation, up to 16×15 mm on the right and up to 14×16 mm to the left (Fig. 2).

As part of the differential diagnosis of the systemic blood disease, an excision biopsy and histological examination of a cervical LN was performed, which showed morphological signs of necrotising lymphadenitis. The material was also sent for immunohistochemistry; the changes correspond to necrotising lymphadenitis in Kikuchi-Fujimoto disease (Fig. 3a, 3b, 3c, 3d).

The clinical presentation and immunohistochemistry results allowed diagnosis Kikuchi-Fujimoto disease.

It was decided to initiate the weekly symptomatic treatment with dexamethasone 12 mg, ascorbic acid 10 mL, cytoflavin 10 mL, Reamberin 500 mL, and omeprazole 40 mg. Since the clinical response to the therapy was poor, daily IV injections of prednisolone 40 mg were introduced. After therapy correction, the symptoms of the disease improved.

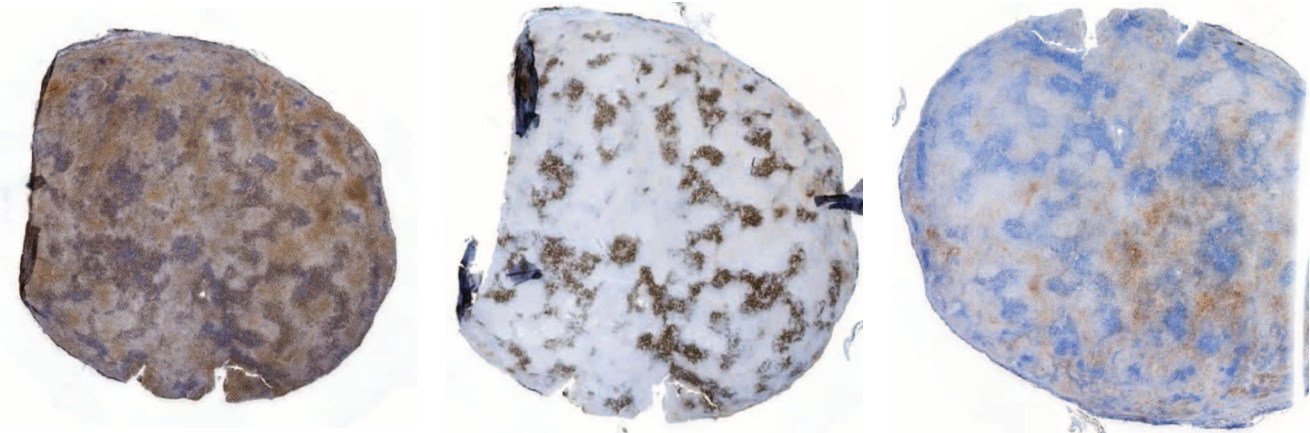


Figure 3b. Enzyme immunoassay, diffuse positive reaction with anti-bodies to CD3 (magnification ×100)

Figure 3c. ELISA reveals a positive reaction in the form of isolated foci with antibodies to CD20 (magnification ×100). Extensive areas of necrosis and infiltrate are unstained

Figure 3d. Enzyme immunoassay, focal positive reaction with antibodies to CD10 (magnification ×100), localized mainly in the germinal centers of lymphoid follicles

Table 1. Dynamics of laboratory parameters

Mark	09.2024	09.2025	11.2025
Total IgG (900-1800 mg/dL)	370 mg/dL	963 mg/dL	928 mg/dL
Total IgM (80-250 mg/dL)	330 mg/dL	262,8 mg/dL	281 mg/dL
Total IgA (100-350 mg/dL)	20 mg/dL	0,001 mg/dL	1 mg/dL
Total IgE (up to 100 IU/ml)	<1 IU/ml	-	<1,00 IU/ml
Hb (120–140 g/l)	143 g/l	118 g/l	115 g/l
PLT (179.00-403.00 10 ⁹ /l)	255 x 10 ⁹ /l	137 x 10 ⁹ /l	132 x 10 ⁹ /l
Leukocytes (4.50-11.00 10 ⁹ /l)	7,8 x 10 ⁹ /l	1,94 x 10 ⁹ /l	9,72 x 10 ⁹ /l
Neutrophils (2.10-8.89 10 ⁹ /l)	3,49 x 10 ⁹ /l	0,86 x 10 ⁹ /l	9,07 x 10 ⁹ /l
Eosinophils (0.01-0.40 10 ⁹ /l)	0,64 x 10 ⁹ /l	0,0 x 10 ⁹ /l	0,0 x 10 ⁹ /l
Basophils (0.00-0.07 10 ⁹ /l)	-	0,0 x 10 ⁹ /l	0,0 x 10 ⁹ /l
Lymphocytes (1.26-3.35 10 ⁹ /l)	3 x 10 ⁹ /l	0,93 x 10 ⁹ /l	0,49 x 10 ⁹ /l
Monocytes (0.25-0.84 10 ⁹ /l)	0,62 x 10 ⁹ /l	0,15 x 10 ⁹ /l	0,16 x 10 ⁹ /l
ESR (0.00-30.00 mm/hour)	21 mm/hour	11,0 mm/hour	23 mm/hour
CRP (up to 5 mg/l)	-	7,77 mg/l	0,19 mg/l

Note: Ig — immunoglobulins, Hb — hemoglobin, PLT — platelets, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein

Discussion

This clinical observation is a case of KFD in a patient with multiple comorbidities. The main diagnostic challenge in this case was the history of PID and MS. From an early age, the patient has had frequent infections and chronic lymphadenopathy, and even being an adult, they were treated as manifestations of PID or its complications. In turn, it resulted in a long-lasting diagnostic search. This case demonstrates the importance of cancer alertness in persistent lymphadenopathy resistant to empiric antimicrobial therapy.

The analysed publications do not report any patients with KFD and PID GVID or MS, evidencing the unique

nature of this clinical case. Vaidya H. et al. described a case of a 35-year-old patient complaining of severe abdominal pain, vomitting, general weakness, episodes of fever, and joint pain both in legs and arms. Lab results demonstrated marked anaemia, and abdominal ultrasound showed enlarged liver and delated portal and splenic veins. The patient also complained of impaired vision acuity. An ophthalmic examination revealed multiple cotton wool-shaped macules on the retina of both eyes, haemorrhage in the left eye along the lower arcade, areas of paracentral acute moderate macular retinopathy to the right, while the left eye had a thickened outer plexiform layer [8].

The case of a 20-year-old patient described by Gurung S. et al. reported standard clinical manifestations of lymphadenopathy, fever, and asthenia. Lab results were within the normal range [9].

There are also numerous cases of disease manifestations following SARS-CoV-2 vaccination. For instance, Ikeda K. et al. described a case of a 20-year-old patient with progressing complains after vaccination. Lab test results demonstrated leukopaenia, inflammatory syndrome, and elevated lactate dehydrogenase levels. G, A and M immunoglobulins, C3 and C4 complement concentrations, and antinuclear antibody titer were normal. SARS-CoV-2 PCR test was negative. Imaging examinations revealed enlarged liver and spleen [10].

Identification of the precise trigger of KFD is rather challenging; therefore, the causes of the disease remain unknown. The theory of the association between KFD and autoimmune diseases is common; however, in the present case the specific markers of SLE and other diffuse connective tissue disorders were negative; a history of MS and a family history of autoimmune pathologies evidence potential general susceptibility to immune dysregulation. This is in line with the theory of excessive or inadequate immune response to various triggers (viral, bacterial) in susceptible individuals.

An analysis of the reported cases and comparison with the described clinical case assume that the classical presentation of KFD (lymphadenopathy, fever, and asthenia) remains the same. However, the patient in this case study had a more lingering and more severe disease, caused by a long-lasting diagnostic search and PID.

Conclusions

KFD is a very rare disease, which should not be negated in the differential diagnosis of lymphadenopathy and idiopathic fever. It can mimic lymphoma or systemic autoimmune diseases, requiring mandatory morphological confirmation. Diagnosis of KFD can be particularly challenging in patients with concomitant immunodeficiencies. This case study underlines the importance of a multidisciplinary assessment of the clinical presentation and prompt biopsy in atypical or refractory lymphadenopathy.

PID GVID and MS in the patient make possible an assumption of the link between transcription factor protein dysregulation, autoimmune susceptibility, and KFD development.

Despite the challenging diagnosing path, the KFD prognosis remains favourable. The disease is self-limiting and responds well to symptomatic therapy, including glucocorticosteroids. This case demonstrates a favourable disease outcome even in a patient with severe KFD and a severe comorbidity.

Therefore, higher KFD awareness among health-care professionals and inclusion of the disease into the differential diagnosis in patients with fever and lymphadenopathy allow timely diagnosis, prevent unnecessary tests and examinations, and ensure adequate treatment.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Аранович Э.В.: разработка концепции, подготовка и редактирование текста

Лисовой В.А.: разработка концепции, получение данных, анализ и интерпретация данных, подготовка и редактирование текста, поиск и анализ научной литературы

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Author Contributions:

All authors made a significant contribution to the preparation of the paper and read and approved the final version of the article before publication

Aranovich E.V.: concept development, text preparation and editing;

Lisovoy V.A.: concept development, data acquisition, data analysis and interpretation, text preparation and editing, search and analysis of scientific literature;

Fefelova V.A.: concept development, data acquisition, data analysis and interpretation, text preparation and editing, search and analysis of scientific literature.

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DOI: 10.20514/2226-6704-2026-16-4-312-320

УДК 616.72-002.771-085.276

EDN: TWWNIS

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ХВДП-ПОДОБНАЯ ДИЗИММУННАЯ ДЕМИЕЛИНИЗИРУЮЩАЯ ПОЛИРАДИКУЛО- НЕЙРОПАТИЯ, АССОЦИИРОВАННАЯ С ТЕРАПИЕЙ БРЕНТУКСИМАБОМ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Brentuximab Vedotin-Induced CIDP-Like Inflammatory Demyelinating Polyradiculo- neuropathy (Clinical Case Report)

Резюме

Брентуксимаб ведотин-индуцированная дизиммунная демиелинизирующая полирадикулонейропатия является редким нежелательным побочным явлением химиотерапии, связанным с патологическим влиянием препарата на функционирование гуморальной иммунной системы. Клиническая картина заболевания характеризуется прогрессирующим развитием вялого тетрапареза и чувствительных нарушений по полиневритическому типу, нередко приводящим к выраженному нарушению качества жизни и инвалидизации пациентов. Результаты нейрофизиологического обследования представлены генерализованным поражением моторных и сенсорных волокон периферических нервов первично демиелинизирующего характера с наличием блоков проведения по моторным волокнам нервов рук в нетипичных для компрессии местах и феномена 'sural sparing pattern'. Клинико-анамнестические данные и показатели объективных методов обследования сходны с клинико-нейрофизиологическим паттерном, наблюдаемым при острой или хронической воспалительных демиелинизирующих полирадикулонейропатиях. Важной особенностью заболевания является положительный ответ на стандартную патогенетическую терапию аналогично классическим дизиммунным полирадикулонейропатиям, которая включает глюкокортикостероиды, препараты иммуноглобулинов человека для внутривенного введения и методы экстракорпоральной гемокоррекции. Обратимость неврологических нарушений на фоне патогенетической иммуносупрессивной терапии обуславливает необходимость повышения осведомленности врачей о тактике ведения данной категории пациентов. Представленный клинический случай демонстрирует пример брентуксимаб-индуцированной дизиммунной демиелинизирующей полирадикулонейропатии с прогрессирующим развитием грубых моторных нарушений, которые в течение 6 месяцев привели к полной обездвиженности пациента. Своевременное назначение патогенетической терапии в оптимальном режиме дозирования, грамотная тактика ведения, подразумевающая медленное и постепенное снижение доз глюкокортикостероидных препаратов, обеспечивает благоприятный исход при рассматриваемой курабельной лекарственно-индуцированной полирадикулонейропатии.

Ключевые слова: брентуксимаб ведотин, химиотерапия, лимфома Ходжкина, хроническая воспалительная демиелинизирующая полирадикулонейропатия, ХВДП, иммуносупрессивная терапия, глюкокортикостероидные препараты, ГКС

Конфликт интересов

Соавтор статьи Супонева Н.А. является членом редакционной коллегии журнала «Архивъ внутренней медицины». Статья прошла принятую в журнале процедуру рецензирования. Супонева Н.А. не участвовала в принятии решения о публикации этой статьи. Об иных конфликтах интересов авторы не заявляли

Сведения об источниках финансирования работы

Авторы заявляют об отсутствии внешних источников финансирования.

Соответствие принципам этики

Пациент дал согласие на опубликование данных инструментальных исследований в статье «ХВДП-ПОДОБНАЯ ДИЗИММУННАЯ ДЕМИЕЛИНИЗИРУЮЩАЯ ПОЛИРАДИКУЛОНЕЙРОПАТИЯ, АССОЦИИРОВАННАЯ С ТЕРАПИЕЙ БРЕНТУКСИМАБОМ (КЛИНИЧЕСКИЙ СЛУЧАЙ)» для журнала «Архивъ внутренней медицины».

Статья получена 12.10.2025 г.

Одобрена рецензентом 04.12.2025 г.

Принята к публикации 17.02.2026 г.

Для цитирования: Зайцевская С.А., Гришина Д.А., Супонева Н.А. ХВДП-ПОДОБНАЯ ДИЗИММУННАЯ ДЕМИЕЛИНИЗИРУЮЩАЯ ПОЛИРАДИКУЛОНЕЙРОПАТИЯ, АССОЦИИРОВАННАЯ С ТЕРАПИЕЙ БРЕНТУКСИМАБОМ (КЛИНИЧЕСКИЙ СЛУЧАЙ). Архивъ внутренней медицины. 2026; 16(4): 312-320. DOI: 10.20514/2226-6704-2026-16-4-312-320. EDN: TWWNIS

Abstract

Brentuximab vedotin-induced inflammatory demyelinating polyradiculoneuropathy is a rare chemotherapy side effect. The underlying cause of disease is thought to be pathological drug effects on the humoral immune system. The typical clinical picture is characterized by progressive development of flaccid tetraparesis and severe polyneuritic manifestations, which typically leads to disability and significant impairment in quality of life. Nerve conduction study results show evidence of generalized primary demyelination, including conduction block and sural sparing pattern. Clinical and anamnestic data and objective observational findings are similar to the clinical and neurophysiological pattern observed in acute or recurrent inflammatory demyelinating polyradiculoneuropathies. It is important to emphasize that brentuximab vedotin-induced inflammatory demyelinating polyradiculoneuropathy response to accepted in guidelines pathogenetic therapy, which includes corticosteroids, intravenous human immunoglobulin therapy and extracorporeal hemocorrection methods. Clinicians should be aware of treatment possibilities due to reversibility of neurological impairment through the pathogenetic immunosuppressive therapy. This clinical case represents a case of brentuximab-induced inflammatory demyelinating polyradiculoneuropathy with progressive development of severe motor impairment, which led to complete immobilization over 6 months. This clinical case report demonstrates optimal management strategy: timely administration of pathogenetic therapy with appropriate dosing, slow and gradual reduction in corticosteroid dosage. Competent management strategy ensures favorable outcome of the curable drug-induced polyradiculoneuropathy.

Key words: *brentuximab vedotin, chemotherapy, Hodgkin disease, chronic inflammatory demyelinating polyradiculoneuropathy, CIDP, immunosuppression therapy, glucocorticoids.*

Conflict of interests

Co-author of the article Suponeva N.A. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure Suponeva N.A. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Brentuximab Vedotin-Induced CIDP-Like Inflammatory Demyelinating Polyradiculoneuropathy (Clinical Case Report)» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

Article received on 12.10.2025

Reviewer approved 04.12.2025

Accepted for publication on 17.02.2026

For citation: S.A. Zaitsevskaya, D.A. Grishina, Suponeva N.A. Brentuximab Vedotin-Induced CIDP-Like Inflammatory Demyelinating Polyradiculoneuropathy (Clinical Case Report). The Russian Archives of Internal Medicine. 2026; 16(4): 312-320. DOI: 10.20514/2226-6704-2026-16-4-312-320. EDN: TWWNIS

BV — brentuximab vedotin, DDP — disimmune demyelinating polyradiculoneuropathy, RCNN — The Russian Centre of Neurology and Neurosciences, CIDP — chronic inflammatory demyelinating polyradiculoneuropathy, ENMG — electroneuromyography, CTCAE — Common Terminology Criteria for Adverse Events, MRC — Medical Research Council

Introduction

Peripheral neuropathy (PN) is one of the most common adverse side effects (ASE) of chemotherapy, impairing patients' quality of life, and is a frequent cause of cancer therapy adjustments. Chemotherapy-induced polyneuropathy is frequently reported as a side effect of drugs, the mechanism of action of which involves damage to microtubules in cancer cell cytoskeleton [1, 2]. Brentuximab vedotin (BV) is a drug conjugate, comprising three components: 1) chimeric monoclonal immunoglobulin G1 anti-CD30 receptor cAC10 antibody; CD30 receptor is a tumour necrosis factor receptor; 2) active substance — microtubule-targeting agent

monomethyl auristatin E; 3) a protease-cleavable linking agent, which links both compounds together. The activity of BV is based on its ability to bind to the cells, which express CD30 receptor, and internalise into cytoplasm of the active substance, which binds to tubulin, impairs microtubule function, and breaks the cell cycle, causing target cell death [3]. In August 2011, BV was registered in the USA; in Russia, the drug was registered in 2016 [4]. Currently, BV is used to treat Hodgkin lymphoma, peripheral CD30+ T-cell lymphoma and primary skin T-cell lymphoma, usually as a third- or fourth-line therapy, where other chemotherapy options or red bone marrow stem cell autologous transplantation

were inefficient [5]. Peripheral neuropathy is the most common ASE of BV therapy. In phase II clinical trials of the drug, the rate of PNs of various degrees of severity varies between 9% and 73%: in 41–44% of cases, sensory polyneuropathy was reported; while 9–11% were motor polyneuropathy [3,6–8]. It has been noted that 11–23% of patients had to interrupt BV therapy because of severe PN [3,6,7,9]. Later it was determined that BV-induced disimmune demyelinating polyradiculoneuropathy (DDP) can account for up to 14.6% of patients with BV-induced NP and up to 7.2% among all patients treated with BV [5].

The objective of this article is to describe a clinical case of disimmune demyelinating polyradiculoneuropathy associated with brentuximab vedotin therapy, and to compare the clinical and neurophysiological pattern of brentuximab-induced demyelinating neuropathy with globally reported cases, as well as with cases of classical chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Clinical Case Report

Patient N., born in 1994, sought help at the Russian Centre of Neurology and Neurosciences (RCNN) for the first time in October 2024, complaining of weakness and numbness in his limbs. His medical history shows that since 2019 the patient has been followed up by an oncohematologist for Hodgkin lymphoma, type 2 nodular sclerosis, stage IVB, with involvement of neck lymph nodes, mediastinum and lungs, with penetration through pericardium and pleural membrane. After his diagnosis, the patient underwent multiagent chemotherapy: in 2019 — BEACOPP 14 (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone), 2022 — Nivo-BeGEV (nivolumab in a combination with bendamustine, gemcitabine, and vinorelbine); as well as radiation therapy in the mediastinum area in 2019; red bone marrow stem cell autologous transplantation in April 2022; lymph node excision in 2023. The therapy did not cause any neurological complications. From July 2023 to May 2024 the patient was treated for cancer relapse with brentuximab vedotin and showed complete reported metabolic response to the therapy in September 2023. In December 2023 (six month into his BV therapy), the patient noticed gradually progressing weakness in his limbs. His condition progressed to complete immobility by June 2024. Follow-up examinations, including positron emission tomography and computed tomography (PET/CT), showed remission of the disease. At the local outpatient clinic, the patient was diagnosed with CIDP-like neuropathy, and in July 2024 he underwent a course of IV pulse therapy with

methylprednisolone (MP) 5 g, then oral MP 64 mg daily for a week, after that the MP dose was reduced to 36 mg for four months. Thus, at the time of his visit to RCNN in October 2024, the patient's daily MP dose was 28 mg. Three weeks of high-dose immunosuppressive therapy resulted in significant improvement in limb mobility: the patient was able to walk with support, get up and sit down unaided. The rate of recovery slowed down after rapid MP dose reduction; however, his condition remained stable.

At the time of the first visit to RCNN in October 2024, the neurological status was prevailed by distal flaccid tetraparesis with diffuse areflexia, hypotonia and muscle hypotrophy: 4 points on the MRC scale in proximal limbs; up to 1–2 points in hand and finger flexors; and up to 0–1 points in hand and finger extensors, interosseal muscle of hands, and feet extensors and flexors. Superficial and deep sensibility impairment (polyneuritic form) was classified as minor. In RCNN, the patient underwent stimulation electro-neuromyography (ENMG), which showed generalised, mostly motor, neural demyelinating impairment with possible conduction in motor fibres of hand nerves in sites, which are not common for neural compression (Table 1).

Clinical and medical history data, namely the temporal association between disease onset and BV therapy initiation, positive response to the immunosuppressive therapy by the time of the visit, as well as neurophysiological examination results allowed confirming the diagnosis “CIDP-like disimmune, mostly motor, demyelinating polyradiculoneuropathy, associated with the therapy with brentuximab vedotin”.

Due to persistent significant neurologic impairment with lower rates of recovery because of the rapid reduction in the dose of MP, glucocorticosteroid therapy was corrected: it was recommended to replace MP 28 mg daily with MP 48/24 mg, alternating the high and the low doses every other day for three months, and then gradually reducing first the low dose, then the high dose of the drug. After the GCS therapy was corrected, considerable positive changes were observed, and clinical symptoms started improving more rapidly: in July 2025 (one year after GCS therapy initiation), the patient's MP dose was reduced to 20 mg once every other day. Upon examination, distal mild to moderate tetraparesis was still observed: up to 4 points (MRC) in hand and finger flexors and up to 3–4 points in finger extensors and feet flexors/extensors. The patient did not need any support while walking; he was able to get up from the chair without the help of his hands and could stand on his toes and heels. Thus, glucocorticosteroid therapy helped changing the clinical pattern from complete immobility to distal mild to moderate tetraparesis. Similar to clinical

manifestations, neurophysiological examination results showed positive changes: improved amplitude and speed parameters, improvement in possible conduction in motor fibres of hand nerves (Table 2). When this case study was reported, the patient was still consulted by RCNN specialists in order to select a maintaining dose of methylprednisolone.

Discussion and literature review

Brentuximab-induced polyneuropathy is the most common adverse effect of BV therapy [3]. In the majority of reported cases, clinical presentation comprises a classical set of symptoms: damage to thick and thin sensitive fibres with the development of predominantly superficial sensitivity impairment; deep sensitivity is reduced less frequently (polyneuritic mild to moderate impairment with signs of primary axon involvement, as demonstrated by stimulation ENMG) [8,10]. It is assumed that axon damage is associated with immediate cytotoxic effects for microtubule functioning from monomethyl auristatin E, a component of BV [11].

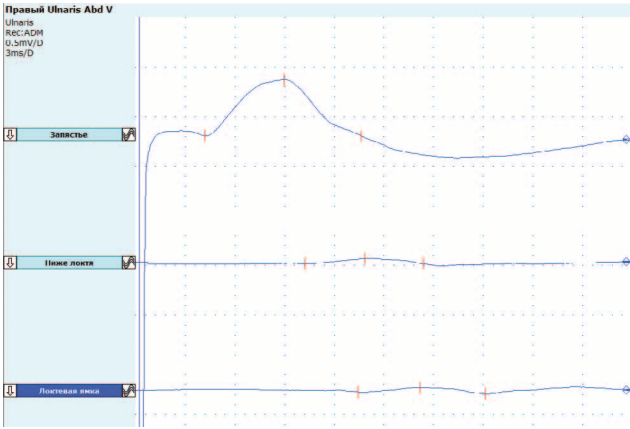
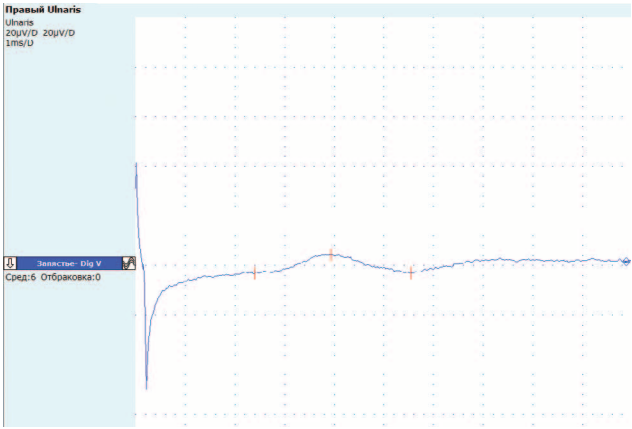
Nevertheless, there are global reports of isolated cases of BV-associated disimmune demyelinating poly-

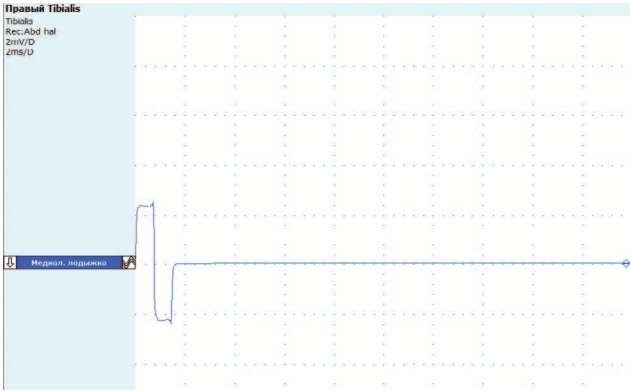
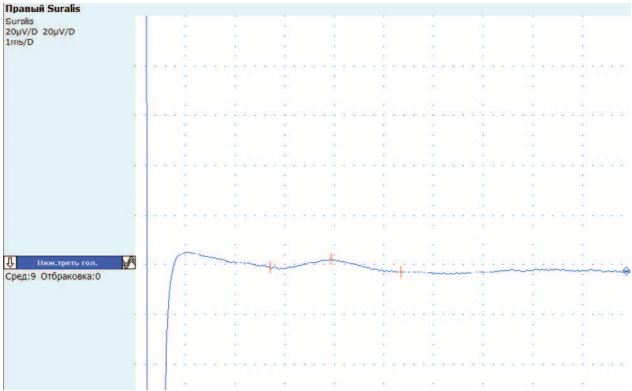
radiculoneuropathy. The first case of BV-induced DDP was reported in 2013 by Pastorelli F. et al. [12]; later, individual observations were published in 2017–2022 [2, 13, 14]. The largest review by Fargeot G. et al. (2020) is a retrospective analysis of three cases (0.4 %) of Guillain-Barre syndrome and 9 cases (1.3 %) of CIDP, which were verified among 700 patients treated with BV during 2013 to 2019 [15]. Later, a single-centre study by Matthys A. et al. (2024) reported 6 clinical cases (7 %) of disimmune NP in 83 patients treated with BV [5]. It is assumed that damages to the myelin sheath may be caused by aberrated immune response as a result of the impact by chimeric monoclonal immunoglobulin G1, i.e. the first component of BV, on CD30-expressing cells, similar to the drugs, which inhibit TNF [15,16]. Histologic examination results of patients with rapidly progressing BV-induced motor neuropathy demonstrate a mixed axonal and demyelinating pattern of the damage: sural nerve biopsy specimens show reduced sheathed fibre density, signs of wallerian degeneration and sporadic accumulation of regenerating fibres. Electron microscopy results show signs of damaged axon cytoskeleton, changes in orientation and overall number of microtubules, mostly in sheathed fibres [2,17].

Table 1. Nerve conduction study results of patient N., first visit in Russian Center of Neurology and Neurosciences (03.10.2024). Electromyography machine Keypoint, Dantec (Denmark).

Nerve conduction study results of the right median nerve	
CMAP parameters (lead with m. APB dexter)	SNAP parameters (lead with dig. II)
Правый Медианс APB Medianus REC:APB 0.3mV/D 3ms/D Заметьте Локтевой сгиб	Правый Медианс Medianus 20µV/D 20µV/D 1ms/D Заметьте- Dig II Сред:11 Отбрасывае:0
CMAP latency, ms (N <3.5): 4.28	CNAP latency, ms (N <3.0): 3.58
CMAP amplitude, mV (N >5.0): 0.35	CNAP amplitude, µV (N >15.0): 5.0
Right median motor study shows significant temporal dispersion on 2 nd stimulation point (elbow)	Conduction velocity, m/s (N >50): 44.7
Distal CMAP duration: 8.3 (N <8.4)	
Proximal CMAP duration: 8.3 (N<8.4)	
Conduction velocity, m/s (N >50) (elbow-wrist segment): 25.5	—

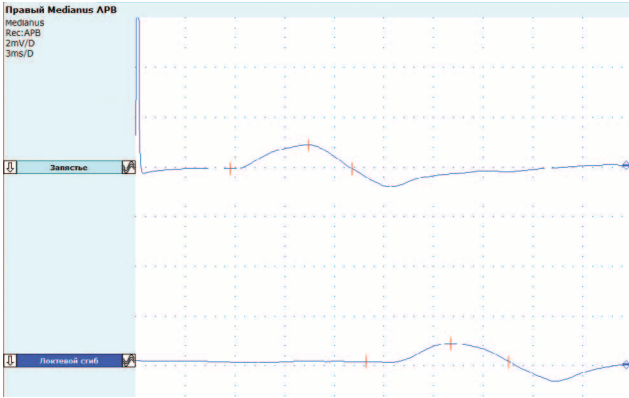
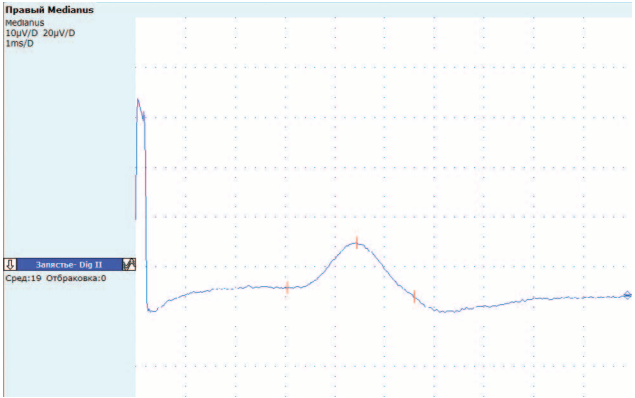
Table 1. (The End).

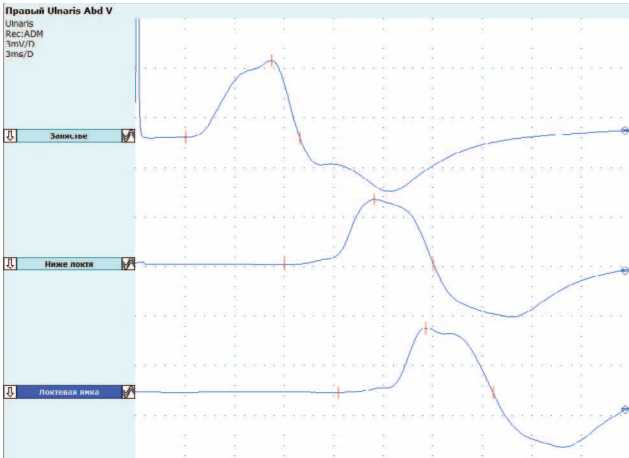
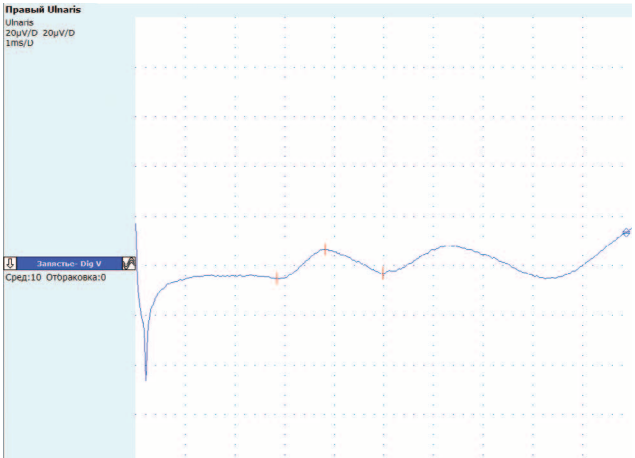
Nerve conduction study results of the right ulnar nerve	
CMAP parameters (lead with m. ADM dexter)	SNAP parameters (lead with dig. V)
	
CMAP latency, ms (N <3.0): 4.28	CNAP latency, ms (N <3.0): 3.58
CMAP amplitude, mV (N>6.0): 0.57	CNAP amplitude, µV (N>15.0): 7.6
Right ulnar motor study shows probable conduction block below elbow: 91 %	—
Conduction velocity, m/s (N>50) (below elbow-wrist and above elbow to below elbow segments): 33.2 — 40.6	Conduction velocity, m/s (N>50): 60.4

Nerve conduction study results of the right tibial nerve	Nerve conduction study results of the right sural nerve
CMAP parameters (lead with m. AH dexter)	SNAP parameters
	
Right tibial motor study showed no responses	SNAP latency, ms (N <4.0): 2.71
—	SNAP amplitude, µV (N>6.0): 4.2
—	Conduction velocity, m/s (N>40): 44.3

Note: ADM — abductor digiti minimi manus muscle; APB — abductor policis brevis muscle; AH — adductor hallucis; CMAP — compound muscle action potential; dig. — digitus; N — norm; SNAP — sensory nerve action potential

Table 2. Nerve conduction study results of patient N., dynamics in 8 months on steroid therapy (03.07.2024). Electromyography machine Keypoint, Dantec (Denmark)

Nerve conduction study results of the right median nerve	
CMAP parameters (lead with m. APB dexter)	SNAP parameters (lead with dig. II)
	
CMAP latency, ms (N <3.5): 5.72	SNAP latency, ms (N <3.0): 3.04
CMAP amplitude, mV (N >5.0): 0.96	SNAP amplitude, µV (N >15.0): 10.0
Conduction velocity, m/s (N >50) (elbow-wrist segment): 26.9	Conduction velocity, m/s (N >50): 47.7

Nerve conduction study results of the right ulnar nerve	
CMAP parameters (lead with m. ADM dexter)	SNAP parameters (lead with dig. V)
	
CMAP latency, ms (N <3.0): 3.05	SNAP latency, ms (N <3.0): 2.84
CMAP amplitude, mV (N >6.0): 4.6	SNAP amplitude, µV (N >15.0): 10.7
Conduction velocity, m/s (N >50) (below elbow-wrist and above elbow to below elbow segments): 36.9 — 42.7	Conduction velocity, m/s (N >50): 44.0

Note: ADM — abductor digiti minimi manus muscle; APB — abductor policis brevis muscle; CMAP — compound muscle action potential; dig. — digitus; N — norm; SNAP — sensory nerve action potential.

According to case studies and individual cases reported in global publications, there is a common clinical and neurophysiological pattern of BV-induced DDP [5,12–15]. The majority of publications report that disimmune BV-induced neuropathy is usually abrupt or subacute in onset; it starts from isolated sensory disorders, mostly paresthesias and neuropathic pain syndrome; then severe ataxia and motor deficit of various degrees of severity develop, which are more noticeable in distal muscles of the limbs. According to Fargeot G. et al. (2020), 73 % of patients required extra support for walking [15]; among the patients described by Matthys A. et al. (2024), complete immobility developed in one out of six patients [5]. Other reported symptoms are diffuse areflexia and impaired vibration sensitivity [5,12,13]. A chronic condition in the publication by Fargeot G. et al. (2020) was reported in 36 % of cases [15]. The studies do not indicate any clear predisposing factors of demyelinating polyradiculoneuropathy development in patients treated with BV. However, the publication by Matthys A. et al. (2024) reported potential impact of a higher cumulative BV dose on the development of disimmune NP [5]. It has been established that disimmune NP appears on the average 10–14 weeks after BV therapy initiation. Polyneuritic disorders start 2 to 36 weeks after BV therapy initiation [5, 15].

This case study is yet another example of BV-induced DDP, which manifested 24 weeks after BV therapy initiation. The condition was chronic; motor disorders progressed and were more prominent distally. In six months, the patient was completely immobile; it corresponds to grade 4 under the Common Terminology Criteria for Adverse Events (CTCAE). The distinctive characteristic of this case is prevailing motor disorders both at the onset and at the peak of clinical symptoms, as well as more prominent muscle involvement (hand and feet extensors).

According to study results, the data obtained during stimulation ENMG in patients with BV-induced DDP correspond to EDX criteria of CIDP and acute inflammatory demyelinating polyradiculoneuropathy (AIDP), i.e. primary demyelinating damage to peripheral nerves are present [5,15]. In 78 % of cases, the sural sparing pattern was observed (reduced amplitude of sensory potential of the sensory section of the median or ulnar nerve with preserved amplitude of sensory potential of the sural nerve) [15], which is a highly specific early marker of AIDP and is observed in CIDP [18]. Of note, in a later observational study by Pezullo L. et al (2025), patients treated with BV also had the sural sparing pattern, despite primary axial changes seen during stimulation ENMG [10]. The common characteristic of BV-induced DDP, noted by researchers, was failure to register any F-waves from hand and feet muscles, as well as conduction in motor

fibres of hand nerves in sites, which are not common for neural compression [5,12–14]. ENMG results in this case study correspond to published data: predominant involvement of motor fibres of peripheral nerves; demyelinating damage; sural sparing pattern.

The differential diagnosis of BV-induced NP includes chemotherapy-induced toxic axonal NPs, paraproteinemic demyelinating NP, as well as paraneoplastic NP and neurolymphomatosis, given that this patient category is treated with BV for lymphatic cancers [5]. Thus, various studies may be required, including anti-neuronal antibody screening, nerve ultrasound under the Ultrasound Pattern Sum Score (UPSS) protocol [19] or brachial plexus magnetic resonance imaging, PET/CT, serum protein electrophoresis, and 24-hour urine test with immunofixation [5].

The severity of BV-induced polyneuropathy is dose-dependant, therefore, recovery depends on BV therapy duration and mode [5]. According to the guidelines on the management of patients treated with BV, who develop CTCAE grade 2–3 NP, BV therapy should be interrupted until clinical symptoms improve to CTCAE grade 1 or resolve completely; then the therapy should be resumed at a lower dose [9, 20]. CTCAE grade 4 NP requires BV therapy discontinuation [9,20]. Based on the therapy results reported in case studies, it can be concluded that BV-induced disimmune NP responds to the standard pathogenetic therapy, similar to classical CIDP [5,12–15]. The sample data by Fargeot G. et al. (2020) demonstrated that in 82 % of cases, the neurological status improved after the IV human immunoglobulin (IVHI) therapy (2 g/kg) together with BV therapy discontinuation; however, complete recovery has not been observed in any of the cases [15]. In the publication by Matthys A. et al. (2024), IVHI helped achieve significant improvement in two cases; in two cases, positive changes were observed with the use of glucocorticosteroid therapy; also, there was one case of spontaneous recovery once BV dose had been reduced [5]. Apparently, pathogenetic therapy duration is determined on a case-by-case basis and depends on the clinical effect, similar to classical variants of disimmune neuropathy. The question of repeated initiation of BV after disimmune NP is resolved remains unanswered. In addition to clinical improvements after pathogenetic therapy, neurophysiological characteristics (as shown by ENMG) also improve: in some clinical cases, motor and sensory responses reverted to their normal levels [12,14]. This case study confirms the overall trend of the positive impact of the standard pathogenetic therapy on BV-induced DDP: pulse therapy with methylprednisolone, then high-dose oral MP therapy with gradual controlled MP dose reduction helped achieving positive changes — from complete immobility to mild distal tetraparesis within a year. It is

worth noting that gradual, slow reduction of glucocorticosteroid therapy ensures higher rates of regression of neurological deficit and optimal return of the quality of life [21].

Conclusion

Brentuximab vedotin-induced disimmune demyelinating polyradiculoneuropathy is a severe debilitating complication of chemotherapy, the course and clinical characteristics of which can resemble acute or chronic inflammatory demyelinating polyradiculoneuropathy. Both acute and chronic muscle weakness, ambulation disorders and sensory ataxia are clinical red flags of possible disimmune origin of impairment and the indication for stimulation electroneuromyography in order to identify the pattern of peripheral nerve damage. Medical professionals following up patients with haematological and neurological conditions should be aware of this complication of brentuximab vedotin therapy, because prompt discontinuation of the drug and initiation of immunosuppressive pathogenetic therapy are the optimal management approach for such patients, ensuring favourable outcome and recovery.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили

финальную версию статьи перед публикацией

Зайцевская С.А.: редактирование и подготовка черновика рукописи

Гришина Д.А.: создание концепции статьи, подготовка черновика и редактирование рукописи

Супонева Н.А.: редактирование и окончательное утверждение рукописи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the

final version of the article before publication

Zaitsevskaya S.A.: writing and editing a draft of the manuscript

Grishina D.A.: definition of the general concept of the article, editing and preparing a draft of the manuscript

Suponeva N.A.: editing the article after reviewing, final approval of the manuscript

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