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ORIGINAL ARTICLE

Rheumatology Quarterly

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ARTIFICIAL INTELLIGENCE IN RHEUMATOLOGY

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Abstract

Aim: In the field of rheumatology, spectacular advances have been observed in digital health technologies, including electronic health records, virtual visits, mobile health, wearable technology, digital treatments, artificial intelligence (AI), and machine learning.

Material and Methods: We conducted bibliometric analysis in the field of "AI in rheumatology". The entire bibliometric study was conducted on 16.01.2023. The Web of Science (WoS) database was scanned from 1975 to 2023. The data were accessed by typing the keyword "AI" in the first line of the research row (406.807 documents) and adding the keyword "rheumatology" in the second line (146 documents). A total of 146 publications were analyzed. The data were analyzed as publication year, document types, authors, WoS category, affiliation, publication titles, countries/areas, publishers, and citation report (number of total citations, number of cited articles, and h-index).

Results: In this field, 40 (27.3%) articles were published in 2022, 29 (19.8%) in 2021, 30 (20.5) articles in 2020, and 17 (11.6%) articles in 2019. Document types were; article (n=65/44.5%), meeting abstract (n=35/23.9%), review article (n=34/23.2%) etc. According to the WoS category, 73.2% were in rheumatology, 6.8% were in Medicine General Internal, 5.4% were in Computer Science AI, etc... When we look at the total number of articles from countries, the USA (n=35) England (n=28), and Germany (n=19) take the first place. Among 146 publications, the number of cited articles was 1.067 (without self-citations 1.037), times cited was 1.184 (without self-citations 1.124) with h-index=16.

Conclusion: Bibliometric analysis of AI in the field of rheumatology will be useful as it creates awareness and provides an objective perspective to the research field.

Keywords: Artificial intelligence, bibliometrics, rheumatology, bibliometric analysis

INTRODUCTION

Artificial intelligence (AI) refers to the use of computers to model intelligent behavior with minimal human intervention. The development of AI is based on the invention of robots. In the medical field, robots cover a wide spectrum, covering medical definitions, statistics, and human biology. There are two main branches in the field of medicine; virtual and physical. The virtual part includes approaches from controlling health management systems to guiding treatment decisions. The physical branch can be used as surgical assistive devices. The social and ethical complexities of these practices require future reflections, evidence of their medical goals, and revealing of their economic values (1).

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The increase in access to these technologies provides opportunities for important aspects of rheumatology. Growth in access, results, compliance, and research. There is no improved standard practical method for digital health technologies yet (2).

Machine learning is a field of AI that is frequently applied in medicine to help patients and physicians. Sound-based databases are created that provide the machine with learning methods acquired from previous experiences. Machine learning applications that include the patient's opinion and the physician's empirical/experimental suggestions will be developed shortly (3). The wave in which the first AI defeated the world chess champion affected the field of rheumatology and many other medical fields (4).

Bibliometric analysis is the application of mathematical and statistical methods to books and other communication media. In more detailed terms, it provides a quantitative analysis of the publications or documents according to the author, subject, publication information, cited sources, etc... Bibliometric analysis helps us identify the most productive researchers on any subject, among countries and institutions. It allows us to make comparisons and objectively see how scientific communication is carried out in various disciplines (5,6).

The Web of Science (WoS) provides subscription-based access to multiple databases that provide comprehensive citation data for disciplines in different academies. Created by the Institute for Scientific Information, the service is now maintained by Clarivate Analytics (7). In the field of rheumatology, we performed a bibliometric analysis in the WoS database to examine and evaluate the research on "AI". In this way, we aim to compile the current data on "AI in rheumatology" to raise awareness and inspire new research.

MATERIALS AND METHODS

Data Collection

The entire bibliometric study was conducted on 16.01.2023. The WoS database was scanned from 1975 to 2023. The data were accessed by typing the keyword "AI" in the first line of the research (406.807 documents were in the AI field) and adding the keyword "rheumatology" in the second line. A total of 146 publications were analyzed. The data were analyzed as publication year, document types, authors, WoS category, affiliation, publication titles, publishers, and citation reports (number of total citations, number of cited articles, and h-index).

Data were taken from the WoS website. We used the following keywords: "AI" and "rheumatology". A total of 146 publications were analyzed.

Statistical Analysis

Analysis and processes were carried out using WoS graphics and tables. Using Microsoft Excel 2010, the data in the tables were converted to absolute values (percentage and frequency). There were no relative frequencies. There were no sophisticated statistical procedures applied, such as mean, median, model, dispersion measures, standard deviation, or statistical tests. Visualizations from the WoS database were also used. Descriptive statistical methods were used in this study.

RESULTS

A total of 146 articles were reached (1975-2023). Of these, 34 were reviewed, 5 were early access, and 7 were open access. The number of publications by years is shown in bar Figure 1. When we look at the total number of articles from countries, the USA

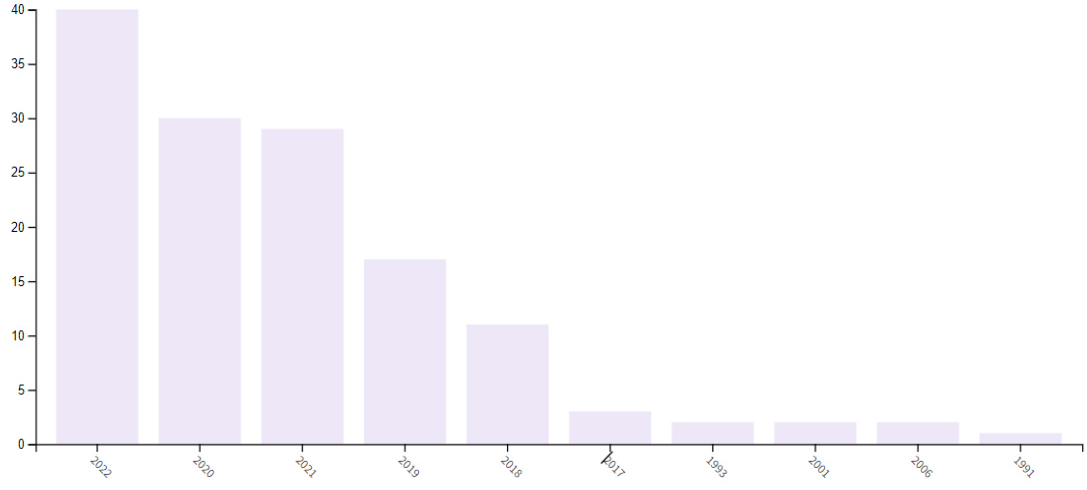

Figure 1. Bar graphs of publications according to years

(n=35), England (n=28), and Germany (n=19) take the first place (Figure 2).

Document types were as follows: article (n=65/44.5%), meeting abstract (n=35/23.9%), review article (n=34/23.2%), editorial material (n=6/4.1%), proceeding paper (n=6/4.1%), early access (n=5/3.4%), correction/addition (n=1/0.6%).

According to the WoS category, 73.2% were in rheumatology, 6.8% in Medicine General Internal, 5.4% in Computer Science AI, 2.7% in Computer Science Interdisciplinary Applications, and 2.7% in Engineering Biomedical (Figure 3).

According to the citation topics meso: 31.5% was in rheumatology; 7.5% was in Computer Vision & Graphics; 3.4% was in Nursing;

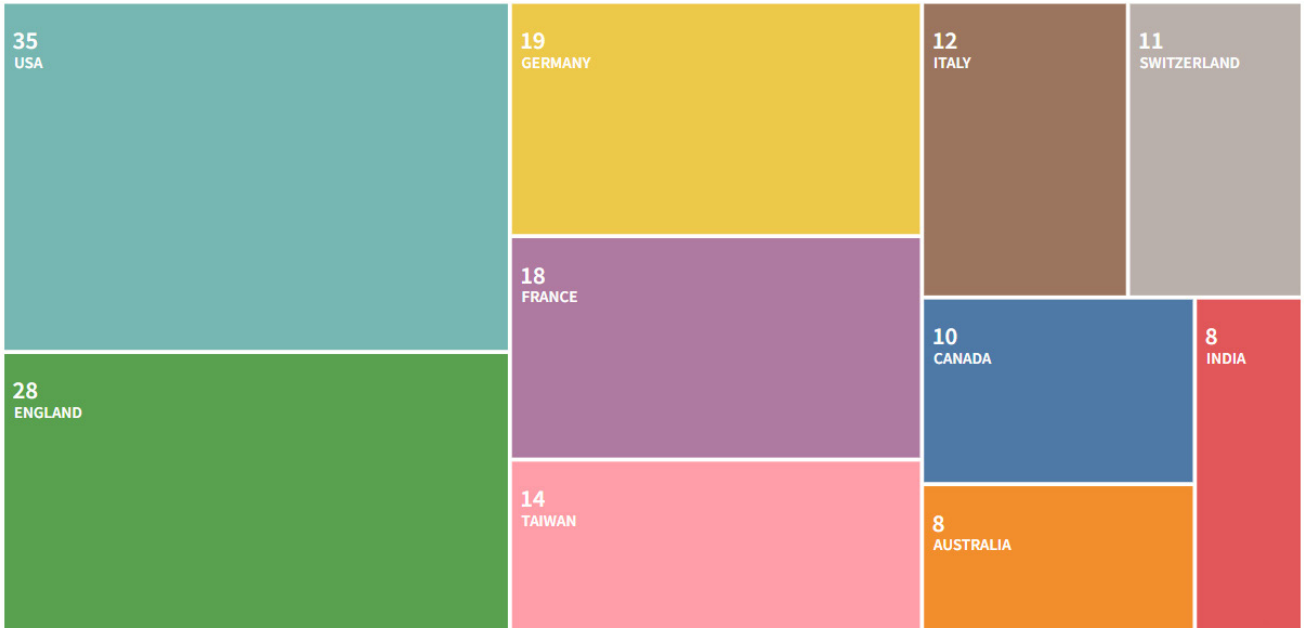

Figure 2. Distribution of documents according to countries/areas

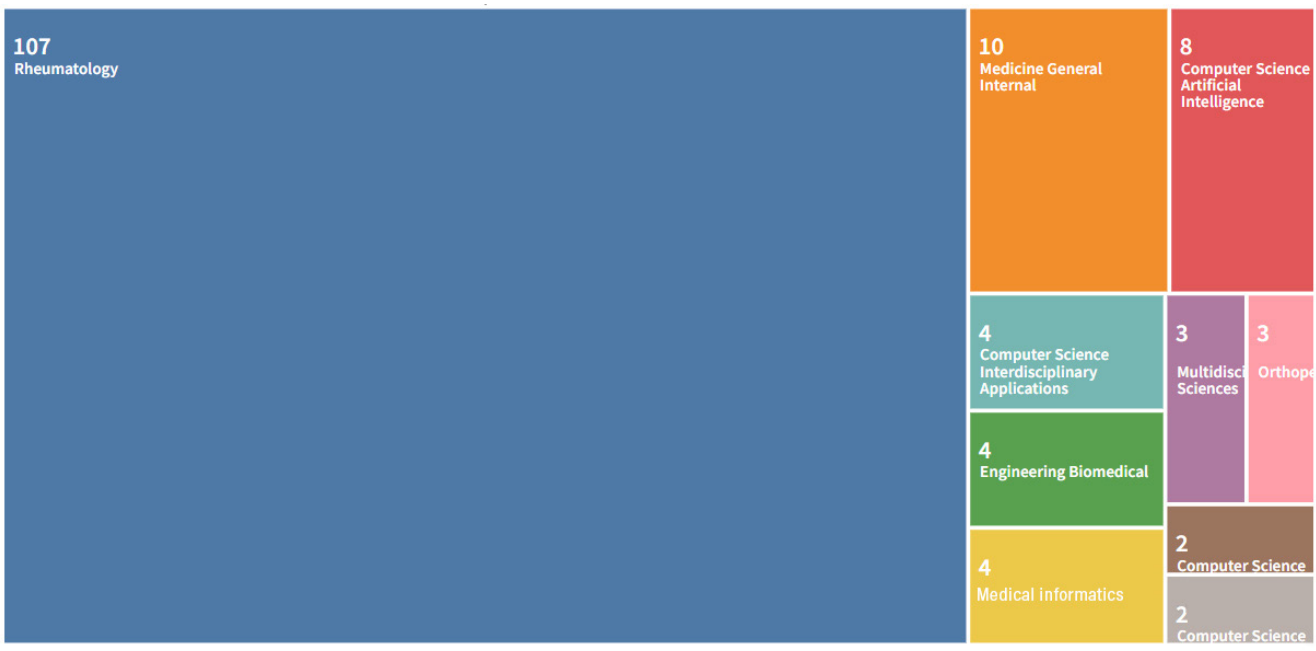

Figure 3. Documents according to the WoS categories
WoS: Web of Science

2.7% was in Orthopedics; and 2.7% was in AI learning (Figure 4). Meso is a level of analysis that examines midrange-sized populations. The top affiliations were as shown in Figure 5.

The characteristics of publication titles are shown in Table 1; publishers in Table 2.

When we look at the countries of the authors with the most articles in this field, Germany, France, and Taiwan take the lead.

Times cited and publications over time are shown in Figure 6. If we look at the graph, an increase in acceleration is seen after 2018.

Among 146 publications, the number of cited articles was 1.067 (without self-citations 1.037), times cited was 1.184 (without self-citations 1.124) with h-index=16.

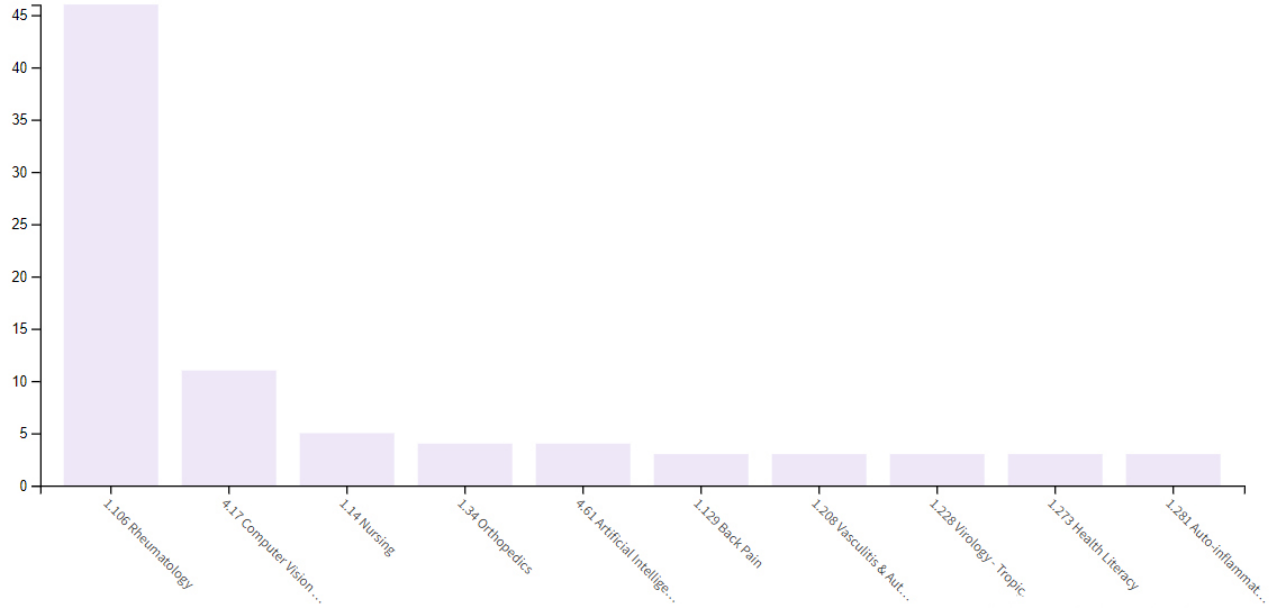

Figure 4. Bar graphs of citation topic meso

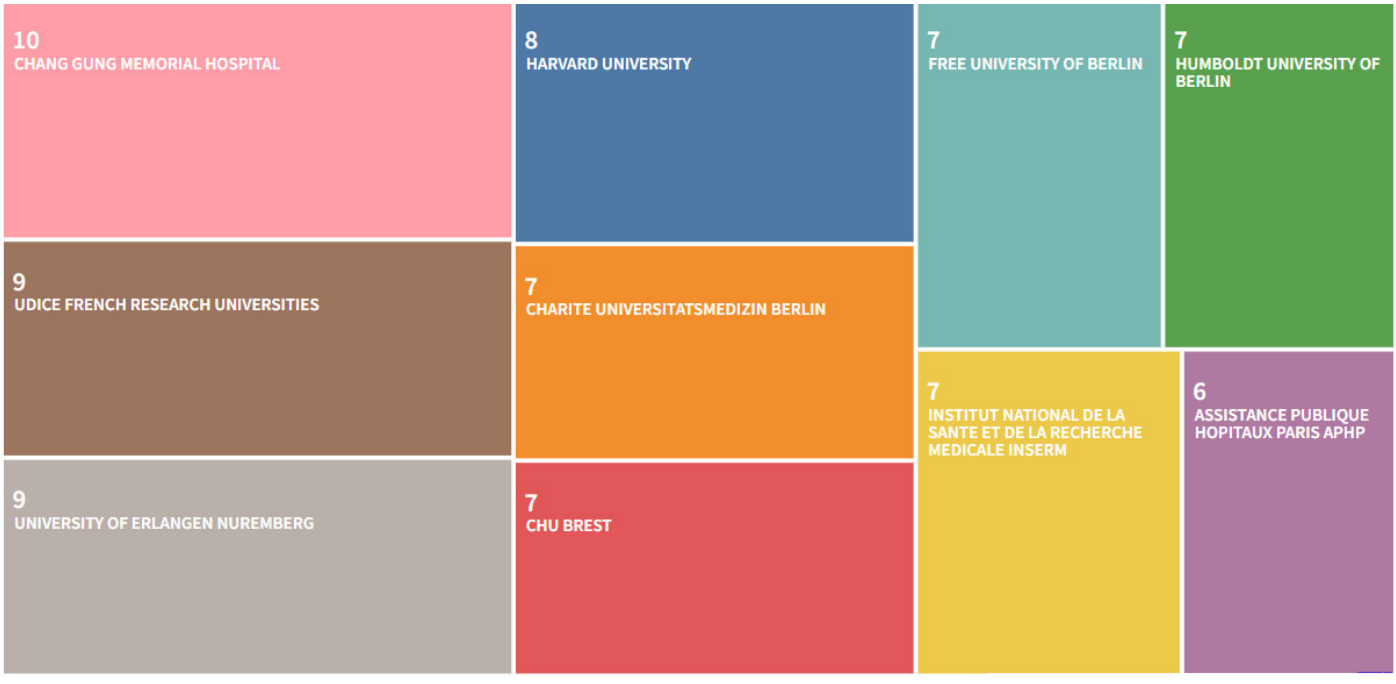

Figure 5. Top affiliations

DISCUSSION

As scientific researches continue at a rapid pace, we should look at them from a broad perspective and compile what we have. Although there are current studies on the use of AI in different areas of rheumatology, bibliometric analysis is few. When we look at our research data, we see that the number of publications in this field has increased in the last decade with the beginning of the digital age. In particular, the increase in the use of the internet and computer technologies throughout the world has also provided its use in the field of health.

Table 1. Characteristics of publication titles

Publication titles	Record count	% of 146
Arthritis Rheumatology	19	13.0
Annals of Rheumatic Diseases	17	11.6
Rheumatology	15	10.2
Clinical and Experimental Rheumatology	6	4.1
Arthritis Research Therapy	4	2.7
Best Practice Research in Clinical Rheumatology	4	2.7
Frontiers in Medicine	4	2.7
Rheumatology and Therapy	4	2.7
Rheumatology International	4	2.7
Clinical Rheumatology	3	2.0

Computer-mediated clinical decision support systems are likely to become more common shortly. The primary aim is to improve the treatment, save time, and reduce the risk of error. These algorithms are already used in the field of rheumatological diseases. Automatic image recognition and prediction of disease in rheumatoid arthritis is the most advanced, but no decision support system is integrated. AI-intermediate decision systems will be hybrid clinical decision systems that include both the expert's and the patient's decision (8,9).

Table 2. Characteristics of publishers

Publishers	Record count	% of 146
Springer Nature	31	21.2
Wiley	21	14.3
BMJ Publishing Group	20	13.6
Oxford Univ. Press	17	11.6
Elsevier	11	7.5
Frontiers Media SA	7	4.7
Clinical and Exper Rheumatology	6	4.1
Mdpi	4	2.7
Journal Rheumatol Publ. Co.	3	2.0
Nature Portfolio	3	2.0
Lippincott Williams and Wilkins	2	1.3
Mdpi: Multidisciplinary Digital Publishing Institute		

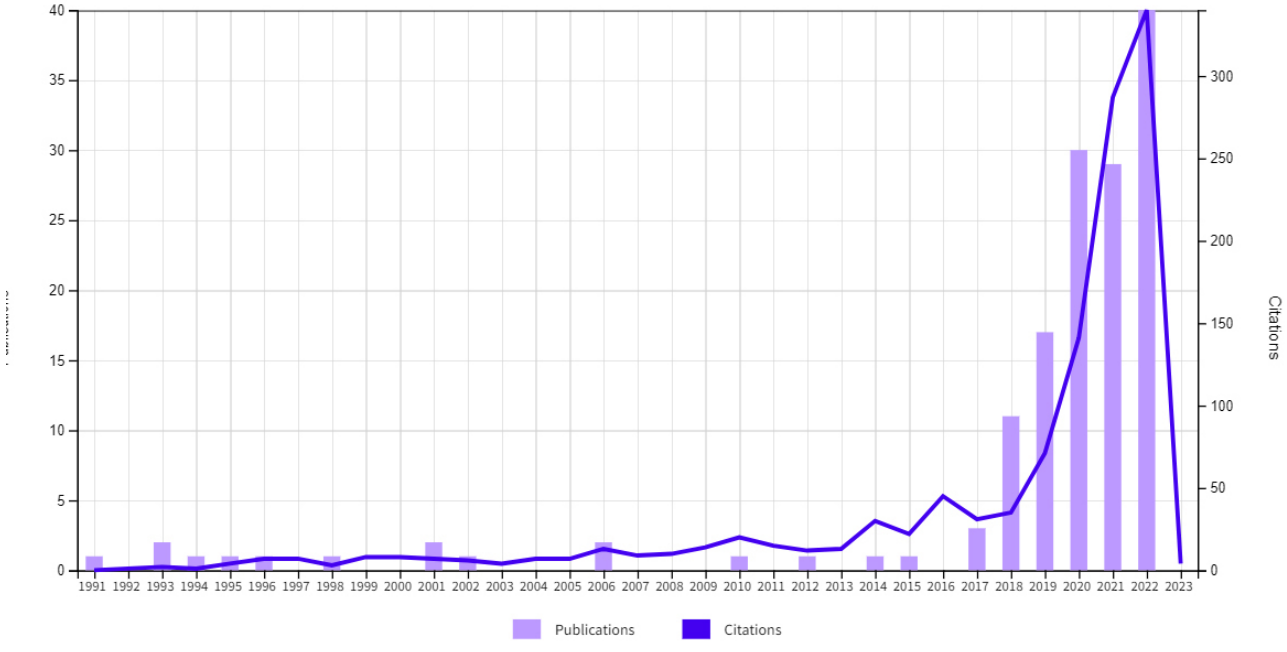

Figure 6. Graphics of citations over time (1991-2023)

Applications in the field of rheumatology have achieved successful advances in detecting joint erosions on plain radiographs predicting future rheumatoid arthritis disease activity, and identifying the halo sign on temporal artery ultrasound. The deep learning method should be based on the clinical experience of rheumatologists (10).

Current studies in the field of rheumatoid arthritis are based on fully demonstrating the applicability of the automatic scoring system and the power of AI. With AI being faster and more sensitive, it will enable the development of effective treatments for rheumatoid arthritis patients (11).

New digital health advances have created opportunities for rheumatologists, patients, and other caregivers through improved outcomes and improved efficiency. The next tier of digital treatments is the Food and Drug Administration approval process. The digitization of healthcare services has gained momentum worldwide in recent years. However, more databases based on observational studies, clinical trials, systematic reviews, and meta-analyses are needed to reach effective and objective results (12,13).

A large proportion of cancer patients do not benefit from a single immune checkpoint inhibitor (ICI) and therefore new combination strategies are needed. AI applications that predict ICI responses are currently being developed. There is increasing data on the applicability of AI in predicting cancer treatment ICI responses (14). Based on this, we can say that in the future, AI may guide us as to which biological/non-biological disease-modifying treatment some rheumatological diseases will respond better to. AI will be able to guide treatment decision-making.

The integration of AI into salivary gland ultrasound, ultrasound-mediated needle biopsy, and known diagnostic and prognostic biomarkers in the diagnosis of Sjögren's syndrome is another promising development in this field (15).

AI applications, including machine learning, provide the opportunity to identify the high-dimensional relationship between large numbers of datasets where human capacity is insufficient. Machine-mediated learning models provide additional information in defining osteoporotic fracture risk and predicting fracture prediction (16). AI tools are finding new applications in medical diagnostics. Machine learning and deep learning models have found a role in osteoporosis. This task is to model the risk of fragility fractures and assist in the identification and segmentation of images (17). In articles before 2017, computational clinical decision models (ChapGPT and other AI tools) containing multiple languages were causing excitement. But today we see that this high expectation has not yet been met.

Study Limitations

Limitations of the study include relying on a single database and documents consist two keywords.

CONCLUSION

We see AI-based publications in the literature on different diseases in the field of rheumatology, such as rheumatoid arthritis, osteoporosis, osteoarthritis, Sjögren syndrome, etc... AI methods based on human experience will of course increase the success of diagnosis, treatment and minimize the risk of error. We hope that our work will raise awareness in this area and shed light on future studies.

Ethics

Ethics Committee Approval: The study complied with the World Medical Association Declaration of Helsinki. Ethics committee approval is not required, as it performs a bibliometric analysis of existing published research.

Informed Consent: There is no human or animal research.

Authorship Contributions

Concept: T.T.K., Design: T.T.K., Data Collection or Processing: T.T.K., Analysis or Interpretation: T.T.K., Literature Search: T.T.K., Writing: T.T.K., C.Z.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE

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EVALUATION OF DRUG SIDE EFFECT PROFILES IN PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASE USING TUMOR NECROSIS FACTOR-ALPHA INHIBITORS

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Abstract

Aim: The use of tumor necrosis factor-alpha (TNF-α) inhibitors is associated with potential side effects such as infusion reactions, anaphylaxis, development of infection, and cutaneous and paradoxical side effects. We evaluated the side effects observed with the use of these agents in patients with rheumatic diseases followed by TNF-α inhibitors in our clinic.

Material and Methods: Patients admitted to our clinic in the last 5 years with a diagnosis of inflammatory rheumatic disease and treated with TNF-α inhibitors were included in the study. Demographic data, diagnoses, treatment, and side effects were recorded. Statistical analysis was performed using SPSS version 21.0.

Results: Forty-two patients with rheumatic disease receiving TNF-α inhibitors were analyzed. Infliximab had cutaneous side effects in 26 patients, including one infusion reaction and two cases of anaphylaxis. These side effects included allergic rash, psoriasis, bullous pemphigoid, dermatitis herpetiformis, erythema AB Igne, dermatitis, and small vessel vasculitis. Golimumab caused neutropenia in two patients. The other adverse events were cervical intraepithelial lesions and Kaposi's sarcoma in one patient with psoriatic arthritis. Infections were the most common adverse events and were reported in four patients.

Conclusion: TNF-α inhibitors are widely used in the treatment of inflammatory rheumatic diseases. These agents have side effects, and it is important to be aware of and cautious about potential side effects.

Keywords: TNF alpha inhibitors, rheumatic diseases, side effects, paradoxical effects

INTRODUCTION

Tumor necrosis factor-alpha (TNF-α) is produced by many immune system cells, such as activated macrophages and lymphocytes. It is involved in inflammation and cell necrosis, proliferation, apoptosis, and differentiation. TNF-α exists in two forms: transmembrane and soluble. Both forms bind to TNF receptors (TNFR1 and TNFR2) but have different effects. TNFR1 is involved in cytotoxic and proinflammatory responses, whereas TNFR2 mediates cell activation, migration, and proliferation (1-5).

TNF-α inhibitors such as etanercept, infliximab, adalimumab, golimumab, and certolizumab can be used in autoimmune diseases in which TNF-α is involved in the pathogenesis, such as inflammatory bowel disease, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis, and non-infectious uveitis. While etanercept inhibits both TNF-α and TNF-beta,

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infliximab, adalimumab, and golimumab specifically bind to TNF-α, and certolizumab is a modified monoclonal antibody that does not contain the fragment crystallizable (Fc) portion (6).

The side effects associated with TNF-α are divided into groups such as alpha, beta, gamma, delta, and epsilon. In alpha-type reactions, clinical findings include flu-like symptoms, arthritis, arthritis, and myalgia and occur because of excessive cytokine secretion (7). Beta-type reactions are immune-mediated hypersensitivity reactions. Protein components can cause immune complex development, complement activation, or mast cell release. Beta-type reactions include IgE-mediated type 1 reactions, type 2-3 hypersensitivity reactions, and T cell-mediated late-type reactions. Gamma-type reactions describe a reduced immune response or immunodeficiency. Examples of this group of side effects include infections, the development of malignancies, and autoimmunity. The development of autoantibodies such as antinuclear antibodies and antiphospholipid antibodies and clinical conditions such as cutaneous vasculitis, uveitis, psoriasis, and demyelinating disease are mediated by these reactions. Clinical regression after discontinuation of treatment supports a cause-and-effect relationship. Delta-type reactions can be defined as the development of autoantibodies and antibody-mediated cross-reactivity against molecular targets or structurally similar proteins. Epsilon-type reactions include non-immunologic side effects of biological agents. The mechanism of these side effects is unknown; the development of heart failure, asthma exacerbation, and granulomatous disease are examples of these reactions (7).

In our study, we evaluated drug side effect profiles in patients with inflammatory rheumatic disease admitted to a rheumatology clinic and treated with TNF-α inhibitors.

MATERIAL AND METHODS

Patients admitted to our clinic in the last 5 years with a diagnosis of inflammatory rheumatic disease and treated with TNF-α inhibitors were included in the study. Demographic data, rheumatologic disease diagnoses, treatment information, and side effects were retrospectively recorded. The observed side effects were classified as infusion reactions, anaphylaxis, hematologic side effects, malignant/premalignant lesions, infectious side effects, cutaneous side effects, and other side effects. The study was approved by the Aydın Adnan Menderes University Non-interventional Clinical Research Ethics Committee (approval no: 2023/17, date: 03.08.2023).

Statistical Analysis

The data of the study were evaluated using SPSS 21.0. Descriptive statistics are given as mean ± standard deviation, median (25-75p), frequency (n), and percentage (%). Univariate and multivariate statistical methods were planned to be used according to the distribution structure of the data. The chi-square test was used to investigate whether two or more variables were independent of each other. Data were calculated at 95% confidence interval, and p-value<0.05 was considered statistically significant.

RESULTS

In this study, 42 patients on TNF-α inhibitors were analyzed. The patients were equally male and female with a mean age of 49.4 years. Twelve patients had RA, 28 had spondyloarthropathy, one had Behçet's disease, and one had juvenile idiopathic arthritis.

Of these patients, 8 were on adalimumab (19%), 7 on etanercept (16.6%), 5 on golimumab (11.9%), 14 on infliximab (33.3%), and 8 on certolizumab. Infliximab treatment resulted in one infusion reaction and two cases of anaphylaxis. In addition, 26 patients experienced cutaneous side effects. Among the side effects observed were allergic rash in 9 patients, psoriasis in 12 patients, bullous pemphigoid in 1 patient, dermatitis herpetiformis in 1 patient, erythema aligned in 1 patient, dermatitis in 1 patient, and small vessel vasculitis in 1 patient. Specifically, 6 of the patients with allergic rash were diagnosed with AS, 1 with enteropathic arthritis, and 2 with RA and are being treated with various biological agents. In the case of psoriasis, 6 patients had palmoplantar pustulosis and 6 had generalized psoriasis.

Golimumab treatment caused neutropenia in two patients. Cervical intraepithelial lesions occurred in one patient treated with infliximab and Kaposi's sarcoma in a male patient with psoriatic arthritis. Infections were the most common side effect of TNF-α inhibitor use. We reported serious infections in four patients. These infections included bacterial pneumonia, aspergillus pneumonia, and tuberculosis. The first patient was a 66-year-old woman who received adalimumab treatment for RA and was hospitalized for bacterial pneumonia. The other patient was a 52-year-old male patient who was diagnosed with enteropathic arthritis, received certolizumab treatment, and had aspergillus pneumonia. Tuberculosis infection was detected in two of our patients. One of these patients was a 59-year-old woman with pulmonary tuberculosis who received infliximab treatment and was diagnosed with psoriatic arthritis. The other patient diagnosed with tuberculosis was a 26-year-old woman who was diagnosed with AS and receiving certolizumab treatment. This patient presented to us because of widespread ascites in the abdomen and was diagnosed with tuberculous lymphadenitis. The side effects observed in patients with rheumatic diseases using TNF-α inhibitors are shown in Table 1.

Table 1. Side effects in patients with rheumatic diseases using tumor necrosis-alpha inhibitors

Side effects	Adalimumab	Etanercept	Golimumab	Infliximab	Certolizumab
Infusion reaction				n=1	
Anaphylaxis				n=2	
Hematological side effects			n=2		
Cervical intraepithelial neoplasia				n=1	
Kaposi's sarcoma				n=1	
Pneumonia	n=1				n=1
Tuberculosis				n=1	n=1
Allergic rash	n=4	n=2	n=1	n=2	
Palmoplantar pustulosis	n=1	n=1	n=1	n=2	n=1
Psoriasis		n=2	n=1	n=1	n=2
Bullous pemphigoid				n=1	
Dermatitis herpetiformis				n=1	
Erythema AB Igne		n=1			
Small-vessel vasculitis				n=1	
Dermatitis					n=1
Sarcoidosis	n=1				
Uveitis		n=1			
Erectile dysfunction					n=1
Asthma exacerbation	n=1				
Psoriasis flare-up					n=1

DISCUSSION

Some reactions may occur with the use of TNF-α inhibitors, which are effective and safe for treating inflammatory diseases. These reactions may be acute or delayed hypersensitivity reactions (8). Infusion reactions or anaphylaxis may occur with infliximab (9,10). Previous studies have reported anaphylaxis rates ranging from 8% to 23% for infliximab (11). Acute reactions can be minimized using steroids or antihistamines.

TNF-α inhibitors may also have various dermatological side effects, including local reactions, serious infections, malignant lesions, and immune-mediated reactions (12,13). Bullous pemphigoid, dermatitis herpetiformis, and erythematous hyperpigmented lesions have been reported in some patients (14,15). A male patient on etanercept for AS developed erythematous hyperpigmented lesions on both ankles. Dermatological evaluation determined that the erythema was unrelated to treatment and was probably caused by heat exposure. Skin findings resolved spontaneously during follow-up (16). Another patient with AS on certolizumab treatment developed erythematous skin lesions on the extremities, which were treated locally and considered unrelated to the treatment. During our follow-up, urticarial skin eruptions were observed in 8 patients, 3 associated with adalimumab, 2 with infliximab, 2 with etanercept, and 1 with golimumab.

Paradoxical reactions may occur during treatment with some biological agents and may lead to psoriasis and inflammatory bowel disease (16). We reported paradoxical psoriasis in 12 (26.2%) of our patients followed by TNF-α inhibitors; six of the patients presented with disseminated disease. Palmoplantar pustulosis was observed in patients on infliximab, certolizumab, etanercept, adalimumab, and golimumab. The skin lesions of four patients with palmoplantar pustulosis resolved with steroid treatment and a change of biological agent. Different drugs have been associated with these reactions, but switching to a different anti-TNF-α agent may help relieve symptoms. Another case of infliximab-associated palmoplantar pustulosis treated with high-dose steroids and methotrexate. The patient is still being followed up at our clinic.

Hematologic side effects of TNF-α inhibitors are rare but may include thrombocytopenia, neutropenia, and aplastic anemia (17,18). The risk of malignancy is not increased with these drugs, but the risk of cervical intraepithelial neoplasia may be higher

in women with RA (17-19). Both of our patients who developed neutropenia were receiving golimumab treatment, and neutropenia regressed with treatment change. Infections are common with TNF-α inhibitors and the risk is highest in the first year of treatment (20). In our clinic, TNF-α inhibitor-associated serious infections were observed in four patients (9.6%): bacterial pneumonia in one patient (2.4%), fungal pneumonia in one (2.4%), and tuberculosis infection in the other two (4.8%).

Sarcoidosis-like reactions may occur with the use of TNF-α inhibitors (21). TNF-α inhibitors may also cause sexual dysfunction, but this may improve with treatment (22). In our study, sarcoidosis developed in only one patient treated with adalimumab. During our follow-up, erectile dysfunction due to certolizumab use was reported in only one patient. The patient's symptoms regressed with the treatment change. There are case reports in the literature regarding the development of mild asthma associated with adalimumab, etanercept, and infliximab (23). Asthma attacks were intensified in a patient who was being followed up in our clinic and was taking adalimumab for RA. The disease was controlled when the treatment was discontinued, but attacks recurred when the drug was restarted. Caution should be exercised in these patients with a family history, and routine asthma treatment recommendations should be applied (23).

CONCLUSION

In conclusion, TNF-α is critical in rheumatic diseases, and its inhibitors are widely used in inflammatory rheumatic diseases. However, these agents have side effects, and it is important to be aware of and cautious about the potential side effects that may result from their frequent use.

Ethics

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Non-interventional Clinical Research Ethics Committee (approval no: 2023/17, date: 03.08.2023).

Informed Consent: Informed consent was not obtained due to the nature of this study.

Authorship Contributions

Surgical and Medical Practices: C.D., G.S., S.Ç., T.Ş., Concept: C.D., G.S., S.Ç., T.Ş., Design: C.D., G.S., S.Ç., T.Ş., Data Collection or Processing: C.D., G.S., S.Ç., T.Ş., Analysis or Interpretation: C.D., G.S., S.Ç., T.Ş., Literature Search: C.D., G.S., S.Ç., T.Ş., Writing: C.D., G.S., S.Ç., T.Ş.

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EVALUATION OF THE DEVELOPMENT OF NEUROLOGICAL DAMAGE IN SEVERE COVID-19 PNEUMONIA WITH SERUM CK-BB LEVELS

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Abstract

Aim: Despite numerous reports of various neurological symptoms observed in Coronavirus disease-2019 (COVID-19) disease, the role of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in the neuropathogenesis and tropism of the central nervous system (CNS) has yet to be fully elucidated. In this study, we evaluated the development of CNS damage related to the severity of COVID-19 pneumonia with creatine kinase BB (CK-BB) serum levels.

Material and Methods: The study included 55 patients hospitalized in the intensive care unit diagnosed with severe COVID-19 pneumonia, 79 in the inpatient service diagnosed with milder COVID-19 pneumonia, and 39 healthy volunteers. CK-BB levels were measured using a quantitative sandwich enzyme immunoassay technique with an Enzyme-Linked Immunosorbent Assay kit. Detection of SARS-CoV-2 was performed by real time-polymerase chain reaction from the respiratory tract (nasopharyngeal swab) according to current guidelines.

Results: While markers that were shown to predict disease severity were higher in patients with severe COVID-19 pneumonia compared with patients with milder pneumonia and the control group, serum levels of the neurological damage marker CK-BB were found to be similar between the groups [respectively 6.84 (5.05-16.2), 7.48 (4.7-22.5), 6.7 (3.8-16.2), p>0.005]. In addition, there was no difference in serum CK-BB levels between patients who developed neurological symptoms and those who did not [respectively 6.78 (5.07-17.21), 7.43 (4.7-22.5), p>0.005].

Conclusion: In COVID-19 pneumonia, serum CK-BB levels do not increase with disease severity and the development of neurological symptoms.

Keywords: COVID-19, central nervous system, creatine kinase BB

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INTRODUCTION

Since the onset of Coronavirus disease-2019 (COVID-19), many reports have been published on the neurological manifestations of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the most common of which are encephalopathy, headache, anosmia, vertigo, ageusia, and seizure (1-4). However, insufficient information exists to explain the pathophysiological mechanisms of neurological symptoms. Neuropathological effects may be associated with hypoxia, proinflammatory cytokines, or a direct result of viral neuroinvasion (5-7). On the contrary, studies show that SARS-CoV-2, due to viral neuroinvasion or antibody levels measured intrathecally, are very low in cerebrospinal fluid (CSF) examinations performed in patients with neurological symptoms (8). Currently, the role of SARS-CoV-2 in central nervous system (CNS) neuropathogenesis and tropism remains unclear, and questions regarding the existence of CNS damage due to SARS-CoV-2 remain unanswered.

Creatine kinase BB (CK-BB), an isoform of CK, is found in the CNS. The transfer of phosphate groups from ATP to creatine phosphate is catalyzed by this enzyme, resulting in energy transfer in tissues with high energy needs, such as the brain. CK-BB, which is found in astrocytes in the CNS, is released into the environment in cases where brain tissue is damaged (9,10). Studies have shown that serum CK-BB levels increase in cases of acute head trauma (10-13) or the development of brain damage due to ischemia after cardiac arrest (14) and subarachnoid hemorrhage (15). In conclusion, many studies have reported that CK-BB is a reliable neurotoxicity biomarker (16-20).

This study was conducted to detect CNS damage that may develop in severe COVID-19 pneumonia. Therefore, we compared serum CK-BB levels between patients with severe COVID pneumonia in the intensive care unit, patients with milder COVID pneumonia in the inpatient service, and healthy volunteers.

MATERIAL AND METHODS

This study was conducted as an analytical case-control study between June 1, 2020 and June 1, 2022. The study included 55 intensive care unit patients and 79 inpatient service patients hospitalized in the Ankara City Hospital diagnosed with COVID-19 pneumonia using a positive nasal SARS-CoV-2 polymerase chain reaction (PCR) test. Forty healthy volunteers with a mean age and gender similar to those of patients with COVID-19 pneumonia were included in the control group. Patients with malignancy, those younger than 18 years of age, and pregnant women were excluded from the study. Individuals with diabetes mellitus, hypertension, coronary artery disease, or chronic lung disease were considered positive for the presence of comorbid diseases. Informed consent was obtained from the individuals included in the study and from the first-degree relatives of the patients who could not provide consent.

Patients who developed symptoms such as confusion, impaired consciousness, sleepiness, agitation, hallucinations, syncope, acute muscle weakness, spasticity, hyperreflexia, Babinski symptoms, or acute central vertigo during the follow-up of patients hospitalized in the COVID-19 service or intensive care units were evaluated by neurology specialists through an in-hospital consultation system. These patients, considered to have developed symptoms localized to the CNS after neuroimaging, were included in the neurological symptom subgroup.

According to current guidelines (21) (Institut Pasteur; World Health Organization technical manual), SARS-CoV-2 detection was performed by real time (RT)-PCR of the respiratory tract (nasopharyngeal swab). The threshold detection limit of this assay, which targets two regions of the RNA polymerase gene in a viral RNA-dependent manner, was 500 copies/mL.

Ten milliliters of venous blood samples were collected in vacutainer tubes and centrifuged at 1300xg for 10 minute. The separated greenhouse was aliquots into Eppendorf tubes and stored at 80 °C until analysis. CK-BB levels were measured with an Enzyme-Linked Immunosorbent Assay kit (USCN, USCN, Wuhan, China; catalog number: SEC030Hu; lot number: L210602384) using a quantitative sandwich enzyme immunoassay technique. The concentration of CK-BB in the samples was calculated by comparing the samples' optical density (OD) to the standard curve. The detection range of the assay was 1.56-100 ng/mL. Intra- and interassay precision were <10% and <12%, respectively. CK levels were measured spectrophotometrically using an ADVIA Chemistry XPT autoanalyzer (Siemens Healthineers, Erlangen, Germany). Mass CK-MB levels were measured by chemiluminescent immunoassay on an ADVIA Centaur XPT autoanalyzer (Siemens Healthineers, Erlangen, Germany).

Statistical Analysis

Statistical analysis of the study was performed using SPSS 22.0. First, the suitability of the numerical variables, whose descriptive statistics will be given, to the normal distribution was examined using visual (histogram, probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were calculated using mean and standard deviation (mean ± SD) for normally distributed variables and median and (minimum-maximum) values for non-normally distributed variables. Categorical variables are expressed as numbers and percentages (%). After Bonferroni correction, comparisons between multiple groups were made using One-Way ANOVA post

hoc Tukey's test for normally distributed numerical variables and with Independent Samples Kruskal-Wallis test for non-normally distributed numerical variables. Independent Sample t-tests were used for normally distributed samples to compare continuous numerical variables between groups, and the Mann-Whitney U test was used for non-normally distributed models. The chi-square test was used to compare categorical data. The correlation relationship between continuous variables was evaluated using Spearman's correlation analysis. The level of relationship between the variables was interpreted as follows according to the r correlation coefficient results: low degree between 0.01 and 0.29, medium degree between 0.30 and 0.70, and high degree between 0.71 and 0.99. The lower limit considered significant was taken as $p<0.05$ in pairwise comparisons, and in multiple comparisons, it was decided according to the Bonferroni correction.

The Ankara City Hospital Ethics Committee approved the research protocol (approval number: E1-21-1813, date: 20.04.2022), and all patients provided written informed consent to participate in the study. Informed consent was obtained from the patients to participate in the study.

RESULTS

Demographic characteristics and laboratory values of the intensive care, inpatient service, and control groups are shown in Table 1. Regarding most values accepted as prognostic markers in COVID pneumonia, there was a significant difference in COVID-19 pneumonia groups compared with controls ($p<0.05$). However, no significant difference was found between the groups regarding CK-BB levels ($p>0.05$).

A comparison of CK-BB levels according to clinical condition and medical treatment type in patients with COVID-19 pneumonia is shown in Table 2. In patients with COVID-19 pneumonia, serum CK-BB levels were similar in the presence of different clinical conditions or treatment types ($p>0.05$).

The correlation between the biochemical markers predicting COVID-19 pneumonia severity and CC-BB is shown in Table 3. No significant correlation was found between CK-BB levels and other biomarkers ($p>0.05$).

DISCUSSION

In this study, we aimed to detect CNS damage that may develop in severe COVID-19 pneumonia. Therefore, we compared plasma CK-BB levels between patients with severe COVID-19 pneumonia in the intensive care unit, patients with milder COVID pneumonia in the inpatient service, and healthy volunteers. Our results showed that elevated CK-BB levels in blood-brain barrier damage remained within normal limits in patients with SARS-CoV-2 and severe pneumonia.

Although neurological symptom development has been widely reported since the onset of the COVID-19 pandemic, SARS-CoV-2 has rarely been reported to cause neuroinvasion. Neurological symptoms that develop in COVID-19 patients may generally result from ischemic injury due to hypoxia, stroke, toxic metabolic reactions, excessive cytokine release, or molecular similarity between COVID-19 antibodies and nervous system glycopeptides and cells (8). In addition, postmortem neuropathological examination results showed that it was not possible to distinguish whether symptoms were the result of hypoxia, viral neuroinvasion, multiple organ failure, decreased immune response, cytokine storm, or stroke. Therefore, it has been reported that large-scale cellular and molecular studies in CSF and brain tissue are needed, together with neurological evaluation and neuroimaging studies, to evaluate the neurological damage due to SARS-CoV-2 (22). One case report demonstrated the presence of SARS-CoV-2 in brain tissue through molecular testing and ultrastructural analysis despite having a negative SARS-CoV-2 PCR in CSF (23). On the other hand, a review study covering 43 postmortem brain tissue examinations reported that the severity of neuroimmune activation was not associated with SARS-CoV-2 in the brain tissue (24).

Although there have been reports of positive SARS-CoV-2 RNA detection in the CSF of COVID-19 patients with neurological symptoms, these reports generally come from a limited number of case reports (25-29). A review study was published by Lewis et al. (8) between December 1, 2019, and November 18, 2020, involving 430 COVID-19 patients with symptoms localized to the CNS and CSF examination. According to the results of this study, the SARS-CoV-2 PCR test was positive in 17 (6%) of 304 patients who underwent the CSF test. SARS-CoV-2 antibody positivity in CSF was observed in 7 (12%) of 58 patients, and evidence of intrathecal antibody synthesis was detected in 3 (2%) of 132 patients with oligoclonal bands. In the examination of CSF for autoimmune antibodies, positivity was found in 4 (5%) of 77 patients. In conclusion, this study reported that viral neuroinvasion and intrathecal antibody synthesis due to SARS-CoV-2 rarely occur in COVID-19 patients with neurological symptoms (8).

Although neuropathological examinations of brain tissue and CSF analysis studies partially explain the neurological symptoms developing in COVID-19 patients, data on the presence of neurological damage due to SARS-CoV-2 are still insufficient. CK-BB, which can be used as a reliable biomarker of neurotoxicity (16-20), has not been previously investigated in detecting

neurological damage that may develop due to COVID-19 pneumonia. In this study, we evaluated plasma CK-BB levels to detect neurological damage that may develop with the severity of COVID-19 pneumonia. In previous studies, parameters such as ferritin, CRP, pro-BNP, troponin-I, fibrinogen, d-dimer, neutrophil-lymphocyte ratio, procalcitonin, and IL-6 were found to be prognostic biomarkers in COVID-19 pneumonia (30-32). In our study, these biomarkers were found to be high in intensive care patients with severe pneumonia symptoms ($p<0.01$), while serum CK-BB levels did not change ($p>0.05$). In addition, our results showed no increase in serum CK-BB levels in COVID-19 patients who developed neurological symptoms compared with those who did not ($p>0.05$).

The small number of patients in the subgroup with neurological syndrome and the inability to evaluate CK-BB levels in CSF simultaneously with plasma CK-BB in this patient group are among the limitations of this study. Another limitation of our study is that serum CK-BB levels may be affected by other secondary infections accompanying COVID-19 pneumonia or immunosuppressive agents used in medical treatment.

Table 1. Comparison of demographic characteristics and laboratory values between the intensive care, service, and control groups

Parameters	Intensive care	Inpatient service	Control	p-value[&]
Gender female/male, n	21\34, 55	32\47, 79	15\24, 39	>0.05
Age, mean ± SD (years)	56.05±13.23	51.48±15.17	52.2±14.1	>0.05
Body mass index, mean ± SD	26.23±4.02	24.34±3.36	27.4±4.69	>0.05
Presence of comorbid disease, n (%)	26 (47.2)	38 (46.9)	18 (43.5)	>0.05
WBC, median (min.-max.) [cells/mm^3]	10140 (1190-48610)*	7110 (22330-2630)	7130 (13670-3640)	**<0.001**
Hemoglobin, median (min.-max.) [g/dL]	10 (6.5-16.3)*	13 (7.2-16.3)	13.6 (8.2-17.2)	**<0.001**
PLT, median (min.-max.) [x10^9/L]	279 (26-788)	260 (137-623)	285 (155-478)	0.589
Creatinin, median (min.-max.) [U/L]	0.73 (0.21-15.1)	0.78 (0.44-1.73)	0.7 (0.1-1.02)	0.131
ALT, median (min.-max.) [U/L]	46.5 (20-3161)	38.5 (10-331)	18 (9-81)$^+$	**<0.001**
AST, median (min.-max.) [U/L]	37 (14-9549)	34 (12-170)	19 (11-42)$^+$	**<0.001**
LDH, median (min.-max.) [U/L]	483 (222-4134)	338 (118-775)	191 (32-242)$^+$	**<0.001**
CRP, median (min.-max.) [mg/L]	85 (0.5-277)*	23.5 (0.6-246)**	3 (0.5-7)	**<0.001**
ESR, mean ± SD [mm/h]	48.5±28.9*	35.05±21.05**	11 (6-54)	**<0.01**
Ferritin, median (min.-max.) [µ/L]	600 (55-68025)*	250 (3.48-3245)**	45 (2.4-135.7)	**<0.001**
NLR, median (min.-max.)	13.8 (2.5-215)*	5.11 (1.1-45.8)**	2.38 (1.27-5.97)	**<0.001**
Pro-BNP, median (min.-max.) [ng/L]	1065 (67-35000)*	219 (35-9614)**	12 (5-36)	**<0.010**
Troponin-I, median (min.-max.) [ng/mL]	22.3 (2.5-1483)*	3.03 (2-271.6)**	1.05 (0.4-2.5)	**<0.001**
CK-MB, median (min.-max.) [µg/L]	0.59 (0.1-4.21)	0.54 (0.1-29)	0,65 (0.12-4.12)	0.48
CK, median (min.-max.) [U/L]	104 (23-2181)*	70 (7-2152)	83 (38-890)	**0.014**
CK-BB, median (min.-max.) [ng/mL]	6.84 (5.05-16.2)	7.48 (4.7-22.5)	6.7 (3.8-16.2)	0.183
Fibrinogen, mean ± SD, [g/L]	5.29±1.83	4.93±1.5	2.1 (1.4-4.6)$^+$	**<0.01**
D-dimer, median (min.-max.) [mg/L]	1.8 (0.1-35.2)*	0.6 (0.01-13.1)**	0.03 (0.01-0.08)	**<0.001**
Procalcitonin, median (min.-max.) [µ/L]	0.2 (0.03-79)*	0.05 (0.03-26.9)**	0.01 (0.004-0.05)	**<0.001**
IL-6, median (min.-max.) [pg/mL]	22.1 (2.7-1268)*	6.08 (2.6-110.04)**	2.1 (1.1-7.3)	**<0.01**

Bold font indicates statistical significance. * Group different from inpatient service and control group,** group different from the control group, $^+$group different from the intensive care and inpatient service group, [&]the significantly lower limit accepted after Bonferroni correction was $p<0.0167$.
Note: After Bonferroni correction, comparisons between multiple groups were made using One-Way ANOVA post hoc Tukey's test for normally distributed numerical variables and with Independent Samples Kruskal-Wallis test for non-normally distributed numerical variables. WBC: White blood cells, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PLT: Platelet, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, NLR: Neutrophil/lymphocyte ratio, BNP: Brain natriuretic peptide, CK: Creatine kinase, IL-6: Interleukin-6, SD: Standard deviation, min.: Minimum, max.: Maximum

Table 2. Comparison of CK-BB levels according to the clinical condition and medical treatment type in patients with COVID-19 pneumonia

Clinical condition		n	CK-BB, median (min.-max.)	p-value
Intubated	Yes	24	7.56 (5.07-16.25)	0.153
	No	110	7.87 (6.42-21.53)	
Non-invasive mechanical ventilator or high O^2 requirement	Yes	39	7.16 (5.7-11.5)	0.571
	No	95	7.33 (4.5-20.4)	
Low O^2 requirement	Yes	36	8.09 (5.23-22.51)	0.483
	No	98	8.41 (6.42-21.53)	
No O^2 support	Yes	35	7.24 (4.7-16.7)	0.694
	No	99	7.32 (4.9-22.45)	
Vasopressor requirement	Yes	15	7 (5.07-16.2)	0.603
	No	119	7.21 (4.7-22.51)	
Neurological symptom	Yes	29	6.78 (5.07-17.21)	0.074
	No	105	7.43 (4.7-22.5)	
Death	Yes	30	6.78 (5.07-16.25)	0.408
	No	104	7.21 (4.7-22.51)	
Medical treatment				
Medium-dose steroid	Yes	9	7.16 (5.45-16.2)	0.569
	No	125	7.38 (5.79-19.1)	
High-dose steroid	Yes	54	7.29 (5.07-22.51)	0.614
	No	80	7.41 (6.92-20.57)	
Pulse steroid	Yes	14	7.29 (5.39-13.1)	0.746
	No	120	7.36 (6.45-19.9)	
IL-1 blocker	Yes	8	7.02 (5.07-14.97)	0.215
	No	126	7.49 (5.32-17.4)	
O^2 therapy only	Yes	49	7.11 (4.91-16.57)	0.102
	No	85	7.49 (5.12-18.59)	

Note: Pairwise comparisons were performed using the Mann-Whitney U test. Bold font indicates statistical significance. CK-BB: Creatine kinase BB, COVID-19: Coronavirus disease-2019, IL: Interleukin, O_2: Oxygen, min.: Minimum, max.: Maximum

Table 3. Correlation between biochemical markers predicting COVID-19 pneumonia severity and CC-BB levels

Parameter (p)	CK	CRP	IL-6	D-dimer	Pro-BNP	Troponin-I	Ferritin	NLR	Creatinin
CK-BB	0.057 (0.454)	-0.073 (0.347)	-0.013 (0.881)	0.054 (0.524)	-0.066 (0.447)	0.037 (0.670)	0.143 (0.077)	-0.003 (0.974)	-0.027 (0.7329)
CK		0.108 (0.164)	0.202 **(0.019)**	0.142 (0.091)	0.083 (0.341)	0.164 (0.056)	0.080 (0.325)	0.097 (0.214)	0.171 **(0.032)**
CRP			0.388 **(<0.0001)**	0.463 **(<0.0001)**	0.248 **(0.004)**	0.484 **(<0.0001)**	0.527 **(<0.0001)**	0.559 **(<0.0001)**	0.074 (0.357)
IL-6				0.350 **(<0.0001)**	0.250 **(0.004)**	0.285 **(0.001)**	0.125 **(0.149)**	0.257 **(0.003)**	0.016 (0.860)
D-dimer					0.421 **(<0.0001)**	0.624 **(<0.0001)**	0.360 **(<0.0001)**	0.555 **(<0.0001)**	-0.001 (0.986)
Pro-BNP						0.446 **(<0.0001)**	0.235 **(<0.006)**	0.433 **(<0.0001)**	0.150 (0.096)
Troponin-I							0.415 **(<0.0001)**	0.494 **(<0.0001)**	0.128 (0.150)
Ferritin								0.566 **(<0.0001)**	0.164 **(0.049)**
NLR									0.133 (0.097)

Note: The correlation relationship between continuous variables was evaluated using Spearman's correlation analysis. Bold font indicates statistical significance.
CK-BB: Creatine kinase BB, CRP: C-reactive protein, IL-6: Interleukin-6, BNP: Brain natriuretic peptide, NLR: Neutrophil/lymphocyte ratio, COVID-19: Coronavirus disease-2019

CONCLUSION

This study showed no increase in serum CK-BB levels, considered an indicator of CNS damage, depending on the severity of COVID-19 pneumonia. Currently, no concrete evidence definitively demonstrates the existence of neurological damage due to SARS-CoV-2, and our results suggest no increase in neurological damage shown by serum CK-BB levels in patients with COVID-19 pneumonia.

However, further studies using imaging methods, CSF studies, and histopathological techniques are needed to clarify the nature of SARS-CoV-2-induced CNS damage and evaluate its relationship with disease.

Ethics

Ethics Committee Approval: The Ankara City Hospital Ethics Committee approved the research protocol (approval number: E1-21-1813, date: 20.04.2022).

Informed Consent: Informed consent was obtained from the individuals included in the study and from the first-degree relatives of the patients who could not provide consent.

Authorship Contributions

Surgical and Medical Practices: D.E., R.G., Concept: Y.M., A.K., E.A., D.E., Ş.E., Design: Y.M., A.K., İ.D., R.G., Ö.E., Data Collection or Processing: Y.M., H.E.K., K.O., Analysis or Interpretation: Y.M., E.A., E.F.O., K.O., Ö.E., Ş.E., Literature Search: H.E.K., İ.D., E.F.O., Writing: A.K., Y.M.

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EVALUATION OF THE RELATIONSHIP BETWEEN SERUM VITAMIN D LEVEL AND CLINICAL ACTIVATION IN PATIENTS WITH RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Aim: In this study, we aimed to analyze the clinical activity relationship between serum vitamin D levels, which are also steroid hormones, and to investigate the correlation between clinical and laboratory data and possible relationships.

Material and Methods: A total of 126 adult patients who met the 2019 systemic lupus erythematosus (SLE) classification criteria and the 2010 rheumatoid arthritis (RA) classification criteria and were treated in the outpatient clinics of Rheumatology and Physical Medicine and Rehabilitation were included in the study. Ten patients were excluded because their data were not suitable for the study. In all patients. Erythrocyte sedimentation rate, C-reactive protein level, vitamin D level, pain assessment with Visual Analog Scale, and Health Assessment Questionnaire (HAQ) were used to assess functional ability and health status in daily life.

Results: Eighty-four patients (72.4%) who participated in the study had RA and 32 patients (27.6%) had SLE. In the SLE group, 27 (84.4%) patients were female, and there was no difference between the two groups in terms of gender. The mean age was 39.32±6.64 years in the SLE group and 50.76±9.07 years in the RA group. While the 25-hydroxyvitamin D [25-(OH)D] level in the SLE group was 10.53±3.52, the vitamin D level in the RA group was 14.20±5.28, and the difference between the two groups was significant ($p<0.0001$). In the RA group, a significant negative correlation was found between the HAQ level and 25-(OH)D measured in terms of clinical activation ($p=0.001$).

Conclusion: In this cross-sectional study, 25-(OH)D levels were lower in patients with SLE, one of the major autoimmune diseases, than in patients in the RA group. A negative correlation of the 25-(OH)D level with HAQ was found in RA patients. Monitoring vitamin D levels and raising them to an optimal level are clinically important in autoimmune diseases.

Keywords: Rheumatoid arthritis, systemic lupus erythematosus, 25-hydroxyvitamin D, disease activation

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, autoimmune disease often affecting women of reproductive age that causes tissue damage in a number of target organs after the development of pathogenic autoantibodies and immune complexes. SLE is characterized by antibodies against nuclear and cytoplasmic antigens. Excessive production of pathogenic autoantibodies by B cells, dysregulation of cytokines, which results in damage to tissues and organs, and abnormal conductivity of T cell receptors also contribute to SLE autoimmunity (1).

As a chronic, inflammatory, multi-systemic disease, rheumatoid arthritis (RA) particularly involves small joints. The etiology of the disease is unknown; however, genetic factors, infectious agents, gender, hormonal factors, and lifestyle factors are considered contributing factors (2).

The presence of hormonal factors is thought to contribute to both RA and SLE, which are autoimmune diseases. Particularly in SLE, estradiol, progesterone, and prolactin, and some pituitary hormones, play a role in regulating the immune system (3). 25-hydroxyvitamin D [25-(OH)D] is a prohormone that is primarily involved in calcium metabolism and has a variety of biological effects, such as antimicrobial activity and modulation of cellular differentiation. Inhibition of autoantibody production by vitamin D leads to suppression of dendritic cell-associated pathways and inhibition of T cell activation (4).

In some studies, vitamin D deficiency has been reported to act not only as a predisposing factor for the development of RA and SLE but also to enhance disease severity and activity (5). There is a higher prevalence of vitamin D deficiency in patients with systemic lupus than in the healthy population. There are some specific risk factors associated with this disease. Less sun exposure due to photosensitivity observed in these patients decreases vitamin D synthesis from the skin. Furthermore, the hydroxylation step of vitamin D is impaired in lupus nephritis, resulting in inadequate conversion to the active form (4,6). Chronic use of commonly used corticosteroids also adversely affects vitamin D metabolism (7).

A number of studies indicate that 25-(OH)D levels are negatively associated with disease activity and mortality risk in RA, but the mechanism for this association has not yet been fully explored (8).

In the literature, there has been little research on the relationship between vitamin D levels and clinical activation in patients with RA and SLE. We conducted this study to investigate the relationship between 25-(OH)D levels and the activity of autoimmune diseases using laboratory data that can be easily obtained from peripheral blood samples.

MATERIAL AND METHODS

This study was planned as a single-center, cross-sectional study to determine the relationship between serum vitamin D levels and disease activity in individuals with RA and SLE.

Sample and Population

There were 84 participants in the study, aged 18 to 65, who applied to Erzincan Binali Yıldırım University, Mengücek Gazi Training and Research Hospital Physical Medicine and Rehabilitation and Rheumatology outpatient clinics between February 2023 and May 2023, who had been diagnosed with RA by a physician depending on the American College of Rheumatology (ACR) and/or American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) 2010 criteria and had been diagnosed with RA for at least a year, as well as 32 individuals who were diagnosed with SLE based on EULAR/ACR-2019 classification criteria. Due to seasonal variation in vitamin levels, the values between February and May were considered.

The exclusion criteria included those who received vitamin D3 replacement within the previous 6 months, pregnant patients, those with severe neurologic impairments that limit perception, and individuals with dysfunction such as uncooperation. Ten patients were excluded because their data were not suitable for the study. These patients were excluded from the study because pregnancy was detected after the examinations in three SLE patients, two SLE patients experienced activation due to discontinuation of their medications and therefore the current treatment was changed, and the other five patients' past vitamin D3 intake was later discovered from their E-nabız records.

Ethical Principles of the Study

Ethics committee approval (date: 08.12.2022; approval number: 2022-7/10) for the implementation of the study was obtained from the Faculty of Medicine Clinical Research Ethics Committee of Binali Yıldırım University.

Data Collection Tools and Data Analysis

The participants were questioned by face-to-face interview using the Patient Information Form prepared by the authors after obtaining verbal and written consent regarding their sociodemographic characteristics, health status, disease activity, sleep quality, fatigue severity, pain levels, and physical activity characteristics. In addition to demographic and clinical laboratory findings, age at diagnosis, disease duration, treatment, and prognosis (age, gender, smoking, diagnosis,

diagnosis duration, treatment and follow-up, acute phase response, hematologic findings, organ involvement findings, disease activation scoring, comorbidity and drug history, antibody levels, and follow-up) were measured and recorded.

All blood samples were drawn from the antecubital vein in the morning. All parameters were studied in the laboratory of the Mengücek Gazi Training and Research Hospital.

Regarding hematological findings, the parameters of complete blood count, erythrocyte sedimentation rate, C-reactive protein (CRP), rheumatoid factor, and anti-cyclic citrullinated peptide were measured (ARCHITECT, refrigerated centrifugation at 400 rpm for at least 15 minutes with thawed samples) and recorded. To evaluate renal involvement caused by SLE, complete urinalysis and 24 hours urinalysis were conducted on the patients. Anti-recurrent antibodies (ANA) and anti-dsDNA levels were determined by ELIZA (Alegria, ORGANTEC Diagnostica, Mainz, Germany), with moderate and high values being considered positive. A nephelometric technique was used to determine the levels of serum complement (C3, C4) (normal values for C3: 85-200 mg/dL, for C4: 20-50 mg/dL).

Using the Agilent Technologies 6460 Triple Quad liquid chromatography (LC)/mass spectrometry (MS) device, high-performance liquid chromatography (HPLC), and MS methods, serum vitamin 25-(OH)D and blood samples collected in EDTA tubes were analyzed. The 25-(OH)D concentration in serum and blood samples collected in an ethylenediamine tetraacetic acid (EDTA) tube was analyzed using an Agilent Technologies 6460 Triple Quad LC/MS device, HPLC, and MS. The reference values for vitamin 25-(OH)D were evaluated according to the device, and vitamin D levels were classified as sufficient at 30 ng/mL, insufficient at 20-30 ng/mL, deficient at 20 ng/mL, and severe at 10 ng/mL (9).

A visual analog scale (VAS) was used to determine participants' pain levels; a Disease Activity Score (DAS-28-CRP) was used to assess RA disease activity; and a Health Assessment Questionnaire (HAQ) was used to assess functional capacity and health status in daily life. Clinical findings regarding SLE, organ involvement, and other follow-up parameters, as well as SLE disease activation scores, were evaluated using the Disease Activity Index (SLEDAI).

VAS

The VAS pain score was evaluated as "no pain" (score=0) and "worst pain possible" (score=10) and divided into three groups according to the pain intensity scale of the World Health Organization: if the score was <3, it was considered mild pain, 3-6 as mild-moderate pain, and >6 as moderate-severe pain (10).

HAQ

This questionnaire consisted of 20 questions and eight activities. The score obtained from each activity was determined according to the highest score obtained from the questions in that activity. The total score was calculated by taking the sum of the scores obtained from the eight activities and dividing by 8, and was evaluated with a score between 0 and 3. Higher scores indicate an increased level of functional dependence (11).

DAS-28 Score Calculation Form

The DAS-28 score was used to assess disease activation in RA. It was calculated using the swollen joint count, tender joint count (over 28 joints), VAS, and CRP (mg/dL) data. A special type of calculator was used for this calculation. As a result of the calculation, values of 2.6 and below were considered "remission" , values between 2.6 and 3.2 as "low level of disease activity", values between 3.2 and 5.1 as "moderate level of disease activity", and values of 5.1 and above as "high level of disease activity" (12).

SLEDAI

In the case of SLE, activity classification was based on the SLEDAI score. Whenever there was no activity, the score was accepted as zero. A score of 1-5 was considered mild activity, 6-10 was moderate activity, 1-19 was high activity, and ≥20 was very high activity. Laboratory parameters included in the DAS were obtained from the patient's examinations in the last month (13).

Statistical Analysis

The analysis was performed using the SPSS 22.0 software package. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as percentages. The normal distribution of the continuous variables was tested using the Kolmogorov-Smirnov test. For the continuous variables, an independent sample t-test or Mann Whitney U test was used. Correlations between the data were tested using Spearman's and Pearson correlation analysis. The chi-square test was used to compare categorical values. For all tests, a two-way p-value of 0.05 for the patients was considered significant. The relationship between variables in the patients group was analyzed using Spearman's correlation analysis (r-value).

RESULTS

A comparison of the demographic and laboratory characteristics of the 126 individuals participating in the study is presented in Table 1.

There were 84 individuals (72.4%) with RA and 32 individuals (27.6%) with SLE. The SLE group consisted of 27 (84.4%) female

Table 1. Comparison of demographic and laboratory characteristics of the RA and SLE groups

Variables	RA (n=84, 72.4%)	SLE (n=32, 27.6%)	p-value
Age (year), (min.-max.)	50.76±9.07 (28-67)	39.32±6.64 (21-52)	**0.001***
Gender, female (n, %)	58 (69.0%)	27 (84.4%)	0.095**
Age of disease onset (years) (mean ± SD)	41.05±9.11	30.03 ±6.85	**0.001****
Disease duration (months) (mean ± SD)	135.36±69.62	126.36±49.32	0.414*
Current smokers (n, %)	28 (33.3%)	10 (31.3%)	0.831**
Hbg, (g/dL)	12.58±1.07	11.73±0.76	**0.001***
MPV	9.59±0.59	9.73±0.74	0.322*
WBC, µL	6.96±7.97	4.08±0.77	**<0.001***
Serum creatinine (mg/dL)	0.76±0.13	0.94±0.28	**0.001***
CRP mean ± SD (mg/dL)	9.52±6.80	8.77±6.96	0.258*
ESH mean ± SD (mm/hour)	26.17±10.18	31.87±13.42	**0.018***
25-(OH) vitamin D (<29.9 ng/mL) (min.-max.)	14.20±5.28 (2.90-25.2)	10.53±3.52 (4.20-23.30)	**0.001***
RF positivity, n (%)	61 (72.6%)	4 (12.5%)	**<0.001****
Anti-CCP positivity, n (%)	35 (41.7%)	2 (6.3%)	**<0.001****
ANA positivity, n (%)	39 (46.4%)	32 (100%)	**<0.001****

*Mann-Whitney U test in an independent sample, **chi square test. In the table, the values are presented as median (minimum-maximum) or number (%), mean ± SD: Mean ± standard deviation (was considered significant at p<0.05), RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, min.: Minimum, max.: Maximum, Std : Standard, n: Number, Hbg: Hemoglobin, MPV: Mean plateau volume, WBC: White blood cell, CRP: C-reactive protein, ESH: Erythrocyte sedimentation rate, 25-(OH) vitamin D :25-hydroxyvitamin D, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, Anti-CCP: Anticyclic citrullinated peptide, ANA: Antinuclear antibody, SD: Standard deviation

patients, and there was no gender difference between the groups. The mean age was 39.32±6.64 years in the SLE group and 50.76±9.07 years in the RA group, which was significantly younger in the SLE group than in the RA group.

The 25-(OH)D level in the SLE group was 10.53±3.52, which was significantly lower than the 25-(OH)D level in the RA group (14.20±5.28) (p<0.0001). In the SLE group, 4 patients (12.5%) had 25-(OH)D vitamin deficiency, 13 patients (40.6%) had 25-(OH)D vitamin deficiency, and 15 patients (46.8%) had severe 25-(OH)D vitamin deficiency. In the RA group, 25-(OH)D was <20 ng/mL in 56 (66.6%) patients.

All patients in the SLE group were ANA-positive. In the RA group, ANA positivity was determined in 39 (46.4%) patients. Anti-dsDNA, C3, and C4 levels were measured in the SLE group. The anti-dsDNA level was found to be higher than the normal reference range (n=>20 IU/L) in 8 patients (25%) in the SLE group. Serum complement (C3, C4) levels of the patients were measured using the nephelometric method (normal values were C3: 85-200 mg/dL, C4: 20-50 mg/dL). C3 complement levels (n=75-135 mg/dL) were found to be lower than normal reference ranges in 12 (37.5%) patients.

A comparison of the treatments between the patient groups is presented in Table 2. While there was no statistical difference

Table 2. Comparison of treatments between the patient groups

Current treatment	RA (n=84, 72.4%)	SLE (n=32, 27.6%)	p*
Corticosteroid, n (%)	62 (73.8%)	24 (75.0%)	0.205
HCQ, n (%)	9 (10.7%)	24 (75.0%)	<0.0001
MTX , n (%)	38 (45.2%)	6 (18.8%)	<0.0001
Anti-TNF-α, n (%)	27 (32.1%)	-	

*chi square test, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, HCQ: Hydroxychloroquine, MTX: Methotrexate, anti-TNF-α: Anti-tumor necrosis factor alfa treatment, n: Number

in terms of the number of patients treated with steroids in both groups, the difference was significant in terms of disease-modifying antirheumatic drugs (DMARDs) treatments (p<0.0001). However, the duration of steroid treatment was longer in the SLE group (8.62±2.6 months) than in the RA group (5.28±1.61), but there was no statistically significant difference, as cumulatively similar doses.

When the treatments of the patients were analyzed, hydroxychloroquine was prescribed to 24 patients (75%) in the SLE group, whereas methotrexate was prescribed to 38 patients (45.2%) in the RA group. The number of patients who used anti-

tumor necrosis factors (TNFs) because of resistant disease despite DMARD treatment was 27 (32.1%) in the RA group. As anti-TNF, adalimumab treatment was administered to 12 (14.2%) patients, golimumab treatment was administered to eight (9.5%) patients, etanercept treatment was administered to four (4.7%) patients, and certolizumab treatment was administered to three (3.5%) patients.

A comparison of disease activation between the groups is presented in Table 3. The difference between VAS and HAQ values between both groups was not significant (p>0.05). The DAS-28 CRP score was 4.21±0.84 in the RA group. In the DAS-28 evaluation, 48 individuals (57.1%) were found to have a moderate level of disease activity. In the SLE group, the SLEDAI was determined to be 6.84±4.54. Six (18.7%) individuals with SLE had a moderate level of activity (SLEDAI 6-10).

When the patients were analyzed in terms of organ involvement, 7 patients (8.3%) in the RA group had interstitial lung disease; therefore, 4 patients (4.7%) were treated with Rituximab (RTX) and 3 patients (3.5%) were administered with a Janus kinase inhibitor (tofacitinib). In the SLE group, 3 patients (9.3%) were treated with Azathioprine, 3 patients (9.3%) with mikofenolat mofetil, and 3 patients (9.3%) with RTX because of renal proteinuria.

Table 3. Comparison of disease activation parameters between the patient groups

	RA (n=84, 72.4%)	SLE (n=32, 27.6%)	p
VAS (unit), (mean ± SD)	5.98±0.99	6.37±1.03	0.068
HAQ, (mean ± SD)	1.27±0.29	1.30±0.26	0.074
DAS-28 CRP score (min.-max.)	4.21±0.84 (2.96-6.84)	-	
SLEDAI (min.-max.)	-	6.84±4.54 (1-20)	

RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, SD: Standard deviation, min.: Minimum, max.: Maximum, VAS: Visual analog scale, HAQ: Health Assessment Questionnaire, DAS-28: Disease Activity Score of 28 joints, CRP: C-reactive protein, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

Table 4. Correlation between the 25-(OH)D vitamin and disease activation parameters in the RA group

Variables	r	p*
Disease duration	-0.112	0.086
CRP	0.043	0.695
ESH	0.132	0.230
DAS-28 CRP	-0.101	0.369
VAS	-0.160	0.147
HAQ	-0.361	**0.001**

*Pearson correlation analysis. 25-(OH) vitamin D :25-hydroxyvitamin D, RA: Rheumatoid arthritis, CRP: C-reactive protein, ESH: Erythrocyte sedimentation rate, DAS-28: Disease Activity Score 28 joints, VAS: Visual analog scale, HAQ: Health Assessment Questionnaire

In Table 4, the correlation between 25-(OH)D and disease activation parameters in the RA group is presented. When the correlation of serum 25-(OH)D levels with parameters was examined, a negative correlation was found with disease duration, DAS-28, and VAS, but it was not significant. The negative correlation between HAQ level and 25-(OH)D was significant (p=0.001).

The correlation between 25-(OH)D vitamin and disease activation parameters in the SLE group is presented in Table 5. When the correlation of serum 25-(OH)D level with the parameters was analyzed, the negative correlation with SLE disease duration was found to be significant (p=0.015). Its negative correlation with SLEDAI, HAQ, sedimentation, and dsDNA levels was determined, but it was not statistically significant (p>0.05).

DISCUSSION

In this study, we examined the correlation between 25-(OH)D levels in peripheral blood samples and disease activation in patients with RA and SLE.

There was no difference between the two groups in terms of gender, with most females in both groups. The SLE group (mean age: 39.32±6.64 years) consisted of younger individuals than the RA patients (mean age: 50.76±9.07 years), as expected.

Sedimentation and CRP levels, which were routinely measured during clinical follow-up, were associated with disease activation

Table 5. Correlation between the 25-(OH)D and disease activation parameters in the SLE group

Variables	r	p*
Disease duration	-0.226	**0.015**
CRP	0.420	0.820
ESH	-0.025	0.892
C3 levels	0.294	0.191
Anti-dsDNA levels	-0.232	0.210
SLEDAI	-0.152	0.408
VAS	0.290	0.873
HAQ	-0.050	0.807

*Pearson correlation analysis. 25-(OH) vitamin D :25-hydroxyvitamin D, SLE: Systemic lupus erythematosus, CRP: C-reactive protein, ESH: Erythrocyte sedimentation rate, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, VAS: Visual analog scale, HAQ: Health Assessment Questionnaire

and prognosis. Patients with active lupus, in contrast to those with RA, had high sedimentation levels as a characteristic finding of the disease (14). According to this study, sedimentation was higher in the SLE group (31.87±13.42), and the difference was statistically significant (p=0.018).

Studies in the literature have revealed that 25-(OH)D deficiency is highly prevalent in patients suffering from autoimmune rheumatic diseases. In our country, many studies have been conducted on this subject, and in the study of Çalışkan Uçkun et al., (15) it was found that 25-(OH)D levels were significantly lower in individuals with RA than in healthy controls, and 73% of individuals with RA were reported to have vitamin D deficiency, similar to our study. This study was cross-sectional, and vitamin D levels were measured in patients who had not been administered 25-(OH)D3 within the past 6 months. In this study, the 25-(OH)D level was found to be 14.20±5.28 in the RA group, and the vitamin D level was <20 ng/mL in 66.6%.

According to a study involving patients with systemic sclerosis, which is an autoimmune disease characterized by skin involvement, 25-(OH)D levels were 11.35±4.09 ng/dL, a value significantly lower than those of healthy controls (16). The presence of skin involvement in lupus patients was also considered as a disadvantage.

Because it is negatively related to vitamin D levels, the cause of this condition is not entirely understood. In the general population and in patients with SLE, female gender is a classic risk factor for D hypovitaminosis. These differences have been attributed to lower body surface area and androgen-related differences in vitamin D-binding protein levels (4,17). This study found that the female gender predominated in both groups, and there was no gender difference between the groups. There was a significantly higher proportion of females in the group suffering from SLE (84.4%).

As reported in the literature, 25-(OH)D levels were lower in the SLE group than in the RA group in this study. The lower 25-(OH)D levels in patients with lupus compared with RA were attributed to intestinal malabsorption, higher corticosteroid levels, renal involvement and proteinuria, different polymorphisms of 25-(OH)D receptors in patients with lupus, and greater sun protection (7,18).

In the study conducted by Bogaczewicz et al. (19) in 2012 on 49 patients with SLE and a control group (49 people), 25-(OH)D deficiency was found in 90.9% of the group with SLE, whereas 25-(OH)D deficiency or insufficiency was observed in 55.5% of the control group. The level of vitamin D was found to be lower and statistically significant in patients with SLE than in the control group (p=0.0005) (19). There was no control group in this study, but 25-(OH)D levels were quite low in the SLE group, with 25-(OH)D deficiency being detected in 13 patients (40.6%) and severe 25-(OH)D deficiency being detected in 15 patients (46.8%). Based on a literature review, some studies found a correlation between vitamin D and RA activity and flare-up frequency, especially in developing countries, whereas other studies found no correlation (8,20).

Although there was a lack of consistency in studies on 25-(OH)D levels and disease activity in SLE, both of the largest studies to date revealed a significant correlation between high disease activity and low 25-(OH)D levels. These studies also identified that improving vitamin D status among patients with SLE could alleviate other common symptoms such as fatigue and cognitive impairment (21).

As part of a prospective follow-up study for 1 year, vitamin D3 supplementation was administered to patients with SLE, and it was observed that disease activity measured by SLEDAI-2K improved, and parallel with this, serum anti-dsDNA levels decreased both at 6 and 12 months from onset (4,18). According to our study, a negative correlation was observed between serum 25-(OH)D levels and clinical activation, but the results were not statistically significant (p>0.05). Quality of life may be negatively affected by low levels of the 25-(OH)D. In the RA group, there was a negative correlation between 25-(OH)D, DAS-28, and VAS, but this correlation was not significant. The negative correlation between the HAQ level and 25-(OH)D was significant (p=0.001).

Vitamin D was found to act as a negative acute phase reactant, thus explaining its decrease in levels during acute inflammatory processes, and its deficiency was associated with an increase in inflammatory cytokines such as interferon alpha and interferon gama and a high autoantibody titer (22). These cytokines play an important role in SLE pathogenesis. An inverse relationship was found between vitamin D levels and disease activity and anti-dsDNA titers in Cutolo et al. (23). However, some studies have found a contrary correlation. It was believed that ethnicity-related genetic differences in vitamin D receptors were responsible for these differences in study results (23).

In our study, a negative correlation was found between 25-(OH)D level and dsDNA, but this result was not statistically significant (p>0.05). Nevertheless, the negative correlation with vitamin D levels should be considered as a parameter that should be evaluated in patients with lupus nephritis.

Serum 25(OH)D levels decrease with decreased glomerular filtration rate in patients with chronic kidney disease (24). In our study, the creatinine value was significantly higher in the SLE group than in the RA group (p=0.001), and 12 patients (37.5%)

in the SLE group were on advanced treatment for proteinuria. When compared with the RA group, the 25-(OH)D level was also significantly lower.

Some studies in the literature have reported that 25-(OH)D serum values in SLE patients were significantly lower than those in RA patients with the same geographical location, D3 supplementation, and other risk factors (7,22,25). Because vitamin D synthesis occurs through the skin and these patients had skin involvement, 25-(OH)D deficiency should be considered more profound in SLE patients.

CONCLUSION

This study suggests that vitamin D levels should be monitored in patients with autoimmune diseases and that this can serve as an effective follow-up parameter for patients with RA in terms of quality of life and clinical activation. By using a treatment as safe, cheap, and widely available as vitamin D in these patients, we believe that morbidity and mortality related to vitamin D deficiency can also be reduced. It is necessary to conduct further large-scale, prospective, and long-term follow-up studies to determine the optimal range of serum 25(OH)D levels for reducing clinical activation and morbidity.

The study was planned cross-sectionally. No healthy control group could be included in addition to the patient groups. A prospective study with a long-term follow-up and including a control group will contribute more to the literature.

Ethics

Ethics Committee Approval: Ethics committee approval (date: 08.12.2022; approval number: 2022-7/10) for the implementation of the study was obtained from the Faculty of Medicine Clinical Research Ethics Committee of Binali Yıldırım University.

Informed Consent: The participants were questioned by face-to-face interview using the Patient Information Form prepared by the authors after obtaining verbal and written consent regarding their sociodemographic characteristics, health status, disease activity, sleep quality, fatigue severity, pain levels, and physical activity characteristics.

Authorship Contributions

Surgical and Medical Practices: K.A.A., B.E., S.E., Concept: K.A.A., Design: K.A.A., Data Collection or Processing: K.A.A., B.E., Analysis or Interpretation: K.A.A., S.E., Literature Search: K.A.A., B.E., Writing: K.A.A.

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EXPLORING THE NEXUS OF SUBCLINICAL ATHEROSCLEROSIS AND SYNDECAN-4 LEVELS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Aim: Systemic lupus erythematosus (SLE) is a persistent inflammatory autoimmune disorder. In an endeavor to juxtapose disease activity against the acknowledged occurrence of subclinical atherosclerosis in patients with SLE, this study sought to evaluate the interrelation between carotid intima-media thickness (CIMT), SLE disease activity index (SLEDAI), and Syndecan-4 (SDC4) levels.

Material and Methods: This study assembled a cohort comprising 70 patients with SLE aged 18 years and older, devoid of concomitant systemic diseases, was assembled, alongside a control group consisting of 68 healthy volunteers attending the rheumatology outpatient clinic. The assessment quantifying SDC4 levels using enzyme-linked immunosorbent assay method. CIMT measurements were conducted for both the patient and control groups. SLEDAI scores, as well as sociodemographic and laboratory data for both groups, were systematically extracted from the hospital's digitalized medical records system.

Results: SDC4 levels within the patient cohort (8.211±9.069) exhibited a statistically significant reduction compared to the SDC4 levels in the control group (26.221±24.653). Furthermore, the CIMT values for the patient group (0.558±0.116) demonstrated a statistically significant variance in contrast to the CIMT values of the control group (0.49±0.117). Remarkably, a noteworthy correlation emerged between SDC4 and CIMT. Additionally, a significant association was identified between SDC4 levels and body mass index ($p<0.05$). Further correlations were discerned between SDC4 levels and SLEDAI in the patient group. Correspondingly, a statistically significant correlation was observed between CIMT and SLEDAI in the patient group.

Conclusion: Despite the statistically significant elevation in CIMT, an essential indicator of subclinical atherosclerosis, within our patient group compared with the control group, we posit that SDC4 levels may not be reliable predictors of atherosclerosis.

Keywords: Atherosclerosis, body mass index, carotid intima-media thickness, Syndecan-4, systemic lupus erythematosus, systemic lupus erythematosus disease activity index

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic connective tissue disorder of undetermined etiology characterized by immunological dysregulation, autoimmune features, and multi-organ system involvement (1). The clinical manifestations of SLE encompass a spectrum of fever, joint swelling, and erythematous skin rashes, and include involvement of vital organs and systems, including but not limited to the kidneys, central nervous system, and lungs.

Atherosclerosis, a condition associated with inflammation, autoimmunity, chronic illness, and dyslipidemia, is well-recognized in the context of SLE, with established links to systemic inflammatory markers, such as C-reactive protein (CRP), fibrinogen, cytokines, chemokines, adhesion molecules, and proteases (2). Cardiovascular complications constitute a leading cause of mortality in patients with SLE (3), with a higher incidence of cardiovascular diseases than in the general population (4). Pignoli et al. (5) highlighted the significance of carotid intima-media thickness (CIMT) as a sonographic marker indicative of early atherosclerosis linked to widespread vascular pathology.

The protein Syndecan-4 (SDC4) encoded by SDC4 in humans has a molecular weight of approximately 20 kDa (6) and is recognized as a well-characterized plasma membrane proteoglycan. Syndecans play a pivotal role in cellular functions by interacting with the intracellular domain of membrane-covering core proteins, the actin cytoskeleton, and signaling molecules within the cell cortex (7). Typically present on the surface of fibroblasts and epithelial cells, Syndecan exhibit binding capabilities with fibroblast growth factors (FGF), facilitating their transport to the FGF receptor on the same cell (8). Studies have elucidated the specific role of SDC4 in determining endothelial alignment, providing atheroprotective signaling, and regulating myofibroblast migration following mechanical stretch or injury (9). A recent study on mice in which SDC4 gene expression was deleted showed that atherosclerosis was accelerated. In this study, ApoE/mice (n=10) and male SDC4/ApoE/mice (n=10) were fed a high-cholesterol diet for 12 weeks. SDC4 −/− ApoE −/− mice have higher lipid contents and a more severe plaque burden. The most important result of the study was that downregulation of SDC4 is not only a consequence of atherogenesis but also a promoter of atherogenesis (10). Notably, SDC4 levels were found to correlate with the extent of myocardial damage observed in myocardial infarction (11). It has been determined that mice genetically suppressed SDC4 protein synthesis are fertile and do not exhibit any morphological defects. It was observed that these mice had a delay in the formation of granulation tissue and that the angiogenesis rates were lower than those of normal mice. This situation raised the question of whether SDC4 is critical for the continuation of life (13).

Previous research indicated an association between SDC4 and atherosclerotic diseases, with increased susceptibility to atherosclerosis observed in SLE. Poor endothelial alignment is an indicator of susceptibility to atherosclerosis *in vivo* (14). The attachment of monocytes and T lymphocytes to the injured endothelium and their subsequent migration to the intima are among the first and most important steps in lesion development. The co-localization of CD4+ T cells and macrophages in the lesion, overexpression of human leukocyte antigen class II molecules, and co-stimulatory molecule CD40 and its ligand indicate the contribution of cell-mediated immunity to atherogenesis (15). Increased oxidative stress, as identified in vitro through endothelial progenitor cell cultures from patients with SLE, is implicated in elevating SDC4 levels (16).

Building on this background, the present cross-sectional study aimed to investigate, for the first time *in vivo*, the relationship between serum SDC4 levels, subclinical atherosclerosis, and SLE disease activity. Employing CIMT as an indicator of subclinical atherosclerosis and the SLE disease activity index (SLEDAI) scale to assess disease activity, this study aimed to elucidate the interplay between SDC4 and these markers in patients with SLE. By comparing SDC4 levels in healthy volunteers and the patient group, our research aimed to establish novel insights into the relationship of SDC4 with CIMT, an established indicator of atherosclerosis, and SLEDAI, a measure of disease activity in SLE patients.

MATERIALS AND METHODS

Approval for our study was received from Necmettin Erbakan University Meram Faculty of Medicine Pharmaceutical and Non-medical Device Research Ethics Committee (approval number: 2020/2928, date: 04/12/2020). For our cross-sectional study, patients diagnosed with SLE, aged 18 years or older, and devoid of any other known systemic diseases were recruited from the rheumatology outpatient clinic of Necmettin Erbakan University Meram Faculty of Medicine. The control group consisted of individuals who sought medical help with non-rheumatological complaints and had no history of heart or systemic diseases. Informed consent was obtained from each participant after providing comprehensive information disclosure.

For the purpose of study inclusion, individuals aged over 18 years must have been diagnosed with SLE for a minimum of 2 months in accordance with the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria. In contrast, the control group was intended to comprise

healthy adults aged 18-65 years. The exclusion criteria include excluding patients with a medical history of coronary artery disease, diabetes, hypertension, and morbid obesity [body mass index (BMI) of 35 or above], given their potential contribution to heart attack. Additionally, participants from all groups who were admitted to the hospital for acute coronary syndrome or stroke within 6 months were excluded from the analysis framework. The 6-month period between April and October 2021 was selected for inclusion in the study. During the study period, 72 patients were included in the patient group and 69 in the control group. The sample group of 50 people was selected using the G*Power program for the 95% confidence interval. Eight patients and 5 control group participants who did not meet the inclusion criteria were excluded from the study.

Bilateral measurements of the internal carotid artery were made by the radiology team involved in the study, and the highest intima media thickness value was recorded.

A 10 mL peripheral blood sample was obtained from the antecubital brachial vein of all participants. The blood samples were allowed to clot at room temperature for 20 min and subsequently subjected to cold centrifugation at 3000 rpm for 20 min. Serum samples were stored at -86 ºC. Carotid ultrasound examinations, using the B (brightness)-mode gray technique, were performed on all participants on the same day as blood collection. A blind radiologist assessed the carotid arteries of both patients and the control group by measuring the CIMT in millimeters.

Serum samples were examined using the sandwich enzyme-linked immunosorbent assay (ELISA) technique with BT LAB Human SDC4 ELISA kits. The specified standard curve range was 0.1-35 ng/mL, with a sensitivity of 0.053 ng/mL. There was no normal SDC4 level range reported by the manufacturer. The ELISA plate was pre-coated with Human SDC4 antibody, followed by the addition of SDC4 from the sample to form a bound complex with the coated antibodies. A biotinylated Human SDC4 Antibody was then introduced and attached to the SDC4 in the sample. Subsequent addition of Streptavidin-HRP formed a complex with a biotinylated SDC4 antibody. After incubation and a washing step to remove unbound Streptavidin-HRP, a substrate solution was added, resulting in color development proportionate to the quantity of Human SDC4. The reaction was halted by adding an acidic stop solution, and absorbance was measured at 450 nm. The recorded results are expressed in ng/mL.

Statistical Analysis

The G*Power program (version 3.1.9.7) was used for sample size calculation. A population of at least 50 individuals is recommended to obtain a 95% confidence interval. Data analysis was conducted using SPSS version 21.0 software. The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics, including mean, standard deviation, minimum, maximum, frequency, and percentage, were employed to present comprehensive data summaries. The correlation between continuous variables within each case group was evaluated using Spearman's correlation test. For the univariate analysis of dependent and independent variables, the chi-square test was used. Model summaries and parameter estimates were generated using linear regression to express the relationship between the dependent variable and a set of independent variables. Statistical significance was determined using p-values below 0.05.

RESULTS

The cohort under investigation comprises 57 females, representing 89% of the total sample, while the control group comprises 56 females, representing 87%. The mean ages of the patient group was determined to be 36.36±13.42, and 34.78±11.798 for the control group. Although the mean age was similar between the patient and control groups (p=0.749), female sex was similarly dominant in both groups. Furthermore, the mean BMI of the patient group was calculated as 26.11±4.28, whereas the mean BMI for the control group was observed to be 25.01±3.71. Renal involvement (lupus nephritis, etc.) of SLE patients was not examined in this study. Patients' medication and serology status are summarized in Table 1. There was a statistically significant difference between the CIMT value of the patient group (0.558±0.116) and the CIMT value of the control group (0.49±0.117) (p=0.001).

The median SDC4 level in the patient group was determined to be 4.085 (2.893-9.702), whereas the corresponding mean in the control group was 18.405 (5.180-42.25). Upon comparative analysis between the patient and control groups, a statistically significant difference in SDC4 levels was observed, with the

Table 1. Medication choices and serologies of patients

Rituximab, n (%)	62 (97%)
Cyclophosphamide, n (%)	63 (98%)
Mycophenolate mofetil, n (%)	53 (83%)
Azathioprine, n (%)	39 (61%)
Corticosteroid, n (%)	19 (30%)
Hydroxychloroquine, n (%)	19 (30%)
C3+C4 mg/dL	14 (22%)
Anti-ds DNA n (%)	42 (66%)

patient group exhibiting a markedly lower level compared with the control group, with a p-value of 0.001 (Figure 1). The laboratory outcomes of the groups are presented in Table 2.

Because the SDC4 data and CIMT values of the control group did not comply with the normal distribution, a correlation test was performed using Spearman's rho analysis. No correlation was detected between CIMT and SDC4 levels in the control group (p=0.327).

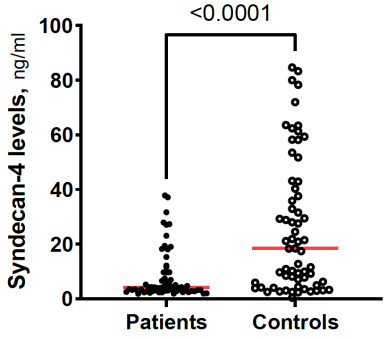

Figure 1. Distribution of Syndecan-4 levels between the patient and control groups

Cumulatively, Figure 2 presents the outcomes derived from linear regression analysis, aimed at delineating conceivable relationships between the pivotal factor SDC4 and patient attributes with disease severity grading.

DISCUSSION

SLE is a chronic disease that increases the risk of cardiovascular disease in the long term. In our study, we aimed to demonstrate subclinical atherosclerosis in SLE patients at an early stage by comparing CIMT values, disease activity indexes and serum SDC4 levels. We also tried to identify statistically significant differences by comparing the SDC4 and carotid intima levels between the healthy volunteers and the patient group.

In an experimental study that inspired this study, the relationship between SDC4 and atherosclerosis was examined. In this *in*

Table 2. Laboratory results of the groups

	Patients	Controls	p-value
WBC, $^{x}10^{9}$/L	6.87±3.07	6.83±1.82	0.926
ANC, $^{x}10^{9}$/L	4.62±2.52	3.95±1.31	0.063
ALC, $^{x}10^{9}$/L	1.5 (1.06-2.13)	0.4 (0.32-0.49)	0.001
AMC, $^{x}10^{9}$/L	0.41 (0.31-0.55)	0.41 (0.32-0.48)	0.359
Hemoglobin, gr/L	12.47±1.98	13.42±1.19	0.001
Platelet, $^{x}10^{9}$/L	237 (191-297)	259 (227-301)	0.043
RDW, fL	14.8 (13.4-16.4)	13.3 (12.9-14)	0.001
MPV, fL	10.31±1.42	13±2.1	0.311
Creatinine, mg/dL	0.76 (0.67-0.92)	0.75 (0.65-0.84)	0.353
AST, U/L	14.8 (12.8-20.4)	14.5 (11.5-17.9)	0.145
ALT, U/L	14.1 (9.9-20.5)	11.8 (9.1-15.6)	0.105
Erythrocyte sedimentation rate, mm/h	15 (6.2-26)	9 (5.3-13.7)	0.002
C-reactive protein level, mg/L	3.14 (1.92-10.57)	0.93 (0.49-2.40)	0.001
Calcium, mg/dL	9.33 (9.06-9.6)	9.29 (9-9.55)	0.502
Ferritin, ng/mL	29.44 (13.01-102.87)	27.02 (12.87-54.92)	0.342
Triglyceride, mg/dL	138.4 (83.5-196)	73.45 (63.12-99.6)	0.001
LDL, mg/dL	89.27±26.84	95.06±29.91	0.250
HDL, mg/dL	47.6±14.61	57.47±12.30	0.001
VLDL, mg/dL	27.37±14.33	18.10±9.61	0.001
TSH, mIU/mL	2.61±1.28	1.93±1.13	0.002
CIMT, mm	0.55±0.11	0.49±0.11	0.001

WBC: White blood cells, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, AMC: Absolute monocyte count, RDW: Red cell distribution width, MPV: Mean platelet volume, AST: Aspartate aminotransferase, ALT: Alanine transaminase, LDL: Low-density lipoproteins, HDL: High-density lipoproteins, VLDL: Very low-density lipoproteins, TSH: Thyroid-stimulating hormone, CIMT: Carotid intima-media thickness

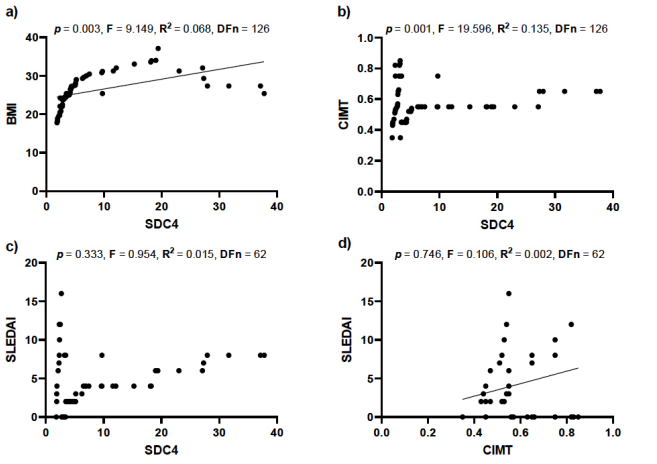

Figure 2. Linear regression results: a) between SDC4 and BMI, (b) between SDC4 and CIMT, c) between SDC4 and SLEDAI, and d) between CIMT and SLEDAI
BMI: Body mass index, CIMT: Carotid intima-media thickness, SLEDAI: Systemic lupus erythematosus disease activity index, SDC4: Syndecan-4

vitro study, in which SDC mRNA responses were monitored, mechanical damage was created to cultured rat aortic smooth muscle cells using a balloon catheter. Serum levels of SDC4 mRNA increase after basic FGF and arterial injury in vascular smooth muscle cells (VSMC) (12). In an *in vitro* study, cardiomyocyte-specific overexpression of SDC4 caused activation of calcineurin-NFAT signaling and intensified cardiac hypertrophy in mice (13). Early detection of subclinical atherosclerosis in patients with SLE plays a vital role in preventing cardiovascular events that do not yet show clinical signs. Cardiovascular complications caused by SLE are the leading cause of mortality and morbidity due to this disease. CIMT measurement, which provides early detection of subclinical atherosclerosis, is performed by ultrasonography, which is quickly accessible, inexpensive, noninvasive, and does not contain ionizing radiation. It has been determined in studies that SDC4 plays important roles in cardiac injury and restructuring process (10). It has been shown that the differentiation of fibroblasts with deleted SDC4 genetic expression into myofibroblast is impaired (14).

However, when the literature is reviewed in general, the relationship between the *in vivo* functions of SDC4 and atherosclerosis has been shown in a limited number of studies. In a study examining the effects of SDC4 on atherosclerosis and cellular alignment in intravascular blood flow, it was found that in hypercholesterolemic mice, stopping the replication step of SDC4 [S4(-/-)] via viral vector greatly increased the atherosclerotic plaque burden, with the appearance of plaque in areas of normal resistance (9). SDC4 has been shown to promote the formation of FGF-2 signaling and subsequently suppress mineralization in VSMC by downregulating transforming growth factor-β signaling (19).

The importance of T-lymphocytes in the development of subclinical atherosclerosis in patients with SLE was also emphasized. During the development of atherosclerotic lesions, the arterial wall is invaded by leukocytes, especially monocytes and T-lymphocytes. This may be important for demonstrating the relationship between lymphocytes and subclinical atherosclerosis in autoimmune disease. We considered the association between T lymphocytes in atherosclerotic plaques and peripheral lymphocytosis as a weak statistical possibility. In our study, the lymphocyte count was significantly higher in the patient group than in the control group. In the control group, lymphopenia was unexpectedly detected in comparison with the population average.

ATP-binding cassette transporters A1 and G1 (ABCA1, ABCG1) are members of the ATP-binding cassette transporter family, and they promote the efflux of intracellular lipids into the extracellular compartment and reverse transport of intracellular lipids to high-density lipoproteins (HDL), thereby inhibiting foam cell formation (20). Deletion of SDC4 expression increased the proinflammatory capacity of mouse macrophages via this pathway. These studies identified SDC4 as a very potent atherosclerosis-inhibiting protein. The increased atherosclerotic plaque burden in mice with SDC4 loss supports this. Studies have determined that SDC4 plays an important role in heart damage and restructuring process (10). In our study, the fact that SDC4 levels were significantly lower in the SLE group than in the control group does not directly support that the atherosclerosis burden increased in the SLE group. Because, as we will explain in detail later, this situation may be caused by the immunosuppressant treatment the patients receive. In our study, we examined whether there is a relationship between subclinical atherosclerosis and SDC4 protein in patients with SLE using CIMT measurement. The CIMT level was found to be significantly higher in our patient group than in the control group. Serum SDC4 levels were associated with blood pressure and cardiovascular parameters in healthy older women, but not with proinflammatory cytokines or arterial elasticity. Significant correlations were detected between SDC4 and MMP-9, heart rate, left ventricular ejection time, systemic vascular resistance, and blood pressure. However, no significant correlation was detected with serum tumor necrosis factor-alpha and interleukin-6 levels, which are proinflammatory markers.

According to the results of this study, systemic inflammation may not cause SDC4 to distribute to the extravascular area

in healthy individuals with aging (21). SDC4 coexistence was examined in a study in which serum osteoprotegerin levels were measured to evaluate oxidative stress in patients with SLE. *In vitro*, the application of osteoprotegerin to endothelial progenitor cells cultured in the peripheral blood of patients with SLE significantly induced the apoptosis of these cells. It was determined that osteoprotegerin treatment increased SDC4 mRNA levels. It is thought that SDC4 may play a role in the development of premature atherosclerosis in patients with SLE by being expressed when oxidative stress increases (15). In a meta-analysis including a total of 80 studies (6085 SLE patients and 4794 controls) evaluating subclinical atherosclerosis in SLE patients, SLE patients had a higher CIMT and increased carotid artery disease compared with controls. plaque prevalence was determined. Additionally, this meta-analysis found that traditional cardiovascular risk factors (age, HDL, and triglyceride of SLE patients) steroids and triglyceride, and lupus-related risk factors (expressed by duration, erythrocyte sedimentation rate, SLEDAI, and steroids) had a significant impact on CIMT and carotid plaque prevalence. In our study, we found no significant correlation between CIMT and SLEDAI values (p=0.746).

A 4-year prospective follow-up study was conducted to evaluate the relationship between BMI and subclinical atherosclerosis in patients with SLE. In this study, CIMT, cumulative steroid doses, and BMI were assessed in 61 Korean female patients with SLE. The average CIMT value of the patients was found to be 0.39±0.09 mm (CIMT value in our study was 0.558±0.116). Additionally, these patients received fewer non-steroidal anti-inflammatory drugs and a higher 4-year cumulative dose of glucocorticoids. The results showed that lower BMI and 4-year cumulative glucocorticoid dose were associated with the progression of subclinical atherosclerosis (22). Although the cumulative steroid dose was not calculated in our study, BMIs were correlated with CIMT.

It has been shown in a longitudinal study that the use of immunosuppressant drugs is effective against plaque progression, regardless of the presence of traditional cardiovascular risk factors (23). Medical treatment methods for SLE have many effects on the prevention of subclinical atherosclerosis. Corticosteroids (CS) have anti-inflammatory properties that should theoretically reduce the risk of atherogenesis, but due to their side effects, such as hypertension, hyperglycemia, dyslipidemia, and obesity, it is possible that these drugs may create paradoxical situations that accelerate atherosclerosis. Hydroxychloroquine (HQ) is an anti-malarial drug that is frequently used for treating SLE. Anti-platelet effects may reduce thrombovascular events, whereas hypocholesterolemic effects may improve lipid profiles (24). Mycophenolate mofetil (MMF), an immunosuppressant, has also attracted attention due to its cardioprotective properties. A high PREDICTS score increases the likelihood of future atherosclerosis in SLE by 28-fold.

In a 12-week study in which Azathioprine, HQ, and MMF treatment were randomized, the PREDICTS atherosclerosis risk score, which is a predictor of cardiovascular events, was found to be significantly lower in the MMF-treated group than in the MMF-treated group (25). Therapeutic drugs used for treating SLE can affect the development of atherosclerosis both positively and negatively (26). In our study, a significant proportion of patients received HQ and CS treatment. Patients receiving MMF, which has been shown to significantly reduce the risk of atherosclerosis, were in the minority. In our study, SDC4 levels were significantly lower in the patient group than in the control group, which may be related to the immunosuppressive treatment the patients received.

Our study patients generally comprised a patient population that did not disrupt follow-up and treatment. Our control group consisted of randomly selected healthy volunteers. We identified patients with asymptomatic subclinical atherosclerosis in our control group despite strict compliance with the inclusion and exclusion criteria. Although patients were excluded from our study, we observed that CIMT was high in the control group with high SDC4 levels. Additionally, we did not detect a significant statistical relationship between the SDC4 levels examined in the control and CIMT groups. We conclude that SDC4 levels are not reliable indicators of subclinical atherosclerosis. Therefore, more studies are needed to clarify the relationship between SDC4 and subclinical atherosclerosis. There is an increased incidence of coronary artery disease and obesity, particularly in the Central Anatolian region where this study was conducted. In our study, the average BMI of the control group was that of the obese group. According to the results of a meta-analysis including 10 studies investigating BMI in adult individuals in our country, the average BMI was 28.2 kg/m^2 in women and 26.5 kg/m^2 in men (27). In our study, the BMI of the control group was below the general country average. In a study conducted on healthy Turkish adults, the CIMT was found to be 0.458±0.116 mm in men and 0.47±0.104 mm in women (28). In our study, the CIMT value of the control group was determined as 0.49±0.117 mm, which was similar to the average for the population. In the patient group, the CIMT was higher than the population average (0.558±0.116 mm).

In a study conducted abroad measuring the CIMT to indicate atherosclerosis in patients with SLE, the average CIMT of the patient group was 0.91 mm. In this study, the highest CIMT

values (1.02±0.27 mm) were observed in patients with lupus nephritis. This value is considerably higher than the CIMT average (0.558±0.116 mm) obtained in the patient group in our study.

SDC4 is a glycocalyx component, and its increased levels in serum reflect glycocalyx damage. Studies on SDC4 levels in coronary artery disease have led to the investigation of SDC4 levels in ischemic stroke. Serum SDC4 levels of 65 patients diagnosed with cryptogenic stroke and 36 healthy volunteers were examined. SDC4 levels were found to be 0.81 (0.78-0.87) (ng/mL) in the patient group and SDC4 levels were 0.79 (0.78-0.88) (ng/mL) in the control group. There was no statistical difference between the SDC4 levels of the patient and control groups (p=0.68). In addition, the CIMTs of the patient and control groups were similar, 0.8 (0.7-1.15) versus 0.8 (0.7-0.9) (p=0.42) (29). In our study, similar to this study, SDC4 serum levels were thought to have a meaningless effect on endothelial dysfunction *in vivo*. There is a need for large-scale population studies on this subject.

Anemia is common in patients with SLE. Autoimmune hemolytic anemia, iron deficiency anemia, CKD, and anemia due to drug myelotoxicity can also be observed in patients with SLE. The other causes of anemia are pure erythroid aplasia, pernicious anemia, myelofibrosis, sideroblastic anemia, hemophagocytic syndrome, aplastic anemia, and thrombotic microangiopathic anemia (30). In our study, hemoglobin values were found to be significantly lower in the patient group than in the control group.

In patients with SLE, on of cardiovascular disease, high-sensitivity CRP (hsCRP) and CRP levels may increase depending on disease activity. In a prospective cohort study evaluating CV mortality in patients with SLE, the serum parameter most associated with CV mortality was hsCRP (31). In our study, hsCRP was not studied. However, the CRP levels of our patient group were significantly higher than those of the control group.

Endocan is a protein whose plasma levels in vascular endothelial cells may reflect endothelial dysfunction. Endocan is a protein expressed in endothelial cells and is associated with subclinical atherosclerosis in patients with SLE (32). We referred to this study because it is similar to our study design and deals with a different endothelial protein. In this study, the CIMT was 0.70 (range: 0.45-1.20) mm in patients with SLE and 0.40 (0.25-0.60) mm in controls. The results were found to be similar to our averages.

Study Limitations

In our single-center study, although the number of cases and controls was sufficient, we experienced limitations in the randomization of participants based on sociodemographic characteristics. The patient group mainly consisted of female patients. Although unequal numbers of patients were included in the patient and control groups, the numbers of patients and control groups were equal due to the exclusion criteria of the study. This led to a statistically unexpected outcome. The patient group generally consisted of a population with an average age of very young who did not skip check-ups and received regular treatment. Contrary to our hypothesis, subclinical atherosclerosis did not progress as quickly as expected in the young group. We believe that the most important reason for this is that patients have easy access to effective treatment. Our patients had access to regular treatment. Our patient population generally consisted of a group that did not interrupt follow-up and visited the outpatient clinic regularly for checkups. In the control group, patients with a high risk of subclinical atherosclerosis were identified despite meeting the exclusion criteria. We think that this is related to the carbohydrate-rich diet in the region where the study was conducted. We believe that large-scale multicenter studies are needed to evaluate SDC4 levels in identifying subclinical atherosclerosis in patients with SLE. We believe that our study will shed light on this issue.

CONCLUSION

We did not find a relationship between SDC4 levels and the progression of subclinical atherosclerosis in patients with SLEs. We believe that SDC4 levels may be related to SLEDAI disease activity in patients with SLE, and further research is needed on this subject. We did not detect any significant correlation between SDC4 levels and CIMT, which reflects subclinical atherosclerosis, in the control group. Although we found that SDC4 levels were positively correlated with CIMT levels in patients with SLE, no significant difference was detected in the control group. We found that the SLEDAI was positively correlated with CIMTs. We believe that this is due to SLE accelerating atherosclerosis processes.

Ethics

Ethics Committee Approval: Approval for our study was received from Necmettin Erbakan University Meram Faculty of Medicine Pharmaceutical and Non-medical Device Research Ethics Committee (approval number: 2020/2928, date: 04/12/2020).

Informed Consent: Informed consent was obtained from each participant after providing comprehensive information disclosure.

Authorship Contributions

Concept: A.Y., C.K., A.K., Data Collection or Processing: A.Y., C.K., Analysis or Interpretation: A.Y., C.K., A.Ç., Literature Search: A.Y., A.Ç., Writing: A.Y., A.Ç., A.K.

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CASE REPORT AND LITERATURE REVIEW

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TRANSVERSE MYELITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS; CASE REPORT

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect any organ, including the nervous system. Estimates of the incidence and prevalence of neurologic and psychiatric symptoms in SLE patients vary widely, largely due to heterogeneity in definition and methodology. In total, studies report that approximately one-third to one-half of SLE patients have neurologic or neuropsychiatric symptomatology. For many of the phenotypic manifestations of neuropsychiatric SLE, no biomarker or diagnostic test is specific enough to link the neurological diagnosis to SLE. Myelitis in SLE is a rare but morbid condition that occurs in approximately 1 to 2 percent of SLE patients in some cohorts. In this case report, we aimed to present the diagnosis and treatment of transverse myelitis in a patient who presented with acute flaccid paralysis in the lower extremity.

Keywords: Systemic lupus erythematosus, neuropsychiatric involvement, myelitis

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease of unknown etiology that is common in women of childbearing age and can affect almost every organ of the body. Acute transverse myelitis (TM) is a rare but serious acquired neuro-immune spinal cord disorder that may present with sudden loss of muscle strength, sensory changes and bowel or bladder dysfunction. It is observed in 1-2% of SLE patients (1-5). Currently, only a very limited number of cases of TM-associated SLE have been reported. A 2010 epidemiologic study showed that the incidence of TM at 3.6 per 100.000 (6). The pathogenesis is largely unknown and the clinical presentation is variable. There are still no established guidelines for diagnosis, management or monitoring and the role of autoantibodies is controversial. Lesions often involve the thoracic medulla and the primary clinical manifestations include paralysis of the limbs below the lesion site, conduction bundle sensory disturbance and dysphoria, and voiding dysfunction (7) In this case report, we aimed to present the diagnosis and treatment of TM in a patient who presented with acute flaccid paralysis in the lower extremity.

CASE REPORT

A 27-year-old woman with SLE since the age of 20 years, married, with one child, presented to the emergency department with the complaint of loss of strength in the legs. Two days ago, antibiotics were started by the dentist due to toothache and the patient discontinued the medication. Sudden loss of strength in the lower extremities develops after a stress. On examination, finger flexion muscle was 3/5 in both hands. Upper extremity

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deep tondon reflexes were normal and no pathological reflex was found. Deep tendon reflexes of the patient with flaccid paralysis in the lower extremity could not be obtained, but no pathological reflex was detected. The patient was taken over by neurology. No abnormality was detected on brain imaging and increased intensity at the C5-T2 level on spinal magnetic resonance imaging (MRI) was interpreted in favour of myelopathy (Figure 1). No abnormality was found in cerebrospinal fluid (CSF) analysis. Laboratory tests revealed white blood count: 7.6/mm^3 (NE# 11.5/mm^3), hemoglobin 11.4 g/dL, normal platelet count, erythrocyte sedimentation rate 40 mm/hour, C-reactive protein level of 53 mg/dL, anti nuclear antibody homogenous 3+ and anti-ribosomal P and anti-histone antibody positivity in the extractable nuclear antigen profile. Anti-neutrophil cytoplasmic anti-body immune florescence, antiPR3, anti-myeloperoxidase Enzyme-Linked Immunosorbent Assay test were negative, anti-dsDNA was positive and C3-C4 was low. In addition, neuromyelitis optica IgG was negative. Liver and renal function tests were within normal limits. The patient was treated with 1 g/day methylprednisolone (MP) and 120 g intravenous immunoglobulin (IVIG) followed by 1000 mg cyclophosphamide (CTX). Plasma Exchange (PLEX) was performed in the patient in whom no significant clinical change was observed. The patient is in the 3rd month of treatment and started to walk with person-assisted walking with rehabilitation.

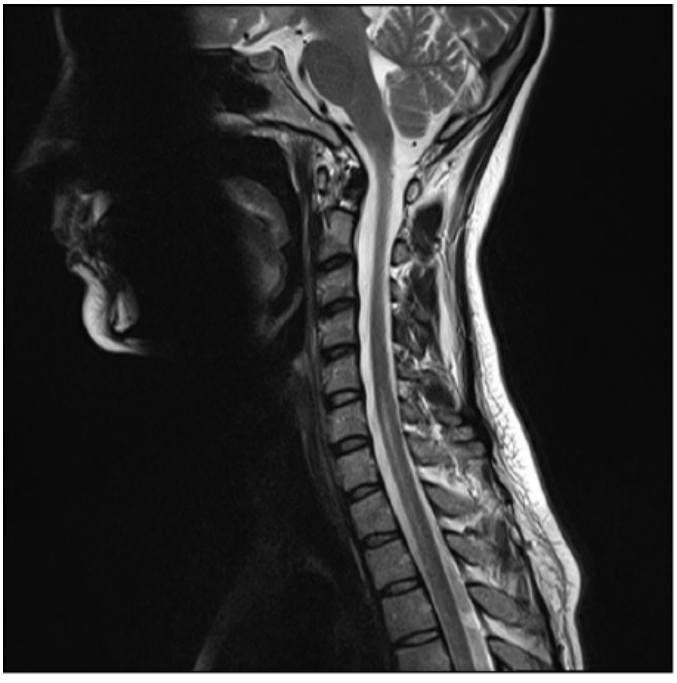

Figure 1. Spinal MR T2 sequence hyperintensity; myelitis

CONCLUSION

TM is one of the neuropsychiatric involvements associated with SLE (NPSLE). Patients present with acute to subacute paraparesis or quadriparesis, usually bilateral but not always symmetrical; sensory impairment, which may be localised at the level of spinal sensation; and/or impaired bowel or bladder function. In SLE-associated myelitis, MRI often shows T2 hyperintensity in the affected area of the spinal cord. CSF examination may show a pleocytosis, usually lymphocytic. The outcome of CSF in SLE patients with TM is currently controversial because some studies have shown that CSF is normal in SLE patients with TM. Treatment is started with pulse glucocorticoids. CTX and Rituximab (RTX) are first-line agents in TM. Plasmapheresis can be applied simultaneously. CTX treatment is usually continued for three to six months and then switched to a less toxic agent for maintenance therapy such as mycophenolate, azathioprine or rituximab to control SLE disease activity and reduce the risk of relapse (8-10). Early aggressive treatment, especially for initially severe myelitis, may be crucial to achieve a favorable outcome. Recently, MP pulse therapy in combination with CTX has been recommended for NPSLE. RTX, a promising modality, has also been reported to be effective in the treatment of new-onset SLE-associated TM (11) and the positive benefits of PLEX and IVIG in patients with refractory NPSLE have also been recognized (12). In recent clinical trials, anti-interleukin 6 agents (tocilizumab and satralizumab) have also shown efficacy in preventing TM attacks (13). Only 40-50% of NPSLE occurs in the presence of active disease in other organ systems of SLE (14). SLE-associated TM can also develop without active disease in other organ systems (15). Therefore, disease activity factors may not predict a worse prognosis. A literature review has shown that recurrence of myelitis will occur several months after the first event, and recurrence occurs at least once in 21-55% of patients (16). Due to its poor prognosis, SLE-TM brings emotional stress and economic burden to the patient's family and society. In the future, there is a need for controlled clinical treatment studies, which can especially inspire the management of this disease.

Ethics

Informed Consent: Informed patient consent form was prepared.

Authorship Contributions

Concept: S.P., A.K., Design: S.P., A.K., Data Collection or Processing: S.P., A.K., Analysis or Interpretation: S.P., A.K., Literature Search: S.P., A.K., Writing: S.P., A.K.

Conflict of Interest: One author of this article, Adem Küçük, is a member of the editorial board of the Rheumatology Quarterly. However, he did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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TAKAYASU ARTERITIS PRESENTING WITH PULMONARY NECROSIS: A CASE REPORT

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Abstract

Takayasu arteritis (TA) is a large vessel vasculitis seen especially in young women who may present with findings such as fever, fatigue, and weight loss. In this disease, lung consolidation or infarction secondary to lung involvement may occur. TA can mimic the other parenchyma-like diseases that we see more frequently in our daily practice because constitutional findings are at the forefront and due to consolidation as a result of lung infarction. Complications associated with chronic processes may result in increased morbidity and mortality in this disease, which often presents with delays in diagnosis. For this reason, TA should be kept in mind in the differential diagnosis of diseases leading to consolidation in the lung.

Keywords: Takayasu arteritis, necrosis, pulmonary, treatment

INTRODUCTION

Vasculitides are a heterogeneous group of diseases that cause tissue damage and organ failure as a result of inflammation in various vessels. Although the pathophysiological backgrounds are different, the symptoms may show similarities or differences concerning the affected site and the affected vessel diameter. The lung is one of these organ systems, and these rare diseases may primarily involve the pulmonary parenchyma as infiltrations, nodules, or cavitary lesions. Lung involvement is more common in small vessel vasculitis, and we see more rare involvement in large vessel vasculitis.

Takayasu arteritis (TA) is a major vasculitis usually found in young women. Contrary to general symptomatology, these patients may rarely present with pulmonary parenchymal findings. We want to emphasize that TA should be kept in mind in a case who presents with lung necrosis as in this case.

CASE REPORT

A 39-year-old female patient presented with a 5-month history of chest pain and backache, exertional dyspnea, fatigue, marked pain, and loss of strength in the left arm. There were no autoimmune rheumatic diseases in her medical and family history. On admission, her temperature was 38.3 °C, her pulse was regular at 110 beats/min, and her respiratory rate was 16 breaths/min. Coarse rales were heard in her right middle lung zone on auscultation. There was no murmur or gallops on cardiac examination. The patient was cachectic and had reduced skin turgor, murmur was heard on abdominal auscultation. The arterial blood pressure was 120/80 mmHg in the right arm and 100/70 mmHg in the left arm. There was considerable increased acute phase response in laboratory tests; [erythrocyte sedimentation rate (ESR)]: 108 mm/hr (normal range: 0-15 mm/hr); [C-reactive protein (CRP)] 98 mg/L (normal range: 0-3 mg/

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dL); (creatinine): 1,4 mg/dL; urea: 40 mg/dL; hemoglobin: 10,9 mg/dL.

Chest radiography showed consolidation in the right peripheral upper/middle lung zones (Figure 1A). The consolidated field was evaluated as atypical pneumonic infiltration and metronidazole, piperacillin, and tazobactam treatment was given for 14 days. Despite the persistence of antibiotic therapy, the patient was investigated for malignancy and tuberculosis (TB); purified protein derivative and acid-resistant bacilli culture were negative in bronchoalveolar lavage and TB was not considered. Thorax tomography showed 53x29x36 mm diameter consolidation in the right upper lobe and occlusion in the right pulmonary artery (Figure 1B, 1C). Transbronchial lung biopsy showed fibrous alveoli, and inflammatory cells, and wright staining showed 15-20 leukocytes in each area. Atypical cells were not observed therefore malignancy was excluded.

The computed tomography (CT) angiography also showed an increase in the thickness of the wall of the descending aorta increase in thickness in the abdominal wall 2/3 of the proximal segment and thickening of the celiac axis proximal wall and distal aneurysmatic expansion. Wall thickening in the branch leading to the lower lobe in the distal segment of the right pulmonary artery and narrowing in the lumen The branch leading to the upper lobe could not be visualized (in favor of occlusion). TA was considered at the forefront due to the high ESR, CRP, weight loss, and fatigue.

The patient's vascular damage index score was 5, the ITAS 2010 score was 11, and the ITAS-A score was 14. Prednisolone (40 mg/d) methotrexate 15 mg/week, and acetylsalicylic acid 100 mg/d were started. After 3 weeks, laboratory values were measured as ESR: 11 mm/hr CRP: 7 mg/L, and creatinine 0.9 mg/dL. Written consent esas obtained from the patient.

DISCUSSION

TA is classified as large vessel vasculitis and affects the aorta and its branches as a primary (1). Disease that first manifests itself with constitutional symptoms, and then includes symptoms associated with vascular involvement. Women are affected in 80 to 90 percent of cases, with an age of onset that is usually between 10 and 40 years. The abdominal aorta and pulmonary arteries are involved in approximately 50% of patients. The inflammatory process within the vessel can lead to narrowing, occlusion, or dilation of involved portions of the arteries, which causes a wide variety of symptoms. Symptoms related to pulmonary arteritis are less common. Pulmonary manifestations include chest pain, dyspnea, hemoptysis, and pulmonary hypertension (2-4). Pulmonary arteritis occlusion is sometimes accompanied by severe symptoms, with some patients' initial symptoms mimicking those of pulmonary thromboembolism (mainly chest pain, shortness of breath, and hemoptysis).

We detected pulmonary artery involvement due to TA in our patient. TA was diagnosed based on clinical, laboratory, and CT

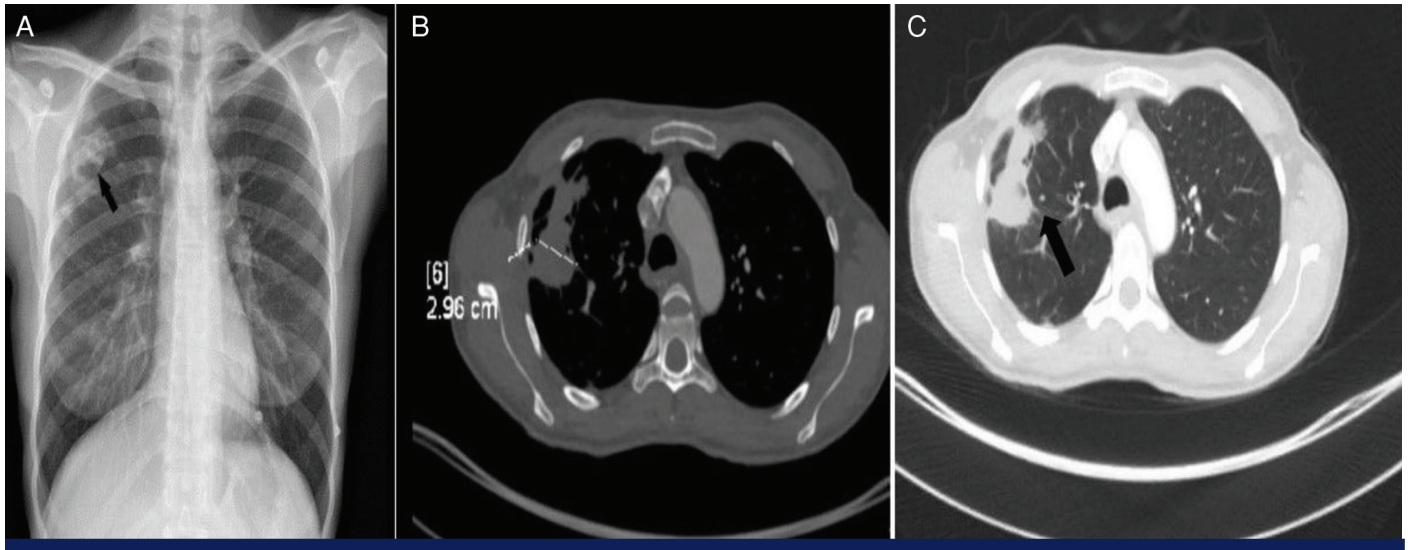

Figure 1. Chest radiograph and CT images. A) Chest radiograph showing consolidation in the right middle/upper lung zones (black arrows). B) Soft nodule with right lung upper lobe apex and cavitation within the size of 53x29x36 mm reaching the anterior and horizontal fissure. C) Interlobular septal thickness increases near the lesion ground-glass density increasing traction bronchiectasis and fibroatelectasis (black arrows)
CT: Computed tomography

findings. There are cases where pulmonary artery involvement may occur before the involvement of the aorta and its branches, and diagnostic delays may occur (5). In our case, we detected the onset of the diagnosis symptoms of aorta and pulmonary artery involvement. Sometimes the diagnosis may be overlooked due to acute pulmonary pneumoniae infiltration. The patient can be given antibiotic treatment and can be observed. TA should be kept in mind and evaluated by tomography. In the case reports, which were previously known, our case was similar to the right pulmonary artery involvement. No sources show that the right or left pulmonary artery is more involved in the literature.

CONCLUSION

Pulmonary infarction may be associated with cases of pulmonary embolism, antiphospholipid syndrome, IGG4-related disease, TB, and pulmonary infiltrative diseases. In these diseases, lesions in different segments of the lungs might be observed. However, it may not always be possible to distinguish this with exact localizations as in the literature. In our case, we have ruled out TB which is one of the other common reasons for involvement in the upper lobe of the right lung. Importantly, after excluding common infective causes such as TB in treatment-resistant diseases, TA should also come to the fore in our minds, especially in women who present with findings such as weight loss and decreased pulse.

Ethics

Informed Consent: Written consent esas obtained from the patient.

Authorship Contributions

Concept: H.K., Design: H.Kü., M.A.Ö., Data Collection or Processing: H.K., H.Kü., M.A.Ö., Analysis or Interpretation: H.K., Literature Search: H.K., H.Kü., M.A.Ö., Writing: H.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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CASE REPORT AND LITERATURE REVIEW

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ANKYLOSING SPONDYLITIS COEXISTING WITH TAKAYASU'S ARTERITIS IN A FEMALE PATIENT: A RARE ENTITY

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects the sacroiliac joints, spine, and enthesis. Typical symptoms include stiffness and gradual functional restriction of the axial skeleton. Takayasu's arteritis (TA) is a condition characterized by chronic inflammation of blood vessels, usually affecting major vessels like the aorta and its branches. It leads to constriction, obstruction, and the development of aneurysms in the systemic and pulmonary arteries. Both AS and TA are rare inflammatory conditions, and their occurrence together in one person is even rarer. Autoimmune mechanisms are likely to have a substantial impact on the onset of TA, similar to AS. Hence, therapy involving steroids and biological medications like infliximab and tocilizumab is expected to be advantageous. In this case report, we present a 24-year-old female diagnosed with TA and AS.

Keywords: Ankylosing spondylitis, Takayasu's arteritis, female, anti-TNF

INTRODUCTION

Ankylosing spondylitis (AS) is a persistent inflammatory condition that primarily affects the sacroiliac joints, spine, and enthesis. Stiffness and gradual functional restriction of the axial skeleton are typical symptoms of this condition, which may also be associated with sleep disturbances. Under the age of 40 years, males are the most likely to be affected by the disease (1-3). AS has a strong genetic component closely linked to the human leukocyte antigen B27 (4). Takayasu's arteritis (TA) is an uncommon chronic inflammation of blood vessels that typically impacts large vessels such as the aorta and its branches. It results in narrowing, blockage, and the formation of aneurysms in the systemic and pulmonary arteries (5). Clinical symptoms consist of pain resulting from inflammation in the arterial wall and, in a later phase, ischemic symptoms due to the narrowing of the arteries. Computed tomography (CT), magnetic resonance (MR), and ultrasound (US) imaging can reveal arterial thickening and stenosis. Classical angiography reveals narrowing or complete blockage of the affected arteries (6). Here we present the case of a 24-year-old female patient diagnosed with AS and TA.

CASE REPORT

Upon initial presentation, the patient reported experiencing pain in the waist, hips, knees, and heels and morning stiffness lasting for 1 hour. Pain was alleviated by movement. The pain was waking her up from sleep. She had oral canker sores more than three times a year. On physical examination, a murmur was detected over the left carotid artery, and pain upon palpation was detected in the knees, ankles, heel, and sacroiliac region. During the patient's most recent hospitalization, her joint pain persisted. The patient with AS was treated with adalimumab for 5 years.

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She discontinued the treatment 3 months 5 months ago and then resumed it. She was diagnosed with cardiac arrhythmia and hypertension. The patient was prescribed amlodipine, calcium dobesilate monohydrate, and doxazosin and was admitted to us for treatment planning. Brain MR imaging angiography revealed that the distal segment of the left vertebral artery was narrower than that of the right, and the right vertebral artery showed slight tortuosity. Both the distal segment of the vertebral arteries and the basilar artery were open. Carotid color Doppler US imaging detected stenosis in the carotid artery. The patient was suspected to have active vasculitis. The carotid walls were found to have stenosis and irregularities. Inflammation of the wall of the superior mesenteric artery was detected. A stenosis of approximately 60% was found in the common carotid artery. Carotid color Doppler US showed that the wall thickening was caused by vasculitis, leading to the development of jet flow due to stenosis, resulting in an audible murmur. Because of CT angiography interpretation, the diameter of the ascending aorta was 35 mm and was found to be at the upper limit of normal for age. The diameter of the aortic arch is 22 mm, and that of the descending aorta is 19 mm. It is in normal filling calibration. In the proximal localization of both renal arteries, secondary to vasculitis, there were vascular wall irregularities in a segment of 1.5 cm on the right and 2 cm on the left, 95% stenosis in the right renal artery, and 80% stenosis in the left renal artery. Inflammatory changes secondary to vasculitis. In the superior mesenteric artery, vascular wall irregularities and inflammatory changes cause 50% stenosis the entire trace. Distally, the superior mesenteric artery and its branches were recanalized with collaterals and were in normal filling calibration. The subclavian arteries, celiac artery, inferior mesenteric artery and its branches, iliac arteries, and proximal parts of the femoral arteries are in normal filling calibration (Figure 1).

The patient with a preliminary diagnosis of TA was scheduled to receive anti-tumor necrosis factor. The patient, who was recently diagnosed with TA, experienced an episode while receiving adalimumab. As a result, adalimumab was withdrawn and replaced with infliximab. In addition, we prescribed methotrexate, folic acid injection, and 16 mg of prednisolone.

DISCUSSION

Both AS and TA are uncommon inflammatory conditions, and their coexistence in one individual is even more infrequent. Research has shown that the presence of TA and AS may be coincidental or simultaneous because of certain underlying factors (1,2). AS typically affects the spine, hip, and enthesis, leading to a limited range of motion. TA is an inflammatory disease primarily affecting the aorta and its branches, leading to limb claudication pain (1,2,7). CT, MR, and US imaging can detect indications of inflammation, such as arterial thickness and stenosis. Classical angiography visualizes the narrowing or complete blockage of the arteries in question (8). A study by Rivière et al. (7) examined 14 patients with both TA and spondyloarthritis (SpA), including AS. Of these patients, 11 individuals with AS were of Caucasian ethnicity, and 10 of them were women. In addition, SpA occurred before TA in 13 individuals, with an average age at onset of 43.5 years, which was higher than the typical age of TA onset. These findings validate that AS is very prevalent in patients who have both SpA and TA simultaneously, and unlike the overall population with AS, the occurrence of TA is elevated. Thus, it is quite probable that the occurrence of these conditions in patients is not accidental but rather a result of an underlying component (7,9).

All of the individuals described in the literature are thought to have large vessel vasculitis characterized by aortic and collateral lesions. Our patient had bilateral sacroiliitis findings that were radiologically indistinguishable from AS. According to the case series documented by Mielnik et al. (2), if we exclude patients with unknown imaging results, peripheral arthritis was observed in 50% of the patients (2,8).

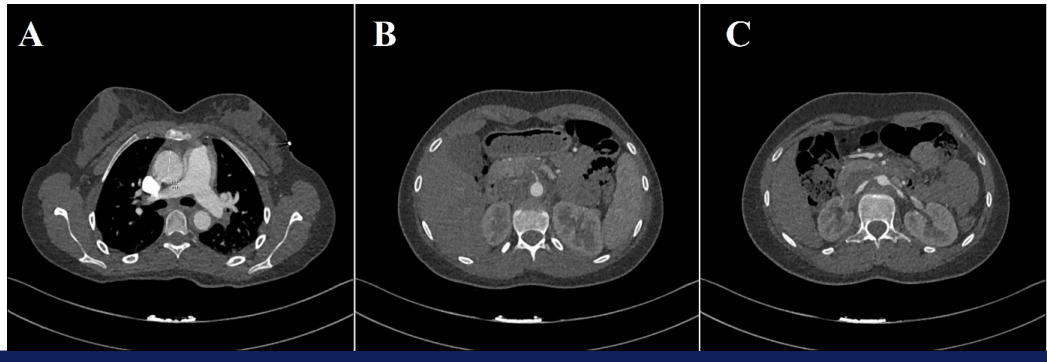

Figure 1. CT angiography images. A) Ascending aorta, B) superior mesenteric artery, C) right and left renal arteries
CT: Computed tomography

TA, like AS, is probably influenced by autoimmune processes. As a result, treatment with steroids and biological agents like tocilizumab is expected to be beneficial (10). Patients who develop TA during AS experience a sudden rise in C-reactive protein (CRP) levels, as observed in this case (1). We measured the peak CRP value in this study at 62.54 and reduced it to 8.03 over a period of 2 weeks.

CONCLUSION

Both diseases share characteristic findings, such as cytokine abnormalities. Although uncommon, AS typically occurs before TA in patients with both diseases, and TA usually develops at an older age.

Our patient was diagnosed with AS 6 years ago, and we diagnosed TA with our recent examinations. While it is possible that treatment for AS may prevent the development of TA, the simultaneous presence of both conditions is intriguing, necessitating further investigation into their relationship.

Ethics

Informed Consent: Written and verbal consent was obtained from the patient.

Authorship Contributions

Concept: M.A.D, B.T., Design: M.A.D, Data Collection or Processing: M.A.D, B.T., Analysis or Interpretation: M.A.D, B.T., Literature Search: M.A.D, Writing: M.A.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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