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Comparable Carotid Vascular Biomechanics in Ankylosing Spondylitis and Psoriatic Arthritis: A Head-To-Head Echo-Tracking Ultrasound Study

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Running title: Carotid vascular biomechanics in AS and PsA

Abstract

Background: Spondyloarthritis, including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), is associated with increased cardiovascular risk that may not be fully captured by conventional risk assessment tools. Arterial stiffness and carotid intima-media thickness (CIMT) represent early markers of vascular ageing; however, direct comparisons of local carotid biomechanical properties between AS and PsA remain limited.

Objectives: To compare structural and functional carotid vascular parameters derived from one-point echo-tracking ultrasound between patients with AS and PsA and to explore clinical, metabolic and haemodynamic correlates of arterial stiffness. **Methods:** In this cross-sectional study, 108 patients with spondyloarthritis (71 AS, 37 PsA) underwent vascular ultrasound assessment including CIMT, local pulse wave velocity (PWV β), β -stiffness index, Peterson's elastic modulus (Ep), arterial compliance (AC) and augmentation index (AI). Clinical

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characteristics, inflammatory markers, lipid profile and cardiovascular risk scores were recorded. Between-group comparisons were performed using non-parametric tests. Spearman correlations and multivariable linear regression analyses were applied to identify factors associated with vascular parameters. **Results:** Baseline demographic and metabolic characteristics were comparable between groups, although sex distribution differed ($p = 0.002$). Most structural and functional vascular indices, including CIMT, PWV β , β -stiffness index, AC and Ep, did not differ significantly between AS and PsA. Augmentation index was higher in PsA compared with AS (median 21.9 vs 12.8, $p = 0.029$). CIMT correlated positively with β -stiffness index ($\rho = 0.404$), PWV β ($\rho = 0.482$) and Ep ($\rho = 0.451$) (all $p < 0.001$). In multivariable regression models, arterial hypertension emerged as the most consistent independent factor associated with vascular parameters, while inflammatory markers showed limited associations. **Conclusion:** Patients with ankylosing spondylitis and psoriatic arthritis demonstrate broadly comparable local carotid vascular profiles when assessed using echo-tracking ultrasound. Higher augmentation index in psoriatic arthritis suggests differences in haemodynamic wave reflection rather than intrinsic arterial stiffness. Vascular alterations appear to be driven predominantly by haemodynamic and metabolic factors rather than disease phenotype alone.

Keywords: ankylosing spondylitis; psoriatic arthritis; arterial stiffness; echo-tracking; carotid intima-media thickness; augmentation index; spondyloarthritis; vascular ageing

1. Introduction

Spondyloarthritis, including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), is associated with a substantially increased cardiovascular risk that cannot be fully explained by traditional risk factors alone. Chronic systemic inflammation contributes to this excess risk through endothelial dysfunction, oxidative stress and adverse vascular ageing, thereby accelerating atherosclerosis and promoting premature cardiovascular disease [1,2]. Importantly, vascular involvement in spondyloarthritis often remains clinically silent for prolonged periods, and subclinical vascular changes may precede overt cardiovascular events.

Large population-based and longitudinal studies consistently report higher rates of ischemic heart disease, cerebrovascular events and cardiovascular mortality in AS compared with the general population [3-10]. Similarly, PsA

is linked to increased cardiovascular morbidity and mortality, with meta-analyses demonstrating higher incidence of myocardial infarction, stroke and heart failure compared with the general population [10-13]. However, commonly used cardiovascular risk prediction models frequently underestimate risk in inflammatory arthritides, supporting the need for approaches that detect early vascular dysfunction beyond conventional risk assessment.

Arterial stiffening represents a key functional manifestation of adverse vascular ageing and integrates the cumulative impact of haemodynamic load, metabolic factors and chronic inflammation. From a haemodynamic perspective, reduced arterial elasticity alters pulse wave propagation and reflection, increases systolic and pulse pressure and augments left ventricular afterload, providing a mechanistic link between arterial stiffness and adverse cardiovascular outcomes (Franklin et al., 1999; Mitchell et al., 2010; Nichols et al., 2011). Although arterial stiffening accompanies physiological ageing, it may be accelerated in chronic inflammatory conditions such as AS and PsA [14-16]. Prior studies in spondyloarthritis have reported heterogeneous results regarding the magnitude and determinants of stiffness and early atherosclerotic changes, likely reflecting differences in study design, populations, and measurement [17-19].

Ultrasound-based assessment enables parallel evaluation of functional and structural vascular alterations. One-point echo-tracking technology provides local carotid biomechanical indices derived from diameter changes throughout the cardiac cycle combined with blood pressure values, including the stiffness index β , Peterson's elastic modulus (E_p), arterial compliance (AC) and augmentation index (AI), as well as local pulse wave velocity (PWV β) calculated at a single arterial [20-22]. Compared with carotid-femoral PWV, local one-point assessment avoids uncertainties related to external distance estimation and heterogeneous arterial segments, offering a focused and reproducible evaluation of carotid wall mechanics [20,23]. In parallel, carotid intima-media thickness (CIMT) provides a validated marker of early structural arterial remodelling and subclinical atherosclerosis [24,25]. Combining echo-tracking-derived stiffness parameters with CIMT may therefore offer an integrated profile of early vascular damage in inflammatory diseases characterised by accelerated vascular ageing.

Despite the growing evidence of increased cardiovascular risk in both AS and PsA, direct head-to-head comparisons of local carotid biomechanical properties between these two spondyloarthritis phenotypes remain

limited. Moreover, augmentation index-reflecting wave reflection and peripheral vascular tone-may capture haemodynamic differences that are not necessarily mirrored by intrinsic carotid wall stiffness. Accordingly, the present study evaluates carotid arterial stiffness using one-point echo-tracking-derived biomechanical indices in combination with CIMT in patients with AS and PsA. We aimed to characterise subclinical vascular damage across the spondyloarthritis spectrum and to explore clinical and metabolic correlates of functional and structural vascular measures.

2. Materials and Methods

2.1. Study design and study population

This cross-sectional observational study included 108 patients with spondyloarthritis, comprising 71 patients with ankylosing spondylitis (AS) and 37 patients with psoriatic arthritis (PsA). Participants were consecutively recruited from the Departments of Rheumatology and Internal Medicine at University Hospital “St. Marina”, Varna, Bulgaria, between January 2023 and December 2024.

Patients included in the present analysis were derived from a larger prospective observational cohort of individuals with spondyloarthritis. To minimise confounding related to age differences between disease groups, frequency matching by age strata was applied during data extraction. Sex distribution was not matched and reflects the underlying epidemiology of the disease populations.

Ankylosing spondylitis was diagnosed according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria, while psoriatic arthritis was classified based on the Classification Criteria for Psoriatic Arthritis (CASPAR). All diagnoses were established by experienced rheumatologists.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Varna (Protocol №133/22.06.2023). Written informed consent was obtained from all participants prior to inclusion.

Predefined exclusion criteria included known ischemic heart disease, cerebrovascular disease, peripheral arterial disease, heart failure, clinically significant arrhythmias, diabetes mellitus, chronic kidney disease stage ≥ 3 , active infection, malignancy, pregnancy, or inability to undergo vascular ultrasonography.

2.2. Clinical and laboratory assessment

Demographic characteristics, smoking status, disease duration (time since diagnosis), and diagnostic delay (time from symptom onset to diagnosis) were recorded. Anthropometric parameters and the presence of arterial hypertension were documented according to current clinical guidelines.

Blood pressure was measured under standardised resting conditions after at least 5 minutes of supine rest using an automated oscillometric device. Systolic and diastolic blood pressure values were recorded, and mean arterial pressure was calculated for descriptive purposes.

Systemic inflammatory activity was assessed by serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), determined using routine laboratory methods at the central hospital laboratory. Fasting lipid profile, including total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), was analysed using standardised enzymatic assays.

2.3. Vascular ultrasound assessment

Vascular ultrasound examinations were performed using a high-resolution ultrasound system (Aloka Hitachi Prosound $\alpha 7$) equipped with a high-frequency linear transducer. All measurements were obtained at the level of the right common carotid artery approximately 2 cm proximal to the carotid bifurcation. The right carotid artery was selected to ensure methodological consistency and minimise examination time variability. Participants were examined in the supine position after a short resting period.

Carotid intima-media thickness (CIMT) was measured at the far wall of plaque-free segments of the common carotid artery using B-mode imaging. Three measurements obtained during separate cardiac cycles were averaged for analysis. Atherosclerotic plaque was defined as focal wall thickening ≥ 1.5 mm or $\geq 50\%$ greater than the surrounding intima-media thickness, and such segments were excluded from CIMT assessment.

Arterial stiffness was evaluated using one-point echo-tracking technology, allowing continuous assessment of arterial diameter changes synchronised with the electrocardiogram. Brachial blood pressure values measured immediately prior to the examination were entered into the system to enable automated calculation of carotid biomechanical parameters. The analysed indices included local pulse wave velocity (PWV β), β -stiffness index, pressure-strain elastic modulus (Peterson's modulus, E_p), arterial compliance (AC), and augmentation index (AI).

All examinations were performed by a single experienced operator blinded to laboratory results. To assess measurement consistency, repeated measurements were performed in a random subset of participants, demonstrating good intra-observer reproducibility.

2.4. Cardiovascular risk assessment

Ten-year cardiovascular risk was estimated using validated prediction models. The Framingham Risk Score and SCORE2 were calculated in accordance with current European Society of Cardiology recommendations. For participants aged ≥ 70 years, the SCORE2-OP algorithm was applied when appropriate.

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0. Continuous variables were assessed for normality using visual inspection and Shapiro–Wilk testing and are presented as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Comparisons between AS and PsA groups were conducted using the Mann–Whitney U test for continuous variables and Pearson’s chi-square test for categorical variables.

Associations between vascular ultrasound parameters, inflammatory markers, lipid profile components, and cardiovascular risk scores were explored using Spearman’s rank correlation analysis. Given the exploratory nature of correlation analyses, results were interpreted with caution and considered hypothesis-generating.

Multivariable linear regression models were constructed to assess factors associated with arterial stiffness indices and carotid intima-media thickness. Covariates were selected a priori based on clinical relevance and included disease type, age, sex, body mass index (BMI), arterial hypertension, and treatment status (targeted therapy vs biologic-naïve). Model assumptions were evaluated using residual diagnostics and multicollinearity assessment. All statistical tests were two-sided, and a p -value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 108 patients with spondyloarthritis were included, comprising 71 patients with ankylosing spondylitis (AS) and 37 with psoriatic arthritis (PsA). Age distribution was comparable between groups (49.4 ± 9.7 vs 52.7

± 10.2 years, $p = 0.083$). Disease duration was also similar (9.7 ± 6.2 vs 9.0 ± 7.0 years, $p = 0.400$).

Sex distribution differed significantly, with male predominance in AS and female predominance in PsA (66.2% vs 35.1% male, $p = 0.002$). The prevalence of current smoking and arterial hypertension did not differ significantly between disease entities. Body mass index was comparable between groups.

Inflammatory markers showed similar erythrocyte sedimentation rate values, whereas C-reactive protein levels were higher in AS compared with PsA ($p = 0.022$). Lipid profile parameters did not differ significantly (Table 1).

Table 1. Baseline demographic, clinical, laboratory and vascular characteristics of patients with ankylosing spondylitis and psoriatic arthritis

Variable	AS (n = 71)	PsA (n = 37)	p-value
Age, years	49.4 ± 9.7	52.7 ± 10.2	0.083
Male sex, n (%)	47 (66.2)	13 (35.1)	0.002
Disease duration, years	9.7 ± 6.2	9.0 ± 7.0	0.400
Current smoker, n (%)	42 (59.2)	23 (62.2)	0.762
Hypertension, n (%)	26 (36.6)	10 (27.0)	0.316
BMI, kg/m ²	28.3 ± 5.8	27.1 ± 4.6	0.447
ESR, mm/h	36.7 ± 26.1	29.8 ± 16.9	0.356
CRP, mg/L	9.5 ± 17.9	3.9 ± 5.7	0.022
Total cholesterol, mmol/L	5.37 ± 1.24	5.51 ± 1.20	0.482
Triglycerides, mmol/L	1.49 ± 1.38	1.48 ± 1.25	0.821
LDL-cholesterol, mmol/L	3.28 ± 1.04	3.23 ± 1.14	0.854
HDL-cholesterol, mmol/L	1.39 ± 0.33	1.57 ± 0.52	0.119
CIMT, mm	0.60 ± 0.17	0.63 ± 0.25	0.510
β -stiffness index	7.64 ± 2.59	8.01 ± 3.42	0.985
PWV, m/s	6.06 ± 0.99	6.16 ± 1.15	0.724
Augmentation index, %	15.8 ± 13.5	21.6 ± 15.3	0.029
Arterial compliance	0.89 ± 0.26	1.09 ± 1.66	0.224
Peterson's elastic modulus	100.5 ± 35.8	105.0 ± 42.6	0.653
Framingham risk score, %	5.8 ± 5.0	5.4 ± 4.4	0.776
SCORE, %	9.4 ± 6.9	11.6 ± 7.1	0.121

3.2. Vascular ultrasound findings

Structural vascular assessment demonstrated comparable carotid intima-media thickness between AS and PsA [0.54 (IQR 0.22) vs 0.61 (IQR 0.22), $p = 0.510$].

Functional arterial stiffness indices were largely similar between groups. The β -stiffness index showed identical median values [7.0 (IQR 3.0) vs 7.0 (IQR 3.9), $p = 0.985$], and local pulse wave velocity (PWV β) was also comparable [5.8 (IQR 1.2) vs 5.8 (IQR 1.5), $p = 0.724$]. Arterial compliance demonstrated overlapping distributions [0.86 (IQR 0.32) vs 0.79 (IQR 0.40), $p = 0.224$], as did Peterson's elastic modulus [88 (IQR 41) vs 93 (IQR 57), $p = 0.653$].

In contrast, augmentation index (AI) was significantly higher in PsA compared with AS [21.9 (IQR 19.65) vs 12.8 (IQR 19.0), $p = 0.029$] (Figure 1).

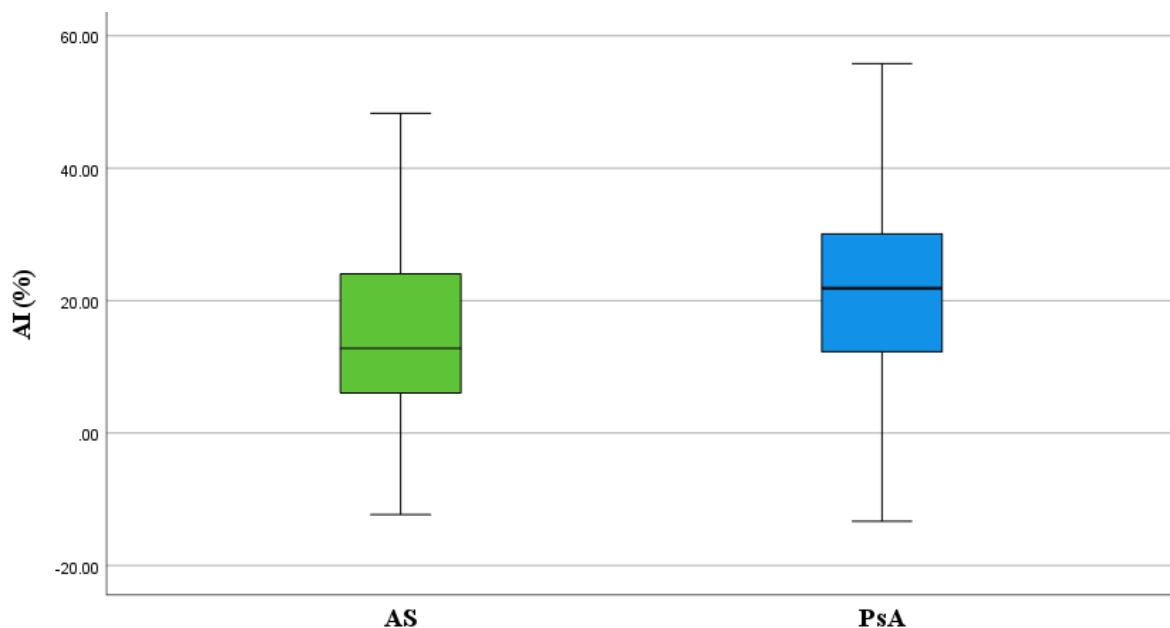


Figure 1. Augmentation index (AI) in patients with ankylosing spondylitis and psoriatic arthritis

3.3. Cardiovascular risk scores

Estimated 10-year cardiovascular risk did not differ significantly between disease groups. Framingham risk score values were comparable ($p = 0.776$), as were SCORE2 estimates ($p = 0.121$).

3.4. Treatment distribution

Targeted antirheumatic therapy distribution differed significantly between AS and PsA ($p < 0.001$). Among patients with ankylosing spondylitis, anti-TNF therapy was administered in 63.4%, anti-IL-17 agents in 15.5%, biologic-naïve status in 15.5%, and JAK inhibitors in 5.6%. In contrast, patients with psoriatic arthritis were more frequently treated with anti-IL-

17 agents (48.6%) and JAK inhibitors (18.9%), while anti-TNF therapy was used in 21.6% and biologic-naïve status was present in 10.8%.

3.5. Correlation analysis

Spearman rank correlation analysis was performed in the overall cohort ($n = 108$). Age correlated positively with cardiovascular risk scores, including the Framingham risk score ($\rho = 0.449$, $p < 0.001$) and SCORE2 ($\rho = 0.558$, $p < 0.001$). Carotid intima-media thickness correlated positively with β -stiffness index ($\rho = 0.404$, $p < 0.001$), PWV β ($\rho = 0.482$, $p < 0.001$) and Peterson's elastic modulus ($\rho = 0.451$, $p < 0.001$). Triglyceride levels demonstrated modest positive correlations with functional stiffness parameters (all $p < 0.05$), while low-density lipoprotein cholesterol correlated positively with augmentation index and cardiovascular risk estimates.

3.6. Multivariable regression analysis

Multivariable linear regression analyses were performed using augmentation index (AI), PWV β , β -stiffness index and carotid intima-media thickness (CIMT) as dependent variables. Covariates included disease type, age, sex, body mass index, arterial hypertension and treatment status.

The regression model for AI was statistically significant ($F = 2.75$, $p = 0.016$; $R^2 = 0.140$), with arterial hypertension independently associated with higher AI values ($p = 0.030$). Disease type showed a borderline association ($p = 0.085$).

For PWV β , the model reached statistical significance ($F = 2.47$, $p = 0.028$; $R^2 = 0.128$), with arterial hypertension and body mass index positively associated with PWV β ($p = 0.040$ and $p = 0.046$, respectively).

The β -stiffness model demonstrated overall significance ($F = 3.25$, $p = 0.006$; $R^2 = 0.162$), with arterial hypertension emerging as the only independent associated factor ($p = 0.009$). The CIMT model showed borderline overall significance ($F = 1.97$, $p = 0.066$; $R^2 = 0.121$), with arterial hypertension independently associated with higher CIMT values ($p = 0.038$).

4. Discussion

In this head-to-head analysis, patients with ankylosing spondylitis and psoriatic arthritis demonstrated broadly comparable structural and functional vascular characteristics when assessed using one-point echo-tracking ultrasound. Most stiffness indices and carotid intima-media thickness values did not differ significantly between the two diseases despite differences in inflammatory burden and treatment exposure. In contrast, augmentation index was higher in psoriatic arthritis, suggesting differences in wave reflection and peripheral vascular tone rather than intrinsic carotid wall stiffness. Arterial hypertension consistently emerged as the strongest determinant of vascular parameters, whereas inflammatory markers showed limited associations with stiffness indices.

A central observation of the present study is the consistent association between structural and functional vascular measures across the cohort. Positive correlations between carotid intima-media thickness and local stiffness indices indicate that arterial remodelling and functional stiffening may evolve in parallel within the spondyloarthritis spectrum. However, the absence of between-disease differences in most local stiffness parameters suggests that disease phenotype alone may not represent the primary driver of carotid biomechanical alterations. The higher augmentation index observed in psoriatic arthritis likely reflects haemodynamic influences related to peripheral vascular resistance rather than intrinsic arterial rigidity, consistent with the known physiological determinants of augmentation index [26]

Across multivariable models, arterial hypertension was the most consistent independent factor associated with vascular alterations. Given the markedly different distribution of targeted therapies between ankylosing spondylitis and psoriatic arthritis, treatment exposure was considered a potential confounder and included as a covariate in multivariable analyses; however, no independent association between treatment status and vascular ultrasound parameters was observed after adjustment. These findings align with evidence demonstrating the central role of haemodynamic stress in elastin fragmentation, collagen accumulation and progressive arterial stiffening [27,28]. Modest associations between metabolic parameters, particularly triglycerides and body mass index, and stiffness indices further suggest a potential contribution of metabolic burden to vascular ageing in inflammatory arthritis, consistent with previous rheumatologic studies exploring vascular and metabolic biomarkers [29].

Inflammatory activity demonstrated limited direct relationships with ultrasound-derived vascular parameters in the present analysis. Previous studies have reported heterogeneous findings, with some cohorts showing associations between disease activity and structural vascular measures but weaker relationships with functional stiffness indices [17,18]. Prospective data in psoriatic arthritis suggest that cumulative inflammatory exposure rather than single time-point inflammatory markers may be more relevant for vascular remodelling [30]. The lack of strong correlations in our cohort may therefore reflect the chronic and cumulative nature of vascular adaptation rather than current inflammatory status.

Most earlier investigations evaluated ankylosing spondylitis or psoriatic arthritis primarily in comparison with healthy controls and reported increased arterial stiffness or carotid intima-media thickness [19,31,32]. In contrast, the present head-to-head comparison indicates that vascular profiles may appear broadly similar when the two spondyloarthritis phenotypes are evaluated directly under comparable clinical conditions. Direct comparisons between spondyloarthritis phenotypes using local echo-tracking-derived stiffness parameters remain limited, highlighting the relevance of the current findings. Previous reports have described variable associations between disease activity and vascular stiffness, including impaired aortic elasticity related to disease burden [33], whereas other studies observed minimal changes in stiffness parameters despite anti-inflammatory treatment [34, 35]. These discrepancies underscore the multifactorial nature of vascular involvement and the influence of study design and measurement methodology.

The use of one-point echo-tracking represents an important methodological aspect of the present study. Local carotid assessment allows precise evaluation of arterial wall motion and avoids uncertainties related to external distance estimation inherent to carotid-femoral pulse wave velocity measurements [22,23]. This regional approach may be particularly sensitive for detecting early functional vascular alterations that are not fully captured by global stiffness indices.

Several limitations should be acknowledged. The cross-sectional design precludes causal interpretation of vascular remodelling processes. Participants were selected from a larger observational cohort to minimise demographic imbalance between groups, which may influence generalisability. Sex distribution differed between ankylosing spondylitis and psoriatic arthritis, reflecting the underlying epidemiology of the diseases, and may have influenced vascular haemodynamic parameters

despite adjustment in multivariable analyses. The absence of a healthy control group limits conclusions regarding absolute cardiovascular risk; however, the primary aim was to compare vascular characteristics between ankylosing spondylitis and psoriatic arthritis. In addition, local carotid measurements may not fully reflect systemic arterial stiffness, and the smaller psoriatic arthritis subgroup may have limited statistical power to detect subtle disease-specific differences.

5. Conclusions

In conclusion, ankylosing spondylitis and psoriatic arthritis demonstrate broadly comparable structural and functional vascular profiles when evaluated directly using echo-tracking ultrasound. The higher augmentation index observed in psoriatic arthritis suggests differences in haemodynamic wave reflection rather than intrinsic arterial stiffness. Arterial hypertension and metabolic burden appear to represent key contributors to vascular alterations, whereas current inflammatory activity shows limited association with stiffness indices. These findings support the concept that vascular ageing in spondyloarthritis may be influenced more strongly by haemodynamic and metabolic factors than by disease phenotype alone.

Author Contributions

Author Contributions: Conceptualization: M.M., T.G.; Methodology: M.M., T.G., M.D.; Formal analysis: M.M.; Investigation: M.M., M.D.; Writing – original draft: M.M.; Writing – review & editing: T.G., M.K., M.D.

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The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Varna (Protocol №133/22.06.2023). Written informed consent was obtained from all participants prior to inclusion.

Informed Consent Statement

Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Сравними каротидни съдови биомеханични характеристики при анкилозиращ спондилит и псориатичен артрит: директно сравнително ехографско изследване чрез echo-tracking

Резюме

Въведение: Спондилоартритите, включително анкилозиращият спондилит (АС) и псориатичният артрит (ПсА), са свързани с повишен сърдечно-съдов риск, който невинаги се отразява адекватно чрез конвенционалните методи за оценка на риска. Артериалната ригидност и дебелината на интима-медия комплекса на каротидните артерии (СІМТ) представляват ранни маркери на съдово стареене. Въпреки това, директните сравнения на локалните каротидни биомеханични свойства между пациенти с АС и ПсА остават ограничени. **Цел:** Да се сравнят структурните и функционалните съдови параметри на каротидните артерии, получени чрез едноточков echo-tracking ултразвук, между пациенти с АС и ПсА, както и да се изследват клиничните, метаболитните и хемодинамичните фактори, свързани с артериалната ригидност. **Методи:** В това напречно (cross-sectional) проучване 108 пациенти със спондилоартрит (71 с АС и 37 с ПсА) бяха подложени на съдов ултразвуков анализ, включващ измерване на СІМТ, локална пулсово-вълнова скорост (PWV β), индекс на β -ригидност, модул на еластичност на Peterson (Ер), артериален комплайънс (АС) и индекс на аугментация (АІ). Регистрирани бяха клинични характеристики, възпалителни маркери, липиден профил и сърдечно-съдови рискови фактори. Сравненията между групите бяха извършени чрез непараметрични тестове. За определяне на факторите, свързани със съдовите параметри, бяха използвани корелационен анализ на Spearman и мултивариантни линейни регресионни модели. **Резултати:** Базовите демографски и метаболитни характеристики бяха сходни между групите, въпреки че разпределението по пол се различаваше статистически значимо ($p = 0.002$). Повечето структурни и функционални съдови показатели, включително СІМТ, PWV β , индекс на β -ригидност, АС и Ер, не показаха съществени разлики между АС и ПсА. Индексът на аугментация беше по-висок при ПсА в сравнение с АС (медиана 21.9 срещу 12.8, $p = 0.029$). СІМТ корелира положително с индекса на β -ригидност ($\rho = 0.404$), PWV β ($\rho = 0.482$) и Ер ($\rho = 0.451$) (всички $p < 0.001$). В мултивариантните регресионни модели артериалната хипертония се очерта като най-

последователния независим фактор, асоцииран със съдовите параметри, докато възпалителните маркери показаха ограничени асоциации. **Заключение:** Пациентите с анкилозиращ спондилит и псориатичен артрит демонстрират в голяма степен сходни локални каротидни съдови характеристики, оценени чрез echo-tracking ултразвук. По-високият индекс на аугментация при псориатичен артрит предполага различия в хемодинамичното отражение на пулсовата вълна, а не в самата вътрешна артериална ригидност. Съдовите промени изглежда се определят предимно от хемодинамични и метаболитни фактори, а не единствено от фенотипа на заболяването.

Ключови думи: анкилозиращ спондилит; псориатичен артрит; артериална ригидност; echo-tracking; дебелина на интима-медия комплекса; индекс на аугментация; спондилоартрит; съдово стареене

Clinical and Functional Results of Transcatheter Arterial Embolization as a Treatment for Knee Osteoarthritis

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Running title: Arterial Embolization in Knee Osteoarthritis

Abstract

Objectives: To evaluate the effectiveness of our first experience in employing transcatheter arterial embolization (TAE) of popliteal artery branches in patients with knee osteoarthritis (OA). **Materials and methods:** The research included 80 people with knee OA grades 1-2, resistant to standard conservative treatment and without indications for surgical intervention. The patients were divided into 2 groups of 40 people each; in group 1, intra-articular injection of sodium hyaluronate (synovial fluid prosthesis) was chosen as minimally invasive therapy; in group 2, TAE of popliteal artery branches was performed. Clinical and functional characteristics of joints were assessed using WOMAC and Lysholm scales at baseline and 3 months after intervention. **Results:** Before surgery, in both groups 1 and 2, high levels of WOMAC scale (150 [138-184] and 162 [140-190] points, respectively) and low levels of Lysholm scale (42 [35-54] and

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40 [38- 60] points, respectively) were recorded. At 3 months after treatment, patients of both groups demonstrated significant improvement in clinical and functional results in the form of decrease in WOMAC scale to 94 [84-120] for group 1, $p < 0.001$; and 52 [40-79] points for group 2, $p < 0.001$. According to Lysholm scale, satisfactory results were obtained in group 1 (68 [60-85] points, $p = 0.001$) and good results in group 2 (91 [85-95] points, $p < 0.001$). On comparison of both groups, patients with TAE achieved lower values of WOMAC ($p = 0.023$) and higher values of Lysholm scale ($p = 0.06$). No complications were recorded in both groups. **Conclusion:** TAE of popliteal artery branches is an effective minimally invasive intervention that significantly reduces severity of pain and improves the function of knee joints. This method requires more studies with larger number of patients, development of selection criteria in order to increase accessibility in practical healthcare.

Keywords: osteoarthritis, knee joint, transcatheter arterial embolization, WOMAC, pain.

1. Introduction

Rheumatic diseases are a heterogeneous group of chronic conditions that are characterized by development of severe concomitant conditions in patients. These ailments cause a tremendous negative impact on the modern society as they act as both physiological and psychological burden on patients and as economic burden on the society. Osteoarthritis (OA) is the most common joint pathology worldwide which is accompanied by chronic pain, disability, and showcases a prediction of further increase in incidence.

In 2020, approximately 595 million patients with OA were identified, corresponding to 7.6% of the world population, this amounted to a 132.2% increase in prevalence compared to 1990 [1]. The incidence rate of OA continues to rise, largely due to the expansion of the “elderly” population and the absence of effective treatment. By 2050 the prevalence of knee OA is projected to increase by 74.9%, hand OA - by 48.6%, hip OA- by 78.6% [1]. In addition to the annual dynamic increase in incidence, a significant rise of this pathology has been noted among the working demographics [2], which is of great medical and social importance for the state.

Management of OA involves the use of a range of methods. According to modern recommendations, treatment should be carried out using a

complex of pharmacological and non-pharmacological methods, taking into account risk factors (obesity, mechanical factors, physical activity), general factors (age, comorbidity, polypharmacy), the level of intensity of pain and functional impairment, the presence or absence of signs of inflammation, localization and severity of structural changes [3, 4]. Despite much research, there is no cure for OA and a distinct lack of disease-modifying drugs persist against the background of reliance on abundant symptomatic pharmacological agents. Another pressing problem of OA is its clinical and pathogenetic variability and pronounced polymorbidity, which in many cases neutralizes the effectiveness of a number of therapeutic strategies [5].

The presence of multiple somatic diseases in an OA patient which are managed by complex combinations of medications creates the need for a proper assessment of the expected benefits and possible risks of a particular treatment method. The chosen intervention should be the safest and most effective one.

One of the promising methods for managing OA is transcatheter arterial embolization (TAE) of popliteal artery branches. It is a new, minimally invasive technique that is used to relieve pain in knee OA and is based on the observation that inflammation causes abnormal neovascularization and sensory nerve fiber growth [6]. It has been identified that pathogenetically excessive angiogenesis in OA is caused by inflammation that aggravates to more inflammation and stimulates an increase in the number of pain receptors, thereby causing persistent pain syndrome [7, 8, 9]. Neoangiogenesis can stimulate the growth of osteophytes that results in pain. Furthermore, this process in the synovium can cause disruption of the homeostasis of hyaline cartilage and hypoxia of chondrocytes [10].

As a rule, the area of pathological vascularization is located in the projection of the medial part of the knee joint and is supplied by a network of branches of the popliteal artery. The TAE method involves catheterization and angiography of the femoral artery, popliteal artery and its branches, followed by embolization of the hypervascular area.

There is relatively little scientific data regarding TAE of the branches of the popliteal artery, and their results are often contradictory. But this method has shown effectiveness in small samples of patients with knee OA grades 2-2 [11, 12, 13]. According to the available data, improvement in pain and joint function is achieved in 86.3% of patients after 6 months, in 79.8% after 3 years [6] and the technique is well tolerated by patients over 50-60 years of age [14]. This intervention demonstrates significantly less pronounced

synovitis after a year, compared with the baseline on verification by MRI using the WOMS scale [15].

It is notable that this method was found to be insufficiently effective in late stage OA [16], but the early stages of the disease with resistance to standard therapy is a considerable indication for this method [13]. Review works presented in literature indicate the success of this technique, especially in cases when conservative therapy was ineffective or contraindications to surgical treatment existed [17].

Unfortunately, the small sample of patients for TAE of popliteal artery does not allow us to determine the current place of this method for employment in management of knee OA. In some patients, insufficient effectiveness is observed, thus further research is necessary to introduce this treatment method into everyday clinical practice.

The aim of research was to evaluate the effectiveness of our first experience in employing the use of TAE of popliteal artery branches in patients with knee OA.

2. Materials and Methods

The research was carried across a time-frame of one year at Orenburg Regional Clinical Hospital named after V.I. Voinov, in the departments of Traumatology and Orthopedics and Endovascular Surgery. Analysis of treatment results of 80 patients with 1-2 grades knee OA aged from 45 to 60 years who underwent minimally invasive therapy due to ineffectiveness of prior pharmacological management were analyzed. All patients received standard pharmacological therapy as prescribed by the National Clinical Recommendations for OA (2021), including NSAIDs, SYSADOA, as well as non-pharmacological treatment in the form of physical therapy and orthotics for a duration of 3-6 months.

The patients were divided into 2 groups of 40 people each; in the first group, intra-articular injection of sodium hyaluronate (synovial fluid prosthesis) was performed and in the second group TAE was done.

Before undergoing procedures, all patients underwent evaluations with collection of complaints and medical history, inspection, and assessment of amplitude of active and passive movements in the knee joints. The diagnosis of knee OA was made taking into account the criteria of Altman R. (1991), and verification of the grading radiographically according to Kellgren-Lawrence criteria. All participating patients of this study provided their

informed voluntary consent. Patients in both groups had no indications for surgical treatment of OA against the background of ineffectiveness or insufficient effectiveness of previous pharmacological treatment. All patients included in the study underwent contrast-enhanced MRI of the knee joint. Particular attention was paid to the presence of abnormal vascular network, indicating active neoangiogenesis. If this was present, patients were candidates for inclusion in the second group, whereas the main exclusion criterion was the absence of a hypervascular network in the knee joint due to the perceived risk of non-target embolization. Patients with allergies or other contraindications to intra-articular administration of hyaluronic acid preparations were excluded in the first group.

All patients underwent a clinical and functional examination using the WOMAC and Lysholm questionnaires. The WOMAC scale was a questionnaire of 24 questions, for each of which the patient selected a number of points from 0 to 10, similar to the visual analogue scale, where 0 points stood for the complete absence of a sign, and 10 points indicated maximum severity. A higher score corresponded to a worse result. The assessment of the knee joint function according to the Lysholm scale was also carried out in points, where the maximum sum was equal to 100 points and corresponded to a healthy knee joint, and dysfunction was determined by a decrease in the total score. The Lysholm score points indicated: less than 64 points – unsatisfactory, 65–83 – satisfactory, 84–94 – good, 95–100 – excellent.

The TAE procedure was performed as follows. Under local anesthesia, arteriography of the lower third of the superficial femoral artery and popliteal artery, including 3D reconstruction, was performed using antegrade transfemoral access (Figure 1). During evaluation of the angiogram, areas of increased vascularization were identified, if any, and the architecture of the arteries was analyzed, with special emphasis on the medial aspect of the knee joint. To identify vessels subject to embolization, as well as to construct the trajectory of target vessels, a specialized Embolization Guidance program (Siemens) was used. This software is for advanced embolization planning and guidance. Knowing the location of the lesion and vessels is essential for complete embolization of pathological process. This program simplifies catheter navigation for any embolization procedure, regardless of the body region. The software's 3D reconstruction of the arterial tree was used to facilitate cannulation of the target branch, including selection of the optimal projection and superimposition of the live image onto the color-coded 3D reconstruction. In most cases, the target artery for embolization was medial genicular artery. The software allowed

for selection of the optimal projection for catheterization of target branch ostium and superimposition of the live image on a color-coded 3D reconstruction to reduce the use of contrast agent. Catheterization of target branch was carried out with a Berenstein catheter or one of the diagnostic coronary catheters, depending on the angle of origin of the artery, after which a microcatheter was inserted through the coronary guidewire. Through a microcatheter, a suspension of microspheres with a diameter of 150-250 μm , diluted in physiological solution with the addition of a contrast agent in a 1:1 ratio, was slowly introduced. To prevent off-target embolization, the authors followed the principles: precise mapping using 3D navigation, neuromicrocatheters, which achieved superselective catheterization of the target artery, and calibrated (the smallest) polyvinyl alcohol particles for embolization. After contrast stasis appeared, control angiography was performed, which confirmed occlusion of the embolized artery (Figure 2). The operation was completed by applying a pressure bandage.

Figure 1. Patient A., 42 years old, knee osteoarthritis grade 2. A: Arteriography of superficial femoral, popliteal artery and its branches. B: 3D reconstruction of



vessels based on data of angiography.

Evaluation of treatment results was done 3 months after the procedure in a consultation where the survey was repeated, complaints, the number of complications, the amplitude of active and passive movements in the knee joints were assessed, the functional result was re-evaluated using the WOMAC and Lysholm scores. The obtained data was compiled into an Excel table and a statistical analysis was then carried out using the Statistica 10.0 program. Quantitative indicators were recorded as median, upper and

lower quartiles (Me [Q1-Q2]), the differences between the groups were determined using Mann-Whitney U test, the significance level, p was 0.05.



Figure 2. Patient A., 42 years old, knee osteoarthritis grade 2. A: Arteriography before TAE showing hypervascular network of the medial genicular artery. B: Arteriography after TAE showing no contrast spread distal to the embolized target artery

3. Results

First group of patients included 35 (87.5%) women, 5 (12.5%) men, the average age was 50 [46-56] years. In the second group of patients there were 32 (80%) women, 8 (20%) men, the average age was 53 [47-58] years. Both groups were comparable in terms of gender and age characteristics.

Assessment of effectiveness of treatment methods revealed the persistence of pain and functional limitations 3 months after intervention in 6 (15%) cases in group 1 and in 9 (22%) cases in group 2. No complications in either group were recorded.

The results of clinical and functional studies of patients in both groups are presented in Tables 1 and 2.

Table 1. Results of a clinical and functional examination of knee joints in patients with knee OA by WOMAC scale.

Group	Sum of WOMAC points before treatment	Sum of WOMAC scores 3 months after treatment	Statistical significance, p -value
Group 1 (synovial fluid prosthesis)	150 [138-184]	94 [84-120]	<0.001
Group 2 (transcatheter arterial embolization)	162 [140-190]	52 [40-79]	<0.001

Statistical significance, p-value	0.840	0.023	
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According to the results in Table 1, before the employment of minimally invasive intervention, significantly high WOMAC scale scores were recorded in both groups of patients, indicating considerable clinical and functional disorders of the knee joints. No substantial differences in this indicator existed prior to the treatment. 3 months later, the patients showed noteworthy improvement, characterized by a significant decrease in WOMAC scores in both groups but the patients in the TAE group achieved significantly lower levels of this scale.

Table 2. Results of a clinical and functional examination of knee joints in patients with knee OA by Lysholm scale

Group	Sum of Lysholm points before treatment	Sum of Lysholm scores 3 months after treatment	Statistical significance, p-value
Group 1 (synovial fluid prosthesis)	42 [35-54]	68 [60-85]	0.001
Group 2 (transcatheter arterial embolization)	40 [38-60]	91 [85-95]	<0.001
Statistical significance, p-value	0.94	0.06	

On pre-intervention analysis of Lysholm scale results of both groups, disappointing data was obtained (less than 64 points), which indicated a pronounced impairment of knee joint functioning. The results of both groups was comparable with no significant differences. 3 months after treatment, in both groups, similar to the WOMAC scale, a significant improvement in the Lysholm index was obtained, and as per the scale, patients who received a synovial fluid prosthesis showed satisfactory results, and patients after TAE indicated good results.

4. Discussion

The first clinical experience of application of TAE of popliteal artery branches in our clinic indicated the method to be an effective minimally invasive therapeutic option, the functional result of which is superior to traditional conservative methods of treating knee OA grades 1-2. These results are comparable to previously published similar studies [11, 15, 17], majority of which had larger samples and thus, reduced risk of statistical error. Decreased pain and no further requirement of NSAIDs is a favorable outcome for prevention of complications in patients with diseases of the gastrointestinal tract and cardiovascular system. Furthermore, there are reduced risks of postoperative complications.

However, the widespread use of this technique presents itself with certain limitations which are primarily associated with little knowledge of the long-term results of its application. Our study included a 3-month follow-up period after the procedure to analyze early complications. However, a 90-day window is insufficient to determine the durability of TAE or the potential late-onset complications like avascular necrosis. Therefore, the results of short-term observation cannot be extrapolated to the efficacy and safety of the method as a whole, and it is necessary to continue monitoring patients for a longer period. It should be noted that the absence of a control group without any interventions limits the internal validity of the reported success rates, which also argues for the need to continue monitoring patients.

No data is available on the use of this technique in patients with concomitant cardiovascular, endocrine and neurological diseases. Theoretically, these pathologies may increase the risk of complications such as ischemic necrosis of the skin and avascular necrosis of the condyles of femur and tibia. Furthermore, it is noteworthy that the number of patients in whom the TAE intervention was ineffective (lack of positive dynamics) with TAE were slightly higher on comparison with the synovial fluid prosthesis group. We analyzed cases of insufficient TAE efficacy. It can be concluded that this is independent of the patient's gender or body mass index, although there is a tendency for unsuccessful results in older patients. Angiographic characteristics also do not provide convincing data, so it is necessary to conduct further search for causes and verification of "suitable" patients, development of clearer indications for this method.

Moreover, it is essential to continue researching the variants of the anatomical structure of the pathological vascular networks that develop in OA of knee joint as it would increase the effectiveness of the method by detailing the causative branches of the popliteal arteries which would be accurately embolized and would lower the risk of development of ischemic complications from surrounding tissues. Above all, insufficient data is available regarding the comparative effectiveness of TAE in OA patients based on grading and age-sex correlation of treatment results. However, we do not recommend TAE in patients with OA grades 3-4, as the procedure is ineffective in advanced stages, according to the literature [16]. It is logical to assume that the significant changes in joint structures observed in late stages, involving the articular bone, subchondral cartilage, and ligamentous apparatus of the knee, will not allow for significant positive clinical results when addressing the vascular factor alone.

5. Conclusions

TAE of popliteal artery branches is an effective minimally invasive intervention that significantly reduces the severity of pain in patients and improves the functional parameters of knee joint. This method has low risk of complications and can be used to alleviate pain in knee OA grades 1-2. On the other hand, this method requires further research, expansion of patient samples, development of a selection criteria in order to increase accessibility for practical healthcare.

Author Contributions

Conceptualization: A.A., V.V.; Methodology: V.V.; Formal analysis: A.G., T.V.; Investigation: V.I., A.Z., K.M.; Writing – original draft: K.K., K.M.; Writing – review & editing: all authors.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Orenburg State Medical University (Nº 357, 02.05.2025).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Proteinuria in Immune-Mediated Glomerular Diseases as a Marker of Disease Activity and Therapeutic Response: A Retrospective Study

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Running title: Proteinuria in immune-mediated glomerular diseases

Abstract

Background: Proteinuria is an established marker of activity, severity, and progression in glomerular diseases. In addition to reflecting damage to the glomerular filtration barrier, it also plays a pathogenetic role in the development of tubulointerstitial inflammation and fibrosis. **Objectives:** To assess the dynamics of proteinuria in patients with chronic glomerulonephritis and its significance as an indicator of therapeutic response. **Methods:** A retrospective study of a total of 57 patients with different morphological forms of chronic glomerulonephritis, treated at the Clinic of Nephrology and Dialysis, St. Marina University Hospital – Varna, were followed for a period of 24 months. Twenty-four-hour proteinuria and the protein-to-creatinine ratio (Pr/Cr) in a spot urine sample were analyzed. All patients received optimal nephroprotective therapy, and immunosuppressive treatment was administered when indicated. **Results:** The mean baseline 24-hour proteinuria was 5.94 g/24 h. By the third month, a statistically significant decrease to 3.65 g/24 h was observed ($p \approx 0.008$), followed by a further reduction to 2.7 g/24 h at month 6 and to 1.72 g/24 h at month 12. The observed reduction indicates an early and sustained therapeutic response in the studied patient population. Analysis

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of the protein-to-creatinine ratio confirmed the same favorable trend and supports its applicability as a reliable marker for monitoring proteinuria in clinical practice. **Conclusion:** Early and sustained reduction of proteinuria is a reliable indicator of therapeutic efficacy in chronic glomerular diseases and is associated with a more favorable renal prognosis. Proteinuria has substantial value both as a prognostic marker and as a surrogate endpoint in clinical follow-up.

Keywords: proteinuria; chronic glomerulonephritis; chronic kidney disease; therapeutic response

1. Introduction

Proteinuria is one of the most common and clinically significant manifestations of glomerular diseases. An increased urinary protein excretion not only reflects damage to the glomerular filtration barrier but also has major implications for long-term renal prognosis [1,2]. In recent years, growing attention has been paid to proteinuria as a modifiable risk factor for progression of chronic kidney disease (CKD).

Accumulated clinical data indicate that the degree of proteinuria is directly associated with the rate of decline in renal function. Patients with persistent proteinuria have a substantially higher risk of developing chronic renal failure [3]. For this reason, reduction of proteinuria is considered an important therapeutic goal and is frequently used as a surrogate marker of treatment efficacy in glomerular diseases [4].

The glomerular filtration barrier consists of endothelial cells, the glomerular basement membrane, and podocytes, which together provide selective filtration of plasma components. In glomerular diseases, structural and functional disturbances of this barrier lead to increased permeability to proteins, predominantly albumin [5].

Filtered proteins reach the proximal tubules where they are reabsorbed via endocytosis. When the amount of filtered protein exceeds the reabsorptive capacity of tubular cells, a series of pathophysiological mechanisms are activated, including inflammatory processes, oxidative stress, and release of profibrotic mediators [6,7]. As a result, tubulointerstitial changes develop that play a central role in progression of CKD.

Several studies demonstrate that even moderate levels of proteinuria may be associated with accelerated loss of renal function. Reduction of proteinuria has been associated with slowing of renal injury progression and improved long-term prognosis [3,7].

Importantly, a substantial proportion of glomerular diseases arise in the context of systemic rheumatologic disorders. Conditions such as systemic lupus erythematosus, ANCA-associated vasculitis, cryoglobulinemic vasculitis and secondary amyloidosis represent key examples in which renal involvement significantly determines overall prognosis. In these settings, proteinuria is not only a marker of renal injury, but also reflects systemic disease activity and therapeutic response. Therefore, evaluating proteinuria as a dynamic and modifiable parameter has direct implications for both nephrology and rheumatology practice.

Conventional endpoints in nephrology clinical trials, such as doubling of serum creatinine or progression to end-stage renal disease, require prolonged follow-up. Therefore, earlier indicators that reflect therapeutic effects on renal function are sought [2,8].

In this context, reduction of proteinuria is accepted as a reliable indicator of favorable renal outcome. Multiple studies show that early decrease in proteinuria after initiation of therapy is associated with a significantly lower risk of CKD progression [8,9]. Achieving proteinuria values below 1 g/24 h is often linked to better renal prognosis across various glomerular diseases [9,10].

ACE inhibitors and angiotensin receptor blockers are a cornerstone of treatment for renal diseases. By reducing intraglomerular pressure, these agents limit protein filtration and produce substantial reductions in proteinuria [11,12].

Moreover, RAAS blockade confers additional nephroprotective effects, including anti-inflammatory and antifibrotic actions [7,11]. There is compelling evidence that long-term therapy with these agents can slow progression of chronic kidney disease [11,12].

SGLT2 inhibitors represent a relatively new class of agents with nephroprotective properties. Their actions include restoration of tubuloglomerular feedback and reduction of glomerular hyperfiltration, resulting in decreased intraglomerular pressure [13,14].

Accumulating evidence indicates that treatment with SGLT2 inhibitors leads to significant reductions in albuminuria and delays progression of CKD in patients with various nephropathies [13,14].

Endothelin-1 participates in the pathogenesis of glomerular diseases by promoting vasoconstriction, inflammation, and fibrosis. Activation of the endothelin system may contribute to podocyte injury and increased proteinuria [15].

Endothelin receptor antagonists have shown promising results in reducing proteinuria in patients with glomerular diseases. Their effects include improvement of glomerular hemodynamics and attenuation of inflammatory processes [15,16].

In immune-mediated glomerular diseases, immunosuppressive therapy plays a key role in disease control. By suppressing the immunologic mechanisms of glomerular injury, these agents can produce marked reductions in proteinuria [1,17].

Achievement of partial or complete remission of proteinuria after immunosuppressive treatment is associated with a more favorable renal prognosis in diseases such as membranous nephropathy, IgA nephropathy, and lupus nephritis [10,17].

2. Materials and Methods

We present the results of a 2-year retrospective, single-center follow-up study including 57 patients from the Clinic of Nephrology and Dialysis at St. Marina University Hospital, Varna. All participants had morphologically verified chronic glomerulopathies and were clinically followed and evaluated using routine diagnostic methods. The analysis of available data includes participants with various morphological forms of immune-mediated glomerular diseases, including IgA nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, minimal change disease, lupus nephritis, and ANCA-associated glomerulonephritis. The exclusion criteria were: (1) age under 18 years; (2) patients with established malignant diseases; (3) pregnancy; (4) status post kidney transplantation; and (5) patients with incomplete laboratory or medical data. Given the retrospective design, informed consent was not required. All data were anonymized prior to analysis.

Descriptive statistics were applied for baseline characteristics. Changes over time were assessed using paired tests, while between-group

differences were analyzed using one-way ANOVA. A p-value <0.05 was considered statistically significant.

Patients were followed for 24 months; 24-hour proteinuria and the protein/creatinine ratio (Pr/Cr) in spot urine samples were analyzed.

All patients received optimal supportive therapy, including RAAS blockade (ACE inhibitors or ARBs), statins, diuretics, and other nephroprotective medications. Immunosuppressive treatment was administered where indicated, tailored to the type and severity of the glomerular disease, and included corticosteroids (parenteral and oral), cyclophosphamide, mycophenolate mofetil (MMF), azathioprine, and calcineurin inhibitors (tacrolimus). In some patients, an SGLT2 inhibitor (dapagliflozin) was added to the therapeutic regimen.

3. Results

The gender distribution of participants was 25 women and 32 men, or 43.86% : 56.14% (Table 1).

Table. 1. Distribution of patients by gender.

Gender	Number	Distribution %
F	25	43.86
M	32	56.14

The average age of all patients with HGN at the time of inclusion in the follow-up is 48.5 years (participants are aged between 19 and 78) (Table 2, Figure 1).

Table. 2. Statistical characteristics of patient age.

	Average value	Minimal	Maximal	Standard deviation.
Age	48.5	19	78	14.9

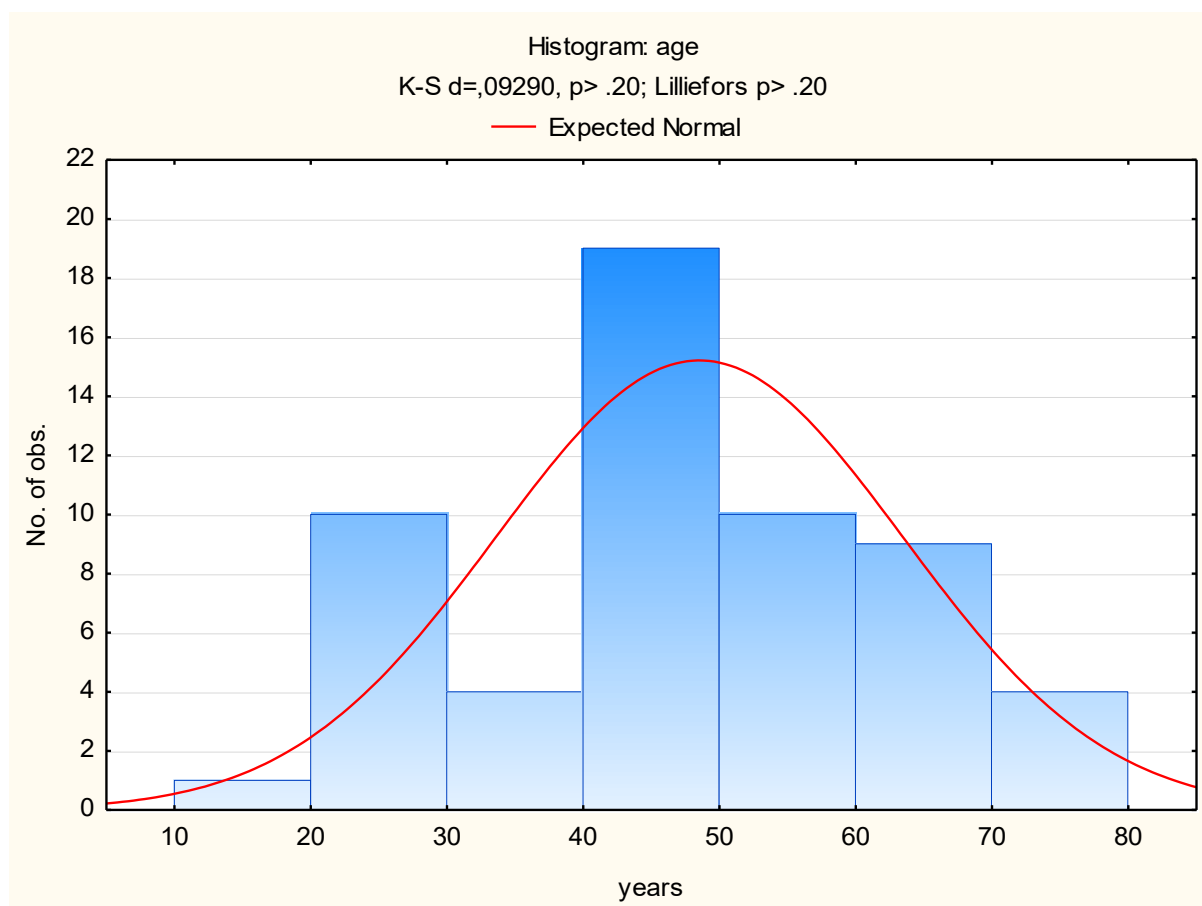


Figure 1. Histogram illustrating the number of participants in the follow-up according to age.

At baseline the mean 24-hour proteinuria among enrolled patients was approximately 5.94 g/24 h, corresponding to the nephrotic range and reflecting a substantial degree of glomerular injury. During treatment a marked reduction in this parameter was observed. By month 3 the mean proteinuria declined to about 3.65 g/24 h ($p \approx 0.008$). The reduction of roughly 2.3 g/24 h is clinically meaningful and demonstrates early therapeutic efficacy. Such a decrease is important because it is associated with stabilization of glomerular function and a reduced risk of progressive renal injury.

By month 6 proteinuria fell further to approximately 2.7 g/24 h. Although the difference versus month 3 did not reach statistical significance ($p \approx 0.148$), the downward trend remained evident. This suggests a sustained therapeutic effect of the interventions, likely reflecting both hemodynamic effects of nephroprotective therapy and gradual suppression of immunologic activity in patients who received immunosuppression.

At 12 months the mean 24-hour proteinuria declined to about 1.72 g/24 h. This value indicates that a substantial proportion of patients achieved partial or complete laboratory remission. Attainment of such levels is an important therapeutic milestone, being associated with markedly better renal prognosis and a lower risk of progression to chronic renal failure (Figure 2).

Additional analysis of the protein/creatinine ratio (Pr/Cr) in spot urine samples confirmed the trend observed with 24-hour proteinuria. Pr/Cr is widely used in clinical practice as a convenient and reliable surrogate for total proteinuria because it correlates with 24-hour collections, although careful interpretation is required at higher proteinuria levels. In the present analysis Pr/Cr values showed a statistically significant reduction at months 3 and 6, consistent with the decreases in 24-hour proteinuria.

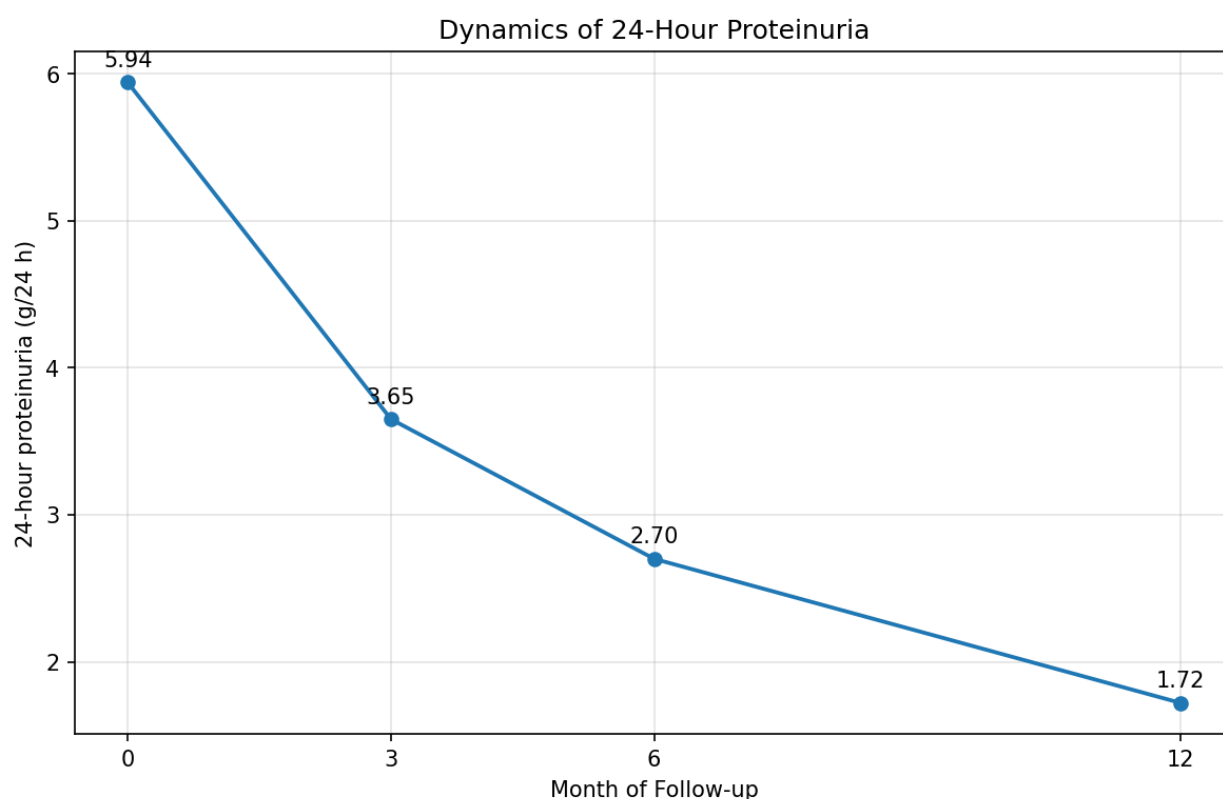


Figure 2. Dynamics of 24-hour proteinuria during follow-up.

One-way analysis of variance (ANOVA) was performed to compare mean protein-to-creatinine ratio (Pr/Cr) at baseline and at month 24 across the study groups (Figure 3 and Figure 4).

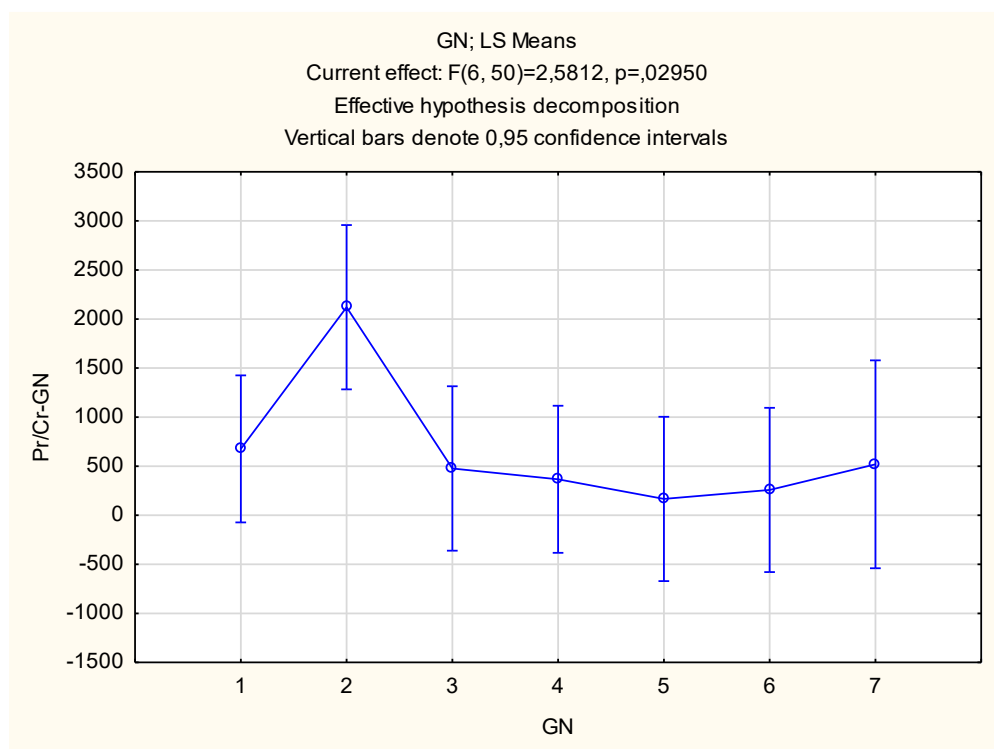


Figure 3. Analysis of variance (ANOVA) assessing differences in mean protein-to-creatinine ratio (Pr/Cr) at baseline.

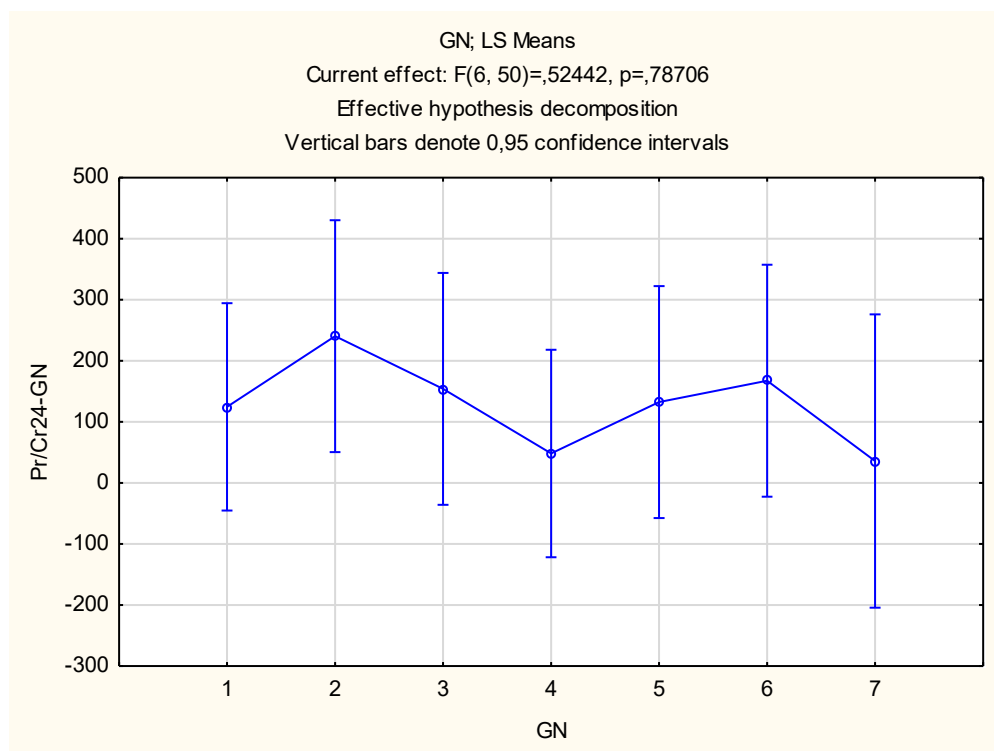


Figure 4. Analysis of variance (ANOVA) assessing differences in mean protein-to-creatinine ratio (Pr/Cr) at month 24.

The analysis of variance (ANOVA) demonstrated no statistically significant differences in the mean protein-to-creatinine ratio (Pr/Cr) at baseline across the study groups ($p > 0.05$). This finding indicates that the groups were comparable at the start of the follow-up period, allowing for a reliable assessment of subsequent changes over time.

At month 24, ANOVA revealed a statistically significant difference in mean Pr/Cr values between the study groups ($p < 0.05$). This suggests a differential treatment response and/or disease progression among the groups during the follow-up period.

4. Discussion

The results obtained from the present follow-up demonstrate a clear trend toward a reduction in proteinuria among patients with chronic glomerular diseases during the course of therapy. Proteinuria is a well-established marker both of the activity of glomerular injury and of long-term renal prognosis. The degree of proteinuria is one of the strongest independent predictors of progression of chronic kidney disease and the development of end-stage renal failure [1,3,7]. For this reason, its reduction is considered a primary therapeutic goal in modern nephrology practice.

A significant subset of glomerular diseases included in this study is directly related to systemic rheumatologic conditions. Kidney-related symptoms in rheumatic diseases are often present, which increase mortality and morbidity of patients with rheumatic diseases [37]. For example, lupus nephritis represents one of the most severe organ manifestations of systemic lupus erythematosus and is characterized by immune complex deposition within the glomeruli, leading to proteinuria and progressive renal dysfunction. Similarly, ANCA-associated vasculitis frequently presents with rapidly progressive glomerulonephritis and significant proteinuria, reflecting active small-vessel inflammation. In addition, cryoglobulinemic vasculitis is associated with immune complex-mediated glomerular injury, while secondary amyloidosis [31], often seen in chronic inflammatory rheumatic diseases such as rheumatoid arthritis, leads to progressive proteinuria due to extracellular deposition of amyloid fibrils within the kidney. These conditions highlight the close interplay between systemic inflammation and renal involvement, further emphasizing the importance of proteinuria as a shared clinical endpoint.

In the present study, the baseline value of 24-hour proteinuria was within the nephrotic range. The presence of high baseline proteinuria is associated

with an increased risk of structural damage to the glomerular filtration barrier, as well as with the development of tubulointerstitial fibrosis, which plays a key role in the progression of chronic kidney disease [6,7].

During the course of treatment, a statistically significant reduction in proteinuria was observed as early as the third month of follow-up. Such an early therapeutic response is considered a favorable prognostic factor, since early reduction of proteinuria is associated with a slower decline in glomerular filtration and a lower risk of reaching end-stage kidney disease (8, 9). The reduction of proteinuria during the first months of treatment is a strong predictor of long-term therapeutic success, regardless of the morphological variant of the glomerular disease [4,8,9]. In addition, a decrease in proteinuria was also observed at the sixth month of follow-up, indicating a sustained effect of the administered therapy. Although the difference between the third and sixth months did not reach statistical significance, the trend toward gradual reduction in proteinuria remained clearly expressed. This likely reflects the combined effect of ongoing nephroprotective therapy, including blockade of the renin–angiotensin–aldosterone system, as well as immunosuppressive treatment in patients with immune-mediated glomerular diseases [11,12,17].

A particularly important observation is the substantial reduction of proteinuria to approximately 1.72 g/24 h at the twelfth month. Achieving proteinuria levels below 2–3 g/24 h is considered partial remission and is associated with a significant improvement in renal prognosis [9,10]. In many glomerular diseases, including IgA nephropathy and membranous nephropathy, reduction of proteinuria below these threshold values is associated with stabilization of renal function and slowing of chronic kidney disease progression [8–10].

The results of the present study are consistent with data from large clinical trials demonstrating that early and sustained reduction in proteinuria is a key factor in improving long-term renal outcomes. Achieving partial or complete remission of proteinuria is associated with a significantly lower risk of developing end-stage renal failure and the need for renal replacement therapy [8–10,17].

In our cohort, all patients received ACE inhibitors or ARBs (unless contraindicated) from the time of diagnosis, which likely contributed to the reduction in proteinuria. It is well established that RAAS blockade has a pronounced antiproteinuric effect; the REIN study demonstrated a ~40–50% reduction in proteinuria and slowing of eGFR decline with ramipril in

proteinuric nephropathies [33]. Our findings are consistent with these observations, as patients receiving ACEi/ARB therapy showed a marked reduction in Pr/Cr ratio.

For instance, patients with moderate proteinuria treated with supportive therapy alone (RAAS blockade, diuretics, statins) achieved a reduction in proteinuria from approximately 1.5–2 g/day to below 0.5 g/day within 6 months. In cases of persistent or resistant proteinuria (>1 g/day despite 3–6 months of optimal supportive therapy), immunosuppressive treatment was initiated in accordance with KDIGO recommendations [23]. The addition of corticosteroids resulted in further reduction in proteinuria [40].

In patients with IgA nephropathy and nephrotic syndrome, a 6-month corticosteroid regimen (including pulse and oral administration) led to remission or significant improvement, consistent with findings reported by Pozzi et al., who demonstrated a reduced risk of doubling of serum creatinine and proteinuria compared to controls [34].

Similarly, in focal segmental glomerulosclerosis (FSGS) and minimal change disease, where corticosteroids are the mainstay of therapy, a substantial reduction in proteinuria was observed. In minimal change disease, initial massive proteinuria (~10–15 g/day) nearly completely resolved after an 8-week course of high-dose prednisolone. In steroid-resistant FSGS, the introduction of calcineurin inhibitors (tacrolimus) resulted in a >50% reduction in Pr/Cr over 6 months, consistent with the reported ~60% remission rate with CNIs in resistant nephrotic syndrome.

Adjunctive therapies such as mineralocorticoid receptor antagonists (e.g., spironolactone) provided additional benefits. Patients treated with spironolactone (25 mg/day) showed a further reduction in Pr/Cr of approximately 20–30% compared to ACEi monotherapy, in agreement with data from Park et al., who reported over 40% reduction in proteinuria within 3 months when low-dose spironolactone was added to ARB therapy [35]. Although a slight increase in serum creatinine was observed in their study, no clinically significant deterioration in kidney function was noted in our cohort, likely due to careful monitoring.

The SGLT2 inhibitor dapagliflozin was administered in selected patients with IgA nephropathy and residual proteinuria. The observed additional reduction in Alb/Cr is consistent with findings from the DAPA-CKD trial, where dapagliflozin reduced albuminuria by approximately 26% compared to placebo [36].

Importantly, the degree of proteinuria reduction after 12 months of treatment is a critical predictor of long-term outcomes. Our data indicate that patients who achieved proteinuria <1 g/day at month 12 maintained stable kidney function without progression. This is consistent with previous studies, such as the Lupus Nephritis Maintenance Trial, which demonstrated that early reduction in proteinuria during the first year strongly predicts favorable long-term prognosis [2,9].

The analysis of the protein/creatinine ratio (Pr/Cr) in a spot urine sample further confirms the observed trend. This parameter is widely used in clinical practice as a convenient and reliable method for assessing proteinuria, although in glomerular diseases and at higher levels of protein excretion, its correlation with 24-hour proteinuria may be moderate rather than absolute [18,19]. In the present analysis, a significant reduction in Pr/Cr was observed even in the early stages of follow-up, corresponding to the observed decrease in 24-hour proteinuria.

The reduction in proteinuria is likely due to the combined effect of the different therapeutic regimens used in the patients. Blockade of the renin-angiotensin-aldosterone system represents a fundamental component in the treatment of proteinuric kidney diseases, as it reduces intraglomerular pressure and decreases protein filtration through the glomerular barrier [11,12]. Additionally, in some patients modern nephroprotective medications such as SGLT2 inhibitors were used; by restoring tubuloglomerular feedback and reducing glomerular hyperfiltration, these agents contribute to lowering proteinuria [13,14].

Immunosuppressive therapy also plays an important role in immune-mediated glomerular diseases. Suppression of the immunological mechanisms of glomerular injury leads to a reduction in inflammatory activity within the glomeruli and consequently to a decrease in proteinuria [1,17]. In diseases such as membranous nephropathy, lupus nephritis, and ANCA-associated glomerulonephritis, achieving remission of proteinuria is considered an important indicator of therapeutic success and better long-term prognosis [10,20].

In a broader clinical context, increasing interest is being directed toward the role of urinary biomarkers in other diseases of the urogenital system, including oncological urological conditions, which emphasizes the importance of early laboratory assessment for diagnosis, follow-up, and therapeutic monitoring [21].

Although the present study was not specifically designed for subgroup statistical analysis, a proportion of patients had glomerular diseases associated with systemic autoimmune conditions, including lupus nephritis and ANCA-associated vasculitis [38,39]. In these patients, the observed reduction in proteinuria paralleled clinical improvement, suggesting that proteinuria may serve as an indirect marker of systemic disease control.

In rheumatologic practice, proteinuria is increasingly recognized as a key therapeutic target, particularly in diseases such as systemic lupus erythematosus and systemic vasculitides. Current treatment strategies in lupus nephritis aim not only at immunological remission but also at achieving a significant reduction in proteinuria, often below 0.5–0.7 g/day, which is associated with improved long-term renal outcomes [22,27]. Similarly, in ANCA-associated vasculitis, reduction in proteinuria reflects control of glomerular inflammation and is used alongside other markers to monitor treatment response [29,30]. Therefore, proteinuria represents a clinically meaningful and measurable endpoint that bridges nephrology and rheumatology, allowing for integrated assessment of both renal and systemic disease activity.

These findings are consistent with rheumatology-focused studies demonstrating that early reduction in proteinuria predicts favorable renal outcomes in lupus nephritis (KDIGO 2021; EULAR/ERA-EDTA recommendations) [23-26]. EULAR recommendations for the management of systemic lupus erythematosus emphasize proteinuria reduction as a primary treatment goal in lupus nephritis [28].

The present study also has certain limitations. The heterogeneity of the included glomerular diseases, differences in the therapeutic regimens used, the relatively small number of patients and the absence of a control group may limit the ability to directly generalize the findings to all forms of glomerulopathies. In addition, the retrospective design is associated with potential biases and incomplete data. Despite these limitations, the study provides relevant real-world insights into the role of proteinuria as a marker of disease activity and therapeutic response and confirms the importance of early therapeutic intervention.

5. Conclusions

Proteinuria is a central biomarker of disease activity, severity, and progression in glomerular diseases, including those associated with systemic rheumatologic disorders. Beyond its role as an indicator of renal injury, proteinuria serves as an important therapeutic target and monitoring parameter in conditions such as systemic lupus erythematosus and systemic vasculitides. The present findings support the concept that early and sustained reduction in proteinuria is associated with improved renal outcomes and may reflect effective control of both renal and systemic disease processes. The reduction of proteinuria is increasingly recognized as one of the main therapeutic goals in the modern treatment of glomerular diseases, as well as a reliable indicator of the effectiveness of the applied therapy. These observations highlight the importance of an integrated nephrology–rheumatology approach in the management of patients with immune-mediated kidney involvement.

Author Contributions

Conceptualization: M.B., S.B.; Methodology: M.B., S.B.; Formal analysis: M.B.; Investigation: M.B.; Writing – original draft: M.B., S.B.; Writing – review & editing: all authors.

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Institutional Review Board Statement

The study was retrospective and statement from the Commission on Institutional Oversight was not necessary.

Informed Consent Statement

Informed consent was waived due to the retrospective nature of the study

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Протеинурията при имуномедиирани гломерулни заболявания като маркер за болестна активност и терапевтичен отговор: Ретроспективно проучване

Резюме

Въведение: Протеинурията е утвърден маркер за активността, тежестта и прогресията на гломерулните заболявания. Освен че отразява увреждането на гломерулната филтрационна бариера, тя играе и патогенетична роля в развитието на тубулоинтерстициално възпаление и фиброза. **Цели:** Да се оцени динамиката на протеинурията при пациенти с хроничен гломерулонефрит и нейното значение като индикатор за терапевтичен отговор. **Методи:** Проведено е ретроспективно проучване на общо 57 пациенти с различни морфологични форми на хроничен гломерулонефрит, лекувани в Клиниката по нефрология и диализа към УМБАЛ „Св. Марина“ – Варна и проследени за период от 24 месеца. Анализирани са 24-часовата протеинурия и съотношението протеин/креатинин (Pr/Cr) в еднократна уринна порция. Всички пациенти са получили оптимална нефропротективна терапия, а при наличие на показания е прилагано и имunosupресивно лечение. **Резултати:** Средната изходна 24-часова протеинурия възлиза на 5,94 g/24 h. До третия месец се наблюдава статистически значимо понижение до 3,65 g/24 h ($p \approx 0,008$), последвано от по-нататъшна редукция до 2,7 g/24 h на 6-ия месец и до 1,72 g/24 h на 12-ия месец. Наблюдаваното понижение е показател за ранен и устойчив терапевтичен отговор в изследваната популация пациенти. Анализът на съотношението протеин/креатинин потвърждава същата благоприятна тенденция и подкрепя неговата приложимост като надежден маркер за мониториране на протеинурията в клиничната практика. **Заключение:** Ранното и трайно намаляване на протеинурията е надежден индикатор за терапевтична ефикасност при хронични гломерулни заболявания и е свързано с по-благоприятна ренална прогноза. Протеинурията притежава съществена стойност както като прогностичен маркер, така и като сурогатен краен показател в клиничното проследяване.

Ключови думи: протеинурия, хроничен гломерулонефрит, хронично бъбречно заболяване, терапевтичен отговор

The History of Cytokines in Rheumatic Disease: An Evolutionary Perspective on Mediators, Inhibitors, and Therapeutics

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Abstract

Cytokines are small, secreted proteins that serve as the principal mediators of the immune system, orchestrating the complex interplay of cells involved in inflammation, immunity, and tissue homeostasis. Their dysregulation is a central feature in the pathophysiology of chronic inflammatory conditions, particularly autoimmune rheumatic diseases such as rheumatoid arthritis. This report provides a comprehensive, structured analysis of the history of cytokines, tracing their evolution from vaguely understood biological activities to precisely defined molecular targets for revolutionary therapies. To provide a conceptual foundation, fundamental definitions and classifications of cytokines are established, with a specific focus on how the core properties of pleiotropy, redundancy, and network complexity have profoundly influenced their study and therapeutic manipulation. The narrative subsequently details landmark discoveries of key pathogenic cytokines in rheumatology—including the TNF- α , IL-1, and IL-6 families—while detailing the paradigm shift prompted by the identification of the IL-23/Th17 axis. Parallel to these discoveries, the evolution of therapeutic agents is mapped from first-generation biologic disease-modifying anti-rheumatic drugs (bDMARDs), such as TNF

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inhibitors, to the oral revolution of targeted synthetic DMARDs like Janus kinase inhibitors, and onward to next-generation strategies including bispecific antibodies and engineered cytokines. In the final sections, the current state of the field is synthesized through a critical examination of unresolved questions and knowledge gaps, such as the mechanisms of treatment non-response, the challenge of cytokine redundancy, and the optimal management of systemic comorbidities. Prospective future directions are outlined, emphasizing an increasing focus on biomarker-driven patient stratification, multi-target combination strategies, and the ultimate pursuit of immune tolerance and curative therapies. Together, these developments represent a clear evolutionary trajectory toward the realization of precision medicine in rheumatology.

Keywords: cytokines, rheumatic disease, DMARDs, monoclonal antibodies

1. Introduction

Cytokines are a diverse category of small, soluble proteins or glycoproteins, typically ranging from 5 to 70 kDa, that serve as the primary regulators of the immune system [1]. Secreted by a wide array of nucleated cells - including immune cells such as macrophages and T lymphocytes, as well as non-immune cells like endothelial cells and fibroblasts - they function as essential intercellular signaling molecules [2]. Historically, their nomenclature reflected specific cellular origins or perceived functions, giving rise to terms such as lymphokines, monokines, and interleukins, though these have since been integrated under the broader "cytokine" umbrella [2,3]. These molecules exert their influence by binding to high-affinity receptors via autocrine, paracrine, or endocrine signaling, thereby directing the maturation, differentiation, and activity of the immune network [2,4].

The biological impact of cytokines is governed by a set of core properties that render their network behavior exceptionally complex. These include pleiotropy, where a single cytokine like Tumor Necrosis Factor-alpha (TNF- α) exerts multiple effects across different cell types, and redundancy, where distinct cytokines perform overlapping functions [1,2,5]. Furthermore, the immune response is fine-tuned through synergy, antagonism, and cascade induction, where the secretion of one cytokine triggers a self-perpetuating loop of secondary mediators [2,6]. This inherent complexity has historically complicated therapeutic efforts; for example, redundancy can lead to treatment resistance when a single cytokine is blocked, while pleiotropy

may result in unintended side effects [5,6]. Such challenges have driven the evolution of the field from simple monoclonal antibodies toward more sophisticated strategies, including Janus kinase (JAK) inhibitors and engineered bispecific molecules designed to navigate these intricate pathways.

To fully understand their clinical relevance, cytokines must be situated within the broader context of inflammatory mediators and biologically active molecules. Inflammatory mediators comprise a heterogeneous group of chemical factors - including vasoactive amines, lipids, and complement proteins - that orchestrate the physiological signs of inflammation [7,8]. More broadly, cytokines are classified as biologically active molecules, a term encompassing all proteins, hormones, and growth factors that elicit specific biological responses to maintain homeostasis [9]. In the field of rheumatology, the dysregulation of these mediators is the cornerstone of disease, as their persistent activity drives the chronic inflammation and joint destruction characteristic of various rheumatic pathologies [8].

The aim of this study is to provide a comprehensive overview of the history of cytokines and the evolution of molecular knowledge surrounding them to define a trajectory for future research in rheumatology. By examining the transition from early phenomenological observations to the current era of precision medicine, we seek to elucidate the role of cytokine involvement in the pathogenesis of rheumatic diseases. Ultimately, this perspective aims to facilitate the development of novel diagnostic biomarkers and next-generation therapeutic strategies centered on the precise modulation of the cytokine network.

2. Classification of Cytokines, Mediators, and Biologically Active Molecules

The expansive diversity of the cytokine network necessitates a multifaceted classification system to organize these molecules into coherent groups. Rather than a single universal standard, cytokines are categorized through several parallel frameworks based on their primary biological function, three-dimensional protein structure, genetic homology, or the specific receptor superfamilies they utilize. Each of these classification schemes provides a distinct perspective essential for understanding cytokine biology and the subsequent development of targeted rheumatological interventions.

2.1 Functional Classification and Context-Dependent Plasticity

From a clinical perspective, cytokines are most intuitively classified by their principal effect on the inflammatory process, established as a functional dichotomy between pro-inflammatory and anti-inflammatory mediators. Pro-inflammatory cytokines, such as TNF- α , Interleukin-1 (IL-1), and IL-6, are the primary drivers of pathogenesis in rheumatic diseases; they are responsible for leukocyte recruitment to the synovium, activation of destructive enzymatic processes, and the perpetuation of chronic tissue damage [1,10]. More recently, the IL-17 and IL-23 families have emerged as critical mediators in this group, specifically in the differentiation of pathogenic Th17 cells [11]. Conversely, anti-inflammatory cytokines, including IL-10, Transforming Growth Factor-beta (TGF- β), and IL-37, serve as regulatory brakes that suppress inflammatory cell activity and promote tissue repair [1,12]. However, this classification is notably context-dependent. The biological outcome of cytokine signaling is dictated by the cellular milieu and timing; for example, while IL-6 is a hallmark pro-inflammatory driver of the acute-phase response, it can also exhibit anti-inflammatory properties by inducing specific inhibitors [5]. Similarly, TGF- β acts as a potent immunosuppressant but can promote highly pathogenic Th17 differentiation in the presence of IL-6 [13].

2.2 Structural and Familial Categorization

Cytokines are also grouped by their tertiary protein structures, which often reflect shared evolutionary origins and mechanisms of receptor engagement. The three primary structural classes include the four- α -helix bundle cytokines (e.g., IL-2, IL-4, IL-6, and GM-CSF), the β -sheet cytokines - characterized by antiparallel beta-strands as seen in the IL-1 and TNF superfamilies - and the cysteine knot cytokines, such as the TGF- β superfamily, which possess an interlocked disulfide bond topology that confers high protein stability [5]. These structural motifs correspond closely with the division of cytokines into major families. The IL family represents the largest and most heterogeneous group, mediating complex communication between leukocytes and various non-immune cells [14]. The Interferon (IFN) family (Types I, II, and III) remains central to antiviral and immunomodulatory responses, while the TNF superfamily molecules are typically synthesized as transmembrane proteins critical for apoptosis and lymphoid organogenesis. Additionally, the chemokine family consists of small proteins (8–10 kDa) defined by their role in leukocyte chemotaxis [2,14], and Colony-Stimulating Factors (CSFs) primarily regulate the proliferation and survival of hematopoietic progenitor cells [15].

2.3 Receptor Superfamilies and the Molecular Basis of Redundancy

The classification of cytokines by their receptor superfamilies offers the most profound insight into their signaling mechanisms and the molecular basis of functional redundancy. Type I cytokine receptors (the hematopoietin family) represent the largest group and are characterized by shared signal-transducing subunits [16]. This is exemplified by the common γ chain (γc) used by IL-2 and IL-15, the common β chain (βc) shared by IL-3 and GM-CSF, and the gp130 subunit utilized by the IL-6 family. Type II receptors include those for interferons and the IL-10 family, while the TNF receptor (TNFR) superfamily is distinguished by repeating cysteine-rich extracellular domains [5]. In contrast, chemokine receptors are seven-transmembrane G protein-coupled receptors (GPCRs) [17,18], and the TGF- β receptor family possesses unique intrinsic serine/threonine kinase activity.

The discovery of shared signaling chains within these receptor families was a watershed moment in immunology, explaining why diverse cytokines often elicit overlapping biological effects. This understanding shifted the therapeutic paradigm in rheumatology: rather than targeting single cytokines, researchers recognized that inhibiting shared intracellular hubs could provide broader control over poly-cytokine-driven inflammation. This logic directly informed the development of JAK inhibitors [19]. Because the JAK-STAT pathway is the primary signaling conduit for Type I and Type II receptors, small-molecule JAK inhibition effectively dampens the signals of multiple pathogenic cytokines simultaneously, offering a potent therapeutic strategy for complex diseases like rheumatoid arthritis (RA) [20].

3. Discovery of Pathogenic Cytokines and Inhibitors in Rheumatic Diseases

The historical progression of our comprehension of RA is intrinsically intertwined with the elucidation of cytokines. This narrative unfolds as a scientific investigative endeavor, progressing from macroscopic biological observations to the precise identification of specific molecular effectors, culminating in the principled development of therapeutic interventions designed to neutralize their activity. Such seminal discoveries that established TNF- α , IL-1, IL-6, and the IL-23/Th17 axis are pivotal constituents within the pathogenesis of rheumatic diseases.

3.1 The Pre-Cytokine Era: From "Endogenous Pyrogen" to "Lymphokines"

Before the advent of molecular biology and recombinant DNA technology, scientists could only characterize the *activities* of soluble factors, not the factors themselves. In the mid-20th century, research into fever led to the concept of an "endogenous pyrogen" (EP) - a substance produced by the host's own cells, rather than by bacteria, that could induce a febrile response [21]. This was a crucial conceptual leap, suggesting the body produced its own inflammatory mediators. Later work would reveal EP to be primarily IL-1 [22].

Simultaneously, in the field of immunology, researchers studying lymphocyte cultures in the late 1960s and 1970s observed that activated lymphocytes released soluble factors that could influence the behavior of other immune cells. These functionally defined substances were given names reflecting their origins: "lymphokines" if they came from lymphocytes and "monokines" if they came from monocytes [2]. The first such lymphokines were isolated from in vitro cultures in 1969 [23]. These terms were placeholders for what was essentially a "black box" of biological activity. The field began to unify in 1979 at the Second International Lymphokine Workshop, where the term "Interleukin" was proposed to describe these molecules that acted as signals *between leukocytes*, marking a transition toward a more unified nomenclature [22,24].

3.2 The TNF- α Revolution: Unifying "Cachectin" and "Tumor Necrosis Factor" and Targeting the Lynchpin of RA

The story of TNF is a classic example of scientific convergence, where two disparate lines of inquiry led to the same molecule, revolutionizing both oncology and immunology.

In 1975, researchers at Memorial Sloan-Kettering, studying the anti-cancer effects of bacterial toxins first noted by William Coley in the 1890s, identified a factor in the serum of endotoxin-treated mice that caused hemorrhagic necrosis of tumors. They named it "Tumor Necrosis Factor" [6,25]. In a parallel field, immunoparasitologist Anthony Cerami and his group at Rockefeller University were investigating the cause of cachexia, the profound wasting syndrome seen in chronic diseases like cancer and tuberculosis. They identified a macrophage-secreted factor that suppressed lipoprotein lipase and induced this wasting state, which they named "cachectin" [26].

The pivotal moment came in 1985 when Cerami's group, including a young postdoctoral fellow named Bruce Beutler, purified cachectin and sequenced

it. They made the stunning discovery that it was the same molecule as TNF [27]. This unified the fields of cancer biology and immunology. More importantly, Beutler and Cerami performed a seminal experiment: they generated antibodies against TNF and showed that passively immunizing mice with these antibodies protected them from the lethal effects of endotoxin shock [28]. This was groundbreaking, as it proved that TNF was not just a correlative marker of disease but a causative mediator of inflammation and pathology. The therapeutic paradigm shifted from using TNF to kill tumors to blocking TNF to treat inflammation.

The focus then turned to autoimmune disease. In the UK, Marc Feldmann and Ravinder Maini were developing a new hypothesis about the pathogenesis of RA, suggesting that cytokine interactions within the synovial tissue were key [29]. In 1989, their group made the critical finding that TNF- α was produced at high levels in synovial cell cultures from RA patients and appeared to be at the apex of the pro-inflammatory cytokine cascade, driving the production of other cytokines like IL-1 and IL-6 [30]. Subsequent work confirmed that TNF and its receptors were abundantly expressed in the rheumatoid joint [31]. This laboratory finding was rapidly translated into animal models, where anti-TNF antibodies were shown to be highly effective at ameliorating collagen-induced arthritis [32]. This provided the direct rationale for human trials. In 1992, Feldmann and Maini initiated the first open-label clinical trial of a chimeric anti-TNF antibody, infliximab, in patients with severe RA [33,34]. The results were remarkably positive, with rapid and dramatic improvements in clinical signs and symptoms, heralding the dawn of the biologic therapy era in rheumatology.

3.3 The Interleukin-1 Axis: A Parallel Pathway of Inflammation and Tissue Destruction

Running parallel to the TNF story was the elucidation of the IL-1 pathway, another critical mediator of inflammation and, particularly, tissue destruction in RA. As mentioned, the story of IL-1 began with research on endogenous pyrogen (EP) in the early 1970s [21]. Charles Dinarello was a key figure in purifying and characterizing EP from human leukocytes [22]. At the same time, in the context of rheumatology, Jean-Michel Dayer and Stephen Krane's group at Harvard made a seminal observation. They found that a factor produced by monocytes, which they termed "mononuclear cell factor" (MCF), could stimulate synovial fibroblasts from RA patients to produce large quantities of collagenase (now known as MMP-1) and prostaglandins - key mediators of cartilage and bone destruction [35]. In 1979, at the same meeting where "Interleukin" was coined, it was recognized that EP, MCF, and another factor called "lymphocyte activating

factor" (LAF) were likely the same entity, which was unified under the name Interleukin-1 [21,24].

The molecular identity of IL-1 was definitively established in 1984-1985 with the cloning of the cDNAs for two distinct but related forms, IL-1 α and IL-1 β , by several groups, including those led by Dinarello and Peter Lomedico [36–38]. The availability of recombinant IL-1 protein confirmed that this single cytokine was indeed responsible for the vast array of biological activities previously attributed to different "factors," from fever to joint destruction.

A unique and critical chapter in the IL-1 story was the discovery of its own natural inhibitor. In 1984, Dayer's group reported that a factor present in the urine of febrile patients could specifically block the activity of IL-1 on synovial cells without affecting TNF [39,40]. This was the first description of a naturally occurring, specific cytokine receptor antagonist. This molecule, named IL-1 receptor antagonist (IL-1Ra), was purified and cloned in 1990 [21,41]. The existence of a dedicated natural inhibitor highlighted the potent and dangerous potential of unchecked IL-1 signaling, and it provided a ready-made template for a therapeutic agent (anakinra) [42].

3.4 The Rise of Interleukin-6: A Pleiotropic Mediator of Systemic Inflammation and the Acute Phase Response

While TNF- α and IL-1 are potent drivers of local joint inflammation, IL-6 emerged as a key mediator of the systemic features of RA. In the early 1980s, Tadamitsu Kishimoto's group in Japan was investigating the soluble factors that drive the final differentiation of B cells into antibody-producing plasma cells. They identified one such factor and named it B-cell stimulatory factor-2 (BSF-2) [43].

In 1986, Kishimoto's team successfully cloned the cDNA for BSF-2. In a remarkable coincidence of scientific discovery, other research groups independently cloned genes for factors with entirely different biological activities: "interferon-beta2" (a protein with antiviral activity), "hybridoma/plasmacytoma growth factor," and "hepatocyte-stimulating factor" (a factor that induced acute-phase protein production in liver cells) [43,44]. Upon sequence comparison, all of these molecules were found to be identical. This pleiotropy was so fundamental to its nature that when the molecule was officially named Interleukin-6 in 1988, it was already understood to have a wide range of functions [45].

In RA, IL-6 was found to be produced at high levels in the synovium, often induced by TNF- α and IL-1 [46]. Its unique role, however, lies in its systemic

effects. IL-6 is the principal driver of the hepatic acute-phase response, leading to the elevated levels of C-reactive protein (CRP) and fibrinogen seen in active RA [47]. It also contributes to the anemia of chronic disease by inducing hepcidin production, and to the thrombocytosis by acting on megakaryocytes [45]. This central role in systemic inflammation made the IL-6 receptor an attractive therapeutic target, culminating in the development of the monoclonal antibody tocilizumab [43,48].

3.5 The Discovery of the IL-23/Th17 Axis and its Redefinition of T-Cell-Mediated Autoimmunity

For many years, the "Th1/Th2 paradigm" dominated immunology, proposing that autoimmune diseases like RA were primarily driven by a T helper 1 (Th1) cell response, characterized by the cytokine IFN- γ [10]. However, the modest success of therapies targeting Th1 pathways suggested this model was incomplete. The breakthrough came from work distinguishing the functions of IL-12 and a newly discovered cytokine, IL-23. These two cytokines are related; they share a common protein subunit called p40, but are paired with distinct second subunits (p35 for IL-12, and p19 for IL-23) [11]. Using gene knockout mice in models of autoimmunity, a team at DNAX research institute led by Daniel Cua made a pivotal discovery. Mice lacking the IL-12-specific p35 subunit still developed severe autoimmune inflammation, but mice lacking the IL-23-specific p19 subunit were completely protected. This seminal finding, published in *Nature* in 2003, demonstrated that IL-23, not IL-12, was the critical cytokine for driving T-cell-mediated autoimmunity [49].

The immediate question was: what is the cellular target of IL-23? It was known that IL-23 could stimulate T cells to produce IL-17, a pro-inflammatory cytokine that had been cloned back in 1993-1995 but whose cellular source and significance were unclear [50,51]. In 2005, landmark papers from several independent groups, including those led by Casey Weaver [52] and Chen Dong [53], described a novel subset of CD4⁺ T helper cells. These cells were distinct from Th1 and Th2 cells and were characterized by their signature production of IL-17, leading to their designation as "Th17" cells [54]. They found that the differentiation of these cells was driven by a combination of TGF- β and IL-6, and that IL-23 was not required for their initial differentiation but was essential for their expansion, stabilization, and pathogenic function *in vivo*.

With the discovery of this new pathogenic T cell lineage, the role of IL-17 in RA was rapidly clarified. IL-17 was found in high concentrations in the RA synovium, where it acts as a potent pro-inflammatory mediator [10]. It

synergizes with TNF- α and IL-1 to drive the production of other inflammatory molecules, is a powerful recruiter of neutrophils into the joint, and directly contributes to bone erosion by promoting osteoclastogenesis [50]. The discovery of the IL-23/Th17 axis revealed an entirely new arm of the immune response driving autoimmunity and provided the clear scientific rationale for developing a new class of biologics targeting IL-23 or IL-17 [11]. Table 1 provides a condensed summary of these landmark discoveries.

Table 1. Summary of the discoveries of key cytokines (TNF- α , IL-1, IL-1Ra, IL-6, IL-23/Th17 axis).

Cytokine/ Pathway	Key Discoverer(s)/ Group	Approx. Year	Seminal Finding/ Publication	Pathogenic Mechanism in RA
TNF-α	Carswell, Cerami/Beutler, Feldmann/Maini	1975-1992	Identification as tumor necrosis factor and cachectin; protection from endotoxin shock with anti-TNF Ab; identification as a pivotal cytokine in RA synovium [25-34]	Apex of the inflammatory cascade; induces other cytokines (IL-1, IL-6); promotes cell adhesion and recruitment; activates osteoclasts
IL-1	Beeson, Dinarello, Dayer/Krane	1940s-1985	Identification as endogenous pyrogen (EP) and mononuclear cell factor (MCF); cloning of IL-1 α and IL-1 β cDNA [21-24, 36-38],	Potent pro-inflammatory mediator; induces fever and systemic symptoms; stimulates production of matrix metalloproteinases (MMPs) leading to cartilage degradation
IL-1Ra	Dayer, Seckinger	1984-1990	Discovery of a specific, natural IL-1 inhibitor in human urine; cloning of the IL-1 Receptor Antagonist (IL-1Ra) [21, 39-42]	Natural brake on IL-1 signaling; its therapeutic form (anakinra) competitively inhibits IL-1 binding to its receptor
IL-6	Kishimoto	1980s-1988	Identification as B-cell stimulatory factor-2 (BSF-2); cloning and unification with other factors (IFN- β 2, HSF) to become IL-6 [43-48]	Key driver of systemic inflammation; induces hepatic acute-phase response (e.g., CRP); contributes to anemia, fatigue, and thrombocytosis

IL-23/Th17 Axis	Cua, Weaver, Dong	2003-2005	Discovery that IL-23 (not IL-12) is critical for T-cell mediated autoimmunity; identification of the Th17 cell subset as the source of IL-17 [10,11, 49-52]	IL-17 recruits neutrophils; promotes inflammation; synergizes with TNF/IL-1; drives osteoclastogenesis and bone erosion
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APC: Antigen-presenting cell, BSF-2: B-cell Stimulatory Factor-2, DMARD: Biologic disease-modifying antirheumatic drug, CD20: Cluster of differentiation 20, CTLA4-Ig: Cytotoxic T-lymphocyte-associated protein 4-immunoglobulin fusion protein, EP: Endogenous pyrogen, EU: European Union, Fab': Fragment antigen-binding, HSF: Hepatocyte Stimulating Factor, IFN: Interferon, IL: Interleukin IL-1Ra: Interleukin-1 receptor antagonist, JAK: Janus kinase, MCF: Macrophage Chemotactic Factor, RA: Rheumatoid arthritis, Th17: T helper 17 cells, TNF- α : Tumor necrosis factor-alpha TYK2: Tyrosine kinase 2, US: United States

4. The Development of Cytokine-based Targeted Therapy in Rheumatology

The elucidation of the cytokine network in RA, as detailed previously, did not remain a purely academic exercise. It directly catalyzed a therapeutic revolution, transforming RA from a progressively disabling condition into a manageable chronic disease for many patients. This section details the evolution of these therapies, tracing a clear trajectory from the first targeted injectable biologics to orally available small molecules and onward to the innovative strategies of the future. This progression represents a continuous effort to improve efficacy, enhance safety, broaden the base of responsive patients, and address the fundamental challenges of cytokine biology.

4.1 First-Generation Biologics: The Era of Monoclonal Antibodies and Fusion Proteins

The late 1990s and early 2000s marked the dawn of targeted therapy in rheumatology. For the first time, drugs were not broad-spectrum immunosuppressants but were rationally designed, genetically engineered proteins aimed at neutralizing a single, specific pathogenic molecule.

4.1.1 TNF- α Blockers

Building directly on the foundational work of Feldmann, Maini, Beutler, and Cerami, TNF- α inhibitors were the first class of biologic disease-modifying antirheumatic drugs (bDMARDs) to be developed and approved [55]. Their dramatic success established the "cytokine blockade" principle and set the

standard for all subsequent biologics. The first approved agents utilized different molecular strategies to achieve the same goal. Infliximab, first approved for Crohn's disease in 1998, is a chimeric monoclonal antibody, meaning it combines mouse variable regions (for antigen binding) with a human constant region (to reduce immunogenicity) [55]. Adalimumab and golimumab are fully human monoclonal antibodies, further reducing the potential for the patient's immune system to recognize the drug as foreign and develop anti-drug antibodies [56]. Etanercept, also approved in 1998, uses a different design. It is a fusion protein that links two extracellular domains of the human p75 TNF receptor to the Fc portion of human IgG1 [57]. It acts as a "decoy receptor," binding to and neutralizing soluble TNF- α before it can engage with cellular receptors. Certolizumab pegol, a PEGylated Fab' fragment of a humanized monoclonal antibody, lacks the Fc region present in other agents and therefore does not mediate cell-killing mechanisms such as apoptosis, complement-dependent cytotoxicity, or antibody-dependent cell-mediated cytotoxicity. To compensate for the poor in vivo pharmacokinetics of the Fab' fragment, a 40 kDa polyethylene glycol moiety is attached to increase its half-life to a level comparable with whole antibody products [58].

The introduction of TNF blockers transformed RA management. However, their limitations quickly became apparent. A significant proportion of patients exhibit a primary non-response, and others lose response over time [59]. Furthermore, as potent immunosuppressants, they carry an increased risk of serious infections and other side effects, and being injectable proteins, they can be inconvenient for patients [60]. These limitations created a clear unmet need for alternative therapeutic mechanisms.

4.1.2 IL-1 and IL-6 Receptor Blockade

The success of TNF blockade validated the cytokine-targeting approach and spurred the development of drugs aimed at other key pathways identified in the synovium, providing crucial options for patients who failed or were intolerant to TNF inhibitors.

Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra) [61]. It competitively inhibits the binding of both IL-1 α and IL-1 β to the IL-1 receptor. While effective, its clinical efficacy in RA was generally found to be more modest than that of TNF inhibitors, and its short half-life requires daily injections, which has limited its use in this indication. However, it proved highly effective in a group of rare autoinflammatory

conditions such as cryopyrin-associated periodic syndromes (CAPS), where IL-1 β is the central pathogenic driver [21].

Tocilizumab is a humanized monoclonal antibody that targets the IL-6 receptor (both soluble and membrane-bound forms), preventing IL-6 from signaling [62]. Approved for RA in 2009, it proved to be a highly effective therapy, not only for joint inflammation but particularly for the systemic features of RA, such as fatigue, anemia, and the acute phase response, which are strongly driven by IL-6 [43]. Its success provided a valuable alternative for TNF-inadequate responders (TNF-IR).

4.2 The Second Wave of Biologics: Targeting the Th17 Pathway

The discovery of the IL-23/Th17 axis as a new, independent pathway of autoimmunity provided a fresh set of targets for drug development, leading to a second wave of biologics.

Secukinumab and ixekizumab are monoclonal antibodies that directly neutralize IL-17A [63,64]. Bimekizumab represents a further evolution in this class; unlike secukinumab and ixekizumab, which selectively target IL-17A, bimekizumab is a humanized IgG1 antibody that dual-neutralizes both IL-17A and IL-17F. This dual inhibition is hypothesized to provide superior efficacy, as both isoforms are overexpressed in inflammatory tissues and synergistically drive synovial inflammation and joint damage [65]. Ustekinumab takes a different approach, targeting the shared p40 subunit of IL-12 and IL-23, thereby blocking both the Th1 and Th17 pathways [66]. Expanding on this, more selective inhibitors have been developed to target the p19 subunit of IL-23 specifically [67,68]. Risankizumab is a high-affinity humanized monoclonal antibody that binds the IL-23 p19 subunit, effectively inhibiting IL-23 signaling without affecting IL-12, which shares the p40 subunit [67]. Similarly, guselkumab is a selective IL-23 inhibitor that has demonstrated significant efficacy in reducing disease activity in both peripheral and axial forms of psoriatic arthritis by suppressing the IL-23/Th17 axis [68].

These drugs have demonstrated outstanding efficacy in psoriasis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS), where the IL-17/23 axis is a dominant pathogenic driver [69,70]. However, their performance in RA clinical trials has been surprisingly modest [71]. This discrepancy between diseases has become a key area of debate and research. It strongly suggests that while the IL-17 pathway is present in the RA synovium, it may not be as central or as indispensable to the disease process as the TNF and IL-6 pathways, or that its role is confined to a specific subset of RA patients

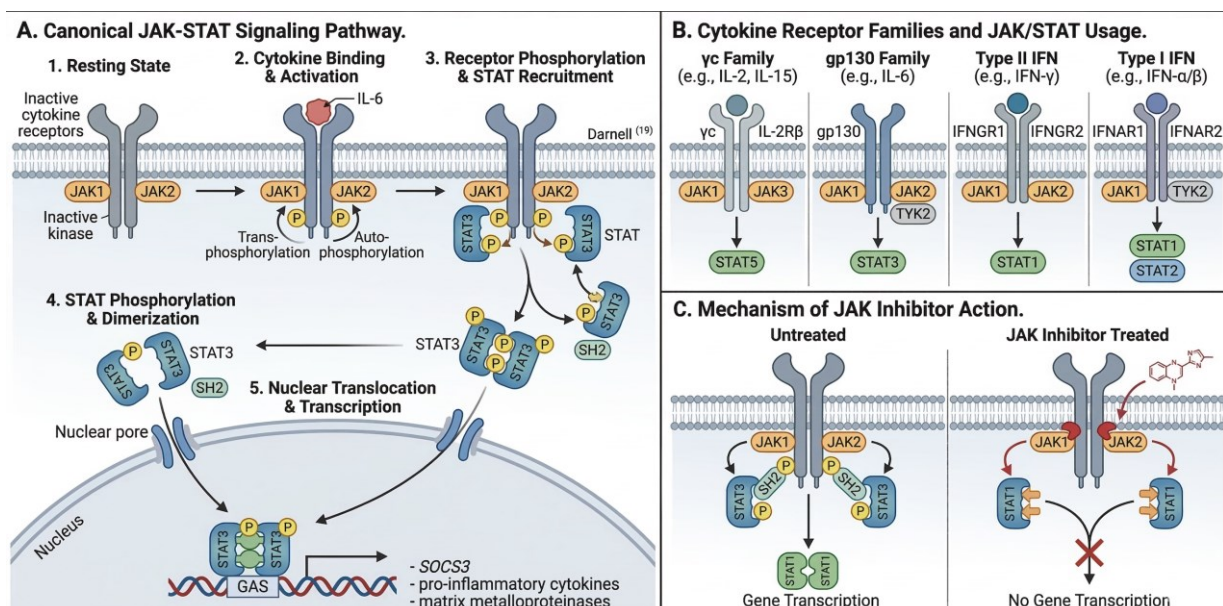
[72,73]. This highlights the critical concept of a "cytokine hierarchy" that differs between autoimmune diseases, even those that appear clinically similar [74].

4.3 The Oral Revolution: Targeted Synthetic DMARDs

A major paradigm shift in RA therapy occurred with the development of targeted synthetic DMARDs (tsDMARDs) [75]. This marked a move away from large, injectable protein-based biologics to orally available small molecules that could penetrate the cell membrane and inhibit key intracellular signaling pathways.

4.3.1 Discovery and Mechanism of the JAK-STAT Pathway

The JAKs are a family of four intracellular tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that are essential for transducing signals from Type I and Type II cytokine receptors [19]. When a cytokine binds to its receptor, it brings the associated JAKs into close proximity, allowing them to phosphorylate and activate each other. The activated JAKs then phosphorylate the receptor itself, creating docking sites for Signal Transducer and Activator of Transcription (STAT) proteins (Figure 1). The JAKs then phosphorylate the STATs, which dimerize, translocate to the nucleus, and act as transcription factors to alter gene expression [76]. This JAK-STAT pathway, elucidated in the early 1990s by researchers including James Darnell, was identified as a critical signaling hub for a multitude of pro-inflammatory cytokines implicated in RA, including IL-2, IL-6, IL-7, IL-15, and interferons [19]. This made the JAK family an exceptionally attractive therapeutic target. A single small molecule inhibitor could, in theory, block the downstream effects of numerous pathogenic cytokines



simultaneously, offering a broader mechanism of action than a monoclonal antibody targeting a single cytokine.

Figure 1. The JAK-STAT Signalling Pathway: Mechanism, Diversity, and Therapeutic Targeting in Rheumatoid Arthritis.

4.3.2 Clinical Development of Pan-JAK and Selective JAK Inhibitors

Tofacitinib, the first-in-class "jakinib", began development in the mid-1990s through a collaboration between the NIH and Pfizer and was approved for RA by the FDA in 2012 [77]. Tofacitinib is considered a "pan-JAK" inhibitor, though it shows greater selectivity for JAK1 and JAK3 over JAK2 and TYK2 [78].

Following the success of tofacitinib, a new generation of more selective JAK inhibitors was developed. The rationale was that by targeting specific JAKs more precisely, one might be able to retain the therapeutic efficacy while minimizing off-target effects associated with inhibiting other JAKs (e.g., effects on hematopoiesis linked to JAK2 inhibition). This led to the development and approval of baricitinib [79], a selective JAK1/2 inhibitor, and upadacitinib, a highly selective JAK1 inhibitor [80]. Filgotinib further exemplifies this trend as a potent, once-daily oral highly selective JAK1 inhibitor that has demonstrated rapid, sustained clinical responses and a favorable safety profile in patients with RA who have had an inadequate response to methotrexate [81]. These oral agents have demonstrated efficacy comparable to, and in some cases superior to, injectable biologics, representing a major advance in the RA treatment armamentarium [82].

4.4 The Next Frontier: Innovative and Future Therapeutic Strategies

The field continues to evolve, driven by the need to treat the remaining population of patients with refractory disease, improve safety, and move toward the ultimate goal of consistent remission or cure. Current research is focused on several innovative frontiers.

4.4.1 Engineered Cytokines and Biosimilars

To address the limitations of natural cytokines (which have short half-lives and high toxicity when used therapeutically), protein engineering techniques are being used to create "smarter" cytokines. Strategies like pegylation (attaching polyethylene glycol) can extend a drug's half-life, reducing dosing frequency [58]. Fusion proteins can be designed to target cytokines to specific tissues, enhancing local efficacy while minimizing systemic side effects [83,84]. In parallel, as patents for the original blockbuster biologics expire, the market for biosimilars - highly similar, officially approved copies of the original drug - is expanding rapidly.

Biosimilars for infliximab, etanercept, and adalimumab are now widely available, offering the potential for significant cost savings and increased patient access to these life-changing therapies [57,85].

4.4.2 Bispecific Antibodies and Multi-Target Approaches

In a direct response to the challenge of cytokine redundancy, bispecific antibodies (BsAbs) are being developed. These engineered molecules have two different antigen-binding sites, allowing them to engage two distinct targets simultaneously [86]. This approach essentially builds combination therapy into a single molecule. In rheumatology, several strategies are being explored in clinical trials, including BsAbs that can neutralize two different cytokines at once or that can bridge two different cells together (e.g., binding to the CD20 marker on a pathogenic B cell and the CD3 marker on a cytotoxic T cell, bringing the killer cell directly to its target) [87]. This represents a logical and sophisticated evolution in therapeutic design, aiming to overcome the therapeutic ceiling seen with single-target agents.

4.4.3 Emerging Modalities

Looking further ahead, several cutting-edge technologies are being explored that could fundamentally change how autoimmune diseases are treated.

MicroRNAs (miRNAs) are small non-coding RNAs that can regulate gene expression post-transcriptionally [88]. Specific miRNAs have been shown to control the production of pro-inflammatory cytokines like TNF- α . Developing drugs that can mimic or inhibit these miRNAs could offer a novel way to fine-tune the inflammatory response at a genetic level [89].

Perhaps the most revolutionary approach is the use of engineered cell therapies. Chimeric Antigen Receptor (CAR) T-cell therapy, which has transformed the treatment of certain blood cancers, involves taking a patient's own T cells, genetically engineering them to recognize a specific target (e.g., the CD19 marker on B cells), and re-infusing them to eliminate the target cell population [90]. Stunningly successful reports of using CD19 CAR-T to induce drug-free remission in patients with severe, refractory systemic lupus erythematosus and systemic sclerosis have ignited immense excitement about its potential for other B-cell-mediated rheumatic diseases [91,92].

5. Discussion

The journey of cytokine research in rheumatology is a remarkable story of scientific progress, illustrating a clear evolutionary path from observing

broad inflammation to designing precision-targeted therapeutics. This journey has fundamentally altered the natural history of rheumatic diseases for millions of people. However, the completion of this journey is not yet in sight. The very successes of the past have illuminated the remaining complexities of the immune system, revealing significant knowledge gaps and unresolved questions. The future of the field lies in addressing these challenges, moving beyond simple immunosuppression toward the ambitious goals of personalized medicine, durable remission, and ultimately, a cure.

5.1 Synthesis of the Evolutionary Trajectory: From Broad Inflammation to Precision Targets

The narrative arc of cytokines' history traces a clear and logical progression. It begins with the earliest immunological studies, which could only describe biological phenomena like fever or inflammation as the work of ill-defined "factors" [21]. The advent of protein biochemistry and molecular biology in the latter half of the 20th century allowed for the identification of the specific molecular culprits, namely cytokines like TNF- α , IL-1, and IL-6 [93]. This knowledge directly enabled the first therapeutic revolution: the development of biologic drugs, such as monoclonal antibodies, that could neutralize these specific targets with high precision [55].

The clinical limitations of these first-generation biologics - namely, non-response in a substantial subset of patients and the inconvenience of injections - drove the next evolutionary step. Scientists looked downstream of the cytokine-receptor interaction to the intracellular signaling hubs, leading to the development of orally available small molecule JAK inhibitors that could block the pathways of multiple cytokines at once [77]. Now, facing the persistent challenges of treatment resistance and the deep-seated complexity of the cytokine network, the field is entering a third era. This new frontier is characterized by even more sophisticated strategies, such as bispecific antibodies designed to overcome redundancy and cellular therapies aimed at resetting the immune system entirely [87,91]. This trajectory is a testament to iterative innovation, where each generation of

therapy is born from the scientific questions raised by the limitations of the last (Figure 2).

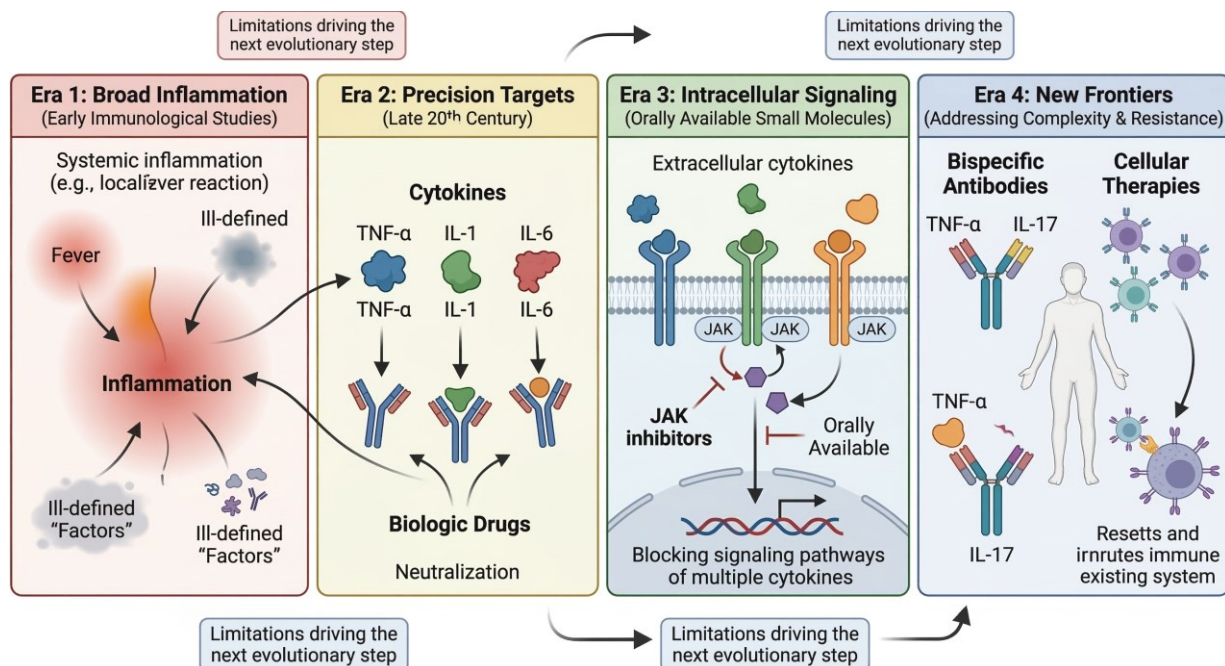


Figure 2. The evolutionary trajectory of cytokine-targeted therapeutics, illustrating the progression from early observations of broad inflammation to the development of precision biologics, intracellular signaling inhibitors, and next-generation cellular and bispecific therapies.

5.2 Current Knowledge Gaps and Unresolved Debates

Despite the powerful therapeutic armamentarium now available, several fundamental questions remain unanswered. These knowledge gaps represent the most active and important areas of current research in rheumatology.

A significant challenge remains: why do 30-40% of patients diagnosed with RA fail to achieve a satisfactory therapeutic response to initial biologic agents, such as TNF inhibitors? [59]. The mechanisms underlying this primary and secondary non-response are poorly understood. It may be due to the dominance of alternative, non-targeted cytokine pathways in those individuals, the influence of genetic background, environmental factors, the development of anti-drug antibodies, or other unknown biological variables [94]. Elucidating these mechanisms is paramount to moving beyond the current "trial-and-error" approach to prescribing.

Our understanding of the cytokine network, with its intricate web of synergistic, antagonistic, and feedback-regulated interactions, remains incomplete [1]. While we can block one or two nodes in this network effectively, we have yet to fully grasp how to modulate the entire system

back to a state of healthy homeostasis. The inherent redundancy of the system means that blocking one pathway may simply lead to compensatory upregulation of another. Developing therapeutic strategies that can account for and overcome this network-level complexity is a major future challenge.

RA is a systemic disease, and chronic inflammation is a known driver of serious comorbidities, most notably accelerating cardiovascular disease (CVD) [95]. A major unresolved debate in clinical practice is how best to manage this excess risk. Should the focus be on aggressively managing traditional CVD risk factors like lipids and hypertension, or should it be on achieving the deepest possible suppression of systemic inflammation through cytokine blockade? While evidence suggests both are important, the optimal strategy and the relative contribution of each approach are still under active investigation and debate [96,97].

The striking difference in the efficacy of IL-17 inhibitors in psoriasis versus RA is a powerful lesson in disease-specific immunology [50]. It demonstrates that even in clinically related autoimmune diseases, the hierarchy and relative importance of pathogenic cytokine pathways can differ profoundly. Understanding the molecular basis for these differences is a key knowledge gap that, if filled, could lead to more rational drug development and application across the spectrum of autoimmune conditions.

5.3 Future Perspectives: Towards Personalized Medicine and Curative Strategies

The future of cytokine-based therapy is shifting from the development of broadly applicable drugs to the creation of intelligent, personalized therapeutic strategies designed to address the specific needs of individual patients and achieve more ambitious outcomes.

The paramount objective within the field of rheumatology is the transition from treatment algorithms based on population-level data to individualized therapeutic approaches [98]. The future lies in the discovery and validation of biomarkers - which could be genetic, proteomic (e.g., serum cytokine profiles), or cellular - that can predict a patient's response to a specific therapy before it is initiated [99]. This would allow clinicians to stratify patients and select the most effective treatment from the outset, maximizing efficacy, minimizing toxicity, and avoiding costly and time-consuming cycles of failed therapies.

Given the complexity and redundancy of the cytokine network, it is likely that combination therapy will be key to treating the most refractory

patients. This can be achieved by combining existing drugs with different mechanisms of action or through the development of novel multi-targeting agents like bispecific antibodies [86,100]. The goal is to break through the "therapeutic ceiling" that limits the efficacy of monotherapy and induce deeper, more durable levels of remission.

The ultimate ambition of the field is to move beyond chronic suppression of the immune system and toward the re-establishment of immune tolerance, potentially leading to drug-free remission or a functional cure. This represents the most challenging frontier, but promising strategies are emerging. These include therapies designed to selectively boost the function of regulatory T cells (Tregs), for example with low-dose IL-2, to restore the body's natural control over inflammation [101]. Even more revolutionary are the cellular therapies, such as CAR-T, which have shown the potential to completely eliminate pathogenic B cell populations and "reset" the autoimmune response [90]. While still in their infancy for rheumatic diseases, these strategies represent the most ambitious and potentially transformative future direction in the long and evolving history of cytokine-targeted therapy.

6. Conclusions

The journey of cytokine research in rheumatology is a remarkable story of scientific progress, illustrating a clear evolutionary path from observing broad inflammation to designing precision-targeted therapeutics. This journey has fundamentally altered the natural history of rheumatic diseases for millions of people. However, the completion of this journey is not yet in sight. The very successes of the past have illuminated the remaining complexities of the immune system, revealing significant knowledge gaps and unresolved questions. The future of the field lies in addressing these challenges, moving beyond simple immunosuppression toward the ambitious goals of personalized medicine, durable remission, and ultimately, a cure.

Author Contributions

Conceptualization: S.D & Z.K; Methodology: S.D.; Formal analysis: S.D & S.B; Investigation: S.D, S.B and Z.K; Writing—original draft: S.D, S.B and Z.K; Writing—review & editing: S.D, S.B and Z.K.

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The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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История на цитокините при ревматичните заболявания: Еволюционна перспектива върху медиаторите, инхибиторите и терапевтичните средства

Резюме

Цитокините са малки, секретирани протеини, които служат като основни медиатори на имунната система, координирайки сложните взаимодействия между клетките, участващи във възпалението, имунитета и тъканната хомеостаза. Тяхната дисрегулация е централна характеристика в патофизиологията на хроничните възпалителни състояния, особено при автоимунните ревматични заболявания като ревматоидния артрит. Настоящият доклад представя цялостен, структуриран анализ на историята на цитокините, проследявайки тяхната еволюция от неясно дефинирани биологични активности до прецизно определени молекулярни мишени за революционни терапии. За осигуряване на концептуална основа са установени фундаментални дефиниции и класификации на цитокините, с особен акцент върху това как основните им свойства - плеiotропност, редундантност и мрежова сложност - са оказали дълбоко влияние върху тяхното изследване и терапевтична манипулация. Изложението впоследствие детайлизира ключови открития на патогенни цитокини в ревматологията - включително фамилиите на TNF- α , IL-1 и IL-6 - като същевременно описва промяната в парадигмата, предизвикана от идентифицирането на оста IL-23/Th17. Паралелно с тези открития е проследена еволюцията на терапевтичните агенти - от първото поколение биологични болест-модифициращи антиревматични лекарства (bDMARDs), като TNF инхибиторите, до „оралната революция“ на таргетните синтетични DMARDs, като Janus киназните инхибитори (JAK-инхибитори), и по-нататък към стратегиите от следващо поколение, включващи биспецифични антители и инженерно модифицирани цитокини. В заключителните раздели съвременното състояние на областта е синтезирано чрез критичен анализ на нерешените въпроси и пропуските в познанията, като механизмите на терапевтична резистентност (липса на отговор), предизвикателството на цитокината редундантност и оптималното управление на системните придружаващи заболявания. Очертани са перспективни бъдещи насоки, акцентирани върху нарастващия фокус върху стратификацията на пациентите чрез биомаркери, комбинираните стратегии с множество мишени и крайния стремеж към постигане на

имунен толеранс и куративни терапии. В своята съвкупност тези разработки представляват ясна еволюционна траектория към реализирането на прецизната медицина в ревматологията.

Ключови думи: цитокини, ревматични заболявания, DMARDs (БПАРС), моноклонални антитела

Osteoarthritis as a Failure of Adaptation: Biological Complexity and the Therapeutic Role of Physical Activity

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Running title: Osteoarthritis as a Failure of Adaptation

Abstract

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder worldwide and a leading cause of chronic pain, disability, and reduced quality of life. Traditionally conceptualized as a degenerative condition driven by mechanical wear and age-related structural deterioration of articular cartilage, this paradigm does not adequately explain the heterogeneity of clinical presentation, the weak correlation between structural damage and pain, or the limited efficacy of many current therapeutic strategies. Growing evidence supports a conceptual shift in which OA is understood as a biologically active disorder of impaired adaptation. Within this framework, OA reflects the reduced capacity of joint tissues to maintain homeostasis in response to cumulative mechanical, metabolic, and inflammatory stressors. Rather than representing an inevitable consequence of aging or mechanical overload alone, OA can be interpreted as a failure of coordinated adaptive responses across the whole joint organ. This narrative review aims to synthesize current evidence from inflammation biology, mechanotransduction, and epigenetic regulation to develop an integrative model of OA as diminished adaptive capacity. Physical activity is examined as a biologically active intervention capable of modulating inflammatory tone, restoring mechanosensitivity, and supporting functional resilience. This review is based on a structured, non-systematic literature search conducted in PubMed and Scopus, focusing on

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publications addressing OA, inflammation, mechanobiology, epigenetic regulation, and physical activity. Emphasis was placed on high-quality reviews, mechanistic experimental studies, and clinically relevant translational research published predominantly within the past 15 years, alongside seminal foundational work.

Keywords: osteoarthritis, physical activity, adaptive capacity of the joint, epigenetic regulation, mechanotransduction

1. Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder worldwide and a leading cause of chronic pain and disability [1]. Emerging evidence challenges the traditional view of OA as a purely degenerative process and instead frames it as a disorder of impaired biological adaptation of joint tissues to cumulative mechanical, metabolic, and inflammatory stressors [2].

This narrative review integrates insights from inflammation biology, mechano-transduction, and epigenetic regulation to propose an adaptive model of OA. Within this perspective, physical activity is considered a biologically active stimulus capable of modulating inflammatory tone, restoring mechano-sensitivity, and promoting joint resilience.

2. Osteoarthritis as a Whole-Joint Disease

OA affects the joint as an integrated biological unit rather than a single tissue. Cartilage, subchondral bone, synovium, periarticular muscles, and neural structures interact dynamically to preserve joint stability and function. Disruption of this coordinated system leads to progressive functional decline and clinical disease (Figure 1).

Articular cartilage, once considered metabolically inert, is now recognized as a highly responsive tissue capable of sensing and adapting to mechanical stimuli. Chondrocytes regulate extracellular matrix turnover through mechano-transduction pathways that maintain tissue integrity under physiological loading. In OA, this regulatory balance becomes disrupted, resulting in a shift toward catabolic activity and matrix degradation [1,2].

Subchondral bone actively contributes to disease progression through altered remodeling, vascular changes, and biomechanical modifications.

Bone marrow lesions, frequently observed in OA, are associated with pain and structural progression, underscoring the functional interdependence between bone and cartilage [3].

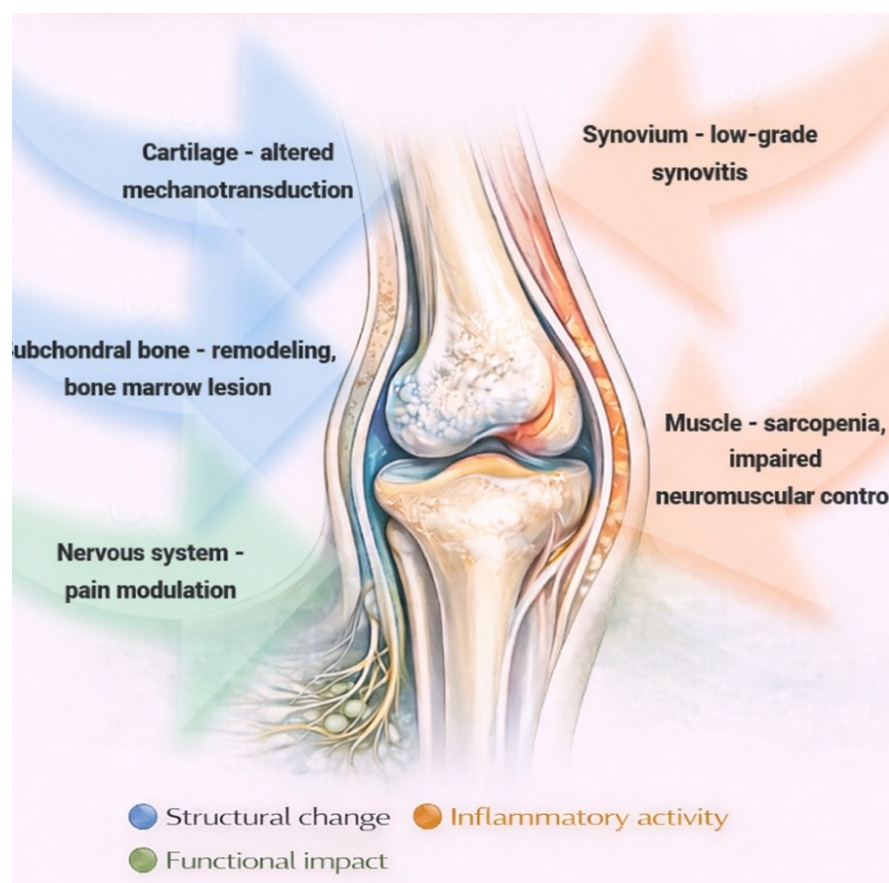


Figure 1. OA as a whole-joint disease. OA affects the joint as an integrated organ involving cartilage, subchondral bone, synovium, periarticular muscles, and neural structures. Interactions among these compartments contribute to pain, functional impairment, and structural progression, supporting the concept of OA as a disorder of the entire joint system rather than isolated cartilage degeneration. The figure is original and created by the authors.

Low-grade synovial inflammation further amplifies joint dysfunction. Unlike the intense inflammatory response seen in inflammatory arthritides, OA-associated synovitis is characterized by persistent but subtle immune activation. Synovial macrophages and fibroblast-like synoviocytes produce cytokines and mediators that influence adjacent tissues and contribute to nociceptive sensitization.

Periarticular muscles are central to load distribution and joint stabilization. Muscle weakness, altered motor control, and impaired proprioception are common in OA and may precede overt structural damage. These neuromuscular alterations increase mechanical stress and reduce adaptive

movement capacity, thereby contributing both to disease initiation and progression.

Together, these interdependent processes support the concept of OA as a disorder of the entire joint organ rather than a localized cartilage disease [4].

This whole-joint perspective raises a fundamental question: what mechanisms drive the progressive decline in adaptive capacity? Increasing evidence suggests that age-related inflammatory processes—collectively termed *inflammaging*—provide a permissive biological background linking systemic aging to local joint dysfunction.

3. Inflammaging as a Biological Background of Osteoarthritis

Aging is accompanied by a chronic, low-grade inflammatory state termed *inflammaging* (Figure 2). Unlike acute inflammation, *inflammaging* is characterized by persistent immune activation driven by cellular senescence, metabolic dysregulation, mitochondrial dysfunction, and impaired immune clearance mechanisms [5].

Substantial evidence supports the role of *inflammaging* as a contributing factor in OA pathophysiology. Senescent cells accumulate in cartilage, synovium, and subchondral bone and adopt a senescence-associated secretory phenotype (SASP), releasing pro-inflammatory cytokines, chemokines, growth factors, and matrix-degrading enzymes [6,7]. This altered microenvironment promotes matrix breakdown, disrupts intercellular communication, and reduces regenerative capacity.

Systemic low-grade inflammation further modulates local tissue responses. Circulating mediators such as IL-6, TNF, and IL-1 β influence synovial activation, bone remodeling, and nociceptive signaling, thereby contributing to pain and functional decline. The association between OA and other age-related conditions—including sarcopenia, metabolic syndrome, and cardiovascular disease—supports the concept of shared inflammatory pathways [8].

While *inflammaging* establishes a permissive biological background, it does not fully determine disease expression. Emerging evidence suggests that the interaction between inflammatory tone and mechanical loading critically shapes tissue responses. In this context, chronic inflammation may

alter cellular mechanosensitivity, amplify catabolic signaling, and lower the threshold for maladaptive responses to biomechanical stress.

Importantly, inflammatory mediators also influence peripheral and central pain processing. Neuroimmune interactions contribute to symptom variability and help explain the frequently observed discordance between structural damage and pain severity.

Recognizing inflammaging as a foundational but modulatory mechanism in OA underscores the limitations of purely structural approaches and highlights the need for strategies targeting systemic biological vulnerability.

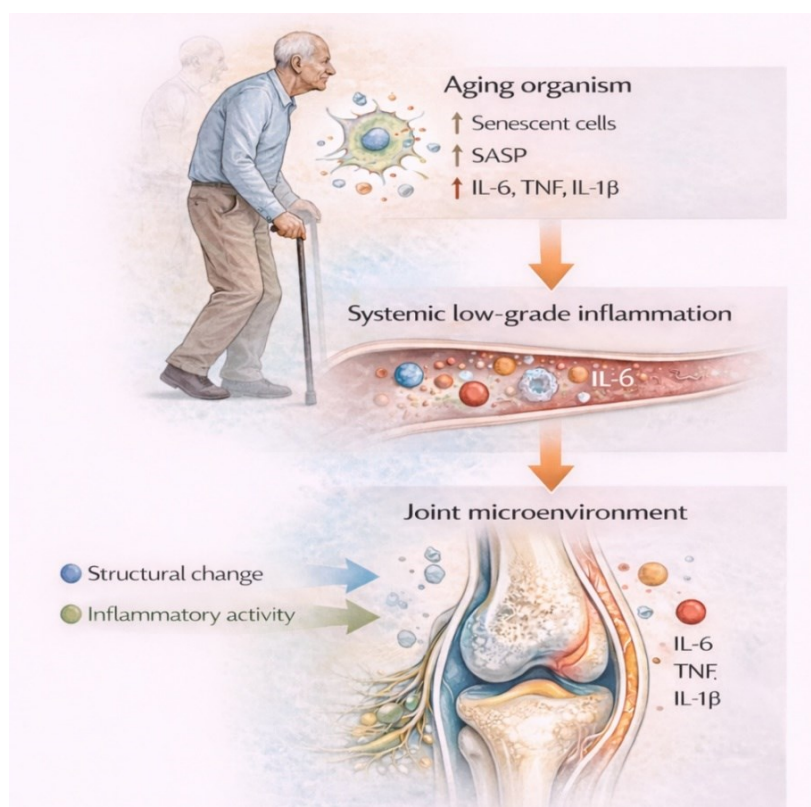


Figure 2. Inflammaging as a biological background of OA. Age-related accumulation of senescent cells promotes a chronic low-grade inflammatory state (inflammaging) characterized by increased secretion of pro-inflammatory mediators, including IL-6, TNF, and IL-1 β . This systemic inflammatory environment influences the joint microenvironment and contributes to synovial activation, cartilage degradation, and pain in OA. Abbreviations: SASP – senescence-associated secretory phenotype; IL – interleukin; TNF – tumor necrosis factor. The figure is original and created by the authors.

4. Mechanotransduction and Epigenetic Regulation

Mechanical loading is a fundamental biological stimulus governing joint health. Extensive experimental and translational research has established that chondrocytes and other joint-resident cells translate mechanical forces into biochemical signals through mechanotransduction pathways that regulate gene expression, extracellular matrix turnover, and cellular behavior [9].

Physiological loading promotes tissue resilience and functional integrity. In contrast, both insufficient and excessive mechanical stimuli disrupt homeostasis and initiate maladaptive responses, including catabolic signaling and matrix degradation. The concept of “mechanoflammation” further supports the close interaction between biomechanical stress and inflammatory pathways in OA (Figure 3) [10].

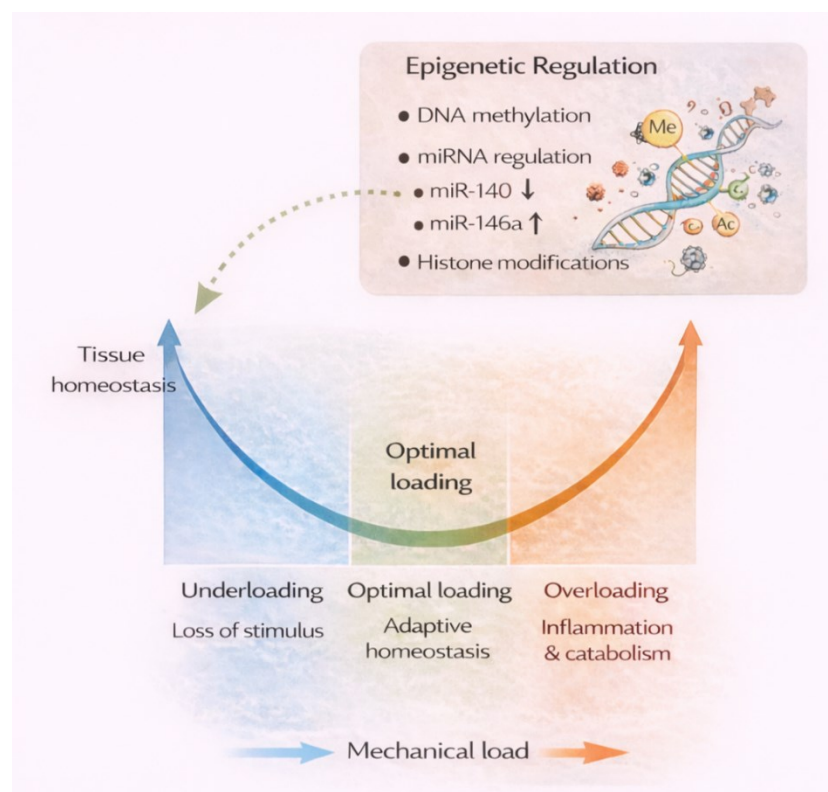


Figure 3. Interaction between mechanical loading and epigenetic regulation in OA. Mechanical loading functions as a biological signal influencing gene expression through epigenetic mechanisms, including DNA methylation, histone modification, and microRNA regulation. Physiological loading maintains tissue homeostasis, whereas both insufficient and excessive loading induce maladaptive responses, inflammation, and matrix degradation contributing to OA progression. Abbreviations: miR – microRNA. The figure is original and created by the authors.

Emerging evidence suggests that mechanical stimuli may influence cellular behavior not only through immediate signaling cascades but also via

epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation [11,12]. Experimental models indicate that mechanical stress can alter epigenetic marks associated with inflammation, extracellular matrix remodeling, and senescence-related pathways. However, the extent to which these mechanisms drive long-term disease progression in human OA remains an area of ongoing investigation.

Chronic low-grade inflammation may further modify cellular mechanosensitivity, lowering the threshold for maladaptive responses to biomechanical stress. This bidirectional interaction between inflammation and mechanotransduction provides a unifying framework for understanding how structural, molecular, and functional changes reinforce one another over time. [13]

Importantly, epigenetic plasticity also represents a potential substrate for therapeutic modulation. Although clinical evidence remains limited, preclinical data suggest that adaptive pathways may be partially restored under favorable mechanical and metabolic conditions.[14]

Recognizing the interplay between mechanical forces, inflammatory tone, and epigenetic regulation reframes OA as a condition influenced by dynamic biological signaling rather than irreversible structural decline.

5. Physical Activity as a Disease-Modifying Intervention

Physical activity represents a biologically active intervention capable of influencing several mechanisms implicated in OA. Beyond its mechanical effects, structured movement modulates inflammatory signaling, metabolic regulation, neuromuscular coordination, and—potentially—epigenetic expression [15].

Robust clinical evidence supports the role of exercise in reducing pain and improving function in OA [16]. In addition to symptomatic benefits, regular physical activity is associated with reductions in systemic inflammatory markers, improved mitochondrial function, and enhanced metabolic resilience. Skeletal muscle acts as an endocrine organ, releasing myokines with immunomodulatory properties that may counterbalance aspects of chronic low-grade inflammation.

At the biomechanical level, physical activity improves motor control, joint stability, and load distribution. Neuromuscular dysfunction—characterized by impaired proprioception and altered activation patterns—contributes to abnormal joint loading. Exercise-based interventions can partially restore

coordinated movement patterns, thereby reducing excessive mechanical stress on vulnerable tissues (Figure 4) [17, 18].

Emerging evidence suggests that physical activity may also influence gene expression through epigenetic mechanisms, including DNA methylation and microRNA regulation. While most data derive from experimental and non-OA-specific studies, these findings support the concept of biological plasticity in response to mechanical and metabolic stimuli [19]. The extent to which such epigenetic modulation contributes to long-term structural modification in OA remains to be fully elucidated.



Figure 4. Physical activity as a disease-modifying biological intervention in OA. Structured physical activity exerts multimodal biological effects, including reduction of low-grade inflammation, improvement of muscle strength and neuromuscular control, and modulation of epigenetic pathways. These mechanisms enhance adaptive capacity and counteract core pathophysiological processes in OA beyond symptomatic relief. The figure is original and created by the authors.

Importantly, the therapeutic effect of physical activity depends on appropriate dosing, progression, and individualization [20]. Excessive loading may aggravate symptoms, whereas insufficient stimulus may fail to induce adaptive responses. Personalized prescription—guided by phenotype, functional capacity, pain sensitivity, and comorbidities—optimizes the likelihood of restoring adaptive capacity.

Within this integrative framework, physical activity should be viewed not merely as adjunctive therapy but as a modifiable biological signal capable of enhancing joint resilience when appropriately applied.

6. Clinical Implications and Future Directions

Reconceptualizing OA as a disorder of impaired adaptation has profound implications for clinical practice. Rather than focusing exclusively on symptom control or structural preservation, management strategies should aim to enhance adaptive capacity across biological systems.

This approach supports personalized, mechanism-based interventions that integrate physical activity, behavioral modification, and, when necessary, pharmacological support. It also emphasizes the importance of interdisciplinary collaboration and longitudinal care.

We propose a conceptual model (Figure 5) integrating biological, functional, and adaptive dimensions of OA:

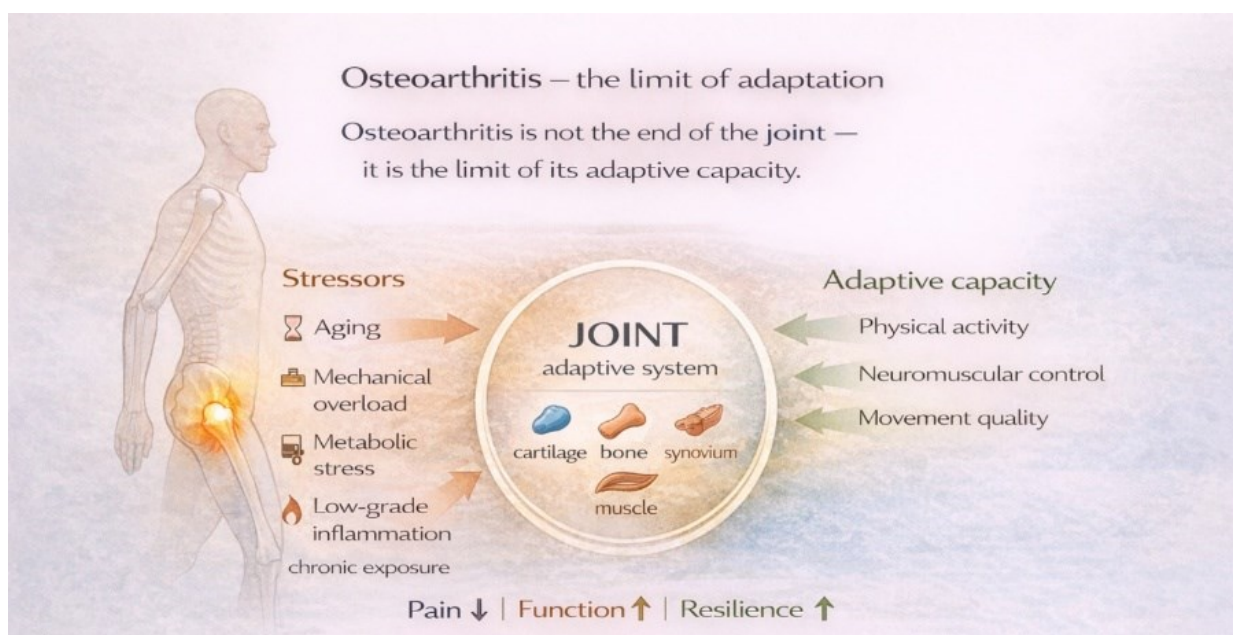


Figure 5. Adaptive capacity model of OA. OA is conceptualized as a failure of joint adaptation resulting from chronic exposure to biological and mechanical stressors, including aging, metabolic dysfunction, mechanical overload, and inflammation. Adaptive mechanisms such as physical activity, neuromuscular control, and movement quality improve resilience, reduce pain, and support joint function. The figure is original and created by the authors.

Future research should focus on identifying biomarkers of adaptive capacity, refining phenotypic classification, and developing interventions

that target both biological and functional dimensions of OA. Personalized management of OA requires identification of dominant phenotypic drivers - mechanical overload, inflammatory activity, metabolic dysfunction, or neuromuscular impairment. Rather than treating these components in isolation, an integrated approach acknowledges their interdependence and cumulative effect on joint adaptation.

7. Conclusions

OA should not be understood solely as the consequence of mechanical wear, but as a condition characterized by diminished adaptive capacity within the joint system. Viewing OA through this lens integrates biological aging, mechanical stress, and functional decline into a coherent conceptual framework.

By shifting emphasis from irreversible degeneration toward modifiable adaptive processes, clinicians and researchers may identify more effective strategies for prevention, personalized intervention, and long-term functional preservation. While structural changes remain central to disease characterization, restoration and support of adaptive resilience may represent a meaningful direction for future OA management.

Author Contributions

Conceptualization: I.M; Methodology: I.M & V.G; Formal analysis: I.M & M.V; Investigation: all authors; Writing—original draft: I.M & M.V; Writing—review & editing: all authors.

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Institutional Review Board Statement

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Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Остеоартрозата като провал на адаптацията: биологична сложност и терапевтична роля на физическата активност

Резюме

Остеоартрозата (ОА) е най-разпространеното заболяване на опорно-двигателния апарат и водеща причина за хронична болка, инвалидизация и влошено качество на живот. Традиционно тя се разглежда като дегенеративно състояние, обусловено от механично износване и възрастово обусловени структурни промени в ставния хрущял. Този модел обаче не успява да обясни клиничното разнообразие на заболяването, слабата корелация между структурните промени и болковия синдром, както и ограничената ефективност на много от съвременните терапевтични подходи. Натрупващите се данни налагат преосмисляне на остеоартрозата като биологично активно и динамично състояние, характеризиращо се с нарушена способност за адаптация към механични, метаболитни и възпалителни стимули. В този контекст ОА може да се разглежда не като неизбежна последица от стареенето, а като резултат от изчерпване на адаптивния капацитет на ставата. Този преглед има за цел да синтезира настоящи доказателства, подкрепящи остеоартрозата като разстройство на нарушената адаптация, интегрирайки данни от възпалението, механобиологията и епигенетиката. Чрез преосмисляне на остеоартрозата като динамичен и модифицируем процес, ние предлагаме концептуална основа за по-персонализирани, базирани на механизми терапевтични стратегии, като физическата активност е позиционирана като централен биологичен модулатор, а не като допълнително лечение.

Ключови думи: остеоартроза, физическа активност, адаптивен капацитет на ставата, епигенетична регулация, механотрансдукция

A Clinical Case of a 74-Year-Old Patient with Overlap of Rheumatoid Arthritis and Axial Spondyloarthritis

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Running title: Overlap of Rheumatoid Arthritis and Axial Spondyloarthritis

Abstract

In the past, rheumatoid arthritis and axial spondyloarthritis were considered mutually exclusive diseases because of their distinct genetic and clinical profiles. We present the case of a 74-year-old man with seropositive rheumatoid arthritis and long-standing axial spondyloarthritis, illustrating the diagnostic and therapeutic challenges associated with this rare overlap. The patient presented with symmetrical erosive-destructive polyarthritis involving joints of the upper extremities, strongly positive immunological markers, a history of chronic inflammatory low back pain beginning at approximately 35 years of age, positive HLA-B27, radiographic sacroiliitis and spondylitis with syndesmophyte formation and complete bony bridges between vertebral bodies. Given the predominant clinical manifestations, the presence of concomitant prostate carcinoma, and having in mind the urological consultation, combination therapy with methotrexate and tocilizumab was initiated, resulting in low disease activity. This case highlights the challenges in diagnosing and treating patients with two

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distinct inflammatory joint diseases and discusses the importance of individualized therapeutic strategies.

Keywords: seropositive rheumatoid arthritis, axial spondyloarthritis, HLA-B27, methotrexate, tocilizumab, synovitis, spondylitis

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by erosive-destructive polyarthritis involving joints of the upper extremities and positive immunological markers. The pathogenesis of RA includes autoimmune activation of B- and T-lymphocytes, formation of autoantibodies (rheumatoid factors, RF and anti-cyclic citrullinated peptide antibodies, anti-CCP), and chronic synovial inflammation leading to erosive joint changes and functional impairment [1].

Modern treatment of RA is based on the recommendations of the European Alliance of Associations for Rheumatology (EULAR) and includes conventional synthetic (csDMARDs), biologic (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), as well as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. The primary therapeutic goal is to achieve and maintain remission or low disease activity, assessed by validated indices such as the disease activity score (DAS28) [1]. Treatment choice depends on disease activity, structural damage progression, comorbidities, and safety profile.

Axial spondyloarthritis (axial SpA) is an immune-mediated chronic inflammatory disease characterized by chronic inflammatory low back pain with onset before 45 years of age and imaging evidence of sacroiliitis, often accompanied by extra-musculoskeletal manifestations. The primary sites of inflammation are the entheses, sacroiliac joints, and facet joints. Clinical features include axial skeleton involvement, peripheral arthritis, enthesitis, and dactylitis [3]. The disease is characterized by new bone formation with syndesmophyte development, complete bony bridges between vertebral bodies, and progressive spinal ankylosis.

The pathogenesis of axial SpA involves genetic predisposition (particularly HLA-B27), immune mechanisms, and a local enthesitis-driven inflammatory response, distinct from the synovial inflammation observed in RA [3].

Current treatment of axial SpA is based on ASAS-EULAR (2022) recommendations [4]. NSAIDs are first-line therapy for pain and stiffness.

In patients with persistently high disease activity despite optimal conventional treatment, bDMARDs are recommended, most commonly tumor necrosis factor-alpha (TNF α) inhibitors, interleukin-17 (IL-17) inhibitors, or tsDMARDs such as Janus kinase inhibitors (JAKi). To date, other biological classes, including interleukin-6 (IL-6) inhibitors, have not demonstrated clinical efficacy in axial SpA.

The therapeutic goal in both RA and axial SpA is control of inflammation, prevention of structural damage, and improvement of quality of life.

Although traditionally regarded as distinct nosological entities, rare cases of overlap syndrome between RA and axial SpA have been reported. Herein, we present the case of a 74-year-old man with seropositive RA and long-standing axial SpA. The coexistence of these two diseases in a single patient is rare and presents unique diagnostic and therapeutic challenges [5].

2. Case Presentation

A 74-year-old man was admitted to the Rheumatology Clinic of University Hospital "St. Ivan Rilski" with a three-month history of pain, swelling, and morning stiffness in the small joints of the hands, wrists, and shoulders. The pain was inflammatory in nature, most pronounced in the morning, with night pain awakening the patient. Morning stiffness lasted approximately 45 minutes.

Additionally, the patient reported the presence of chronic inflammatory back pain for approximately 40 years, with limited cervical and lumbar spine mobility. He reported no history of psoriasis, inflammatory bowel disease, acute anterior uveitis, enthesitis or dactylitis.

He had not received systemic anti-rheumatic treatment previously. He had been taking NSAIDs on demand for back and peripheral joint pain, with partial and temporary clinical efficacy. He had not been treated with targeted therapies.

In March 2021, he was diagnosed with well-differentiated prostate adenocarcinoma (Gleason score 3+3=6) and was treated with radiotherapy and hormonal therapy, currently being in remission. There was no history of allergies or family history of rheumatic disease. He had long-term occupational exposure to physical strain as a truck driver, likely contributing to misinterpretation of spinal symptoms as mechanical.

On physical examination, the patient was in good general condition with a hypersthenic body habitus, the skin was normally coloured without any

rashes. No abnormalities were detected on examination of the internal organs. Musculoskeletal examination revealed tenderness in metacarpophalangeal and wrist joints, synovitis of the left wrist, pain and limited shoulder motion, and restricted spinal mobility in all segments (Bath Ankylosing Spondylitis Metrology Index (BASMI) score 2).

Laboratory tests showed elevated CRP (55.7 mg/L) and ESR (76 mg/L). Immunology revealed strongly elevated rheumatoid factor IgM (>500 U/mL) and anti-CCP antibodies (1000 U/mL). The patient was HLA-B27 positive.

Radiographs demonstrated erosive-destructive changes in the hand joints, as well as spondylitis (syndesmophytes and complete bony bridges between vertebral bodies) and bilateral sacroiliitis stage IV. (Figures 1-3).

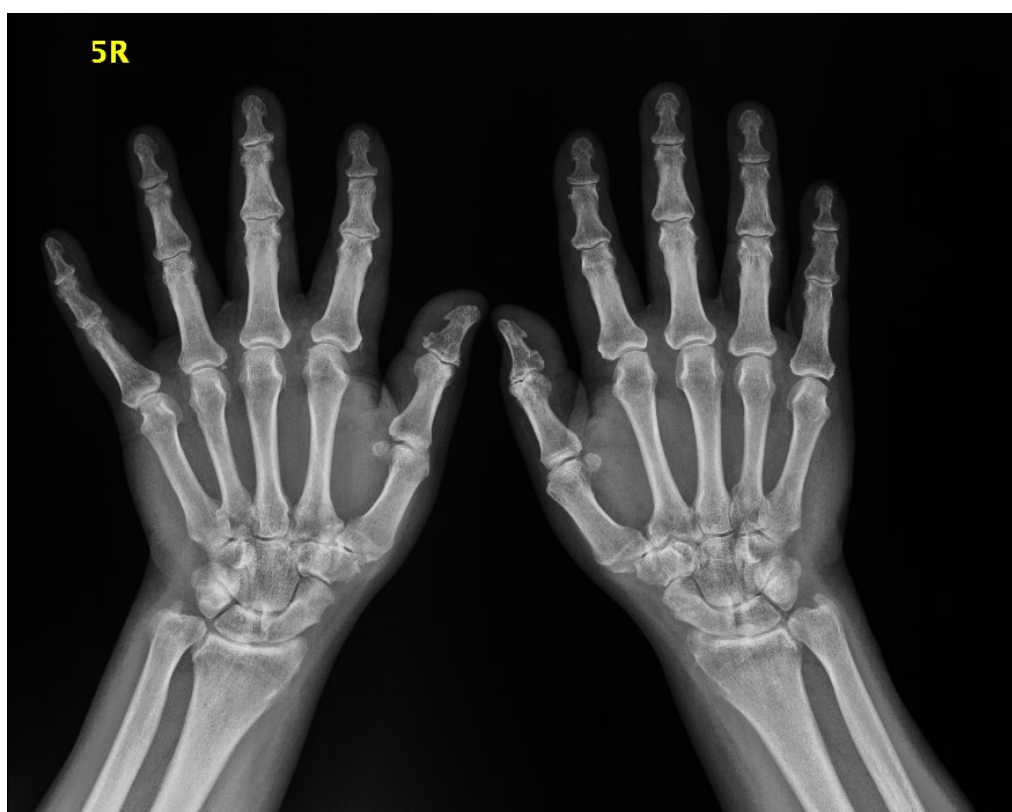


Figure 1. Radiography of wrists with palms and fingers at the time of diagnosis.

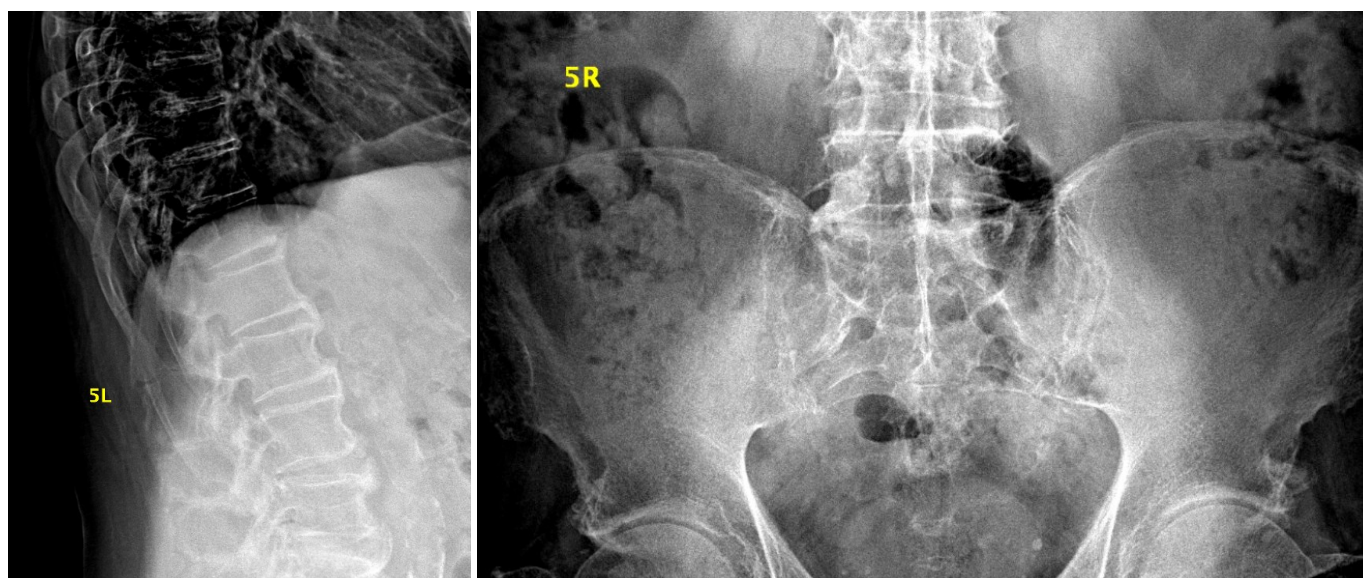


Figure 2. Lateral radiography of thoracolumbar segment of the spine and the sacroiliac joints at the time of diagnosis.



Figure 3. Computed tomography of the sacroiliac joints at the time of diagnosis.

Ultrasound confirmed bilateral synovitis in wrist and small joints of the hands – gray-scale grade II on the right and III on the left, with positive

Power Doppler (PD) signal grade I on the right and II on the left, as well as synovitis of PIP II on the right, without PD signal.

Ultrasound of shoulder joints demonstrated bilateral proliferative tenosynovitis of the long head of the biceps tendon, erosions along the humeral head contour, bilateral glenohumeral joint effusion with marked synovial hypertrophy and bilateral subacromial-subdeltoid bursitis.

The patient had very high peripheral arthritis activity with DAS using CRP (DAS28-CRP) of 6.6, an Ankylosing Spondylitis Disease Activity Score using CRP (ASDAS-CRP) of 3.9 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 5.8.

A diagnosis of seropositive RA with high disease activity combined with long-standing, previously untreated radiographic axial SpA was made. Treatment was initiated with methotrexate 15 mg/week orally with folic acid supplementation and NSAIDs for axial SpA.

After 3 months, remission or low disease activity was not achieved. Despite significant improvement in back pain and stiffness, synovitis persisted in wrists and shoulders. Addition of a bDMARDs was recommended. Due to concomitant prostate carcinoma, consultation with the treating urology team advised avoiding TNF α inhibitors. Considering prevailing recommendations and limited safety data at that time, anti-TNF α therapy was not initiated.

Given the predominance of active seropositive RA, treatment with the IL-6 inhibitor tocilizumab 162 mg/week was started. JAKi were considered unsuitable due to the patient's age, the lack of specific safety data regarding JAKi use in patients with a history of carcinoma and concomitant risk factors (cardiovascular risk).

After 6 months of treatment with methotrexate 15 mg/week and tocilizumab 162 mg/week, low disease activity was achieved – chronic synovitis in shoulder joints persisted, but with improved range of motion. The patient reported significant reduction in pain and stiffness, there was no night pain and no functional deficit. Control indices of activity were calculated – DAS28-CRP 2.4, ASDAS-CRP 2.1, BASDAI 3.2. Acute-phase reactants normalized.

At 12 months, clinical remission was achieved – there was no synovitis of peripheral joints, morning stiffness was significantly reduced, there was no night pain and acute-phase markers remained within normal range. Control

indices of activity were calculated – DAS28-CRP 1.6, ASDAS-CRP 1.2, BASDAI 1.3.

At 24 months, on continued tocilizumab (162 mg/week) and reduced methotrexate (5 mg/week), the patient remained in persistent clinical remission with no radiographic progression (Fig. 4).

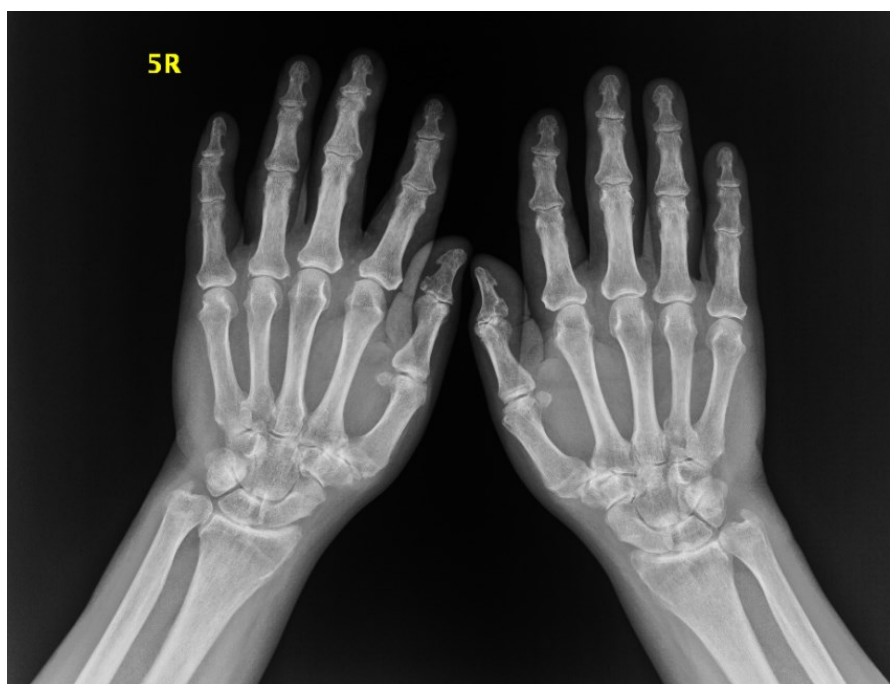


Figure 4. Radiography of wrists with palms and fingers at the 24th month of follow-up.

3. Discussion

The coexistence of seropositive RA and axial SpA is exceptionally rare. Until the mid-1990s, approximately 40–50 confirmed cases were reported, with an estimated prevalence of approximately 1:100 000 [5], although subsequent reports suggest wide variability, ranging from 1:50 000 to 1:2 000 000 [6]. This reflects the lack of population studies and the fact that the available data originate predominantly from individual clinical cases and small studies.

RA and axial SpA have distinct pathogenetic mechanisms, resulting in different clinical manifestations and requiring a disease-specific therapeutic approach. In RA, inflammation is primarily synovial, leading to synovitis, erosions and joint deformities. In contrast, axial SpA is characterized predominantly by enthesitis and perifibrocartilaginous osteitis. This distinction is particularly relevant in overlap cases such as the

present one, in which both synovial inflammation typical of RA and enthesopathic inflammation characteristic of axial SpA were observed.

An additional important aspect of this case is the concomitant prostate carcinoma. In routine clinical practice this represents a frequent therapeutic challenge. In this case, close collaboration with a urologist is essential to minimize potential treatment-related risks. Therapeutic decisions must therefore be carefully individualized, balancing rheumatic disease activity with oncological considerations and current recommendations. More recent EULAR recommendations and expert opinions regarding the initiation of biological therapy in patients with inflammatory joint diseases and a history of malignancy suggest that TNF α inhibitors may be an appropriate therapeutic option in selected patients [2]. In the present case, however, modification of the therapeutic strategy was not required due to the achievement of low disease activity and a stable clinical condition.

This case also illustrates the diagnostic challenges in such overlap. The presence of erosive-destructive polyarthritis involving the small joints of the hands, together with strongly positive anti-CCP antibodies and RF fulfilled the classification criteria for seropositive RA with high disease activity (DAS28 6.6). Additionally, a history of chronic inflammatory low back pain with onset before the age of 45 years, reduced spinal mobility, HLA-B27 positivity, and radiographic evidence of bilateral grade IV sacroiliitis, syndesmophytes, and complete vertebral bony bridging fulfilled the ASAS criteria for radiographic axial SpA [4].

On the other hand, the limited cervical spine mobility raised an important differential-diagnostic consideration. In patients with seropositive RA, atlantoaxial joint involvement must always be considered, as it is a well-recognized complication, particularly in long-standing or highly active disease [7]. Careful clinical and imaging evaluation is therefore required to differentiate ankylosis related to axial SpA from potential RA-associated cervical instability.

The therapeutic approach in patients with overlapping RA and axial SpA requires an individualized strategy, based on predominant clinical manifestations, disease stage and comorbidities [12]. In the present case priority was given to controlling the high RA activity. Methotrexate was initiated as a conventional synthetic DMARD in accordance with international RA treatment recommendations [13]. Anti-TNF α therapy was not implemented due to the concomitant oncological disease and the

consultation by the attending urology team, taking into account the limited safety data available at that time regarding TNF α inhibitors in patients with prostate carcinoma. At the time of therapeutic decision-making (2022–2023) no recommendations endorsed the use of TNF α inhibitors as an appropriate treatment option in patients with inflammatory arthritis and a history of malignancy. The existing EULAR and ASAS–EULAR recommendations emphasized individual risk assessment and a multidisciplinary approach. In clinical practice caution generally predominated regarding the use of TNF α inhibitors in patients with a recent history of malignancy [2]. More recent 2024 EULAR “points to consider” support the use of TNF α inhibitors as a potential therapeutic option in selected patients with a history of solid tumors [11].

The potential use of JAKi was also considered, as this therapeutic class is recommended for both RA and axial SpA. However, in this case the patient was 74 years old, had concomitant oncological disease and increased cardiovascular risk. Available data indicating a higher incidence of cardiovascular events and venous thromboembolism in patients over 65 years of age treated with JAKi led to avoidance of this therapeutic class [8].

Tocilizumab was chosen due to marked systemic inflammation and persistent high RA activity despite methotrexate therapy. Although IL-6 inhibitors have not shown efficacy in axial SpA [9], axial disease in this patient was longstanding with established structural damage, shifting the primary therapeutic focus to peripheral arthritis. Combination therapy with methotrexate and tocilizumab resulted in low disease activity at 6 months and clinical remission at 12 months.

Similar cases of overlap between seropositive RA and axial SpA have been reported in the literature, however, available data remain limited to individual case reports or small series. The publications highlight the complexity and the absence of established therapeutic algorithms, as these two conditions have traditionally been regarded as mutually exclusive entities, often leading to delayed diagnosis [5,6,14]. Combined biological therapy (e.g., anti-IL-17 plus anti-IL-6) could theoretically provide more control of both diseases, however, no randomized trials have demonstrated its safety or efficacy, and the risk of infection remains a major limitation [10].

4. Conclusions

The coexistence of RA and axial SpA is rare but clinically meaningful. The presence of classic seropositive RA does not exclude axial SpA in patients with a history of longstanding inflammatory back pain.

Treatment should be individualized, based on the predominant clinical manifestations, with the aims of achieving sustained remission, preventing radiographic progression, and optimizing quality of life. Early recognition and personalized therapy can significantly improve clinical outcomes and overall quality of life in patients with rheumatic diseases.

Author Contributions

Conceptualization: G.K.; Methodology: G.K., V.T.; Formal analysis: V.T., P.E.; Investigation: G.K., V.T., P.E., M.I.; Writing—original draft: G.K., V.T.; Writing—review & editing: G.K., V.T., P.E., M.I.

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Declaration

The case report was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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КЛИНИЧЕН СЛУЧАЙ НА 74-ГОДИШЕН ПАЦИЕНТ С ПРИПОКРИВАНЕ НА РЕВМАТОИДЕН АРТРИТ И АКСИАЛЕН СПОНДИЛОАРТРИТ

Резюме

В миналото, ревматоидният артрит и аксиалният спондилоартрит са се считали за взаимно изключващи се заболявания поради различните им генетични и клинични профили. Представяме клиничен случай на 74-годишен мъж със серопозитивен ревматоиден артрит и дългогодишен аксиален спондилоартрит, който илюстрира диагностичните и терапевтичните предизвикателства, свързани с това рядко припокриване. Пациентът се представя с клинична картина на симетричен ерозивно-деструктивен полиартрит, ангажиращ ставите на ръцете, със силно положителни имунологични маркери, анамнеза за хронична възпалителна болка ниско в гърба (low back pain) възникнала около 35-годишна възраст, положителен HLA-B27 и рентгенографски сакроилиит и спондилит с формиране на синдесмофити и пълни костни мостове между прешленните тела. С оглед водещата симптоматика, отчитайки наличието на придружаващ карцином на простатата и проведената консултация с уролог, пациентът е лекуван с комбинация от метотрексат и тоцилизумаб, с постигане на ниска болестна активност. Представеният случай подчертава предизвикателствата при диагностицирането и лечението на пациенти с две различни възпалителни ставни заболявания и обсъжда значението на индивидуализираните терапевтични стратегии.

Ключови думи: серопозитивен ревматоиден артрит, аксиален спондилоартрит, HLA-B27, метотрексат, тоцилизумаб, синовит, спондилит