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EDITORIAL

ORIGINAL ARTICLES

REVIEW ARTICLES

CASE REPORT

CONFERENCE REPORT

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"A horse, a horse, my kingdom for a horse"! Why do we still not know everything about systemic sclerosis?

This post-holiday issue of the "Rheumatology Forum" focuses on one of the rather rare disease in rheumatology — systemic sclerosis (SSc). This is probably because this year we celebrated the tenth anniversary of the World Scleroderma Foundation (WSF) and the twentieth anniversary of the European Scleroderma Trials and Research group (EUSTAR) and the main anniversary gala was held on 30 May 2023 in the halls of the Leonardo da Vinci National Museum of Science and Technology in Milan. There were plenty of Polish accents during the ceremony as, Polish physicians and Polish rheumatology centres actively participate in EUSTAR's work [1].

In line with this, in this issue we may also find two more scleroderma highlights. Bultrowicz et al. [2] reviewed the current strategies in the treatment of systemic sclerosis. Contrary to the common belief, the treatment of SSc is far more complicated than we used to think, therefore we await the second part of this paper that will appear in the last issue of this year. But the treatment is not the main area of interest in the field of scleroderma and more generally in the field of connective tissue disorders. For several years our philosophy in disease management was to provide a high level of quality of life and to maintain a satisfactory level of physical performance. Palka et al. [3] addressed this issue in their paper entitled "Vital activity of patients with systemic sclerosis". In this study, it was found that in despite the severity of the disease 37.7% of the respondents are employed, including more than a quarter of responders working full-time. These data are consistent with the findings of studies from other European countries which indicated a similar frequency of full professional activity among SSc patients. This clearly shows that despite their disability, patients strive for independence and self-sufficiency by taking up employment. Our role as physicians is to help them to fight for full independence.

It was not editors' intention but this issue is dominated by psychosocial aspects of the rheumatic patient's life. Findings form scleroderma patients' lives were substantiated by two more papers addressing psychosocial aspects in rheumatology. In detail "Comparison of the prevalence of fibromyalgia in pre-clinical and clinical years among medical students of the Collegium Medicum of the University of Warmia and Mazury in Olsztyn" has been made by Knapik et al. [4]. Results from the study raise some important questions as to whether the training of medical students is organized optimally and whether medical study may be an area where certain changes should be made to make the first yards in the medical career pathway less stressful. This potentially may bring many serious consequences as low quality of life and experienced traumatic situations may influence the next steps in medical career and personal development among medical students. As a supplement to the psychological aspects of the medical study may serve a paper by Jeka et al. [5] who focused on the

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psychodemographic characteristics of patients with rheumatic diseases in clinical trials. The authors were able to fully characterize subjects enrolled on clinical trials. Keeping in mind many discrepancies between Poland and other European countries, patients enrolled on clinical trials suffer from a disease for many years and have many comorbidities significantly reducing their quality of life, are professionally active and seek new therapies by participating in clinical trials. It is still an open question whether the level of education may at least potentially influence the decision on participation in clinical trials The truth is that most patients are graduates from colleges or have a formal academic education.

Even though rheumatology is a mysterious area where many not fully understood immunological mechanisms play a role, modern rheumatology is still an area where a proper understanding of metabolic processes and metabolic pathways helps to understand the plethora of signs and symptoms in rheumatic diseases. That is absolutely true when pyrophosphate arthropathy and bone mineral density (BMD) are taken into consideration. Both clinical problems are elegantly addressed in this issue by Suszek et al. [6] and Jeka [7] respectively. In the first paper entitled "Pyrophosphate arthropathy — a literature review", the Authors characterized pyrophosphate arthropathy as still a chronic, but self-limiting disease characterized by the presence of the symptoms of acute inflammation usually lasting for a few days or weeks after the start of treatment. The prognosis depends on the number of affected joints and the frequency and exacerbations and varies significantly between the patients. Calcium pyrophosphate crystals when deposited on the surface of the joints can cause structural damage thus directly leading to disability development. Moreover, several episodes of CPPD promote the formation of palpable nodules that resemble gout nodules, making differential diagnosis a bit difficult. Paper by Daniel Jeka entitled "The importance of bone mineral density and structure in fracture risk assessment of patients with rheumatoid arthritis and ankylosing spondylitis — perspectives" Fracture risk assessment in AS" [7] focuses on diagnostics challenges in osteoporosis among patients with ankylosing spondylitis (AS). Indeed, in the general population, BMD assessment, the gold standard for diagnosis of osteoporosis, does not work too well in inflammatory arthropathies in general and in AS in particular. New bone formation may increase BMD value thus leading to falsely negative results. Moreover, inflammation commonly observed in patients with AS or rheumatoid arthritis may have a strong influence on bone metabolism that translates directly to impaired bone structure. That is why the Authors proposed the trabecular bone score as a practical tool to assess the real structure of bone in AS patients.

The "Rheumatology Forum" was designed as a platform to exchange ideas and knowledge as well as to share personal experiences. Ciba-Stemplewska et al. [8] presented at series of case reports of patients with giant cell arteritis, the most common form of vasculitis in patients aged over 50. The Authors discussed in detail the typical characteristics of patients. However, the unmet need in GCA is a delay in diagnosis and treatment. Therefore, we should be aware of this disease, and diagnose it properly which give a chance to halt the progression of the disease and prevent serious complication including blindness of affected patients. Talking about ocular complications we moved finally to the last paper by Bachta et al. [9] — "Uveitis in rheumatic diseases — therapeutic management". The paper is the result of the high interest that ocular presentation of rheumatic diseases attracts among rheumatologists. It provides a "road map" on how to diagnose uveitis clearly indicating that only some ocular presentations may be liked with rheumatic diseases. Unfortunately, most of them may be recognized as idiopathic and should be treated by well-experienced ophthalmologists.

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ORIGINAL ARTICLE

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Everything you always wanted to know about systemic sclerosis but were afraid to ask: Part 3. Vital activity of patients with systemic sclerosis

ABSTRACT

Systemic sclerosis is an inflammatory connective tissue disease of autoimmune origin, characterized by progressive fibrosis of the skin, internal organs and damage to blood vessels referred to as vasculopathy. Although the most visible symptom of the disease is hardening of the skin, the involvement of internal organs leading to their extreme insufficiency determines the severity of the disease, resulting in a severe course for the patient.

The method used to carry out this test is the diagnostic survey method. The paper used a questionnaire that contained 22 questions, including 7 open-ended questions and 2 multiple choice questions.

The aim of the work is to show how systemic sclerosis affects the patient's vital activity, with particular emphasis on those activities of everyday life that cause the greatest difficulty. In addition, an attempt was made to determine how the progression of the disease affects the physical and mental sphere of patients with systemic sclerosis.

Studies show that systemic sclerosis is a disease that affects the life activity of patients to varying degrees. It penetrates both the physical sphere of the patient, gradually limiting his independence, but also into his mental sphere.

Rheumatol. Forum 2023, vol. 9, No. 3: 96–104

KEY WORDS: systemic sclerosis; vital activity; inflammatory connective tissue disease

INTRODUCTION

Systemic sclerosis (SSc) is an inflammatory connective tissue disease of autoimmune origin marked by progressive fibrosis of the skin, internal organs and damage to blood vessels termed as vasculopathy. Although the most visible symptom of the disease is sclerosis of the skin, the involvement of internal organs leading to their extreme failure determines the severity of the disease, resulting in a severe course for the patient.

The first detailed description of SSc dates back to the 18th century. Dr Carlo Curzio of Naples published a monograph in 1753, where he gave a description of a seventeen-year-old patient, Patrizia Galiera. He described the patient's skin as dry, hard in the likeness of wood. In his monograph, he wrote "A patient with diffuse skin tightening and hardening of the skin all over the body and thickened eyelids…, cold skin, difficulty opening the mouth…".

The disease most commonly affects people aged between 30 and 50. This means that people become ill in the most active period of their lives. As it progresses, SSc affects the simplest activities of daily living. Patients often have to reduce their responsibilities or give up their jobs. Reduced independence is often associated with reduced contact with friends and family. Patients usually stay in a home or hospital environ-

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ment. All this has an impact not only on the physical well-being but also on the patient's depressed mood [1, 2].

The disease process can develop slowly and gradually or, in the case of an aggressive form of disease, manifest suddenly. The problems that patients will face are not only those from the physical sphere but also from the mental sphere. The period of the illness coincides with an age when the patients are economically active but also take an active part in family and social life, all of which means that the illness often limits their activities, bringing with it a depressed mood. This results in SSc patients becoming dependent on third parties at an age when their healthy peers are independent. Therefore, nursing care should focus on the patient's physical and psychological needs [1, 2].

The main problem is a limitation and, in advanced stages of the disease, a deficit in self-care. Activities of daily living (ADLs), such as toileting, putting on clothes and preparing meals, can be very difficult for patients whose limb mobility is restricted. Therefore, patients often have to use third-party assistance.

AIM OF THE STUDY

This study aims to show how systemic sclerosis affects the patient's ADLs, with a focus on those ADLs that cause the greatest difficulty. Moreover, an attempt was made to determine how the progression of the disease affects the physical and psychological spheres of SSc patients.

MATERIAL AND METHODS

METHOD, TECHNIQUE AND ORGANISATION OF THE STUDY

The method used for conducting this study is the diagnostic survey method. The study used a questionnaire that contained 22 questions, including seven open-ended questions and two multiple-choice questions. The questions in the questionnaire focused on the patient's assessment of their ADLs and the changes that had taken place in their lives after being diagnosed with SSc.

The surveys were collected *via* an online questionnaire. Participation in the survey was voluntary and anonymous. The questionnaire was completed by 77 people. The respondents are those who struggle with diffuse SSc (dSSc) or limited SSc (lSSc).

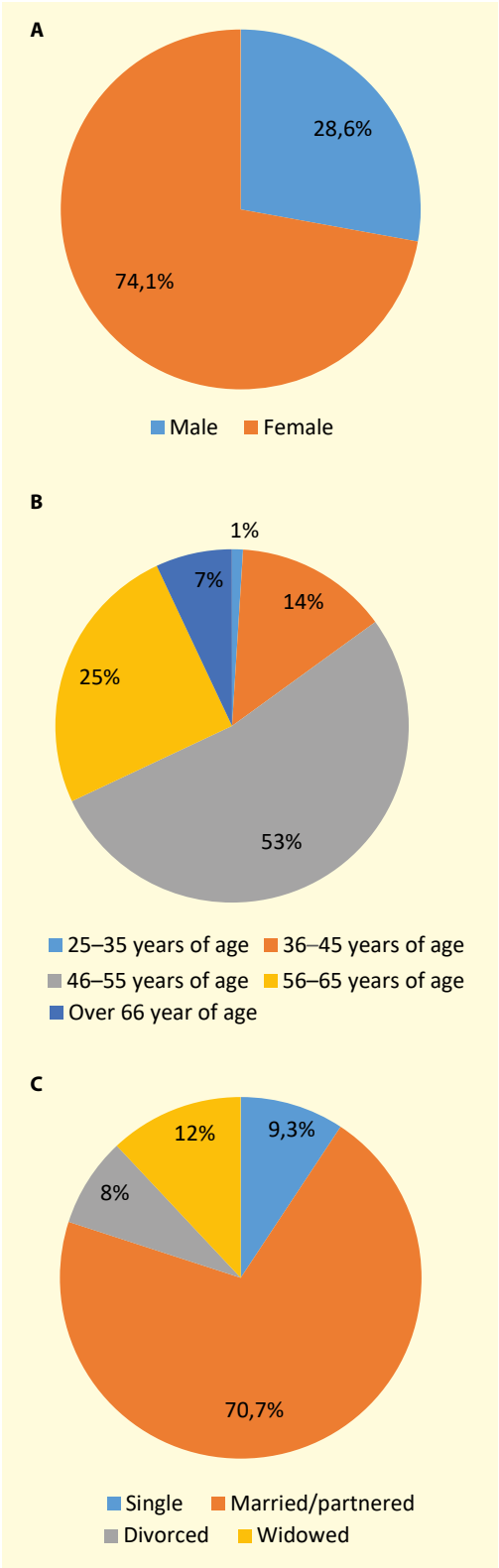

Figure 1. Demographics of patients with systemic sclerosis: **A.** Sex of respondents; **B.** Age of respondents; **C.** Marital status of respondents

The study group consisted of patients diagnosed with SSc based on European Alliance of Associations for Rheumatology (EULAR)/ /American College of Rheumatology (ACR)

classification criteria, including 56 women and 21 men aged between 25 and 68 years (Fig. 1A). In this group, 42 patients with dSSc were identified based on the Le Roy and Medsger criteria, while the remaining 35 were diagnosed with lSSc (Fig. 3A). Among this study group, as many as 46.8% of people were diagnosed with the disease between the ages of 36 and 45 years, while only 1.3%, or one person, was diagnosed between the ages of 18 and 25 years (Fig. 1).

CHARACTERISTICS OF THE STUDY GROUP

The largest group was those between 46 and 55 years of age — 53%. The majority of respondents were women — 71.4%. A significant proportion of respondents were married or in a civil partnership — 70.7%.

Respondents also provided answers regarding the fact of having children. The majority of respondents, 84.2%, confirm that they have children; the largest number of them have two children — 35.1% of respondents.

Respondents also identified their education, with the largest number of respondents having a secondary education, i.e., 45.5% (Fig. 2A). More than half of the patients surveyed are economically active with 26% working full-time and 24.7% undertaking part-time activity.

The impact of the illness on the difficulty of becoming gainfully employed resulted in 35.1% of respondents receiving disability benefits (Fig. 2B).

RESULTS

Systemic sclerosis was diagnosed most frequently between the ages of 36 and 45, with 46.8% of respondents giving this answer, followed by people diagnosed with SSc between the ages of 46 and 55, i.e,. 35,1%. Only one person surveyed was diagnosed earlier, between the ages of 18 and 25.

The results show that SSc is a chronic disease with 32.9% of respondents having been diagnosed with the disease for more than 6 years. The next largest group was found to be patients whose disease diagnosis had been known for three to 4 years — 27.6%.

Diagnostic difficulties in SSc patients are the reason for the significant delay between the onset of the first symptoms and when a formal diagnosis is made. In the study group, 19.7% were people who had known the diagnosis for 5 to 6 years. An identically sized group of patients, 19.7% , were diagnosed between 1 and 2 years after the onset of symptoms. It should be emphasised that the first symptoms and health problems that have been associated with SSc probably occurred much earlier in patients, while the time from actual diagnosis is relatively short. None of respondents had a confirmed diagnosis for less than a year (Tab. 1).

Systemic sclerosis, due to its significant musculoskeletal involvement, directly affects the patient's independence.

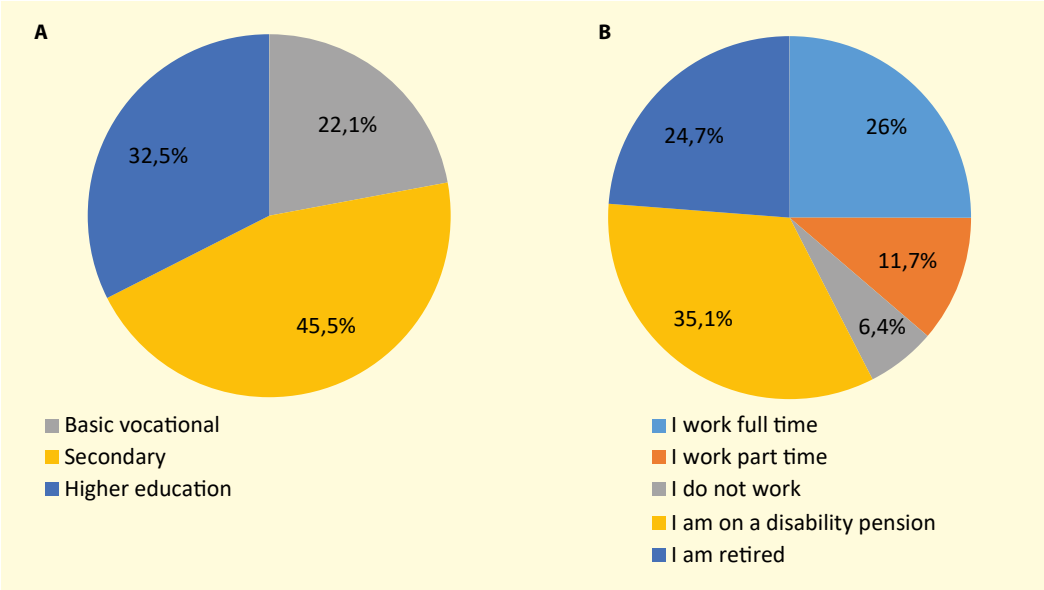

Figure 2. Education level and occupational status of respondents: **A.** Education level of respondents; **B.** Occupational status of respondents

In this study 55.8% of respondents declared completely independent mobility, while 42.9% of patients specified mobility with the help of orthopaedic equipment to facilitate movement, including 12 respondents using an orthopaedic cane or elbow crutches, and 6.5% of respondents using an orthopaedic walker. A wheelchair is a mobility aid for 18 respondents. One person among the respondents is a bedridden person (Fig. 3B).

Among the main groups, complaints occurring in the course of SSc were identified as 6 main groups. These included musculoskeletal symptoms occurring in 67.3% of respondents, pain affecting 62.3% of respondents. Cardiovascular symptoms in 55.1% of respondents, respiratory symptoms in 21% of respondents. Skin lesions in 42.4% of respondents, gastric symptoms in 14.5% of respondents.

In the surveyed population, the survey revealed the frequency of symptoms reported by the respondents. Among them, 58.4% of the patients reported experiencing the disease symptoms as quite frequent, while 32.5% of the participants described them as very frequent symptoms. This means that 70 participants out of 77 are significantly affected by their illness (Fig. 4A). It is also significant that none of the participants reported never experiencing the symptoms. They always accompany the patients to varying degrees. Physical well-being has a direct impact on mental well-being, which in turn affects family relationships and social interactions. Among the respondents, a positive result is that as many as 84.4% of respondents reported that the disease did not affect their family relationships. Three participants even noticed a positive impact

Table 1. Age at which systemic sclerosis was diagnosed among respondents and time since systemic sclerosis (SSc) diagnosis among respondents

Age at which the respondent was diagnosed with SSc					
Age	18–25 years of age	26–35 years of age	36–45 years of age	46–54 years of age	Over 55 year of age
% of respondents	1.3	3.9	46.8	35.1	13
Time since diagnosis of SSc among respondents					
Time since diagnosis	1–2 years	3–4 years	5–6 years	More than 6 years	
% of respondents	19.7	27.6	19.7	32.9	

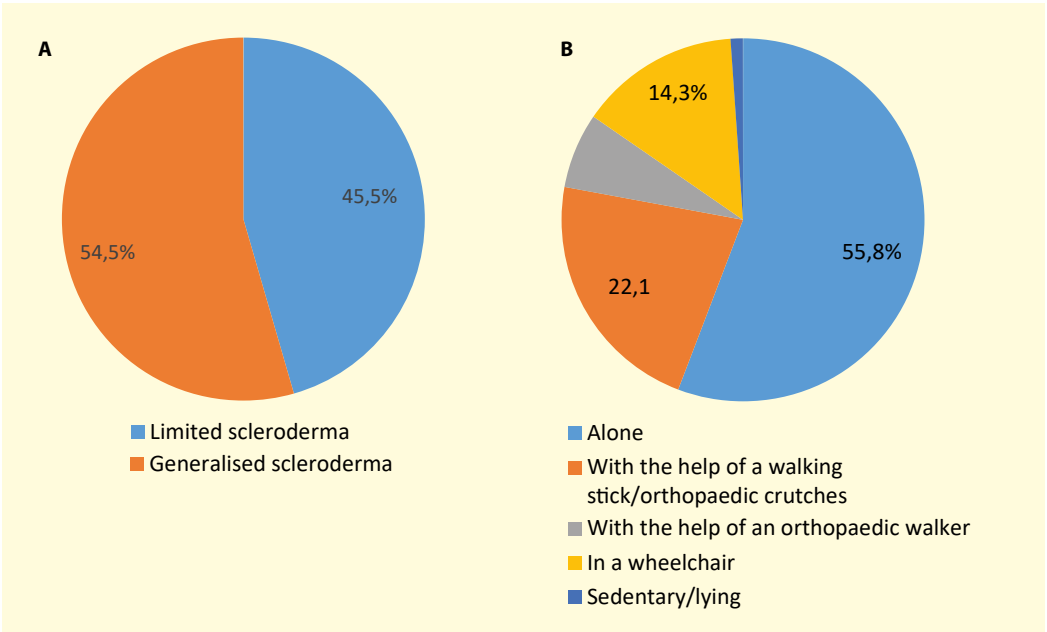

Figure 3. Characteristics of the type of sclerosis and the need for orthopaedic supplies of the respondents: **A.** Forms of systemic sclerosis among respondents; **B.** The way respondents move

of the disease on strengthening their family bonds (Fig. 4C). Given social interactions, 35 respondents perceived a negative impact of the disease, which they described as frequent. Moreover, 6.5% of the participants stated that the disease had a continuous impact on their social interactions. Rare impact was identified by 28 respondents, while 9 respondents stated that the disease had no impact on their social interactions.

The respondents specified in which ADLs they need assistance. The need for assistance in meal preparation was reported by 76.7% of the participants. A significant number of respondents, 46.8%, declared their ability to independently prepare and take medication. However, among them, 2.6% stated that they constantly require assistance, while 7.8% reported needing assistance in this activity all the time or frequently. Household chores are another ADL. Among the surveyed individuals, 13 respondents reported needing permanent assistance in household chores, while a significant percentage — 48.1% of the patients — stated that they require frequent help in this regard. Buying groceries is an activity during which assistance was required all the time or frequently by 54.6% of the respondents; 22 individuals rarely used this form of assistance. In terms of doing shopping, 15.6% of the respondents reported not needing any assistance. Moving around the home is another activity that can be difficult for SSc patients. Permanent assistance is required by 26% of respondents, frequent use of assistance is declared by 5.3%. Assistance is used rarely or not at all by 92% of respondents.

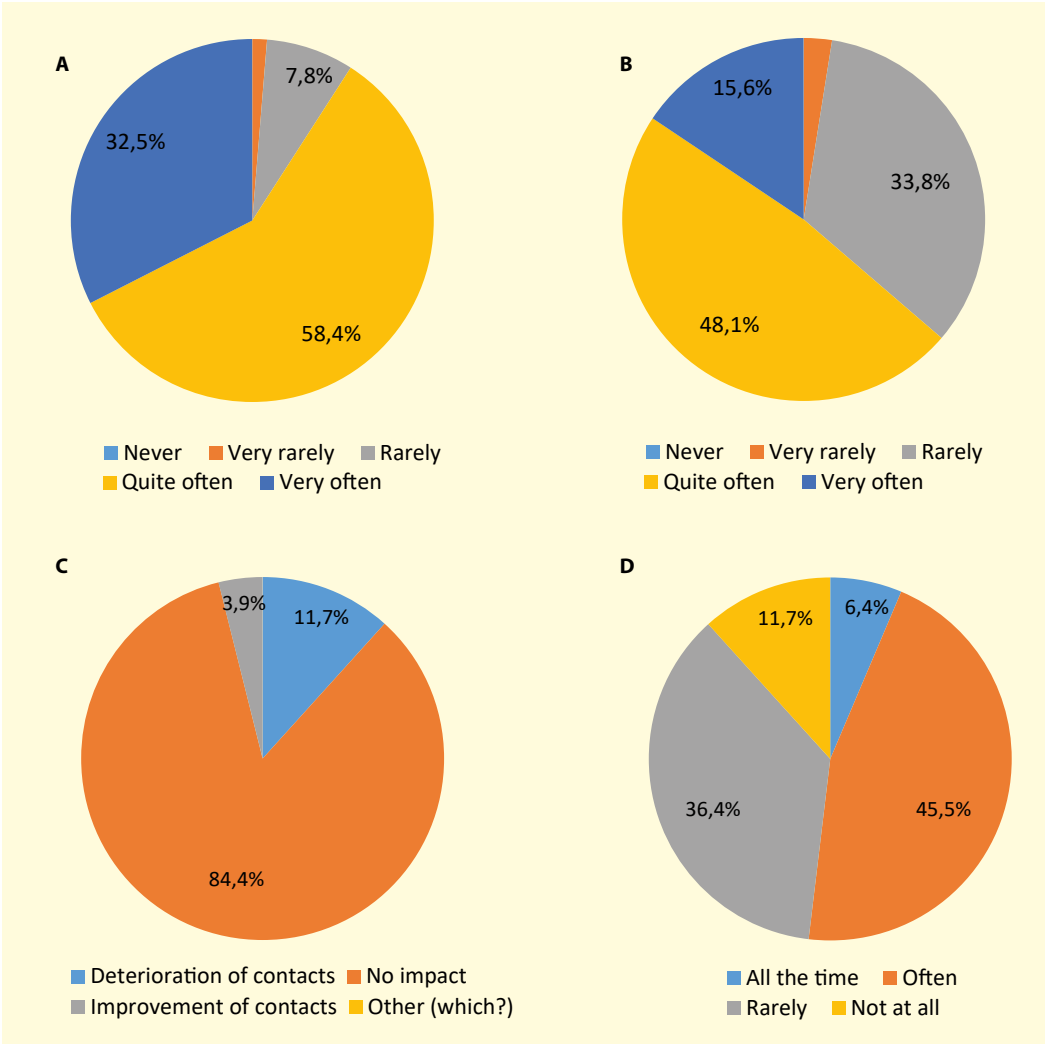

Figure 4. Emotional wellbeing of patients with systemic sclerosis: **A.** Frequency of perceived symptoms among respondents; **B.** How often do the experienced symptoms disrupt work among respondents?; **C.** Impact of the disease on family interactions of respondents; **D.** The impact of physical wellbeing and emotional wellbeing on social interactions of the respondents

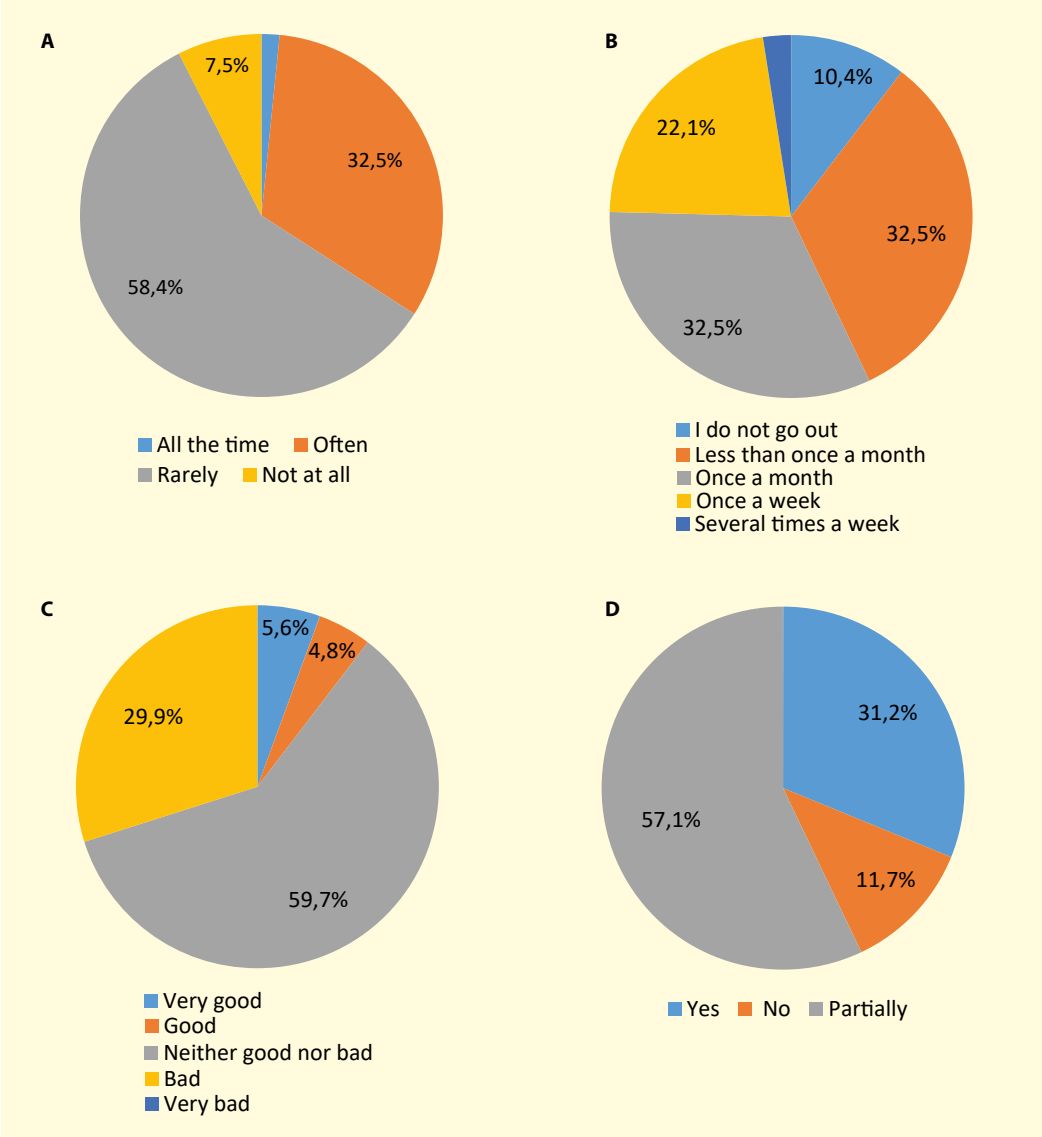

Figure 5. Social activity of respondents: **A.** Perception of loneliness among respondents; **B.** Frequency of leaving home among respondents; **C.** Assessment of own health status among respondents; **D.** Perception of life fulfilment among respondents

Moving outside the home can pose greater difficulties, as indicated by the results where 8 respondents require permanent assistance in this regard. Moreover, 20.8% of the participants described their need for such assistance as frequent. Maintaining personal hygiene is an important activity that affects the wellbeing of the body and the wellbeing of the patient.

Permanent assistance with hygiene is required by 3.9% of respondents, while 11 respondents stated that they need frequent assistance. A higher percentage of respondents, 45.5%, indicate that they do not currently require assistance in maintaining personal hygiene, while 37.7% of respondents reported rarely relying on assistance. Putting on and taking off clothes is a seemingly simple activity for healthy people. Among SSc patients, 2.6% of the respondents require permanent assistance, while 9 respondents frequently rely on assistance. Patients strive to remain independent in basic ADL for as long as possible, as reflected in the survey results. According to the survey, 41.6% of the respondents rarely rely on assistance when dressing up, while 44.2% do not require any assistance in this regard.

Using the toilet is one of the very intimate activities identified in this questionnaire, the results show that patients want to remain independent in this activity for as long as possible. Therefore, 71.4% of respondents do not require assistance, 19.5% rarely use assistance. Frequent assistance, or permanent assistance, is declared by 6 respondents. All the results are given in Table 2.

Table 2. Frequency of use of assistance in activities of daily living

	Meal preparation	Preparation and administration of medication	Doing the housework	Doing shopping	Moving around the flat	Moving outside the residence	Personal hygiene	Dressing up	Use of the toilet
All the time	5.2%	2.6%	16.9%	18.2%	2.6%	10.4%	3.9%	2.6%	2.6%
Often	27.3%	7.8%	48.1%	36.4%	5.2%	20.8%	14.3%	11.7%	5.2%
Rarely	49.4%	42.9%	28.6%	28.6%	40.1%	28.6%	37.7%	41.6%	19.5%
Not at all	18.2%	46.8%	6.5%	15.6%	51.9%	40.1%	45.5%	44.2%	71.4%

Questions about feelings of loneliness, frequency of leaving home, assessment of one's own health status and feelings of life fulfilment among respondents were also important points in the survey. Systemic sclerosis can affect all these areas of life. Loneliness and depression are rarely or not at all felt by 66.2% of respondents. Unfortunately, a sense of loneliness and depression often or constantly occurs in 33.8% of the respondents (Fig. 5A). Following that, the frequency of leisure outings is also varied among the respondents. There were 10.4% of respondents who did not leave their homes for recreational purposes. Moreover, 32.3% of the respondents reported going out for recreational purposes less than once a month. More than once a week, 2 individuals among the respondents engage in recreational activities (Fig. 5B). The self-assessment of health status revealed that unfortunately no one rated their health as very good. Their health status was rated as very bad or bad by 36.4% of respondents. A significant majority, 59.7%, rated their health as neither good nor bad, while only three respondents rated their health as good (Fig. 5C). The respondents were also asked about their feelings of fulfilment in life. Partial fulfilment was felt by 57.1% of respondents. Furthermore, 31.2% of the respondents reported feeling fulfilled in life. Lack of life fulfilment among respondents is felt by 9 respondents (Fig. 5D).

DISCUSSION

Research shows that SSc is a disease that affects patients' ADL to varying degrees. It penetrates both the patient's physical sphere, gradually limiting his or her independence, but also his or her mental sphere.

The majority of respondents were women. The questionnaire was completed by 55 women and 22 men. Systemic sclerosis is diagnosed more frequently among women than men. These results are consistent with epidemiological data indicating a 3–8 times higher susceptibility to illness among women compared to men [3–5] (Fig 1A). The age at which SSc is most commonly diagnosed is between 30 and 50 years of age [2, 6]. This fact was confirmed by the respondents' answers to the question about the age at which the disease was diagnosed in them. Among 46.8% of the respondents, 36 individuals, systemic sclerosis was diagnosed between the ages of 36 and 45. In 35.1% of respondents, 27 people, the diagnosis was made between the ages of 46 and 55. Systemic sclerosis is a chronic disease, and this is confirmed by the results of this survey as well. In the survey as many as 32.9% of the respondents (25 individuals) reported having the disease for more than 6 years. The length of patient survival depends on the form of the disease and its dynamics. The prognosis for systemic sclerosis is generally serious. It is estimated that 55% to 80% of patients survive ten years [7].

A larger portion of the respondents in this survey, 54.5% (42 individuals), have been diagnosed with dSSc . Almost half, 45.5%, of respondents struggle with lSSc. These data are in contrast to literature data indicating a higher prevalence of lSSc [8].

When analysing these discrepancies, it is worth noting that the surveyed group were patients of a unit specialising in the diagnosis and treatment of systemic sclerosis, which may have resulted in a "negative selection of patients" by accepting more severe and advanced forms of the disease. This fact significantly influenced the prevalence of different forms of the disease in the group described.

Systemic sclerosis is a chronic and progressive disease. Patients' awareness of the sequelae of systemic sclerosis and their current health status have an impact on their depressed mood. These data are in line with the results of this study, where as many as one third of pa-

tients feel lonely and depressed. In this study, physical well-being and emotional well-being were shown to have a significant effect on social interactions. Patients with systemic sclerosis are significantly more susceptible to depressive disorders, according to research. The percentage of patients with depression among those with rheumatological conditions is higher than the percentage of individuals with depression in the general population [9]. These observations align with the existing literature, which indicates a significant reduction in the quality of life among individuals with SSc.

Thirty-five individuals, 45.5% of respondents, state that their current health status often affects their interactions with friends. The disease has caused them to limit their contact with the external environment, and most often they spend their time in a familial environment. For the respondents, the disease has an impact on social relationships and social life. These observations are in perfect agreement with the results of a large Italian study showing a significant reduction in the social life of SSc patients [10]. The largest number of respondents also rely on family support. A total of 65 individuals responded that they use the help of their wife/husband, parents or children.

Assistance is necessary given the complications associated with systemic sclerosis, which gradually limit the patient's independence in performing ADLs. The complications experienced by SSc patients are related to the form they have been diagnosed with. Each of these complications also affects the quality of life of SSc patients [11]. Despite the discomfort experienced, 55.8% of respondents (43 individuals) move independently. However, as shown in the literature, individuals with systemic sclerosis significantly less frequently engage in physical recreational activities, which further contributes to a sense of reduced quality of life [12].

In this study, it was found that 37.7% of the respondents are employed, including 26% (20 individuals) working full-time. These data are consistent with the findings of a study from Sweden, which indicated a similar frequency of full professional activity among SSc patients. These data are in line with the results of a study from Sweden indicating a similar frequency of full professional activity of SSc patients [13]. Restrictions on the ability to perform gainful employment and social roles, which are also related to the mismatch between jobs and the needs of the employee. Despite their disability, patients strive for independence and self-sufficiency by taking up employment (Fig. 4B). The impact and significance of occupational work have been raised in an article discussing nursing care for patients with functional impairments. This study highlighted the positive impact of occupational work on reducing feelings of isolation and improving the quality of life for individuals across different age groups [14].

However, the factors limiting the ability to perform gainful employment still remain the axial symptoms of SSc, such as damage to the respiratory system, musculoskeletal system and weakness.

There are also symptoms that cause discomfort and affect the emotional and physical well-being of the patient; however, these symptoms do not limit physical activity. The majority of the respondents, despite being diagnosed with systemic sclerosis, try to maintain a positive outlook on life and appreciate their current health status, which may deteriorate at varying rates as the disease progresses. When asked about their health, the majority of respondents described their health as "neither good nor bad". The majority of respondents also feel fulfilled in life and such results can be seen as a positive. Despite the difficulties and negative assessments related to their own health and life, the research revealed that these respondents are a minority of individuals.

CONCLUSIONS

The survey results allow the following conclusions to be drawn:

1. Patients diagnosed with systemic sclerosis do not feel the impact of the disease on family interactions.
2. A chronic disease such as systemic sclerosis negatively affects the wellbeing of patients. Patients gradually limit social interactions and leisure outings.
3. Patients most often benefit from assistance during work-related activities that require the use of muscular force and activation of the musculoskeletal system. Most often they need help with various household chores and grocery shopping.
4. Patients wish to remain independent for as long as possible despite their deteriorating health and physical limitations. This is particularly true in the area of self-care and self-grooming.
5. The occupational status of the respondents also shows that patients try their best not to

give up their ADLs for as long as possible. Therefore, a large proportion of respondents continue to take up professional work. Certainly, the type of work performed and the progression of the disease do not always allow patients to continue working in their profession, so a significant portion is currently on disability pension.

6. Systemic sclerosis is a chronic disease. Its course and the symptoms that patients experience have a huge impact on their ADLs. The more advanced the stage of the disease, the more the patient's ADLs decrease.

ARTICLE INFORMATIONS AND DECLARATIONS

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

Concept: KP, BBP, KN, MB, MK, PK, EM; Data collection: KP, BBP, KN;

Data analysis: MB, MK, EM; Text creation: KP, PK.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Not applicable.

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Comparison of the prevalence of fibromyalgia in pre-clinical and clinical years among medical students of the *Collegium Medicum* of the University of Warmia and Mazury in Olsztyn

ABSTRACT

Introduction: Fibromyalgia is a chronic soft tissue rheumatic disease of unknown aetiology and marked by chronic, multi-sited pain persisting for at least three months and concomitant fatigue. The pathogenesis is still not precisely understood; disturbances of biochemical, metabolic, and immunological processes are suspected, and the impact of chronic stress is also undeniable. This study aims to compare the prevalence of fibromyalgia among students of different years of medical course at the University of Warmia and Mazury in Olsztyn.

Material and methods: The Fibromyalgia Survey Questionnaire (FSQ) incorporating the 2011 and 2016 diagnostic criteria for fibromyalgia was used for the survey. Questionnaires were distributed in hard copy during lectures (1–2 years of study) or credits (3–6 years of study).

Results: A total of 451 students representing all years were surveyed, sequentially from the first (n = 125), second (n = 96), third (n = 80), fourth (n = 62), fifth (n = 68) and sixth years (n = 20). Seventeen respondents (3.77%) met the diagnostic criteria for fibromyalgia according to the ACR 2016. In the pre-clinical years, fibromyalgia was slightly more frequent, however, the difference was not statistically significant (p = 0.1867). In contrast, in the pre-clinical years there was a statistically significantly higher prevalence of symptoms such as headaches, fatigue, trouble thinking or memory problems, waking up feeling tired, and pain in various parts of the spine. Also, students in their pre-clinical years were significantly more likely to meet fibromyalgia criteria such as symptom severity scale, widespread pain index and duration of symptoms of more than 3 months.

Conclusions: Although this study did not reveal an increased incidence rate of fibromyalgia among medical students compared to the general population, nor was there a statistically significant difference in terms of the prevalence of fibromyalgia between the first two years of study and the remaining years of study, it clearly highlighted the reduced quality of life in this population group.

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KEY WORDS: fibromyalgia; medical students; stress; fatigue

INTRODUCTION

Fibromyalgia (FM) is a chronic soft tissue rheumatic disease of unknown aetiology and is marked by chronic multi-sited pain in at least four out of five areas of the body, persisting for at least three months, and concomitant fatigue [1–3]. At the onset of the disease, pain is most often located in the spinal region.

The pain present in FM is not related to tissue inflammation; moreover, in these patients, there is no damage to or deformation of the affected tissues [4].

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The WPI (widespread pain index) is used for assessing the extent of pain while the SSS (symptom severity scale) is used for assessing the severity of symptoms.

Moreover, patients affected by fibromyalgia experience sleep disturbances, fatigue, and body stiffness, as well as a tendency to anxiety and depression, and there are also vegetative and functional disorders of varying severity [1–5]. Fibromyalgia is not an immediately life-threatening condition for patients [4], however, the complaints they experience are intractable, leading to a deterioration in daily functioning [3].

Fibromyalgia is estimated to affect approximately 2–8% of the population [1, 5, 6], however, this may be an underestimation as the Polish population is under-researched. FM is suspected to be a syndrome of complex aetiology. Despite the increased incidence rate of FM in recent years and our knowledge of this disease entity, the exact pathomechanisms still remain unknown [5, 7]. The contribution of biochemical, metabolic, and immunological processes is marked, and the influence of psychological predispositions is also undeniable [1, 4]. There is a noticeable prevalence of this entity among relatives. Genetic susceptibility may be due to the involvement of genes responsible for serotonin action [2]. This compound has a modulatory effect on the nervous system in the process of pain sensation through presynaptic inhibition of the release of neurotransmitters involved in pain sensation (e.g. substance P) [1]. Interestingly, 5-HT levels are reduced in patients with a diagnosis of FM [1], which may explain the frequent co-occurrence of depression in FM patients. Chronic psychological stress, severe psychological trauma or low self-esteem appear to have a significant impact on the development of the disease [5, 7].

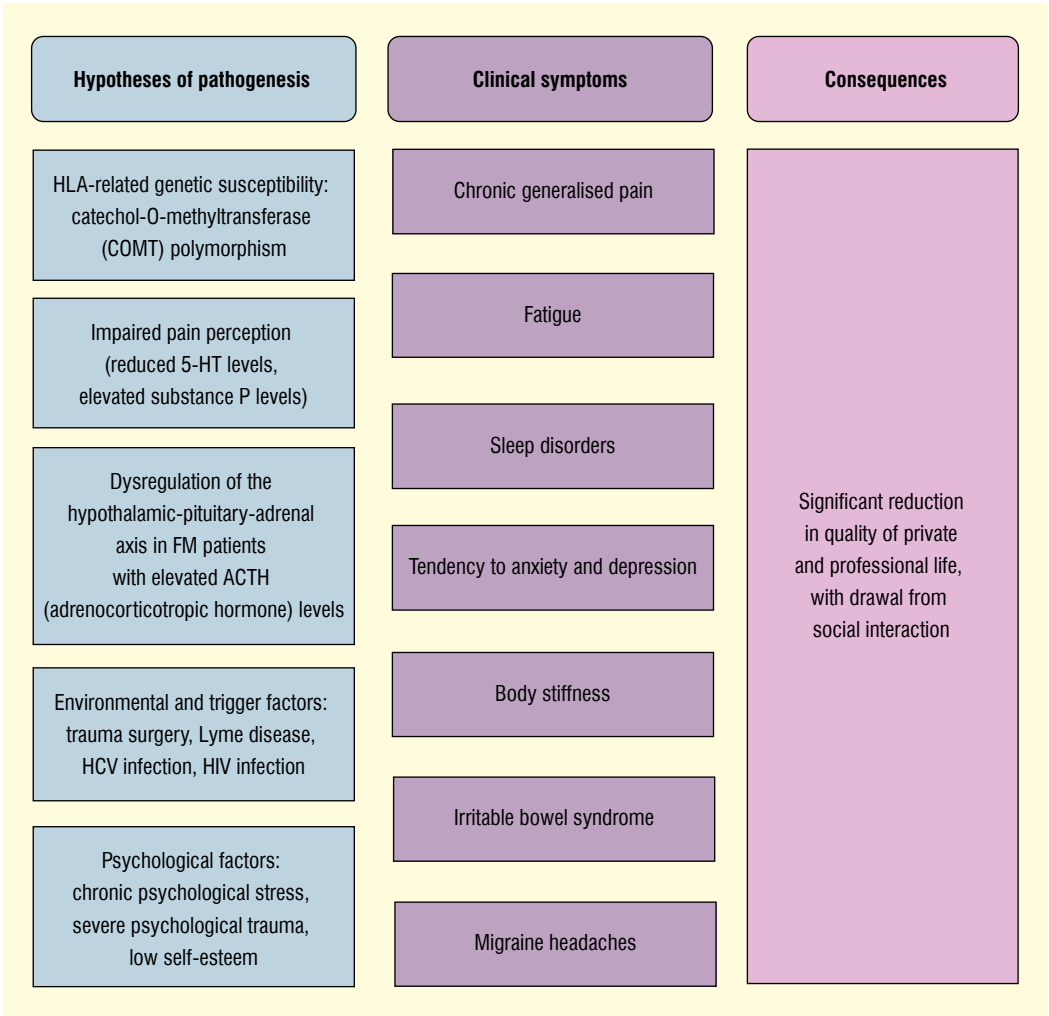

Figure 1. Pathogenesis of the development of fibromyalgia

The available literature points out that health-related students, particularly medical students, are exposed to chronic high-frequency stress [3, 5, 7, 8]. This stress is due to the nature of the studies — a large amount of material that has to be learnt in a short period of time, peer pressure, high expectations from relatives and one's own expectations mean that there is a deterioration in psychological well-being of medical students with the commencement of their studies [5, 7, 8].

To cope with the tasks set before them, students often work beyond their means and have little leisure time [8], and this, combined with the huge responsibilities associated with patients' lives, makes them a group at particular risk of developing chronic stress-related syndromes [7], including FM.

However, there is still a small amount of research that takes into account such a specific research group (Fig. 1).

MATERIAL AND METHODS

This study aims to compare the prevalence of fibromyalgia among students of different years of medical course at the University of Warmia and Mazury in Olsztyn.

A total of 451 students representing all years were surveyed, sequentially from the first (n = 125), second (n = 96), third (n = 80), fourth (n = 62), fifth (n = 68) and sixth years (n = 20).

The survey of third-year–sixth-year students took place in May/June 2022 while first- and second-year students were surveyed in October 2022. Questionnaires were distributed in hard copy during lectures (1–2 years of study) or credits (3–6 years of study). It is key to note that the timing of the completion of the questionnaires by third-year–sixth-year students coincided with the stressful moment for survey participants to pass their final tests, just before the start of the summer exam session. In contrast, the first- and second-year students were surveyed in the second week of the newly started academic year.

The Fibromyalgia Survey Questionnaire (FSQ) incorporating the 2011 and 2016 diagnostic criteria for fibromyalgia was used for the survey. This questionnaire contains a set of three questions assessing the mental state of the study participants in terms of the presence of selected symptoms listed in the questionnaire and their severity over the past seven days, as well as questions about symptoms observed over the past 6 months, such as lower abdominal pain/cramps, depression, headaches. Moreover, respondents were asked to indicate the areas of the body in which they had experienced pain in the last seven days and specify whether the symptoms mentioned in the previous questions had been experienced collectively for a period of at least three months.

The 2016 ACR criteria for a diagnosis of FM are met by individuals who score WPI ≥ 7 and SSS ≥ 5 or WPI 4–6 and SSS ≥ 9 on the FSQ, have generalised pain in at least 4 out of 5 areas of the body, and a period of sustained symptoms of persistent severity is ≥ 3 months. The WPI specifies the number of painful points, while the SSS is the symptom severity scale used for the first 6 questions of the questionnaire.

Data were compiled using Excel and Statistica. A non-parametric χ^2 test of concordance was used for the development and analysis of statistical data.

RESULTS

A total of 451 medical students took part in the survey. The survey included 125 first-year medical students (27.7%), 96 second-year medical students (21.3%), 80 third-year medical students (17.7%), 62 fourth-year medical students (13.7%), 68 fifth-year medical students (15%), and 20 sixth-year medical students (4.4%). The diagnostic criteria for fibromyalgia were met by 17 participants (3.77%).

Seventeen participants (3.77%) met the diagnostic criteria for fibromyalgia according to the ACR 2016, which meant that they met all conditions: WPI ≥ 7 and SSS ≥ 5, or WPI 4–6, and SSS ≥ 9. In addition, there was generalised pain, occurring in ≥ 4 out of 5 body areas. Those symptoms persisted for ≥ 3 months.

The prevalence of fibromyalgia was compared by year of study among the participants

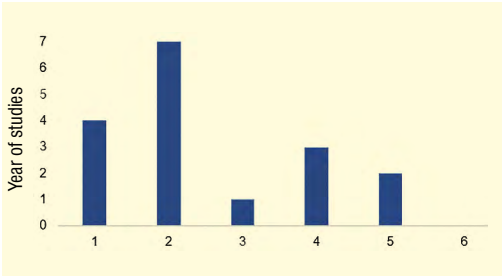

Figure 2. Distribution of persons with fibromyalgia in each year of the medical course

to determine the impact of chronic stress. Four participants (23.5%) of those with fibromyalgia were first-year students, seven (41%) were second-year students, one person (5.9%) was a third-year student, three (17.6%) were fourth-year students, five (29.4%) were fifth-year students, while there was no single participant among sixth-year students who met the diagnostic criteria for fibromyalgia (Fig. 2). Pre-clinical years were defined as the first two years of study — 11 participants (64.7%) met the criteria — and clinical years were defined as the 3rd-6th year of study — 6 participants (35.3%). In the pre-clinical years, fibromyalgia was slightly more frequent, however, the difference was not statistically significant ($p = 0.1867$).

Furthermore, it was noted that both SSS and WPI were significantly more likely to meet the diagnostic criteria for fibromyalgia in pre-clinical years — 71 (32%) than in clinical years — 22 (9.6%). A greater number of participants in their pre-clinical years had been experiencing those symptoms for more than 3 months 92 (41.6%) compared to 57 (24.8%) in their clinical years. The differences were statistically significant ($p < 0.001$). Generalised pain occurred with similar frequency in the pre-clinical 17 (7.7%) and clinical 12 (5.2%) years ($p = 0.2841$).

The presence of the following FM symptoms was also assessed over the previous six months: depressive states, headache, lower abdominal pain/cramps (Fig. 3). There were 164 participants (36.36%) who reported symptoms of depression, 241 (53.4%) experienced abdominal pain/cramps and 337 (74.72%) reported headaches. Depressive symptoms were reported in 87 participants in their pre-clinical years (39.4%) and 76 participants in their clinical years (33%). Headache was experienced by 183 participants (82.8%) in their pre-clinical years and 150 participants (65.2%) in their clinical years. Abdominal pain/cramps were reported by 131 participants in their pre-clinical years (59.3%) while 110 participants in their clinical years (47.8%). There was no statistically significant relationship in terms of the frequency of depression and abdominal pain ($p = 0.1623$; $p = 0.0148$), however, there was a significant difference for headaches ($p < 0.001$).

In addition, the severity of symptoms was assessed: fatigue, trouble thinking, and waking up feeling tired. Participants rated the severity of their symptoms during a given week on a scale of 0–3, where 0 meant “no problem”, 1 “mild, transient”, 2 “moderate, significant problems, present frequently or of moderate severity”, 3 “severe, persistent, disruptive problems”.

The prevalence of those problems was compared between students in their pre-clinical and clinical years fatigue was reported by 173 participants (78.3%) in their pre-clinical years and 91 (39.6%) in their clinical years. Trouble thinking or memory problems were experienced by 115 participants (52%) in

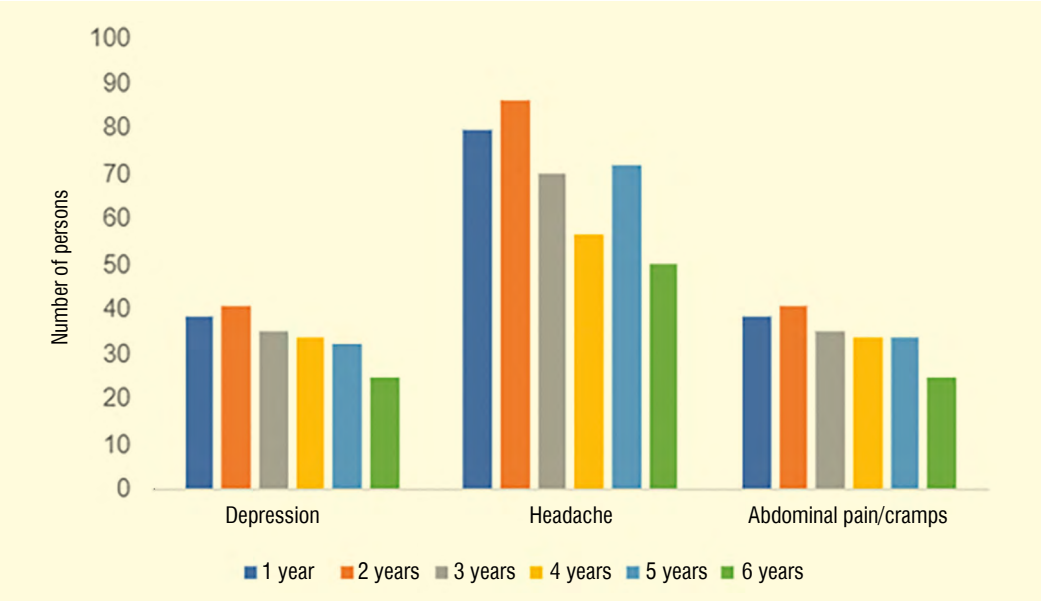

Figure 3. Distribution of prevalence of depression, headaches, and abdominal pain/cramps by year of study

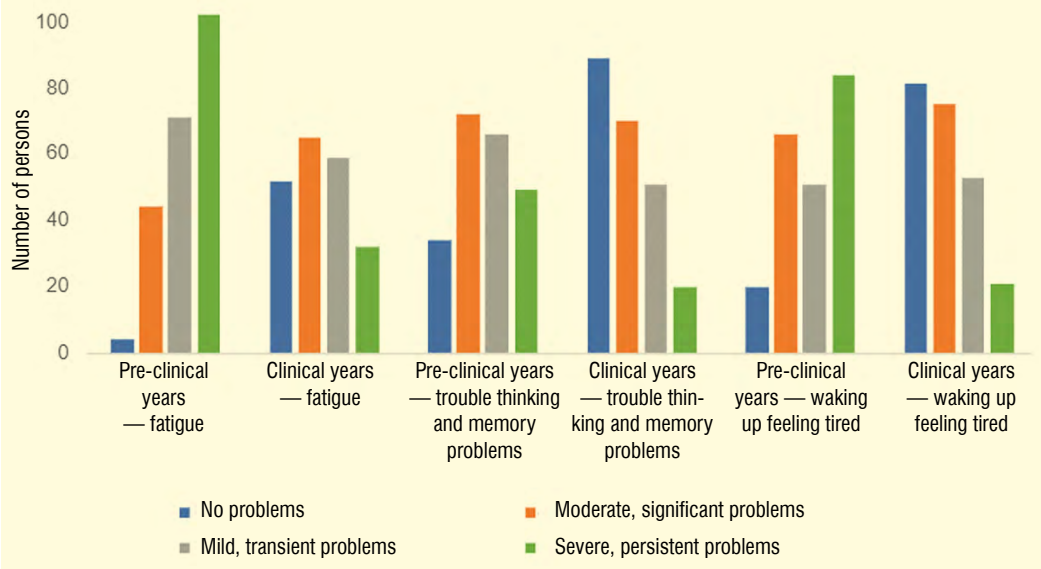

Figure 4. Increase in symptoms of fatigue, trouble thinking and memory problems according to the stage of training

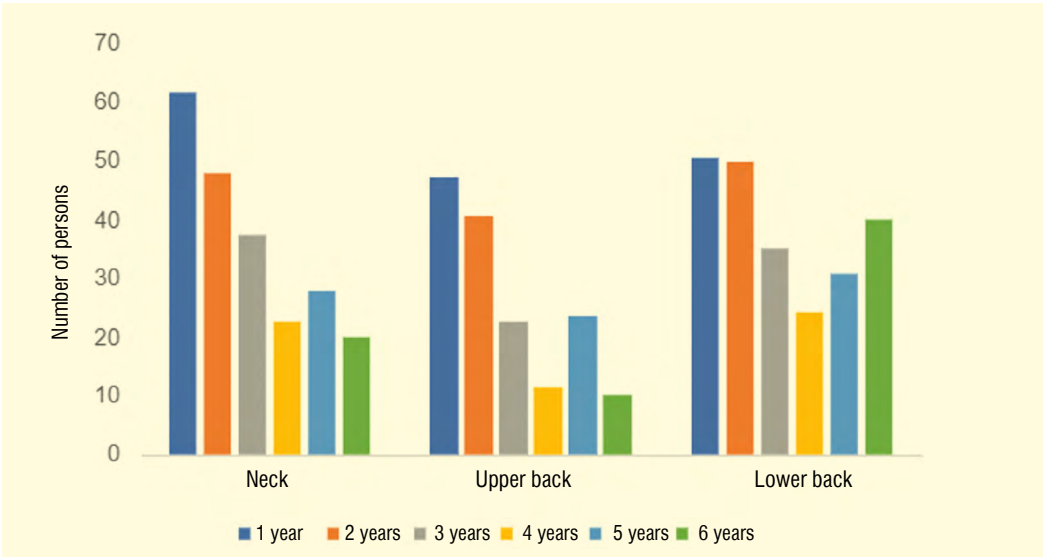

Figure 5. Prevalence of neck, upper and lower back pain symptoms by year of study

their pre-clinical years and 71 (30.9%) in their clinical years. Waking up feeling tired was reported by 135 participants (61.1%) in their pre-clinical years and 74 (32.3%) in their clinical years (Fig. 4). All variables had statistically significant relationships ($p < 0.001$).

It was also noted that there was a high proportion of participants who suffered from pain in various spinal segments. Neck pain was reported in 123 participants (55.65%) in their pre-clinical years and 67 (29.1%) in their clinical years. Upper back pain was experienced by 98 participants (44.3%) in their pre-clinical years and 43 (18.7%) in their clinical years. Lower back pain was reported in 111 participants (50.23%) in their pre-clinical years and 72 (31.3%) in their clinical years (Fig. 5). All these data revealed statistically significant differences ($p < 0.001$)

DISCUSSION

This study aims to assess the prevalence of FM among medical students as a group that is particularly exposed to chronic stress, which is an important risk factor for the development of FM. This is probably the second study of its kind in Poland. The first study was conducted in 2021 by students of the medical faculty of the Medical University of Gdansk [5].

The prevalence of FM among medical students in our study was 3.77%, which is not different from the prevalence of FM in the general population (2–8%) [1, 5, 6]. Similar results are reported in papers from Turkey and Japan. According to those studies, 2% of 306 Turkish medical students, met the criteria for FM diagnosis, while 1.48% of 539 Japanese working in healthcare met the criteria [9, 10]. However, it should be emphasised that both of those studies were based on the 1990 ACR diagnostic criteria.

In contrast to ours, in studies from the Medical University of Gdansk and King Abdulaziz University in Saudi Arabia, the prevalence of FM among medical students was higher than in the general population. In a study by the Medical University of Gdansk, it was 10.48% while in a study by King Abdulaziz University — 9.6% [5, 7]. Similar results were also reported among pharmacists and pharmacy students in Saudi Arabia [3].

The differences in results between this study and those from Gdansk and Saudi Arabia may be due to the different ethnic groups taking part in the survey. In ours, only Poles took part, while the study from Gdansk also surveyed English Division students, most of whom were of Arab origin like the participants in the study from Saudi Arabia.

In our study, we compared the prevalence of FM between pre-clinical (first-year–second-year) and clinical (third-year–sixth-year) year students. The criteria for a diagnosis of FM were met slightly more often by first- and second-year students, however, this was not a statistically significant difference. However, students in their first two years of study were significantly more likely to meet the diagnostic criteria for FM in terms of SSS and WPI. Symptoms also persisted for more than three months in more pre-clinical year students. Based on these findings, it can be concluded that although students in their first years of study do not meet the FM criteria significantly more often than clinical year students, their quality of life is significantly worse.

Similar results were obtained in the study from King Abdulaziz University in Saudi Arabia [3].

Our study also assessed the prevalence of symptoms such as depressive states, headache and lower abdominal pain/cramps occurring within 6 months preceding the survey period. The analysis revealed that almost 40% of students struggle with depressive states and more than half with headaches and abdominal pain. For these symptoms, a significant difference in prevalence was only observed in headache, which is more common in pre-clinical students. These results clearly show that the stress and pressure to which medical students are subjected have a significant impact on their quality of life. The higher prevalence of headaches among students in their first 2 years of study may be due to the fact that they spend considerably more time on pure theory from textbooks and learning remotely, whereas clinical year students spend more time on practical learning. Clinical year students are likely to have already developed more effective methods of learning that reduce the time spent studying from books. A high incidence of headaches and depressive states may also be due to sleep deprivation [11, 12], which undoubtedly accompanies medical students throughout their studies, but mostly affects students in their initial years of study. It is evident from symptoms such as fatigue, trouble thinking or memory problems and waking up feeling tired, which are significantly more frequent in the pre-clinical years.

The high rate of depression among medical students was confirmed in independent studies [13, 14].

Students in their first 2 years of study were also significantly more likely to report spinal pain than students in their clinical years. Again, this may be due to the number of hours spent studying theoretical subjects and the lack of physical activity.

Based on the above results, it is clear that medical students are exposed to factors that favour the development of fibromyalgia, such as chronic stress and sleep deprivation [15].

A limitation of this study was the relatively small sample size, especially among final year students. Furthermore, the gender distribution and several other factors that may affect the development and diagnosis of fibromyalgia were not taken into account, such as physical activity, stimulants, other chronic diseases.

CONCLUSIONS

Although this study did not reveal an increased incidence rate of fibromyalgia among medical students compared to the general population, nor was there a statistically significant difference in terms of the prevalence of fibromyalgia between the first two years

of study and the remaining years of study, it clearly highlighted the reduced quality of life in this population group.

It clearly appears from the study that students in their first two years of study cope less well with stress and experience more fatigue than clinical year students, however, all face high rates of depressive states, headaches, abdominal pain, and back pain.

These results give food for thought as to whether the training of future doctors is being delivered optimally and whether certain changes should not be made so that young people taking their first steps in the medical profession do not begin their professional path burdened physically and mentally by the shortcomings of the system, as this may have a negative impact on the quality of their work and thus on the well-being of patients.

ARTICLE INFORMATIONS AND DECLARATIONS

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Uveitis in rheumatic diseases — therapeutic management

ABSTRACT

Treatment of uveitis requires a special approach because of the risk of significant complications, including loss of vision. The causes of the disease cannot always be determined, but a significant proportion of cases have a strong association with systemic connective tissue disorders, particularly spondyloarthropathies. This indicates the need for cooperation between an ophthalmologist and a rheumatologist in order to provide the patient with proper care. Several stages can be distinguished in the course of treatment, depending on the duration of therapy and the persistence of symptoms. Current research data justify the use of topical and systemic corticosteroids, as well as immunosuppressive drugs in subsequent lines of therapy. The article summarizes current recommendations and clinical observations, and presents a therapeutic regimen based on them.

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KEY WORDS: iritis; rheumatic disorders; glucocorticoids; disease-modifying antirheumatic drugs; uveitis

All structures of the eye can be involved in the course of rheumatic disorders, as part of extra-articular manifestations.

The most common is the dry eye syndrome, keratoconjunctivitis sicca, also known as Sjögren's syndrome. It is present in approximately 30% of patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Less commonly, isolated corneal inflammation (keratitis) occurs in the rare Cogan syndrome, but also in RA, SLE, or ANCA-associated (anti-neutrophil cytoplasmic antibody) vasculitis.

The second most common manifestation is uveitis, which occurs in a wide variety of disorders, including rheumatic ones. It should be noted that uveitis is not synonymous with a diagnosis of rheumatic disorder, although certain features in the clinical presentation of uveitis can suggest a rheumatic origin.

Episcleritis is rarely associated with rheumatic disorders, while scleritis is a manifestation in 40% of cases. It is most common in RA (up to 1% of patients) and ANCA-associated vasculitis (up to 15% of patients), but also in SLE, inflammatory bowel disease, and recurrent cartilage inflammation. The mainstay of therapy is aggressive treatment of the underlying condition with additional ophthalmic treatment. Retinal vasculitis is a fairly typical manifestation of Behçet's disease, and rarely occurs in systemic vasculitis or systemic lupus erythematosus. Retinal vein occlusion, which may accompany antiphospholipid syndrome, should also be kept in mind. Involvement of periorbital structures in the form of granulomas occurs in ANCA-associated vasculitis and optic nerve ischemia occurs in giant cell arteritis [1, 2].

Anatomically, uveitis can involve the anterior segment of the eye (anterior uveitis, which includes iritis, iridocyclitis, anterior cyclitis), the intermediate segment (intermediate uveitis, the vitreous — pars planitis, posterior cyclitis, and hyalitis), the posterior segment (posterior uveitis, the retina, choroid, or optic nerve — choroiditis, retinitis, chorioretinitis, neuroretinitis), and all of the above (panuve-

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itis). In 75–90% of patients it affects the anterior segment of the uvea [1, 2].

In Polish studies, a definitive diagnosis was established in 76.3% of patients, of which specific ocular disorders accounted for 31.8% of cases, infections for 27.9%, and systemic disorders for only 16.8% (5.7% of patients had the HLA B27 antigen, all of whom had anterior uveitis). In 23.6% of the cases, a diagnosis could not be determined. It follows, therefore, that the primary obligation is to refer the patient to an ophthalmologist to rule out a specific or infectious cause [3]. Only after these have been excluded, an autoimmune disorder can be considered. The HLA B27 antigen is found in over 50% of patients in this group. Among systemic disorders, it is most commonly associated with ankylosing spondylitis (AS) and other spondyloarthropathies (SpA) (9.6% of cases), autoimmune thyroiditis (4.8%), inflammatory bowel disease (4.8%), sarcoidosis, juvenile idiopathic arthritis, and less commonly rheumatoid arthritis, multiple sclerosis, tubulointerstitial nephritis, vasculitis, Still's disease (no more than 1% of cases each) [4]. These diseases account for 17–30% of all cases of uveitis; the remaining inflammations are treated as idiopathic if no diagnosis is made despite targeted diagnostics. However, after years of observation, approximately 40% of patients in the last group are diagnosed with spondyloarthritis [5, 6].

Observations of large groups of patients with spondyloarthropathies showed that in 26.4% of cases, uveitis preceded the symptoms of SpA, in 58% it occurred during the first 10 years of the disease, and in 15% it appeared after 10 years. 24% of patients had more than 10 episodes, 25.4% had more than 2 exacerbations per year, and 13% had chronic uveitis that lasted over 3 months. Isolated iridocyclitis was found in 84% of patients, panuveitis in 8%, and isolated posterior uveitis only in 0.01%. 87% of patients had unilateral uveitis, 13% had bilateral uveitis, 45% had alternating uveitis. After many years in the course of the disease, complications that negatively affected the quality of vision occurred in 29% of cases, and these included: synechiae (18%), vitreous floaters (14%), cataracts (23%), glaucoma (9%), maculopathy (4%), band keratopathy (4%), optic nerve atrophy (2%), blindness (6%, and up to 10–20% in children). The presence of the HLA B27 antigen, psoriasis, and inflammatory bowel disease have been identified as independent predisposing factors for uveitis. Thus, it can be summarized that uveitis associated with SpA occurs mainly during the first 10 years of the disease, is predominantly unilateral, is recurrent, and impairs vision in about 1/3 of patients [7, 8].

Clinically, uveitis poses the greatest problem in children with juvenile idiopathic arthritis, as it occurs in 10–20% of cases, and in 70–75% of patients, it presents with scant symptoms and is chronic. Predisposing factors for this form of uveitis are early onset of arthritis, oligoarthritis, and an aggressive disease course. Only 25–30% have acute inflammation associated with the HLA B27 antigen, and arthritis takes the form of juvenile spondyloarthritis. As mentioned previously, it can lead to blindness in 10–20% of patients, which is why it is of special concern and has separate diagnostic and therapeutic recommendations from both EULAR (European League Against Rheumatism) and ACR (American College of Rheumatology). The EULAR recommendations, supplemented by later ACR recommendations, are presented in Tables 1, 2, and 3. The authors emphasize that the cessation of immunosuppressive treatment is a critical moment, which can provoke new uveitis as well as exacerbations of previously treated uveitis within 2 years [9, 10].

According to the recommendations, close cooperation between ophthalmologists and rheumatologists experienced in uveitis treatment is essential, especially in the absence of strictly developed criteria for assessing disease

Table 1. Recommendations for diagnosis of anterior uveitis in juvenile idiopathic arthritis (JIA) [9, 10]

1. All patients with suspected JIA should be screened for uveitis according to the current and audited protocol. The protocol should be used in all centers where children with suspected JIA are screened
2. The frequency of ophthalmologist visits must be based on disease activity and is up to the ophthalmologist's decision
3. Patients who have discontinued all immunosuppressive treatment have a high risk of new or recurrent uveitis, despite the prolonged remission. After discontinuing systemic immunosuppressive therapy, it is recommended that all JIA patients be examined by an ophthalmologist at least every 3 months for at least one year. The ACR recommends that during the treatment of uveitis, visits should be at least every 3 months in stable disease, within a month of every change in glucocorticoid treatment, and at least every 2 months after any change in immunosuppressive drug dosage

Table 2. Recommendations for the assessment of uveitis activity in patients with juvenile idiopathic arthritis (JIA) [9, 10]

4. Close communication between the ophthalmologist and pediatric rheumatologist is crucial in terms of changes in disease activity and responsibility for monitoring treatment
5. There is a need to develop common endpoints to facilitate decision-making during systemic treatment
6. There are currently no validated biomarkers useful for monitoring uveitis activity
7. There are currently no universally accepted definitions of inactive uveitis in JIA. The goal of treatment should be the absence of any cells in the anterior chamber. The presence of macular and/or disc edema, ocular hypotony, and rubeosis iridis may require anti-inflammatory treatment, even in the absence of cells in the anterior chamber
8. Experts recommend 2 years of inactive uveitis without topical steroids before tapering systemic immunosuppressants (both DMARDs and biologic therapy)

Table 3. Recommendations for the treatment of uveitis in the course of juvenile idiopathic arthritis (JIA) [9, 10]

9. Active uveitis in the course of JIA requires immediate treatment
10. The first line of treatment is topical steroids (prednisolone acetate or dexamethasone are preferred)
11. Topical and systemic NSAIDs have no significant effect on uveitis as a monotherapy but can be used as an adjunct treatment
12. Systemic immunosuppression in active uveitis is recommended if poor prognosis factors are identified during the first visit. The appearance of poor prognosis factors and lack of remission later in the course of the disease require systemic immunosuppression
13. Systemic immunosuppression is recommended if uveitis remission has not been achieved within 3 months or if there has been an exacerbation during steroid tapering
14. Methotrexate is a first-line drug as a systemic immunosuppressant; according to the ACR, subcutaneous administration is preferred
15. In the event of ineffectiveness or intolerance of methotrexate, addition or replacement with biologic drugs is recommended
16. In patients with persistent uveitis or resistant to DMARD treatment, mainly methotrexate, the introduction of biologic drugs is recommended (adalimumab > infliximab > golimumab)
17. Based on current data, etanercept should not be considered for treatment
18. If uveitis is resistant to first-line anti-TNF treatment, switching to another anti-TNF drug may be beneficial, even though the data comes from a small case series or preliminary studies
19. In case of ineffectiveness, consider testing for the presence of anti-drug antibodies and drug concentration. If the patient does not have anti-drug antibodies or the drug concentration is low, consider increasing the dose or shortening the intervals between doses
20. Tocilizumab, rituximab, and abatacept may be potential therapies in cases of resistance to prior anti-TNF treatments

activity or a definition of an inactive disease. It is important that the treatment is continued for an appropriate length of time, as tapering of systemic immunosuppression should not occur earlier than 2 years after discontinuation of topical steroids.

In uveitis in adults, the recommendations developed by the FOCUS Initiative should be followed regardless of etiology and after an infectious cause has been excluded. They omit the first line of treatment, which is oral and potentially systemic glucocorticoids (GCs), and focus on the issue of systemic immunosuppression in case GCs are ineffective [11]. The recommendations are presented in Table 4.

The indications for the introduction of systemic immunosuppressive treatment are similar to those in the recommendations for juvenile idiopathic arthritis. Unlike the latter, failure of at least one periocular administration of glucocorticosteroids and oral GCs treatment, their intolerance, or the need to discontinue them were taken into account in addition to topical treatment. The authors of the recommendations do not specify GC doses, referring to daily clinical practice. Recommendations in this regard were developed in 2000 and are still valid today (Tab. 5 and 6) [12].

The FOCUS Initiative does not specify which immunosuppressant drug should be selected. Effective choices include mycophenolate mofetil, tacrolimus, cyclosporine, azathioprine, methotrexate (MTX), and cyclophosphamide, although mycophenolate mofetil (not reimbursed by the National Health Service) and methotrexate seem to

Table 4. Indications for initiating systemic immunosuppressive therapy according to the FOCUS Initiative [11]

1. Ocular and anatomic Onset and course: — Acute disease that is sight threatening — Chronic persistent inflammation Exudative retinal detachment Posterior and macular involvement Binocular sight-threatening diseases
2. Therapeutic Regional failure to respond to: — Periocular steroid administration — Topical steroid administration in JIA Systemic therapy failure: — Active uveitis while taking doses of 30 mg or 0.5 mg/kg prednisone per day or more — Recurrence of uveitis after reduction of oral corticosteroid dose to less than 7–10 mg/day prednisone Steroid intolerance Need for steroid dose reduction
3. Severity (in adults) Visual acuity worse than 20/100 Increase in vitreous haze of grade > 2 Recurrence of cystoid macular edema Disease that impacts the quality of life
4. Severity in JIA, including prognostic factors for vision loss, such as: Poorer presenting visual acuity Posterior uveitis Uveitic complications of glaucoma Advanced cataract Macular edema Synechiae Severe band keratopathy Ocular hypotony Rubeosis iridis

Table 5. Topical treatment for the entire period of inflammation [12]

Prednisolone acetate 1% or dexamethasone 0.1%	1 drop every 1h for 1–3 days, then 1 drop every 2h; gradual dose tapering over 6 weeks to ≤ 3 drops per day
Methylprednisolone acetate	Periocular injections
Dexamethasone phosphate 2–4 mg	Subconjunctival or intravitreal injections
Triamcinolone acetate 20–40 mg	Periocular or intravitreal injections
Fluocinolone acetonide	Intravitreal drug-releasing implant
Short-acting mydriatics	Prevention of synechiae

Table 6. Recommended GC doses in inflammatory diseases of the uvea

Initial dose	1 mg/kg/d prednisone (may be preceded by 3 × 1 g *i.v.* methylprednisolone) for < 1 month
Dose tapering schedule	> 40 mg/d — decrease by 10 mg/d every 1–2 weeks 40–20 mg/d — decrease by 5 mg/d every 1–2 weeks 20–10 mg/d — decrease by 2.5 mg/d every 1–2 weeks < 10 mg/d — decrease by 1–2.5 mg/d every 1–4 weeks
Maintenance dose	≤ 10 mg/d
Additional recommendations	Monitoring visit every 3 months, calcium and vitamin D supplementation

be preferred [11]. The efficacy of methotrexate was shown by Bachta et al. However, the study involved a small study group. Out of 19 patients with recurrent acute anterior uveitis treated with 25 mg methotrexate per week, despite discontinuation of glucocorticoids, 16 patients (84%) had no symptom exacerbations over a 3-year follow-up (19–59 months), 3 patients had the interval between exacerbations increase from 4.8 months to 18.3 months, and the number of exacerbations in the entire group decreased from 2.12 patient/year to 0.11 patient/year ($p < 0.001$) [13].

Recommended doses of immunosuppressive drugs are shown in Table 7.

Biologic therapy should be considered in patients for whom standard treatment (corticosteroids + immunomodulators) is ineffective. Monoclonal anti-TNF antibodies are recommended — adalimumab (first choice), infliximab (less data available for certolizumab or golimumab), and also interferons. Etanercept and secukinumab are not recommended, as they neither decrease nor increase the number of exacerbations [14–16].

Table 7. Doses of immunosuppressive drugs used in uveitis treatment

Drug	Recommended dose
Methotrexate	25 mg/week, preferably subcutaneously
Mycophenolate mofetil	2–3 g/day
Azathioprine	2–3 mg/kg/day
Cyclosporine A	3–5 mg/kg/day (max. 10 mg/kg/day with serum concentration monitoring)
Cyclophosphamide	1–3 mg/kg/day (oral)
Tacrolimus, chlorambucil	According to the SmPC

Janus kinase inhibitors may be the future treatment of uveitis resistant to the therapies described above. At present, there are no randomized trials, but a meta-analysis by Wen et al. showed that out of 11 patients with various forms of active ocular involvement (6 with uveitis), despite biologic therapy, 8 patients achieved good outcomes in terms of ocular symptoms, regardless of the effects on joint symptoms. Adverse effects were rare, only 1 patient had to discontinue baricitinib due to leukopenia [17].

The authors of the recommendations emphasize that in case of treatment failure, the possibility of a different diagnosis (masquerade syndromes, e.g. ocular neoplasm, retinal degeneration), lack of patient cooperation, or an infectious cause of the inflammation. If the diagnosis is confirmed, the first step should be to optimize drug dosage, change to a different immunosuppressant, add periocular or intravitreal treatments, and also consider surgical or non-medical treatments (vitrectomy, cryotherapy) [11].

The management algorithm shown in Figure 1 should be useful in daily practice.

Treatment of uveitis should be initiated by an ophthalmologist, and the process itself can be divided into several stages, depending on the patient's clinical condition and response to medication (the so-called stepladder approach).

The first step is topical treatment with steroids, non-steroidal anti-inflammatory drugs, and short- and long-acting mydriatics. These drugs act on the anterior segment of the eye and do not penetrate further. Another route of drug administration is periocular steroid injections in slow-release (depot) form — methylprednisolone or triamcinolone.

In case of intense inflammation with macular edema, vitreous exudate or posterior segment involvement, drugs can also be administered intravitreously as a bridge therapy until remission is achieved with the use of systemic drugs. Long-acting, intravitreal implants that release small doses of steroids for 6–24 months are also available.

In severe inflammation, after an infectious cause has been excluded, systemic glucocorticoid therapy is initiated and, depending on the clinical condition of the patient, is administered intravenously (in most severe cases) or orally. The dose should be later reduced, depending on the clinical situation.

Although topically administered steroid drops are the first line of therapy, it is important to remember that chronic use can cause cataracts (rarely when < 3 drops per day are administered, perhaps not at all when < 2 drops) and post-steroid glaucoma (regardless of the dose). Systemic steroids can only be used in children in cases of severe inflammation with macular edema. In case of remission, GCs should be discontinued first, regardless of administration route.

The next stage of therapy is immunosuppressants. However, their effects are only visible after 6 weeks of use. It is therefore necessary to wait at least 3 months to assess the final effect.

Risk factors for poor prognosis requiring early use of systemic immunosuppression are the onset of uveitis before arthritis, posterior synechiae, male gender, band keratopathy, glaucoma, cataracts, hypotony, macular edema, dense vitreous floaters, and lack of remission despite topical treatment (patient requires at least 1–2 drops/day after 3 months of treatment). Systemic immunosuppression reduces the risk of vision loss by about 60%.

Methotrexate plays a leading role in immunosuppression, according to the ACR it should be always administered subcutaneously as its bioavailability is much higher than in oral preparations. Methotrexate allows for control of inflammation and discontinuation of GCs, improves, and maintains visual acuity. In case it is ineffective, the maximum tolerated dose should be administered before switching to another immunosuppressive drug.

Other DMARDs (leflunomide, mycophenolate, cyclosporine) may be used if MTX is ineffective or poorly tolerated.

According to the ACR, starting a combined MTX and anti-TNF treatment is recommended in severe cases [14]. In case of ineffective first-line immunosuppressant therapy (methotrexate, preferably subcutaneously; failed if after 3 months of therapy patient needs 1–2 GC drops/day), the addition of a biologic drug is recommended (monotherapy only in case of contraindications or intolerance of methotrexate), although there is no data that, as is the case in rheumatoid arthritis, it increases the efficacy and survival of biologic drugs. Anti-TNF antibodies are preferred; the use of a false receptor like etanercept or anti-IL-17 is not recommended. If the first anti-TNF drug is ineffective, it should be

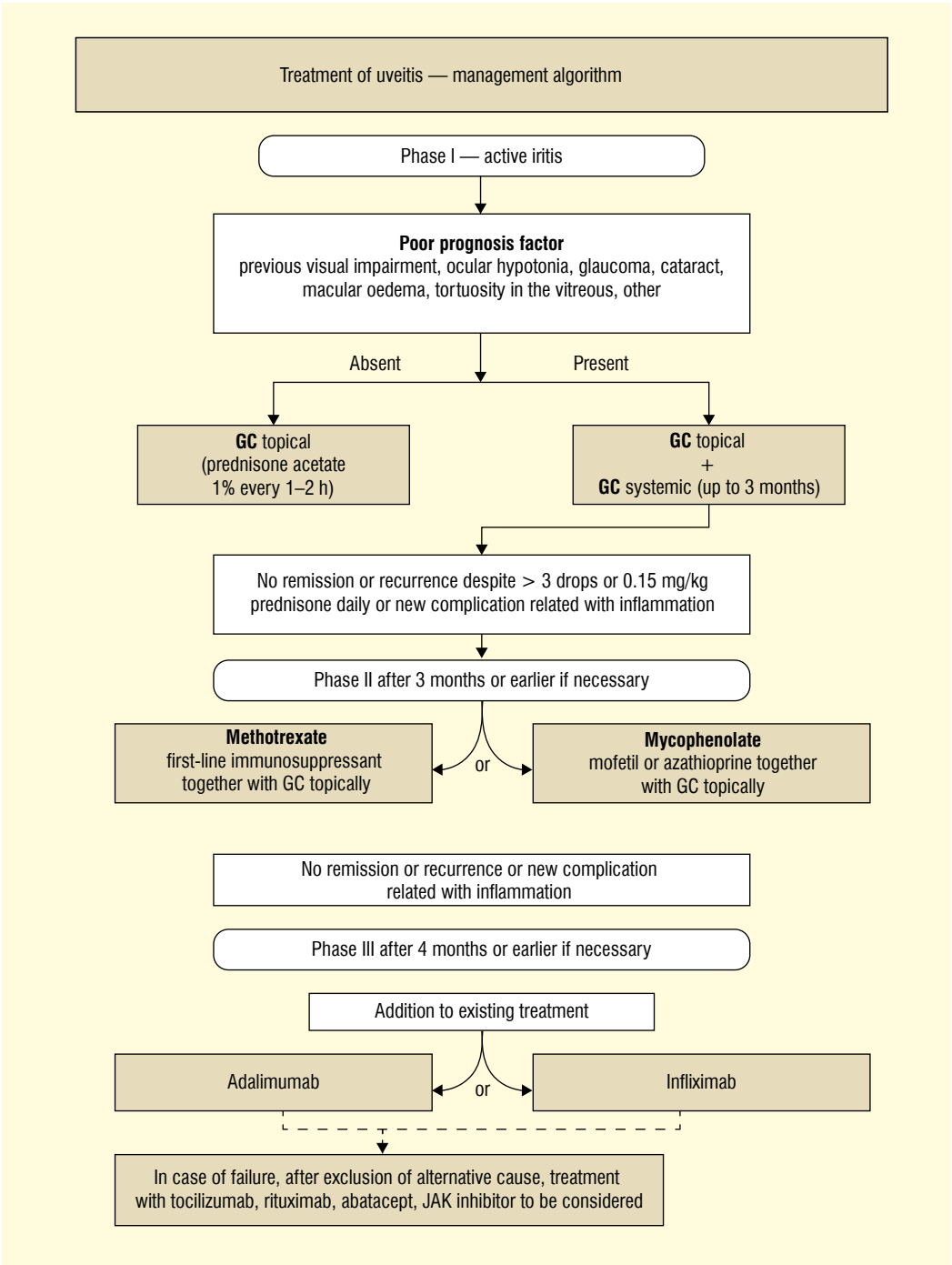

Figure 1. Management algorithm for uveitis treatment; GC — glucocorticoids

switched to another anti-TNF drug. The reason for its ineffectiveness should be considered. If the concentration of the drug is too low, the dose should be increased or intervals between doses shortened; if drug antibodies are present, switch it to a different one (combined treatment with methotrexate plays an important role in reducing the risk of their appearance). In case of anti-TNF antibody failure, tocilizumab, rituximab, and abatacept may be an option, but the ACR recommends they be used after at least 2 failed anti-TNF therapies.

In conclusion, uveitis can cause significant visual impairment, sometimes resulting in blindness, especially in children, and requires appropriate care. One of the more commonly identifiable causes may be juvenile idiopathic arthritis and spondyloarthropathies. Early diagnosis and appropriate treatment result in good outcomes in at least 60% of patients.

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Pyrophosphate arthropathy — a literature review

ABSTRACT

Joint diseases associated with calcium pyrophosphate crystals (calcium pyrophosphate dihydrate deposition disease, CPPD) are classified as crystallopathies. They clinically present as chondrocalcinosis, acute or chronic arthritis. The main risk factors are age, injuries and degenerative changes in the joints. One or more joints may be affected. Knees, wrists and shoulders are the most commonly affected joints. CPPD may be primary or secondary, and may be associated with hemochromatosis, hyperparathyroidism, hypothyroidism, and hypomagnesemia. Treatment is mainly symptomatic, most commonly using non-steroidal anti-inflammatory drugs, colchicine, or glucocorticoids.

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KEY WORDS: crystals; calcium pyrophosphate; arthritis

INTRODUCTION

Calcium pyrophosphate dihydrate deposition disease (CPPD), along with gout, is one of the most common crystallopathies and involves the deposition of calcium pyrophosphate (CPP) crystals in cartilage and periarticular structures. It may be asymptomatic, or present as acute or chronic arthritis.

EPIDEMIOLOGY AND CLASSIFICATION OF CPPD

Joint diseases associated with calcium pyrophosphate crystals affect the elderly population and their risk of occurrence increases with age. The majority of patients with acute arthritis are over 65 years old, with 30–50% of patients over 85 years old [1]. In the British population, the incidence of CPPD in people aged 55–59 years is 3.7%, and in those aged 80–84 years, it is 17.5% [2]. No difference in incidence was found between men and women. There is an association between CPPD and osteoarthritis (OA), as advanced osteophytosis correlates with intra-articular deposition of CPP [3, 4]. CPPD comes in primary and secondary forms (generalized and localized). Primary CPPD may be familial and has an autosomal dominant inheritance pattern. Secondary, generalized form of CPPD may be associated with hemochromatosis, gout, hyperparathyroidism, alkaline phosphatase deficiency, hyper- or hypothyroidism, and hypomagnesemia [5]. Localized CPPD can develop in patients with joint instability or after meniscus removal surgery.

PATHOGENESIS OF CPPD

The pathogenesis of CPPD has been shown to be influenced by transglutaminases involved in extracellular matrix mineralization and affecting chondrocyte hypertrophy. A pathogenetic link with IL-8 is suggested, which causes chondrocyte hypertrophy through the CXCR1 receptor (CXC chemokine type 1 receptor). In familial CPPD, the association of two gene loci, CCAL1 (long arm of chromosome 8) and CCAL2, with the

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ANKH gene (short arm of chromosome 5) has been confirmed. The former is associated with a severe form of OA, while the latter encodes a protein that affects the transport of phosphorus across cell membranes and influences the activity of enzymes related to mineral metabolism. A change in the phenotype of chondrocytes near crystallization foci has also been demonstrated [6, 7]. The cause of CPPD in patients with hemochromatosis or alkaline phosphatase deficiency is unknown. Hypomagnesemia promotes CPP crystallization.

CLINICAL PRESENTATION OF CPPD

The clinical presentation of CPPD depends on its phenotype (Tab. 1). Joint diseases associated with calcium pyrophosphate crystals can take the form of:

— chondrocalcinosis;
— acute arthritis (pseudogout);
— chronic arthritis (pseudo-rheumatoid arthritis);
— pyrophosphate arthropathy associated with OA [7].

Pyrophosphate arthropathy most commonly affects weight-bearing joints: hips, knees, and shoulders. Crystal deposits accumulate mainly in fibrous and hyaline cartilage [8, 9].

Chondrocalcinosis is defined as the presence of calcium salt deposits (not just CPP) in articular cartilage, which have been detected by imaging or histological examinations. Chondrocalcinosis is the most common form of CPPD, and is usually asymptomatic [10].

Patients with acute arthritis have symptoms similar to an acute gout flare such as pain, swelling, and redness of the joint area. Unlike gout, symptoms build up more slowly. A pseudogout flare affects a single joint, most often the knee, followed by wrists, shoulders, ankles, and elbows. Sometimes the inflammation can involve ligaments, tendons, bursae, and spinal joints [11]. Half of the patients have general symptoms: subfebrile state, fatigue. Factors that induce the onset of acute pseudogout include: joint trauma, myocardial infarction, infections, treatment with thyroxine, bisphosphonates, intra-articular administration of hyaluronic acid.

Chronic arthritis associated with CPPD affects 11% of patients and is characterized by periods of exacerbation and remission. Periods of exacerbation occur asynchronously and most often affect the wrist and metacarpophalangeal (MCP) joints. The main symptoms are morning stiffness, joint pain and swelling, elevated ESR and CRP values.

Chronic arthropathy in the course of CPPD presents similarly to OA and often accompanies it. What distinguishes this form of CPPD from primary OA is the involvement of the wrist, shoulder, ankle, and elbow joints. Unlike OA without CPPD, the lesions are mainly symmetrical, and there is usually a narrowing of the lateral aspect of the knee joint gap and the development of valgus. It is not known whether chondrocalcinosis is the cause of OA or a consequence of the changes that occur in the articular cartilage during its course. The co-occurrence of both diseases significantly accelerates the progression of OA. CCP has been found in 25–43% of patients with advanced OA undergoing knee arthroplasty [12–14]. Pyrophosphate arthropathy can affect all structures of the spine, including facet joints, intervertebral disc cartilage, interspinous, supraspinous, yellow and posterior longitudinal ligaments. Accumulation of CPP in the fibrocartilage of the axial skeleton is a common phenomenon in patients undergoing spinal surgery, but symptomatic spinal involvement in CPPD is quite rare. Changes in spinal structures can cause acute pain syndromes, and more massive crystals can cause nerve compression, myelopathy, and symptoms of cauda equina syndrome. The cervical and lumbar spine are most commonly affected. Axial CPPD requires differentiation from septic arthritis of the spine and ankylosing spondylitis [15–17].

DIAGNOSIS OF CPPD

Joint fluid analysis and imaging are used in the diagnosis of CPPD. A reliable diagnosis of CPPD can be made by analyzing synovial fluid collected during arthrocentesis. During acute inflammation, the fluid is cloudy, slightly bloody, and inflammatory. Fluid analysis using polarized light microscopy reveals the presence of CPP crystals, which are characteristically rhomboid or rod-shaped and are mainly located in the cytoplasm of granulocytes/macrophages. CPP crystals are characterized by weakly positive birefringence [8, 18–23]. X-ray is the most commonly used diagnostic imaging method. Calcification of the hyaline cartilage of a joint, which appears in the form of narrow linear shadows, is the most characteristic trait. CPP deposits are also seen in tendons, ligaments, fascias, joint capsules, as well as in the

Table 1. Clinical presentations of CPPD [7]

Clinical presentation	Clinical symptoms
Chondrocalcinosis	Usually asymptomatic, typical radiological features
Acute arthritis	CPP deposits in articular cartilage and synovium; usually inflammation of one joint, mainly the knee
Chronic arthritis	Joint deformities caused by chronic CPP deposition
Pseudo-OA	Co-occurrence of CPPD and OA symptoms
Pseudo-RA	Symmetric polyarthritis, mainly PIP and MCP, morning stiffness, elevated inflammatory markers
Pseudo-neuropathic arthropathy	Radiological features of Charcot joints, without nervous system dysfunction

CPP — calcium pyrophosphate crystals; OA — osteoarthritis; CPPD — calcium pyrophosphate dihydrate deposition disease; MCP — metacarpophalangeal joints; PIP — proximal interphalangeal joints; RA — rheumatoid arthritis

meniscus (knee joints) or intervertebral discs (spine). A common radiologic sign of CPPD is isolated stenosis of the patellofemoral joint or degenerative changes in the metacarpophalangeal joints of the hands. X-rays also show cystic degeneration, bone and cartilage fragmentation. In patients with suspected CPPD, X-rays of knees, pubic symphysis, hips, and wrists are most often performed. The presence of characteristic X-ray changes may confirm CPPD, but their absence does not rule out the disease. Ultrasound is helpful in the early stages of the disease, as it shows synovitis and CPP deposits in cartilage in the form of hyperechoic bands or foci (monosodium urate crystals are present on the cartilage surface). Ultrasound has a higher sensitivity and specificity than X-ray. Magnetic resonance imaging also detects the presence of CPP with high accuracy. Despite the fact that computed tomography accurately shows calcification, it is not routinely used to diagnose pyrophosphate arthropathy [12, 15, 24–28]. Conventional radiography and computed tomography remain the gold standard in imaging diagnostics. MRI scans are of limited value [29].

Due to the association of CPPD with metabolic diseases, the levels of calcium, phosphorus, magnesium, iron, alkaline phosphatase, ferritin, thyroid hormones, and ceruloplasmin should be determined in each patient with a recent diagnosis of CPPD [7, 30–32].

TREATMENT OF CPPD

Treatment of CPPD includes non-pharmacological and pharmacological therapies.

Non-pharmacological treatment includes reducing stress on the affected joint, applying cold compresses during acute inflammation, and controlling modifiable risk factors. There is no cure for the cause of pyrophosphate arthropathy. Unlike gout, no effective treatment has been found to eliminate calcium pyrophosphate crystal deposits. The goal of CPPD treatment is to reduce inflammation and compensate for metabolic abnormalities that could predispose to CPP deposition.

Asymptomatic CPPD does not require treatment [33, 34].

In the case of acute inflammation of one or two joints, glucocorticoids (GCs) are administered intra-articularly. When at least three joints are involved, systemic treatment is used: non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and in the absence of improvement, oral or parenteral GCs at a gradually reduced dose [11, 35–36]. The use of NSAIDs and colchicine has been carried over from acute gout treatment. In many patients, these drugs should be used with great caution, keeping in mind that the vast majority are elderly with multiple comorbidities. Short courses of low-dose oral steroids are preferred in patients with polyarticular CPPD. Low-dose NSAIDs or colchicine (0.5–1 mg/day) can be administered as a preventive measure in frequent exacerbations of acute arthritis.

NSAIDs and/or colchicine (0.5–1 mg/day), or low-dose GCs, can be used in chronic arthritis [14].

If the above-mentioned drugs are ineffective, contraindicated or poorly tolerated, an alternative form of therapy is the use of methotrexate or hydroxychloroquine. However, studies have shown low efficacy of these drugs. There are isolated reports on the use of biologic drugs: anakinra and tocilizumab. The use of these drugs may be considered in patients for whom NSAIDs/colchicine/GCs are ineffective [37–40]. Intra-articular administration of hyaluronic acid should be avoided as it may induce acute arthritis. To date, the effect of diet on the occurrence of CPPD has

Table 2. Treatment of CPPD [7]

Conventional treatments	
NSAIDs	Low-dose naproxen/indomethacin. Effective in CPPD exacerbations, reduces the risk of exacerbations
GCs	Effective only in CPPD exacerbations. Oral/intramuscular GCs are preferred in polyarthritis; intra-articular GCs in mono- or oligoarthritis
Colchicine	Effective in CPPD exacerbations in combination with NSAIDs. Beneficial in the prevention of exacerbations
Alternative treatments	
Methotrexate	May be used in CPPD exacerbations if conventional treatment is ineffective/contraindicated. Prevents CPPD exacerbations
Hydroxychloroquine	Effective in chronic arthropathies in the course of CPPD
IL-1 receptor antagonists	May be used in CPPD exacerbations if conventional treatment is ineffective/contraindicated. Prevents CPPD exacerbations
Radiosynovectomy	Best treatment outcomes for hemophilia patients
Future treatments	
CPP-inhibiting drugs (e.g. probenecid)	Prevention of CPP formation

CPPD — calcium pyrophosphate dihydrate deposition disease; CPP — calcium pyrophosphate crystals; GCs — glucocorticoids; IL-1 — interleukin 1; NSAIDs — non-steroidal anti-inflammatory drugs

not been established. In the case of secondary CPPD, treatment of the underlying condition is necessary [2]. Table 2 presents the drugs used in the treatment of CPPD [7].

DIFFERENTIAL DIAGNOSIS OF CPPD

The diverse clinical presentation of CPPD requires extensive differential diagnosis.

Joint diseases associated with calcium pyrophosphate crystals require differentiation from gout (20% of CPPD patients have hyperuricemia), rheumatoid arthritis (10% of CPPD patients have a positive rheumatoid factor test), inflammatory spondyloarthropathy, OA, or septic arthritis [2, 11, 14]. Synovial fluid testing for the presence of CPP and X-ray/USG of the joints are very helpful in the differential diagnosis [41].

PROGNOSIS AND COMPLICATIONS OF CPPD

Pyrophosphate arthropathy is a chronic, self-limiting disease and the symptoms of acute inflammation usually disappear after a few days or weeks after the start of treatment. Long-term prognosis depends on the number of affected joints and the frequency and exacerbations, among other factors. Calcium pyrophosphate crystals can lead to the destruction of joint surfaces. Multiple exacerbations of CPPD promote the formation of palpable nodules that resemble gout nodules [42].

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CONFLICT OF INTEREST

None.

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REVIEW ARTICLE

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Everything you always wanted to know about systemic sclerosis but were afraid to ask: Part 4. Treatment of patients with systemic sclerosis characteristics and recommendations concerning treatment of skin involvement, Raynaud's phenomenon, calcinosis

ABSTRACT

Systemic sclerosis (SSc) is a systemic connective tissue disease marked by diffuse microangiopathy and excessively immune-stimulated fibroblast activity, leading to fibrosis of the skin and internal organs. In the literature, the first report of the disease dates back to 1753 and is attributed to the physician Carlo Curzio of Naples, who described the case of a 17-year-old girl who developed sclerosis of the skin all over her body. The disease is a rare condition. It is estimated that 1 in 10 000 people in Poland suffer from SSc. Women predominate among the patients, with a 3–4-fold prevalence compared to men. Typically, the disease has its onset between 30 and 50 years of age. Early detection and treatment of organ complications are key to improving quality of life and reducing mortality in patients with SSc. Given the significant variability in the clinical course, an individualised approach to patients and multidisciplinary collaboration appear to be justified, both in the diagnostic and treatment phases. The treatment is based on the organ-specific therapeutic strategy, which involves tailoring the pharmacotherapy to the clinical presentation, disease stage, and organ complications. Treatment of patients should include, in addition to pharmacology, education of the patient and family and, if necessary, surgical treatment or other necessary interventions.

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KEY WORDS: systemic sclerosis; recommendations; treatment; management; rituximab; nintedanib; tocilizumab

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INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease in which internal organs, usually the lungs and kidneys, skin fibrosis and microcirculatory abnormalities occur. The pathogenesis takes into account genetic factors, autoimmune disorders, disturbances in collagen synthesis, and environmental factors.

The current classification of SSc according to LeRoy et al. since 1988 distinguishes two main clinical subtypes of the disease based on the extent of cutaneous sclerosis, i.e., SSc with limited cutaneous sclerosis (lcSSc) and SSc with diffuse cutaneous systemic sclerosis (dcSSc). Cutaneous sclerosis in lcSSc includes the hands, feet, forearms and lower legs but does not extend beyond the level of the elbows and/or knees. Cutaneous sclerosis in the form of dcSSc exceeds proximally beyond the level of the elbows and/or knees and involves the trunk. The disease in both forms can involve the facial skin. Indeed, from a treatment perspective, both forms of SSc differ in terms of disease progression dynamics, time of Raynaud's phenomenon onset, immunological profile, type of organ complications, and patient survival. The heterogeneity of the disease is the reason for the constant search and raising questions about a new classification of the disease form. The proposed amendment should take into account, in addition to the extent of skin involvement, the immunological profile of the individual patient, the molecular profile of the skin lesions (inflammatory, fibro-proliferative, normal), genetic variation, sex and stage of disease. Taking into account the aforementioned factors can help in offering the patient a personalised and targeted treatment approach.

The disease has a high mortality rate due to its numerous complications and the lack of effective targeted treatment [1]. It is marked by a wide variation in the clinical picture due to the different rate of development and type of organ complications. At present, there are no drugs that can effectively delay the progression of the disease in all patients.

Current treatment is mainly aimed at ameliorating the symptoms of SSC, which is why early identification of organ complications and assessment of the risk of disease progression is so important. Altered body image is a cause of low self-esteem and depressive disorders in patients. It should be remembered that SSc is primarily a debilitating disease that leads to irreversible disability.

TREATMENT OF PATIENTS WITH SYSTEMIC SCLEROSIS

The decision on treatment should be made individually for each patient after analysing the severity of the skin lesions, duration of the disease, disease activity, complaints and changes in internal organs. The patient's serological profile, which can indicate which organ lesions can be expected in the course of the disease, is not without significance:

— antibodies against topoisomerase I (anti-Scl-70) are associated with an increased risk of developing interstitial lung disease (ILD);
— antibodies against RNA polymerase I and III (anti-RNAP) are associated with an increased risk of renal crisis;
— anticentromere antibodies are typically associated with a milder course of the disease.

It should be noted that male gender and old age at onset are also poor prognostic factors. To assess the disease severity, the European Scleroderma Study Group has developed a Disease Activity Index (DAI) (Tab. 1). The disease is active when the DAI > 3. This index can be helpful in qualifying patients for immunosuppressive treatment.

RECOMMENDED ORGAN-SPECIFIC TREATMENT

Due to the lack of universal disease-modifying drugs and given the considerable clinical heterogeneity, the treatment of SSc is based on so-called organ-specific therapy. This method involves the use of drugs with proven or probable efficacy in the treatment of particular organ complications in patients with these complications. It is an organ-specific intervention aimed at protecting the organ, possible early treatment of the pathologies that have arisen and possible remodelling of the lesions that have already arisen, taking into account the complexity and individualisation of the management. It presupposes the avoidance of the use of drugs that may cause harm in this particular disease entity. Organ-specific therapy in the course of SSc should also include education of the patient and family, physical therapy and kinesitherapy (as prevention of joint contractures in joint complaints and myopathy), occupational therapy and psychotherapy.

If left untreated, the disease, especially dcSSc, quickly leads to serious organ compli-

Table 1. Systemic Scleroderma Activity Index (based on [53])

No.		Scoring	
1.	Rodnan index >14	1	Evaluation of skin hardness from 0 to 3 in 17 areas (0–51)
2.	Sclerodactyly	0.5	
3.	Skin	2	Exacerbation of skin lesions as assessed by the patient in the last month
4.	Digital ulcers	0.5	Presence of minor ulcers to necrosis of the fingers
5.	Vascular lesions	0.5	Raynaud's phenomenon, patient assessment within the last month
6.	Arthritis	0.5	Symmetrical swelling and pain of peripheral joints
7.	DLCO	0.5	< 80%
8.	Heart/lungs	2	Deterioration of cardiopulmonary function as assessed by the patient within the last month
9.	ESR	1.5	> 30 mm after one hour
10.	Hypocomplementemia	1	Decrease in complement C3 or C4 concentration

DLCO — diffusing capacity of the lungs for carbon monoxide; ESR — erythrocyte sedimentation rate

cations and thus disability and death. Early detection of organ lesions and appropriate implementation of treatment offers patients the chance to improve their quality of life (Tab. 2).

RECOMMENDED ORGAN-SPECIFIC THERAPIES

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is an abnormal contractile response of the blood vessels to cold temperatures or emotional stimuli. This disorder affects approximately 5% of the population and is slightly more common in women (11–20%) than in men (1–8%) [2]. It is classically marked by a 3-stage course.

Non-pharmacological management

Above all, patients should be informed about the nature of the disease and how to prevent its attacks. Patients should be advised to avoid provoking factors such as:

— emotional stress;
— consumption of beverages containing caffeine;
— smoking;
— the effect of contraceptive use on the occurrence of Raynaud's phenomenon.

The effects of drugs that cause vasoconstriction (clonidine, ephedrine, pseudoephedrine, bromocriptine, ergotamine, β-blockers and serotonin receptor antagonists) should be discussed with the patient and the use of amphetamine or cocaine should be absolutely prohibited. In addition, patients should be instructed on the principles of protection against exposure to low temperatures, which should consist of appropriate protection (warm clothing, wearing gloves) in winter, during changing weather conditions in other seasons or when using the refrigerator (at home, when shopping). The patient's attention should be drawn to the impact of occupational work in exposure to cold, vibration and finger trauma — these are definitely not recommended situations.

Importantly, the treating physician should also know what dietary supplements the patient is taking, as uncontrolled use of complementary therapies may cause pharmacological interactions.

Pharmacological management

The first-line therapy in SSc patients with Raynaud's phenomenon according to European Alliance of Associations for Rheumatology (EULAR) expert recommendations and French and UK recommendations should be a group of calcium channel antagonists. Given the accepted safety profile and long-term experience with this group of drugs [3–5]. The most effective in such cases are nifedipine and amlodipine that block calcium channels in the cell membranes of vascular wall smooth muscles and in the myocardium. As a result of the drugs, the influx of calcium ions into the cells is inhibited, which in turn leads to vasodilation and improved blood supply to the tissues [6]. The most commonly used preparations include nifedipine — 30 mg *p.o.*, amlodipine — 5 mg/day, diltiazem — 120 mg/day). If there is no improvement within 2 weeks of use, then the dose should be increased over 2–4 weeks to the highest dose, i.e., nifedipine — 90 mg/day, amlodipine — 20 mg/day, diltiazem — 360 mg/day, or to a lower dose if adverse effects occur.

As indicated in the literature, treatment with calcium antagonists may be associated

Table 2. Organ-specific treatment of systemic sclerosis (own elaboration based on [3, 5]

No.	Clinical manifestation	Treatment
1.	Skin involvement	Mycophenolate mofetil
		Cyclophosphamide
		MTX
		RTX
		TOC
		IVIG
		GCs
		Colchicine
		Cyclosporin A
		HSCT
2.	Raynaud's phenomenon	CCBs — nifedipine, amlodipine
		Prostacyclin analogues — iloprost, alprostadil
		Fluoxetine
		Phosphodiesterase-5 inhibitors: sildenafil (digital ulcer healing), tadalafil
		Topical nitrates
		a1-prazosin receptor antagonists
		ARB — losartan
		Statins
		ACEIs — captopril
		N-acetylcysteine
		Botulinum toxin
		Autologous fat grafting
		Sulodexide
		Surgical treatment
3.	Fingertip ulcers	CCBs — nifedipine, amlodipine
		Prostacyclin analogues — iloprost, alprostadil
		Endothelin A and B receptor antagonists: bosentan (prevention of new digital ulcers)
		Phosphodiesterase-5 inhibitors: sildenafil (digital ulcer healing), tadalafil
		Topical nitrates
		Platelet aggregation inhibitors for macroangiopathy
		Statins
		RTX
		Antibiotic therapy
		Pain treatment
		Surgical treatment
		Botulinum toxin
4.	Calcinosis	Minocycline
		Colchicine
		Ceftriaxone
		Probenecid
		Aluminium hydroxide
		IVIG
		Salicylates
		GCs
		ESWL
		CO2 laser
		Infliximab
		RTX

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5.	Lung involvement	Cyclophosphamide
		Mycophenolate mofetil
		GCs
		HSCT
		RTX
		TOC
		Nintedanib
		Oxygen therapy
		Lung transplantation
6.	Scleroderma renal crisis	ACEIs
		Intravenous CCBs
		Alpha-blockers
		Dialysis
		Kidney transplantation
7.	Heart involvement	NSAIDs/colchicine
		CCBs
		ACEIs or ARBs or angiotensin II inhibitors, -blockers,
		Diuretics
		Antiarrhythmics
		Defibrillator/artificial cardiac pacemaker
		Sometimes immunosuppressants or GCs in case of myocarditis
		Heart transplant
8.	Pulmonary arterial hypertension	Oxygen therapy
		Diuretics
		Endothelin receptor antagonists: bosentan, ambrisentan, macitentan
		Phosphodiesterase-5 inhibitors: sildenafil, tadalafil, riociguat
		Drugs affecting the prostacyclin pathway: epoprostenol, treprostinil, beraprost, iloprost, selexipag
		CCBs
		Lung or heart-lung transplantation
9.	Gastrointestinal involvement	Oesophagus: proton pump inhibitors, prokinetics (metoclopramide, domperidone)
		Stomach: proton pump inhibitors, erythromycin (125–250 mg × 2/day), clavulanic acid, prokinetics (metoclopramide, metopimazine)
		Small intestine: for motility disorders and/or pseudo-obstruction of the intestines: octreotide (50–100 μg/day)
		Large intestine: in case of constipation, balanced diet with fibre, adequate hydration, regular physical activity, laxatives and enemas, prokinetics for a limited time (metoclopramide, domperidone)
		Enteral and parenteral nutrition: in cases of severe small bowel damage or swallowing disorders
		Bacterial overgrowth of the small intestine: sequential antibiotic therapy (amoxicillin, metronidazole, fluoroquinolones, gentamicin, etc.).
10.	Musculoskeletal involvement	NSAIDS
		GCs
		Abatacept,
		RTX
		TOC
		Oral corticosteroid therapy
		Methotrexate
		Colchicine
		Azathioprine
		IVIG

CCBs — calcium channel blockers; ESWL — extracorporeal shock wave lithotripsy; GCs — glucocorticosteroids; HSCT — haematopoietic stem cell transplantation; IVIG — intravenous immunoglobulin; MTX — methotrexate; NSAIDs — non-steroidal anti-inflammatory drugs; RTX — rituximab; TOC — tocilizumab

with numerous side effects including hot flushes, facial flushing, palpitations, fatigue, headaches and peripheral oedema, and constipation [7]. Particular caution is required if blood pressure is very low.

The second group of applicable drugs are phosphodiesterase-5 (PDE-5) inhibitors, used primarily in patients who have not had a satisfactory response to treatment with calcium channel inhibitors or in patients with severe Raynaud's phenomenon. Some experts consider this group of drugs to be more effective and associated with a lower risk of adverse effects. It is advised to administer sildenafil (25–50 mg 2–3 times per day, starting with a dose of 12.5 mg/day and gradually increasing the dose with good tolerance) or tadalafil (20 mg/day). Side effects that may occur include hypotension, palpitations, tachycardia, temporary hearing loss, peripheral oedema, temporary visual disturbances. A meta-analysis of randomised clinical trials using PDE-5 inhibitors revealed that they were effective in reducing the incidence and severity of Raynaud's phenomenon [3]

According to studies, iloprost administered intravenously (0.3–3 ng/kg b.w./min for 3–5 days) reduces the frequency, severity and duration of Raynaud's phenomenon and promotes healing of ischaemic ulcers [8]. In two randomised clinical trials, iloprost (administered intravenously 0.5–2 ng/kg b.w./min for 3–5 days every 6–8 weeks) was found to be more effective than nifedipine (30–60 mg/day) in reducing the frequency of seizures and the severity of Raynaud's phenomenon [3]. An alternative is the use of another prostanoid, alprostadil (*i.v.* pulses of 20–60 μg every 4–6 weeks).

Despite the relatively low strength of evidence for efficacy, EULAR experts believe that fluoxetine 20 mg/day may be helpful in the treatment of Raynaud's phenomenon, especially in patients who cannot tolerate vasodilators. Attention should be paid to possible side effects including those associated with abrupt cessation of treatment [3].

Other forms of therapy include:

— **Topical nitrates** — nitroglycerin ointment 2% or transdermal patch 0.2 mg/h applied daily for 12 hours for 1 week.
— **Alpha-1 adrenergic receptor** antagonists (prazosin — 1–5 mg/day) — these drugs block the release of norepinephrine, which prevents vasoconstriction. Unfortunately they are usually poorly tolerated.
— **Angiotensin receptor blocker (ARB)** — losartan (25–100 mg/day, usually 50 mg/day) — the efficacy of losartan was significantly higher in patients with primary Raynaud's phenomenon than in patients with symptoms in the course of SSc.
— **Statins** — positive treatment effects were observed [2].
— **N-acetylcystain** — some studies revealed that it reduces the frequency and severity of Raynaud's phenomenon [2].
— **Botulinum toxin (BTX-A)** — some reports show benefit in patients with digital ischaemia, with or without ulceration [6]. The mechanism of action of BTX-A is most likely based on increasing blood flow, reducing pain sensation by blocking the effects of the sympathetic nervous system [9]. The use of BTX-A is a minimally invasive method with a low complication rate and appears to be an effective alternative therapy [10]. This therapy is currently recommended by the British Society of Rheumatology [4]
— **Autologous adipose tissue transplantation** — recent studies show the efficacy of this treatment, while it is required to use adipose tissue-derived stem cells during the procedure (they have a favourable cytokine profile favouring neovascularisation) [11].
— **Angiotensin-converting-enzyme inhibitors (ACEIs)** — captopril (20 mg/day) may be offered to patients intolerant of calcium channel blockers (CCBs) or in cases of concomitant pulmonary arterial hypertension (PAH). Captopril improves the blood supply to the skin but does not reduce the incidence of vasospasm episodes or the severity of symptoms. Enalapril, on the other hand, shows no therapeutic effect in Raynaud's phenomenon [8].
— **Pentoxifylline.**
— **Vitamin PP.**
— Sulodexide — has a prophylactic effect covering all 3 stages of the pathogenetic process in SSc (endothelial cell damage, inflammatory phase and fibrosis period); it improves vascular flow and has a protective effect on the endothelium. Oral preparations of sulodexide are used at 500 LSU per day in 2 divided doses and intravenously at 600–1200 LSU per day [12]. One paper described [13] the therapeutic use of sulodexide as an alternative drug (administered parenterally at 1 ampoule twice a day). Good treatment tolerance was ob-

served, and no adverse effects were noted. An analysis of this work and a review of the literature lead to the conclusion that this drug can be used in patients with Raynaud's phenomenon; the suggested dose is one ampoule every 12 hours for 3 or 4 days a week over 4–6 weeks [13].

— **Surgical treatment and other invasive procedures** — recommended only in the most severe cases of Raynaud's phenomenon after other therapies have failed [8]. One such procedure is sympathectomy, which involves blocking the nerves responsible for the vasculopathy.

— Alternative therapies such as **acupuncture** — insufficient data from clinical trials available at present.

PHALANGEAL ULCERS IN PATIENTS WITH SYSTEMIC SCLEROSIS

Damage to the microcirculation in patients with SSc results in the development of difficult-to-heal and painful ulcers on the fingertips, leaving behind so-called digital pitting scars. Progressive disruption of the blood supply to the distal phalanges leads to bone resorption and shortening of the phalanges, soft tissue necrosis and, in extreme cases, autoamputation [14]. Ulcer development is promoted by changes found in the course of sclerodermic microangiopathy leading to vasoconstriction, remodelling of the vessel wall, fibrosis and narrowing of the vessel lumen, which, together with imbalances in coagulation and fibrinolysis processes, impairs blood flow and promotes prothrombotic states. It is noteworthy that ulcers in SSc are decidedly chronic (healing takes a long time, 3–15 months) and recurring [15]. Also noteworthy is that approximately 4–6% of scleroderma patients also suffer from ulcers of the lower extremities with heterogeneous aetiology. They are usually found in patients with SSc with a long-term course. Leg ulcers in SSc are particularly difficult to treat; they are painful and negatively affect the quality of life and ability to work. According to the literature, ulcer infections were found in more than 2/3 of patients. Infection was most commonly caused by *Staphylococcus aureus* [2], and about 25% of cases were complicated by infection with enteric bacteria (*Escherichia coli* and *Enterococcus faecalis*) [2]. Infection often also involved bone and marrow [16]. Despite proper treatment, digital gangrene was observed in 22.6% of patients [15]. This complication was more common in dcSSc patients.

The treatment of ulcers in patients with SSc is difficult, requires a multidisciplinary therapeutic approach, and includes topical as well as systemic treatment (Tab. 3). Patients should be careful to avoid factors that exacerbate Raynaud's phenomenon, such as cold and stress, and should take proper care of their hands using barrier creams and protect their skin [5].

TOPICAL TREATMENT

Finger ulcers can be treated with nitrates but their use is limited. It is advisable to avoid topical antiseptics due to their cytotoxic effect,

Table 3. Vasodilators recommended for the prevention and treatment of digital ulcers in systemic sclerosis (own modification according to EULAR recommendations [3])

No.		Dosage
1.	Calcium channel blockers	Nifedipine 10–20 mg 3 times a day
		Amlodipine 5–20 mg/day
2.	Phosphodiesterase-5 inhibitors	Sildenafil 25–50 mg 2–3 times a day
		Tadalafil 20 mg every other day or every day for 8 weeks
3.	Angiotensin receptor blockers	Losartan 25–100 mg/day
4.	Selective serotonin reuptake inhibitors	Fluoxetine 20 mg/day
5.	α1-adrenergic receptor antagonists	Prazosin 1–5 mg twice daily
6.	Topical nitrates	2% nitroglycerin ointment 1/4–1/2 fingertip unit daily
7.	Prostanoids	Iloprost 0.5–2 ng/kg b.w./min *i.v.* for 3–5 days every 6–8 weeks
		Alprostadil 0.1–0.4 μg/kg b.w./min *i.v.* for 2–5 days every approx. 4–6 weeks
8.	Endothelin receptor antagonists	Bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice daily for 12 or 20 weeks

and it is best to use saline solution. Necrotic tissues can be removed mechanically or chemically (enzymatically, e.g. using preparations containing collagenase, papain, trypsin). The choice of dressings depends on the condition of the ulceration — in dry lesions, it is best to use dressings that create a moist environment (hydrocolloid and hydrogel dressings), and in ulcers with exudate — dressings with absorbent properties (hydrofibre dressings — hydrofiber-type dressings, alginate dressings, hydropolymer foam dressings) [17]. There was also a beneficial effect of vitamin E gel on the healing progress of digital ulcers.

VASCULAR TREATMENT

The cornerstone of pharmacological and non-pharmacological management of fingertip ulcers is treatment aimed at improving the vascular disorders associated with Raynaud's phenomenon, in the simplest terms, its effective treatment. In cases of progression of the condition (Raynaud's phenomenon) and ulcer formation, it is always necessary to optimise vascular therapy. This modification should depend on the severity of the symptoms. It should involve increasing the drug dose already in use, adding to it or replacing it with an alternative vasodilator/vasoconstriction inhibitor. A change of therapy is recommended every 3–6 weeks in the absence of clinical improvement. It is worth noting that vascular drugs play an important role in treating skin ulcers in a location other than the fingertips.

A recent meta-analysis of several randomised placebo-controlled clinical trials has shown that PDE-5 inhibitors accelerate ulcer healing [18]. Consequently, they occupy a special place in their treatment [18, 19] which is a direct result of their mechanism of action, as they are stimulators of soluble guanylyl cyclase responsible for cyclic guanosine monophosphate (cGMP) production and lead to an increase in nitric oxide. It inhibits vascular smooth muscle cell proliferation and induces vasodilation. As is well known, reduced nitric oxide production (due to endothelial cell dysfunction) is characteristic of scleroderma microvasculopathy. There are also reports that they may have the effect of reducing the risk of new ulcers — this can be observed with sildenafil as well as tadalafil. Their possible adverse effects include headache, nausea, facial flushing and jaw pain [3].

Intravenous drugs should be considered if oral therapies are ineffective, in refractory Raynaud's phenomenon or with the progression of trophic lesions of the fingertips. Such intensive in-patient treatment is always required in critical ischaemia of the distal phalanges.

Another group of drugs recommended for the treatment of finger ulcers are prostacyclin analogues (iloprost). In 2 randomised placebo-controlled clinical trials, intravenous prostanoids have been shown to be effective in healing finger ulcers [3, 20]. The mechanism of action of iloprost is twofold: it dilates blood vessels and inhibits platelet activity. Studies have shown that iloprost reduces the frequency, severity and duration of Raynaud's phenomenon and promotes the healing of existing ulcers. In particular, it should be emphasised that there is a toxic effect as the dose of iloprost increases. Adverse effects of prostanoids include facial erythema, diarrhoea, headache, drop in blood pressure and skin exanthema. Prostanoids administered orally have proven to be of limited efficacy [21].

In patients with multiple phalangeal ulcers who have not improved after treatment with calcium channel antagonists, PDE-5 inhibitors and prostanoids, endothelin 1 receptor antagonists and bosentan are indicated [18]. In patients with ulcerations over bony prominences and on the lower limbs, significant improvement was observed after using bosentan [19]. Bosentan has not been shown to be effective in the treatment of active finger ulcers; however, it has been shown to be effective in preventing the formation of new finger ulcers, especially in patients with a history of multiple finger ulcers (demonstrated in the RAPIDS-1 and RAPIDS-2). The most common medication regimen is: 62.5 mg twice a day for 4 weeks, then 125 mg twice a day for another 12 or 20 weeks [3]. It is important to be aware of the adverse effects of the preparation, including but not limited to hepatotoxicity, headaches, peripheral oedema, anaemia, teratogenicity of the drug or interactions with other drugs metabolised by cytochrome P450. A particular risk of interaction relates to oral contraception — bosentan may reduce its effectiveness.

Intravenous preparations of pentoxifylline and alprostadil may also be helpful in the treatment of ulcers.

ANTICOAGULANT AND ANTIPLATELET DRUGS

Taking into account the pathogenetic mechanism in SSc, where imbalances in coag-

ulation processes are also observed, it seems reasonable to use acetylsalicylic acid or clopidogrel in all patients with fingertip ulceration, necrosis of the fingers or peripheral arterial insufficiency [20], while short-term heparin therapy should be introduced in the case of acute ischaemia or during exacerbation of finger ischaemia [20]. The use of sulodexide as a method of preventing the risk of vascular thrombosis in SSc is reported extensively in the literature [22]. Its anticoagulant action is based on the inhibition of factor Xa and platelet aggregation and activation of the fibrinolytic system.

The long-term use of platelet aggregation inhibitors or oral anticoagulants in SSc depends on the individual indications. A thorough analysis of the benefits and potential losses should precede it.

Statins

Although there is insufficient evidence to support the efficacy of treatment with statins, it is worth considering these drugs as complementary therapy given their antioxidant, anti-inflammatory and antifibrotic effects.

Rituximab

Two scientific reports are worth noting here. The first concerns the healing of therapy-resistant phalangeal ulcerations after rituximab (RTX) treatment [23]. The second concerns its efficacy in 2/3 of patients with lower limb ulcers in the course of lSSc coexisting with cryoglobulinemia and vasculitis [24].

Antibiotic therapy

It should be reserved strictly for cases of ulcers with clinical signs of infection. It is worth noting that in chronic fingertip ulcers, however, this complication is common. Antibiotic therapy should then be started quickly, and the antibiotic should be selected based on the antibiogram. In cases of suspected central osteitis, antibiotic treatment should be administered intravenously.

Pain management

Fingertip ulcers are usually very painful for the patient. The perception of pain affects adrenergic receptors and can exacerbate vasospasm and ischaemia. Administration of acetaminophen is preferred, but sometimes opioid drugs are necessary; however, great caution should be exercised because there is evidence that they slow wound healing processes [25].

Surgical treatment

The indications for surgical intervention are relatively limited. They mainly involve surgical debridement in cases of gangrene to remove necrotic tissues or amputation of the necrotic finger. In therapy-resistant ulcers, it is advisable to consider allogeneic skin grafts.

Other methods

Beneficial outcomes have been described for treating phalangeal ulcers using hyperbaric oxygen therapy, negative pressure therapy, acoustic waves and intermittent pneumatic compression [26]. Trials of botulinum toxin in the prevention and treatment of fingertip ulcers are also reported in the literature, with promising results. Botulinum toxin has also been used in treating Raynaud's phenomenon, as discussed at the beginning of this article.

SOFT TISSUE CALCINOSIS

In some SSc patients, calcium deposits develop in the skin, causing local inflammation, secondarily leading to the development of ulcerations and fistulas of the skin [14, 27]. The most common locations for deposits are the fingers and the extensor surfaces of the elbow and knee joints. Severe calcinosis in the course of SSc is called the Thibierge–Weissenbach syndrome. Calcinosis is observed to be particularly common in people with anti-centromere antibodies present.

Various drugs have been tried to reduce skin calcification, but therapeutic effects have been mediocre and occurred only in isolated cases. Calcium channel antagonists are proposed as first-line drugs, with most studies investigating the use of diltiazem. Its action reduces the amount of calcium that fills cells and macrophages in damaged tissues; it is used at doses of 240–480 mg/day for 1–12 years [28, 29].

There are reports in the literature on the use of bisphosphonates, however, mainly in cases of concomitant osteoporosis. It is worth noting that data on their efficacy in reducing calcification are scarce [30]. Alendronate is used orally at 70 mg/week and pamidronate intravenously at 90 mg/week.

Warfarin has also been suggested to have a beneficial effect in the treatment of skin calcinosis [28, 29] — this applies to low-dose warfarin treatment (at 1 mg/day) in patients who have small and relatively recent calcifications.

Other drugs that have the potential to inhibit the accumulation of calcium deposits include the following:

— **Minocycline** — reduced skin calcinosis and associated inflammatory reactions and ulcerations were observed in a clinical trial conducted between 1994 and 2000 [31]. Its mechanism of action involves inhibiting metalloproteinases present in the intercellular substance, resulting in reduced inflammation; in addition, it chelates calcium. The drug is used at a dose of 50–100 mg/day.
— **Colchicine** — the most exploited property of colchicine is its ability to reduce inflammation around calcifications, rather than its ability to reduce the calcifications themselves; the risk of adverse effects with long-term use should be emphasised; these include diarrhoea, abdominal pain and numerous drug interactions.
— **Ceftriaxone** — affects metalloproteinases, chelates calcium and has anti-inflammatory effects. It is recommended to use at a dose of 2 g/day for 20 days.
— **Probenecid** — inhibits uric acid reuptake in the kidneys and increases phosphate secretion. It is used at a dose of 1.5 g/day.
— **Aluminium hydroxide** — can be used to reduce soft tissue calcinosis in patients with scleroderma and dermatomyositis [32].
— **Intravenous immunoglobulin (IVIG)** — a positive effect is reported in some scientific reports, including a case report of an lcSSc patient by Schanz et al. [33], who used IVIG treatment for 5 months, achieving complete regression of the lesions. It is customarily administered at a dose of 2 mg/kg body weight [29].
— **Salicylates.**
— **Glucocorticosteroids (GCs)** injected into different sites — used in lcSSc.
— **Extracorporeal shock wave lithotripsy** — a minimally invasive, safe and well-tolerated method; isolated cases of good patient response to this therapy have been described
— **CO2 laser** is used for the treatment of small and superficial deposits; it is a bloodless technique, and there have been cases reported in the literature of complete removal of deposits using this method.
— In severe cases, **surgical removal of deposits** may be useful.
— **Infliximab** — there are isolated reports, including one of a patient with SSc and polymyositis overlap syndrome and concomitant calcinosis who was treated with infliximab at 3 mg/kg administered intravenously at 0.2 and 6 weeks and every 8 weeks after that. After 41 months, a significant reduction in the size of calcifications and no development of new ones was described [34].
— **Rituximab** — appears to be the most promising of the therapies to date. During therapy with RTX, improvements have been observed in the resolution of calcinosis foci and pain in CREST syndrome [35]. Daoussis et al. described a case of an lcSSc patient with multiple deposits who had a significant reduction in the size of the calcifications and a significant improvement in pain one year after treatment. Two cycles of RTX were administered (4 weekly infusions at 375 mg/m^2 each) with an 18-month interval between each cycle [35]. Another case report concerns a female patient with lcSSc, who was treated for ILD and arthritis, incidentally achieving complete regression of deposits in her hands 7 months after treatment [36]. Giuggioli et al. described 10 cases of patients treated with one or more cycles of RTX (4 infusions of 375 mg/m^2 at weekly intervals). Due to ILD, skin or joint involvement, 3 of the 6 patients with calcium deposits had a significant reduction in deposits 6 months after the first treatment cycle. It continued to improve gradually over the following months [21]. There is also a report by Hurabielle et al., in which the researchers describe a case of a woman with deposits in the wrist area. In a patient who received two (2 weeks apart) infusions of RTX 1 g each for ILD and arthritis, progression of existing calcifications and formation of new deposits in other locations was observed [37].

SKIN INVOLVEMENT

The skin in SSc patients undergoes 3 phases: swelling, hardening and atrophy. The skin loses its elasticity, there is a loss of sweat and sebaceous glands as well as hair follicles and hair, and there may also be pigmentation and/or depigmentation of the skin. There may also be telangiectasias, especially of facial skin (also mucous membranes) and pruritus (mainly in dcSSc). The modified Rodnan skin score (mRSS) is used to assess the severity of skin lesions. This method involves assessing the thickness of the skin on a four-point scale by

palpation of 17 areas of the body. The total of all measurements is the final score, and it can range from 0 to 51.

The treatment of cutaneous scleroderma should be guided by the phase of the fibrotic process (early *vs.* late), disease activity and progression of fibrosis. General measures include protecting the skin from cold and trauma, skin care with moisturising creams, lymphatic drainage and active physiotherapy to prevent contractures. These general measures may suffice in mild, non-progressive forms of scleroderma.

The skin should be treated topically to ensure it is well hydrated. Moisturising and softening creams and lotions are recommended to be applied several times a day. Paraffin baths for hands or castor oil have not been thoroughly researched scientifically. Personalised physiotherapy with massages to soften the skin or subcutaneous tissues can be offered, although no studies have been conducted on this topic to date [5]. Antihistamines may be offered for pruritus. Additional treatment may include UV therapy.

METHOTREXATE

According to EULAR expert recommendations, methotrexate (MTX) (initially 15 mg/week *administered subcutaneously* for 24 weeks or 10 mg/week administered orally, then increasing the dose) is recommended as first-line therapy for cutaneous scleroderma. In case of adverse effects or ineffectiveness, intravenous mycophenolate mofetil (MMF) or cyclophosphamide (CYC), low-dose GCs or RTX may be used [3].

Two randomised controlled trials have shown that MTX reduces skin fibrosis in early dcSSc. A positive effect on other organs, such as the lungs, has not been demonstrated [38, 39]. The recommended dose should not exceed 0.3 mg/kg/week, administered orally or subcutaneously. There is no set duration of treatment, but in case of clinical improvement, treatment for at least 2 years is recommended [5]

MYCOPHENOLATE MOFETIL

The use of MMF is recommended by the EULAR Scleroderma Trials and Research (EUSTAR) group as second-line therapy after MTX. The recommended standard dose is approximately 1–2 g/day (target 2–3 g/day if treatment is well tolerated) for at least 2 years [40].

In the Scleroderma Lung Study-II (SLS-II), MMF use was associated with a reduction in the mRSS after 24 months. An analysis of the SLS-II *vs.* placebo Scleroderma Lung Study-I (SLS-I) group would suggest that MMF use was associated with an improvement in the mRSS compared with the placebo group at 24 months.

Reports from US researchers at Thomas Jefferson University (Philadelphia, USA) indicate that more than a quarter of patients with rapidly progressive dcSSc who discontinue MMF therapy or have their drug dose reduced experience progression of skin lesions over the following 5 years.

CYCLOPHOSPHAMIDE

An analysis of the results of 85 SLS-I patients with dcSSc who received CYC for 12 months showed a significant improvement and difference in the mRSS compared with a placebo group [41]. In the SLS-I, oral CYC resulted in a reduction in the mRSS, which was significant after 12 months of assessment. This effect disappeared one year after the discontinuation of CYC. Cyclophosphamide is recommended after the failure of MTX and MMF due to the high incidence of adverse effects [40]. According to EULAR recommendations, CYC should be considered, particularly in patients with progressive ILD. It also appears to be a drug worthy of consideration for rapidly progressive skin lesions in dcSSc. The dose and duration of CYC treatment should be considered individually depending on the clinical condition and response to treatment. The potential risk of bone marrow inhibition, teratogenic effects, gonadal failure and haemorrhagic cystitis should always be considered.

GLUCOCORTICOSTEROIDS

The systemic use of GCs, which is considered standard therapy for most autoimmune diseases, does not play a role in the treatment of fibrosis in patients with SSc [3]. In addition, glucocorticosteroid treatment is associated with an increased risk of scleroderma renal crisis (SRC).

INTRAVENOUS IMMUNOGLOBULIN

Numerous papers reported a significant reduction in skin involvement, although most reports had no control groups or a small number of patients [40]. It is worth mentioning that IVIG may be an effective adjunctive therapy, along with other immunosuppressive therapies, for the treatment of active dcSSc in

patients in whom other therapies have failed. The detailed results of the therapy used in improving the patient's skin thickening are described in a 2015 article [42].

COLCHICINE

There appears to be no basis for using colchicine to treat cutaneous lesions in SSc. Evidence for its efficacy is lacking, and the risk of adverse effects with long-term use of high doses is high.

CYCLOSPORIN A

The use of cyclosporine in scleroderma patients is controversial, mainly due to the potential nephrotoxicity of this drug. However, cyclosporine used long-term at doses of 1.5–5 mg/kg b.w./day was found to reduce cutaneous sclerosis to some extent. It was not found to have a significant effect on organ changes.

RITUXIMAB

There are very numerous reports of beneficial effects of RTX on the skin in SSc. The beneficial effects of RTX on the respiratory system and skin are confirmed by an observational study conducted under the aegis of the EUSTAR group of 63 patients and the control group of 25 patients. In most cases, RTX was administered in 2 intravenous infusions of 1000 mg, 2 weeks apart. After a follow-up period of approximately 7 months in the RTX-treated group, the mean forced vital capacity (FVC) did not change significantly compared to the decrease in FVC in the control group. The mRSS decreased by an average of approximately 15%. In the group of patients with the most severe lesions according to the mRRS — the score above or equal to 16 – the decrease in the mRSS was even more significant [43].

In another retrospective EUSTAR study, 248 patients were randomised; the indication for RTX treatment was lung involvement, joint symptoms and skin involvement. Over the course of the study, the mean mRSS decreased from 15 to 10, and FVC improved. The number of painful and swollen joints decreased in patients with joint symptoms [44].

Daoussis et al. studied 8 patients who received 4 cycles of RTX. Each cycle consisted of 4 weekly infusions of RTX (375 mg/m^2), with a follow-up of 2 years. Improvements in skin tone were observed, as well as improvements in skin histopathology — in the form of a reduction in skin collagen deposits and myofibroblast score [45, 46]. Similar observations were made by Smith et al. [47] and Lafyatis et al. [48], who showed a close relationship between the number of myofibroblasts and the mRSS, which confirms the role of these cells in skin fibrosis. The number of myofibroblasts decreased in both studies after RTX treatment. In addition to the apparent improvement in the mRSS during RTX therapy, there is also a reduction in the severity of other skin symptoms, including hypermelanosis, pruritus and calcinosis.

TOCILIZUMAB

High levels of interleukin 6 are found in both skin and serum of patients with SSc. A correlation has been shown between interleukin 6 levels and the severity of skin lesions. The efficacy of the therapy in SSc has been demonstrated in 2 double-blind clinical trials: the focuSSed study and the faSScinate study. The first study covered 212 patients — 105 received TOC and 107 received placebo, with no significant change in mean FVC in the TOC group. While it was reduced in the placebo group, no significant differences were found between the 2 groups in the skin assessment. The second study found subjective but not statistically significant improvement in FVC and mRSS values in the group treated with TOC [49, 50]. There are more reports that skin lesions may resolve after TOC treatment [51, 52].

SUMMARY

The recommendations are based on contemporary literature and take into account elements of current recommendations from other scientific societies, including dermatological societies, EULAR Scleroderma Trial and Research Group recommendations [3], British recommendations [4], French recommendations [5], and European Society of Cardiology recommendations.

In each case, treatment should be tailored to the individual needs of the patient, the clinical form of the disease, the stage of the disease, and organ complications. Treatment of patients should include not only pharmacology but also patient and family education.

ARTICLE INFORMATIONS AND DECLARATIONS

AUTHOR CONTRIBUTIONS

The authors declared that the percentage contribution to the manuscript is as follows: MB 70%, MKM 10%, OGS 10%, KP 5%, PK 5%.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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REVIEW ARTICLE

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Psychodemographic characteristics of patients with rheumatic diseases in clinical trials: Preliminary findings

ABSTRACT

Introduction: Clinical trials are an integral part of medical progress. Today, it would be difficult to imagine modern medicine without them. Clinical trials make it possible not only to assess the efficacy of new therapies but also their safety profile. Unfortunately, the increase in complexity of clinical trial protocols that have been observed in recent decades makes patient recruitment for clinical trials increasingly difficult. Patients not only have to meet strictly defined inclusion and exclusion criteria but also have to adapt their daily lives to the requirements of clinical trials.

Aim: This study aims to develop psychodemographic characteristics of patients with rheumatic diseases who had completed at least one clinical trial.

Material and methods: Sixty-nine (50K/19M) patients with rheumatic diseases were included in the study. The mean age of patients included in the study was 50.8 ± 12.9 years and the mean duration of disease was 13.1 ± 9.3 years. The inclusion criterion for the study was the completion of at least one clinical trial. Patients enrolled in the study completed **a** questionnaire in which questions covered demographic data, subjective assessment of financial status and health status, and reasons for participating in the clinical trial.

Results: Patients participating in clinical trials include 66.5% of those with a secondary or higher education. Fifty-nine percent of patients rate their financial status as average and 61% of patients are economically active. Eighty-nine percent of patients rate their health status as poor or very poor before entering the clinical trial.

Conclusions: Patients participating in clinical trials are generally those with long disease duration, poor health status and a financial status that does not allow them to buy biologics.

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KEY WORDS: clinical trials; rheumatoid arthritis; psoriatic arthritis; systemic lupus erythematosus; rheumatic diseases

INTRODUCTION

Modern medicine is developing much more rapidly than it did in the past. However, many diseases still require the introduction of new therapies to effectively treat patients. Therefore, it is necessary to continue scientific research into new therapies and, as a result, also conduct clinical trials. Clinical trials can be considered as a bridge between science and routine medical practice. Their aim is to both assess the efficacy and safety of new therapies.

Currently, the top priority in clinical trials is to protect the rights of each study participant — to ensure safety. The regulations are defined by the 1964 Declaration of Helsinki and, in the case of clinical trials, Good Clinical Practice (GCP) is the basis.

Clinical trials aim to produce reliable data so that drugs that are both effective and have a very high safety profile can be brought to

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market. Regulations in this area are governed by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in Europe and the United States, respectively.

In previous decades, clinical trials were not always conducted according to ethical principles. Currently, clinical trial protocols are much more rigorous and great emphasis is placed on patient safety. Before this change, many myths about clinical trials emerged, which can still divide and electrify the public opinion today.

Unfortunately, the bad reputation of clinical trials is not without a real basis. In the history of medicine, drugs such as rofecoxib (Vioxx) or thalidomide have left a bad mark [1, 2]. It is also worth recalling the recent history of the AIDS drug trial in New York, which sparked controversy even within the medical community [3, 4].

Thalidomide, which causes phocomelia, was a drug marketed in a completely different era. The 1950s and 1960s in terms of scientific research methodology significantly differed from today's standards.

However, rofecoxib is no longer such a distant history. In a way, rofecoxib shows how the analysis of research results can be difficult — even for specialists. It would seem that the statistical analysis is a tool that provides a very objective assessment of the data. In reality, it turned out to be quite the opposite. The research findings, including the safety profile of the drug, were published in one of the most prestigious journals in the medical field — "New England Journal of Medicine" [6]. The story of this publication has shown that even the best reviewers cannot guard against mistakes. In addition to editors and reviewers, for a certain period of time even readers failed to catch some inconsistency in the conducted analysis [6].

It should be noted that rofecoxib was also used in patients with rheumatoid arthritis (RA). Before rofecoxib was withdrawn from the market, there were even published findings indicating that not only was it more effective than placebo but also its safety profile was similar to placebo [7].

The Internet, which is now the first source of knowledge for patients, is home to many such stories. Some of them, like those presented above, may be true but others have more in common with science fiction than truth.

From a scientific perspective, the stories discussed above are fortunately the infamous exceptions. Hundreds of clinical trials are currently underway around the world, which are conducted with integrity i.e., respecting ethics, legal standards, and modern scientific methodology. Naturally, well-conducted clinical trials do not generate much interest from the media.

However, the current problem of finding patients who are willing to participate in clinical trials is not only related to the bad reputation of clinical trials. Paradoxically, difficulties in recruiting patients also result from the previously taken remedial steps, which have led to minimising stories like the three mentioned above.

Over the past two decades, there has been an unprecedented increase in the complexity of protocols in the history of clinical trials [8]. Changes to clinical trial protocols resulted in two major consequences. First and foremost, the cost of conducting clinical trials has increased. A second, much more serious effect that has a measurable impact on patient recruitment is the increased duration of clinical trials [8].

The process of including a patient in a trial is time-consuming – both from the perspective of the potential patient and the researcher. Moreover, patients usually have to meet very strict inclusion and exclusion criteria. For this reason, increasing importance is being placed not only on finding patients who meet all the criteria but also on finding patients who will not drop out of the clinical trial within a few months.

Modern trial protocols are highly demanding for patients. They heavily interfere with their lifestyle — for example, through frequent visits to the doctor or the need to spend several hours at the centre to complete all the procedures required by the trial protocol. For this reason, there is an increasing emphasis on patient education aimed at encouraging patients to participate in clinical trials. The problem of patient recruitment is so serious that both the EMA and the FDA have begun to promote clinical trials to potential participants [8].

In addition, a psychological profile of the average clinical trial participant can also be attempted. This makes it possible to identify a group of patients who are very likely to be interested in participating in clinical trials and will not drop out during the course of the trial.

AIM

This study aims to try to establish the profile of patients with rheumatic diseases who would agree to participate in a clinical trial — therapy with biologics, the availability of which is still limited in Poland.

Table 1. Demographics of the study group by sex

	Entire group
Number of patients [n]	69 (50K/19M)
Average age [years] (± SD; median; min.; max.)	50.8 (± 12.9; 51; 23; 74)
BMI [kg/m^2] (± SD; median; min.; max.)	27 (± 5; 26; 20; 39)
Number of patients with BMI ≥ 25 [n] (%)	43 (62%)
Average duration of disease [years] (± SD; median; min.; max.)	13.1 (± 9.3; 10; 1; 40)

Source: authors' own study; BMI — body mass index; SD — standard deviation

MATERIAL AND METHODS

Sixty-nine (50K/19M) patients with rheumatic diseases who had completed at least one clinical trial were included in the study. The mean age of patients included in the study was 50.8 ± 12.9 years and the mean duration of disease was 13.1 ± 9.3 years. In the study group, 40 (32K/8M) patients had RA, 17 (8K/9M) patients had psoriatic arthritis (PsA), 7 (6K/1M) patients had systemic lupus erythematosus (SLE) and 5 (4K/1M) patients had other rheumatic diseases.

Baseline data on the patients included in the study are shown in Table 1.

Patients included in the study came from four different clinical trial centres located in Bydgoszcz (two centres), Torun and Warsaw, and signed an informed patient consent form to participate in the proposed study.

The study was conducted in 2021. The only criterion for inclusion in the study was the completion of at least one clinical trial before completing the questionnaire — a self-administered survey.

Height and weight were measured in each patient.

Each patient was asked to complete a questionnaire. The questionnaire was used for collecting demographic data, including subjective assessment of both financial status and health status before and after the clinical trial, reasons for enrolling in the clinical trial and hopes associated with it.

Patients were informed before completing the questionnaire that the survey was anonymous and were asked to answer each question as honestly as possible. Patients completed the questionnaires independently, in a comfortable environment and without time pressure.

The questionnaire was designed to collect demographic data on the patients, assessing their socioeconomic status, quality of life and emotions related to their participation in the clinical trial. The answers to the questionnaire were meant to be used for creating a description and identify characteristic features of patients participating in clinical trials.

STATISTICAL ANALYSIS

Results are presented as mean ± standard deviation (SD) for continuous variables. For categorical data, the results were presented as a numerical value and percentage.

For independent continuous data, an independent t-test was used when comparing two groups. A χ^2 test was used for comparison of categorical data. $P \leq 0.05$ was considered statistically significant.

MedCalc® Statistical Software version 20.120 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) was used for calculation and drawing of graphs.

RESULTS

Tables 2–5 show the basic data on the socioeconomic status of the patients included in the study.

Table 6 shows the subjective assessment of patients' health status before and after inclusion in the clinical trial.

DISCUSSION

When analysing the data presented in Tables 1–7, the profile of a patient participating in clinical trials forms a logical whole. It is important to note the conditions specific to Poland before attempting to describe the average patient who participates in and, most importantly, completes a clinical trial.

Access to biological therapies in Poland under the National Health Fund (NHF) is very low. The percentage of patients with rheumatic diseases who receive biological therapies is in the order of 2% [9]. This is partly related to the criteria a patient has to meet to start this type of treatment under the NHF. For example, in Drug Programme B.33, patients must

Table 2. Education level of patients included in the study

	Entire group (n = 69)
Incomplete primary [n]	0 (0%)
Primary [n]	4 (6%)
Vocational [n]	19 (27.5%)
Secondary [n]	27 (39%)
Higher [n]	19 (27.5%)

Source: authors' own study

Table 3. Subjective assessment of patients' financial status

Financial status	Number of patients [n]
Poor	4 (6%)
Average	41 (59%)
Good	23 (33%)
Very good	1 (1%)

Source: authors' own study

Table 4. Patient status

	Entire group (n = 69)
Patient lives with their family [n]	59 (86%)
Patient lives alone [n]	10 (14%)

Source: authors' own study

Table 5. Source of livelihood

	Entire group (n = 69)
Professional work [n]	42 (61%)
Invalid pension as a result of rheumatic disease [n]	9 (13%)
Early retirement pension as a result of rheumatic disease [n]	4 (6%)
Invalid pension/early retirement as a result of other diseases [n]	11 (16%)
Dependent on family [n]	3 (4%)

Source: authors' own study

Table 6. Subjective health status assessment

Health status assessment	Before trial [n]	After trial [n]	p
Excellent	0 (0%)	1 (1%)	< 0.0001
Very good	3 (4%)	15 (22%)	
Good	4 (6%)	47 (68%)	
Poor	39 (56%)	4 (9%)	
Very poor	23 (33%)	0 (0%)	

Source: authors' own study

have previously been treated for at least three months with a minimum of two disease-modifying drugs (DMARDs), and in both cases the therapy must have been ineffective and the patient must have high disease activity at the time of trial inclusion [9]. Under the terms of Drug Programme B.33, the disease activity score (DAS28) must be greater than 5.1 which, compared to most European countries with a required DAS 28 greater than 3.2, is a significant limitation in the availability of therapy. From a clinical point of view, the conditions for inclusion in such programmes are very restrictive, resulting in a low percentage of patients who are eligible for this type of treatment in Poland.

Unfortunately, it is not the case that disease progression in e.g., RA is only apparent when disease activity is high. Several large scientific studies indicate that also patients with low disease activity or even clinical remission may experience deterioration over the following months, including progression of radiological changes that are irreversible [10].

Table 7. Presence of comorbidities

	Entire group (n = 69)
At least one comorbidity [n]	41 (59%)
Degenerative disease [n]	12 (17%)
Diabetes [n]	10 (14%)
Hypertension [n]	26 (38%)
Other* [n]	17 (25%)

*Heart diseases, diseases of the digestive system, diseases of the urinary system, thyroid diseases, osteoporosis; Source: authors' own study

According to the current knowledge, even joint inflammation at a subclinical level — i.e., when the patient has no pain or swelling in the joint and only vascular flow is visible on power Doppler ultrasound or magnetic resonance imaging — may lead to an exacerbation of the disease within a few months [10].

For the above-mentioned reasons, conducting aggressive treatment according to the treat-to-target strategy is advisable in patients with moderate or low disease activity. This not only reduces the risk of disease progression but also provides patients with a better qua-

lity of life. Patients treated with biologics are much more economically and socially active, as their physical health and mental health improve thanks to this type of therapy.

Modern therapies, especially for chronic diseases, are associated with high costs when patients attempt to access treatment privately. Even in the current situation, where biosimilars are already on the market, the cost of this type of treatment can be considered high in the Polish reality.

Therefore, if patients do not meet the eligibility criteria for Drug Programmes, their treatment options are very limited. Hence, clinical trials may be an attractive alternative for them.

These are predominantly people with a secondary or higher education. As a result, they are able to filter information, which makes them see the benefits of participating in a clinical trial, and the clinical trial stories mentioned in the introduction do not discourage them in such a case.

The majority of patients enrolling in clinical trials rate their health status as poor or very poor. This may be considered not to be an entirely subjective assessment if the average disease duration, prevalence of comorbidities and high body mass index in the study group are taken into account. This means that, from a clinical point of view, these patients are also people on whom the underlying disease has already made its mark and they are looking for ways to improve or maintain their current health status.

An additional motivation to participate in clinical trials in this group of people is that most of them live with their families and are economically active. This gives them an incentive to take care of their health for both social and economic reasons.

CONCLUSIONS

Based on the analysis of the results obtained, the following conclusions were drawn about the patients participating in clinical trials:

1. These are people who have been ill for many years and who have also developed comorbidities, which further reduce their quality of life;
2. These are economically active people with an average financial situation, which in a way forces them to seek access to modern therapies by participating in clinical trials;
3. These are very often people with secondary or higher education.

ARTICLE INFORMATIONS AND DECLARATIONS

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None declared.

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REVIEW ARTICLE

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The importance of bone mineral density and structure in fracture risk assessment of patients with rheumatoid arthritis and ankylosing spondylitis — perspectives

ABSTRACT

Osteoporosis is a metabolic bone disease that is associated with an increased risk of fractures. The increased risk of fractures in osteoporosis occurs both due to a decrease in bone mineral density (BMD) and bone microarchitecture impairment. Dual-energy X-ray absorptiometry (DXA) is the current gold standard in osteoporosis diagnosis. In a DXA scan, fracture risk is only assessed based on a BMD measurement. This is sufficient to estimate true fracture risk in the general population. Unfortunately, in rheumatic diseases, such as rheumatoid arthritis (RA) or ankylosing spondylitis (AS), BMD often increases. However, the incidence of fractures in RA/AS patients is higher than in the general population. Put together, it becomes obvious that a BMD measurement alone is not sufficient to estimate the risk of fractures in rheumatic diseases. The increase in fracture incidence is strongly associated with bone microarchitecture impairment, which is not evaluated in a standard DXA scan. Therefore, it is necessary to introduce other diagnostic methods. One such assessment is the trabecular bone score (TBS). TBS is a numerical method that can be used during a DXA scan. It allows for a fracture risk assessment in patients with rheumatic diseases, much more accurately than just a BMD measurement.

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KEY WORDS: densitometry; ankylosing spondylitis; rheumatoid arthritis

INTRODUCTION

Osteoporosis is a relatively common metabolic bone disease that increases the risk of fractures. It is estimated that approximately 9 million osteoporotic fractures occur annually worldwide, which means that an osteoporotic fracture occurs approximately every three seconds [1]. In Europe alone, it is estimated that about 32 million people over the age of 50 suffer from osteoporosis, which is about 5.6% of the population at that age — in total it is about 25.5 million women (22.1% of the population) and 6.5 million men (6.6% of the population) [2].

Osteoporosis is a serious problem from both a social and a clinical point of view. Osteoporotic fractures and their sequelae have a significant impact on patients' lives. They are associated with limited physical activity, pain, and, consequently, a decrease in the quality of life.

The development of the disease is usually asymptomatic — early diagnosis is therefore extremely important, especially in patients with an increased risk of osteoporosis.

The current gold standard in osteoporosis diagnosis is a bone mineral density (BMD) measurement based on dual-energy X-ray absorptiometry (DXA). Unfortunately, de-

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spite DXA being the gold standard, this method of fracture risk assessment has some limitations.

It is important to remember that an increase in fracture risk is not only associated with a decrease in BMD. Bone microarchitecture impairment also has a real impact on the increased risk of bone fractures. The DXA scan assesses fracture risk based only on a decrease in BMD, which is sufficient in most cases. However, clinical practice shows that there are cases in which BMD values are high, e.g. type 2 diabetes or ankylosing spondylitis (AS), but bone microarchitecture is impaired, which in turn leads to an increased risk of fractures [3]. Degenerative changes in the lumbar spine may also result in a falsely increased BMD and thus an underestimated fracture risk [4]. Therefore, it is recommended to perform scans of both the lumbar spine and the femoral neck in people over 60 years of age in the general population.

In the case of rheumatic diseases, especially AS or rheumatoid arthritis (RA), the measurement of BMD is also often insufficient. In addition, diagnostics in RA/AS patients may be made more complicated by their relatively young age — the decrease in femoral neck BMD occurs later than in the lumbar spine due to differences in bone turnover rates [4].

Therefore, fracture risk assessment based on BMD is not always reliable in patients with RA and AS. This is a great challenge from a clinical perspective, as fractures occur more frequently in both diseases than in the general population [5, 6]. Osteoporotic fractures and the progression of each disease significantly increase the degree of physical disability in patients, which leads to both therapeutic problems and a decrease in the quality of life.

For this reason, other methods of fracture risk assessment are sought in the diagnosis of osteoporosis. Quantitative computed tomography (QCT) is one such method. QCT allows for a quick and very accurate assessment of bone density that excludes the cortical bone, where degenerative changes most often occur and which have the greatest impact on BMD measurements in a DXA scan. In case of degenerative changes, QCT may be a more sensitive method than DXA in the diagnosis of osteoporosis [7, 8]. However, QCT is currently not routinely used in osteoporosis diagnosis, which may be partly related to the very large role of computed tomography (CT) in routine clinical practice. Performing QCT scans would be an additional burden for radiology departments for this method to be widely used.

Therefore, another widely available method is needed to assess bone structure. The assessment of bone microarchitecture with the use of DXA may be such a method.

TRABECULAR BONE SCORE

The trabecular bone score (TBS) was initially used in CT scans, and only later was it adopted for DXA [9]. The TBS algorithm has been implemented into DXA in such a way as to not affect how the scan is performed and, most importantly, TBS can be measured retrospectively. From a clinical standpoint, this is very important as it does not extend the duration or modify the protocol of the scan. Thanks to this, it does not constitute an additional burden for densitometric laboratories, which is one of the disadvantages of QCT in the case of radiology departments.

In a DXA scan, the assessment of bone density is based on the Beer-Lambert law [10]. As a result, a three-dimensional (3D) object that is the bone, gets turned into a two-dimensional (2D) object during the BMD calculation. Therefore, the measurement is reported as areal bone density in g/cm^2.

In the case of TBS, there is also a transition from a 3D object into a 2D model. In TBS, the differences in grayscale between pixels that make up the bone image in DXA are assessed. The greater the grayscale differences between pixels, the lower the TBS value. In turn, this means a greater bone structure impairment and thus higher fracture risk. A detailed theoretical description of TBS was presented by Pothuaud et al. in 2008 [10].

In the case of BMD, a T-score of –2.5 is the cut-off point below which osteoporosis can be diagnosed — a high risk of fractures. The cut-off value is based on empirical research. An estimated 30% of postmenopausal women have a T-score of less than or equal to –2.5, which roughly corresponds to a lifetime fracture risk [11].

In the case of TBS, there is currently no established cut-off point. It is assumed that a TBS ≤ 1.200 means a strongly impaired bone structure, which may result in a higher risk of fractures [12]. It is worth noting here that TBS has no units — it is a dimensionless quantity. This is because the TBS measurement itself is actually a numerical method and not an actual physical measurement as is the case with BMD.

TBS assessment is currently associated with several significant limitations. The first is the body mass index (BMI). Currently, it is assumed that a patient's BMI should be in the range of 15–37 kg/m^2 for an accurate TBS. Outside of this range, TBS is prone to greater

measurement error, which is directly related to the absorption of radiation by soft tissues. In addition, the TBS index is so far recommended only in the case of Caucasian patients, as further research is needed for other ethnic groups [13]. This limitation is related to differences in bone tissue microarchitecture.

In addition, there may be significant differences in the assessment of TBS between DXA devices from different manufacturers [13]. These differences may result from both differences in scanner resolution and methods of measurement. Finally, it is also worth noting that older DXA devices that use the so-called pencil beam cannot be used to measure TBS.

For the reasons mentioned above, there are no official guidelines for the use of TBS in fracture risk assessment. One of the largest societies dealing with osteoporosis diagnosis — the International Society of Clinical Densitometry (ISCD) — indicated in its latest guidelines from 2019 that a TBS measurement alone cannot be the basis for osteoporosis treatment [14]. However, it stated that TBS is associated with fracture risk in postmenopausal women, men over 50, and women with type 2 diabetes [14].

Results from the Manitoba Registry study show how important TBS may be in the future of fracture risk assessments [15]. The study retrospectively analyzed DXA scans of 47736 women and 4348 men aged at least 40, taken in 1999–2011. The analysis showed that in the case of diseases such as RA, AS, type 2 diabetes or patients treated with glucocorticosteroids (GCs), the incidence of osteoporotic fractures is higher than in the general population, despite high BMD values [15]. However, despite the high BMD measurements, TBS values were low, which reflected fracture risk much better.

IMPORTANCE OF TBS IN RHEUMATIC DISEASES

Patients with rheumatic diseases have a higher risk of osteoporotic fractures than people from the general population [5, 6]. This stems from several factors, primarily the use of GC treatments, reduced physical fitness as a result of underlying disease progression, which directly affects the risk of falls and thus increases fracture risk, or bone remodeling caused by the underlying condition.

As mentioned earlier, osteoporotic fractures in rheumatic patients are a serious problem. They worsen a patient's disability and complicate therapy.

The disease itself and the treatments used may increase BMD, therefore it is necessary to use other methods of fracture risk assessment.

Most studies examining the usefulness of TBS in rheumatic diseases indicate that in this group of patients, TBS reflects the actual risk of fractures much better than BMD alone [16].

An example of possible differences between BMD and TBS is presented in Figures 1 and 2. They present the case of an AS patient who had already suffered an osteoporotic fracture.

In the case of AS, the importance of TBS in the diagnosis of osteoporosis is demonstrated by studies carried out by two independent research groups of Richards et al. and Żuchowski et al. [5, 17]. The studies included 188 and 67 AS patients, respectively. Both studies came to identical conclusions — TBS reflects the risk of osteoporotic fractures much better than the BMD score.

In addition, Żuchowski et al. also assessed the relative risk of fractures in the study group [5]. The presence of syndesmophytes and TBS values ≤ 1.310 were associated with a more than two-fold increase in the relative risk of fractures. It is worth noting that for the general population, it is assumed that only TBS values ≤ 1.200 are associated with a significant increase in fracture risk [12].

In turn, Choi et al. conducted a study on a large population of patients with RA [18]. 279 RA patients over 50 years of age were included in the study. In the study group, 34 (13%) patients had vertebral body fractures. No significant differences were observed in BMD scores between groups of patients with and without fractures. However, as was the case with AS studies mentioned earlier, significant differences in TBS results were found. They were lower in the group of patients with fractures.

The authors of the study also drew attention to the fact that RA patients constitute one of the largest groups of patients for whom GCs are a standard treatment [18]. Glucocorticoid treatment changes the structure of the cortical bone and the trabecular bone, where significant bone structure impairment occurs [18]. This is why TBS may be a much more sensitive method for assessing fracture risk than BMD. Especially given the fact that the biggest degenerative changes occur in the cortical bone, which further increases the BMD score and thus masks the real fracture risk.

SUMMARY

TBS is an extremely useful tool in assessing the risk of fractures in patients with rheumatic diseases. This is related to an increase in BMD due to the rheumatic disease itself and the treatment used.

At the moment, the greatest limitation in the use of TBS is the lack of strict recommendations regarding diagnosis and treatment, but it can be expected that this situation will change in the coming years.

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Giant cell arteritis: Diagnostic difficulties

ABSTRACT

Giant cell arteritis (GCA) is the most common form of vasculitis present in adults. Its symptoms result from ischemia of the areas supplied by the arteries or the severity of the inflammatory reaction: headache, jaw and limb claudication, visual disturbances, blindness, stroke, polymyalgia, and fever. Because of the variety of symptoms, the disease is often overlooked in diagnostics, possibly leading to permanent ischemic complications. The current classification criteria and the gold standard for diagnostics – temporal artery biopsy – apply to the cranial form of the disease. European Alliance of Associations for Rheumatology guidelines have systematized diagnostics, based mainly on simple and reproducible ultrasound examination (ultrasonography). Despite the widespread availability of this imaging method, GCA is still diagnosed too late, and therefore the authors analyzed the possible diagnostic difficulties, based on a group of 21 patients.

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KEY WORDS: giant cell arteritis; blindness; ultrasonography

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of vasculitis diagnosed in patients over the age of 50 (15–25 cases/100 000 people). Women develop the disease twice as often [1]. The essence of the disease is an inflammatory process involving the walls of large and medium-sized arteries, usually the aorta and/or its branches, initiated from the adventitia (vasa vasorum), leading to the formation and infiltration of giant cells, hypertrophy of the intima-media layer (IMT, intima-media thickness), and subsequent deformation of the entire vessel wall [2, 3]. The symptoms are due to ischemia in the supplied areas, while the disrupted structure of the artery wall promotes the formation of aneurysms. The symptoms most commonly identified with GCA are due to extracranial artery involvement: headaches, jaw claudication, tenderness of the temporal region, visual disturbances, and irreversible blindness. There is coexisting polymyalgia rheumatica in 40% of cases. Nevertheless, more nonspecific symptoms may also predominate, related to the extracranial localization of the inflammation and the severity of the inflammatory response: limb claudication, mesenteric ischemia, myocardial infarction, cerebral stroke, fatigue, fever [1]. Giant cell arteritis should be treated as an emergency because of the consequences of vascular complications in cases of delayed diagnosis. The authors analyzed cases of patients hospitalized in the Department of Internal Medicine and Ophthalmology between 2012 and 2023, who were eventually diagnosed with GCA during the diagnostic process.

CASE REPORT

The characteristics of the patients are shown in Table 1.

Medical records of 21 patients (18 patients with the cranial form of GCA and 3 patients with the extracranial form) were analyzed. The mean age was: 75.1 years. Women accounted for 66.7%. At the time of admission, as many

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Table 1. Patient characteristics

Clinical Data	All patients (n = 21)	GCA, cranial phenotype (n = 18)	GCA, extracranial form (n = 3)
Age (mean ± SD)	75.1 (8.6)	77.4 (6.2)	61.3 (8.6)
Sex			
Female	14 (66.7%)	13 (72.2%)	1 (33.3%)
Male	7 (33.3%)	5 (27.8%)	2 (66.7%)
ESR [mm/h] (mean ± SD)	83.7 (44.6)	79.6 (46.1)	108.3 (28.9)
CRP [mg/L] (mean ± SD)	78.8 (46.5)	75.3 (47.5)	100 (40.9)
Headache (%)	n = 19; 12 (63.2%)	n = 16; 11 (68.8%)	1 (33.3%)
Jaw claudication	n = 19; 9 (47.5%)	n = 16; 9 (56.2%)	0 (0.0%)
Tenderness of the temporal area	8 (42.1%)	8 (50.0%)	0 (0.0%)
Polymyalgia	n = 19; 12 (63.2%)	n = 16; 9 (56.2%)	3 (100.0%)
Weight loss	n = 19; 7 (36.8%)	n = 16; 4 (25.0%)	3 (100.0%)
Subfebrile states	n = 19; 11 (57.9%)	n = 16; 8 (50.0%)	3 (100.0%)
Duration of symptoms (months), mean ± SD	n = 19; 4.1 (2.9)	n = 16; 3.4 (2.2)	8.0 (3.5)
Monocular blindness	n = 17; 11 (64.7%)	n = 14; 11 (78.6%)	0 (0.0%)
Binocular blindness	n = 17; 4 (19.0%)	n = 14; 4 (22.2%)	0 (0.0%)
CT or MR imaging diagnostics with contrast	16 (76.2%)	13 (72.2%)	3 (100.0%)

CRP — C-reactive protein; CT — computed tomography; ESR — erythrocyte sedimentation rate; GCA — giant cell arteritis; MR — magnetic resonance; SD — standard deviation

as 64.9% had monocular blindness, while 19% had binocular blindness. The mean erythrocyte sedimentation rate (ESR) value was: 83.7 mm/h, wherein patients with the extracranial form of GCA had a higher ESR value (108.3 mm/h). Patients with the cranial phenotype declared headaches (68.8%) and jaw claudication (56.2%). The mean duration of symptoms until diagnostics was 4.1 months. The duration of symptoms was longer (8 months) in patients with the extracranial form.

During hospitalization, all patients underwent ultrasound of the head and neck arteries (temporal, carotid, and vertebral arteries, axillary arteries were not evaluated). The IMT complex was not measured in all patients. The examination was performed by radiologists. The halo sign of the temporal artery was visualized in two cases. Computed tomography (CT) or magnetic resonance imaging scan of the head was performed in 72.2% of patients with the cranial form. An magnetic resonance imaging device with a magnetic field strength of 1.5 T (Tesla) was used. Computed tomography scans of the thorax, abdomen, and pelvis with contrast were performed in all patients with the extracranial form. One case included thickening of the aortic wall on a CT scan in a patient without cranial symptoms, diagnosed because of high inflammatory parameters. The suspicion of GCA was suggested by the radiologist in that case. Ultimately, the diagnosis was confirmed by positron emission tomography (PET)/CT with fluoro-18-deoxyglucose radiopharmaceutical (^{18}F-FDG-PET/CT) or temporal artery biopsy. The diagnosis was based on the typical clinical picture and response to treatment in 6 patients of the Ophthalmology Department when a biopsy of the temporal artery was impossible. Treatment based on steroid pulses was started in all patients with visual disturbances before the biopsy result was obtained, based on the high clinical probability, with diagnostics carried out at the same time.

DISCUSSION

It seems that GCA is characterized by low awareness among doctors. The pre-hospital diagnostics took several months. Visual disturbance or diagnostics of elevated parameters of inflammation were the reason for hospitalization. The percentage of patients with visual impairment was high.

What causes diagnostic difficulty and how to improve it?

The current 1990 American College of Rheumatology classification criteria refer to cranial symptoms [4]. These include 5 clinical aspects:

— age > 50 years;
— ESR > 50 mm/h;

— new localized headache;
— tenderness of the temporal artery on palpation;
— temporal artery biopsy result.

These criteria have limitations. Neither of these constitute diagnostic criteria. They concern cranial localization and do not include progress in terms of new imaging methods. New validated 2022 classification criteria include:

— age ≥ 50 years;
— six clinical criteria (morning stiffness of the neck or shoulder girdle, sudden blindness, jaw or tongue claudication, new headache of the temporal region, tenderness of the scalp area, abnormalities on temporal artery examination);
— lab, imaging, and biopsy results (ESR > 50 mm/h or C-reactive protein > 10 mg/L, positive temporal artery biopsy or temporal artery "halo" sign on ultrasound, bilateral axillary artery involvement on imaging tests, abnormal glucose uptake in the descending and abdominal aorta on PET scan) [5].

The 2018 European Alliance of Associations for Rheumatology (EULAR) recommendations systematized diagnostics, recommending temporal artery ultrasound as the first imaging method in patients with suspected cranial manifestations of GCA [6]. The sensitivity of this test is 77%, with a specificity of 96%. The "halo" signs, which are not subject to compression, is representative of GCA [7–9]. If temporal artery evaluation does not yield valid diagnostic results, the axillary arteries or other extracranial arteries should be evaluated next. This is because the axillary arteries and other large vessels may be involved in 50% of cases [10]. Atherosclerotic lesions are localized less frequently in the axillary arteries than in the carotid arteries, making reliable imaging assessment difficult.

The Omeract Group (Outcome Measures in Rheumatology Clinical Trials) for ultrasound in large vessel vasculitis defines normal appearance of the extracranial artery ("pulsatile, hardly compressible, with anechoic lumen"), IMT complex ("homogeneous, hypoechoic or anechoic structure delineated by two hyperechoic lines"), and halo sign as "homogeneous, hypoechoic thickening of the wall, well delineated in the direction of the lumen, visible in both longitudinal and transverse planes, usually concentric in transverse scans" [11]. The cutoff points for minimum IMT in GCA are not established in the recommendations. Atherosclerosis is a common pathology in the GCA patient age group, and results in an IMT increase [12]. Various studies have used different IMT cutoff points, yet there is no defined consensus to date [13–18]. Giant cell arteritis on the axillary artery ultrasound is characterized by the specific "slope sign" — the nature of increased IMT thickness transition to normal thickness [19]. EULAR recommendations also specify the technical parameters of the equipment: 15 MHz linear transducers for temporal arteries and 7–15 MHz for extracranial supra-aortic arteries, and sectoral or convex transducers for aortic arch evaluation. The sensitivity and specificity of ultrasound in GCA were estimated based on tests involving equipment with recommended parameters. CT angiography can be used as a tool in extracranial artery assessment. The thickening of the arterial wall and post-contrast enhancement of the vessel wall in the delayed venous phase, which can manifest as a double ring (inner hypoechoic ring and outer hyperechoic ring), are typical for this condition. Berthod et al. [20] suggest 2.2 mm for assessing aortic thickness as the optimal threshold for diagnosing GCA.

EULAR guidelines recommend using equipment with a magnetic field strength of 3 T (3 Teslas) in GCA diagnostics, particularly for extracranial artery evaluation. The sensitivity and specificity of this test are 75% and 89%, respectively. ^{18}F-FDG-PET/CT allows evaluation of all arteries, including aortic branches, which can be difficult with CT alone, due to vessel size, and also enables differential diagnosis of diseases with similar symptoms (tumors, infections). The sensitivity of the test is estimated at 67–77%, with specificity at 66–100%.

The value of positive radiographic imaging results is increased by EULAR's recommendation not to perform temporal artery biopsies in cases with high clinical probability [6].

Based on history, physical examination, and diagnostic imaging, a rapid diagnostic pathway algorithm for confirming or ruling out GCA was proposed by Sebastian et al. [21]. Southend Pretest Probability Score classifies patients into low, intermediate, and high clinical probability categories for GCA. Probability is assessed based on clinical data: age, sex, duration of symptoms, CRP value, headache, polymyalgia symptoms, ischemic symptoms, visual disturbances, and temporal and extracranial artery abnormalities that are

scored accordingly. The next step is to recommend further diagnostic tests if GCA is likely, with the first test being ultrasonography of the temporal and axillary arteries (a value > 0.29–0.42 mm was considered to be abnormal wall thickness in the temporal, and > 1 mm in the axillary artery, respectively), possibly followed by other imaging tests.

It should be noted that the foregoing algorithm is based on cooperation between the clinician and the ultrasonographer.

The examples provided by our patients prove that this disease is overlooked in diagnostics. The authors hoped that the awareness of both its symptoms and radiological picture, already well documented in the literature and recommendations, will be increased among physicians, resulting in an accelerated diagnostic pace and reduced severe complication rate.

SUMMARY

Giant cell arteritis is overlooked in outpatient diagnostics, as evidenced by months of symptoms and a high rate of ischemic complications in patients admitted to the hospital. At the same time, the paper points out that diagnostic imaging is problematic in facilities with less experience. An ultrasound protocol aimed at ultrasonographers and radiologists describing the arterial evaluation, IMT values, ultrasound signs of GCA well documented in the literature, and technical parameters of medical devices could be helpful.

ARTICLE INFORMATIONS AND DECLARATIONS

DATA AVAILABILITY STATEMENT

The authors declared that the manuscript meets the requirements of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

ACS and JRW — development of concepts and assumptions, writing of the paper. EP — methodology. DK and AK —statistics and data analysis. MDŚ — interpretation of results.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

SUPPLEMENTARY MATERIAL

None.

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CONFERENCE REPORT

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World Scleroderma Foundation and European Scleroderma Trials and Research Group Jubilee

The celebrations of the tenth anniversary of the World Scleroderma Foundation (WSF) and the twentieth anniversary of the European Scleroderma Trials and Research group (EUSTAR) were held on 30 May 2023 in the halls of the Leonardo da Vinci National Museum of Science and Technology (Museo Nazionale della Scienza e della Tecnologia Leonardo da Vinci) in Milan. The WSF is a non-governmental, non-profit foundation established in Switzerland with the aim of initiating, developing and supporting research into systemic scleroderma and supporting patients with the disease. The WSF is committed to improving the quality of life of patients and conducting research, as well as cooperating with other organisations and associations to achieve these goals while remaining independent of regional authorities, political organisations and industry. Among its objectives, the WSF pursues its goals by organising world congresses on systemic scleroderma, supporting research projects, providing research grants, setting up expert teams and supporting education on systemic scleroderma. The Journal of Scleroderma and Related Disorders is the official organ of the WSF.

The idea of multicentre collaboration in systemic scleroderma research originated at the end of the 20th century. In 2002, the EUSTAR group was established with Marco Matucci Cerinic from Florence as one of its main initiators. Florence was also the venue for the group's working meetings and the first Systemic Sclerosis World Congress. In 2004, EUSTAR was awarded the status of an EULAR-supported group and the name of the group was the acronym for EULAR Scleroderma Trials and Research. According to the EULAR statutes, the research group should have become independent after ten years, which posed a problem for the EUSTAR group because the pharmaceutical industry was less interested in systemic scleroderma than in other diseases. After the establishment of the WSF, the group became part of the WSF and changed its name to European Scleroderma Trials and Research while retaining the same acronym. Today, EUSTAR brings together more than 200 clinical and research centres working on the disease and holds an immense database, which has been instrumental in publishing more than 50 valuable scientific papers that significantly advance various aspects of systemic scleroderma. EUSTAR also organises training courses and activates young researchers.

Figure 1. Milan, 30 May 2023. Dame Carol Black accompanied by Przemysław Kotyla and Eugeniusz J. Kucharz

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Figure 2. Milan, 30 May 2023. From right: Przemysław Kotyla, Maurizio Cutolo, Eugeniusz J. Kucharz, Daniel Furst, Anna Kotulska-Kucharz

The anniversary celebrations began with a short film, after which the audience was welcomed by Marco Matucci Cerinic, for many years the tireless *spiritus movens* of the worldwide movement for research on systemic scleroderma. This was followed by a presentation by Thomas Krieg on the WSF research grant system, and then he and Ulrich Schanbacher introduced this year's scientific award winners. This year, additional special research grants were awarded to young scientists from Ukraine, enabling three off them to carry out work in Italy and one in France.

The next item on the agenda was a session led by Piet van Riel and Sue Farrington presenting the history, achievements and plans of WSF and EUSTAR. The opening lecture was delivered by Dame Carol Black. It was entitled: "The Pillars of Scleroderma" and spoke about the pioneers of research on systemic scleroderma, including Stefania Jabłońska. The background of the founding of EUSTAR and WSF was interestingly presented by Allan Tyndall, and the history of EUSTAR courses was discussed by László Czirják. It was nice to hear him speak warmly about the course held with the support of the Polish Society of Rheumatology in Katowice in 2015, as well as about the participation of Poles (lecturers and trainees) in training during the courses. Yannick Allanore told the story of cooperation between EULAR and EUSTAR. Daniel Furst presented the history of the development of classification criteria for systemic scleroderma, Ulf Müller-Ladner spoke about the DeSSCipher study aimed at optimising therapeutic strategies, and the participation of a group of young researchers in the work of EUSTAR was presented by Corrado Campochiaro, Michael Hughes, Maria Grazia Lazzaroni and Tania Santiago.

The current EUSTAR leaders (Francesco Del Galdo, Marie Elise Truchelet, Madelon Vonk) presented the current activities and future plans of the group.

Masataka Kuwana (one of the two editors-in-chief) discussed the development of the "Journal of Scleroderma and Related Disorders", and Maurizio Cutolo presented a brief outline of the history of capillaroscopy and its application in the diagnosis of systemic scleroderma. The sessions were concluded by Marco Matucci Cerinic, recalling, among other things, the links with the family of Paul Klee (1879–1940), a painter who suffered from systemic scleroderma. His grandson, Alexander Klee, supported the establishment of the WSF and also gave permission to use the star motif from two of Paul Klee's paintings in the emblems of EUSTAR and the WSF. The ongoing interaction of the WSF and EUSTAR with the patient associations affiliated with the Federation of European Scleroderma Associations (FESCA) was also mentioned.

The last element of the conference component of the jubilee were speeches discussing the philological aspects of the term TEAM (Gianluca Giadima di Maulo Errico) and orchestra as an example of teamwork (Irina Khodossevitch). It should be mentioned that the motto of the meeting, and in a sense of all activities of the WSF and EUSTAR, are the words once uttered by Frank Wollheim: "United we win".

After a coffee break in the museum's columned hall, the participants listened to a piano concert and then attended a gala dinner held in the museum's gallery, in a former monastery building.

Figure 3. EUSTAR emblem featuring a star motif from a painting by Paul Klee

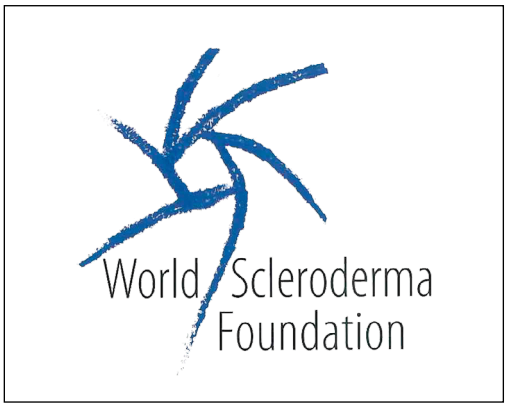

Figure 4. WSF emblem also featuring a star motif from a painting by Paul Klee

There was no shortage of Polish highlights at the ceremony. Since the first years of EUSTAR's establishment, Polish physicians and Polish rheumatology centres have participated in its work. The most significant contribution to the international movement for the research of systemic scleroderma has been made by Otylia Kowal-Bielecka, who was unable to come to Milan. She is the coordinator of the successively updated therapeutic recommendations and has also participated in many of EUSTAR's research and organizational projects. During the presentation of past and present activities of the WSF and EUSTAR, the successful organisation of the 2015 scleroderma course in Katowice was mentioned, and in the historical part, the contributions of Stefania Jabłońska to the understanding of systemic scleroderma as well as the International Conference on Scleroderma and Scleroderma-Like Diseases held on 24–28 June 1991 organized by Stanisław Sierakowski and Krystyna Bernacka and colleagues in Świeradów-Zdrój were mentioned. In backstage conversations, scientific visits to Poland were warmly recalled by Dame Carol Black, Maurico Cutolo, Daniel Furst and László Czirják, among others. Poles have taken an active part in all previous Systemic Sclerosis World Congresses. The jubilee meeting in Milan was attended by invited Polish rheumatologists Przemysław Kotyla, Anna Kotulska-Kucharz and Eugeniusz J. Kucharz.

Systemic scleroderma is a disease that persistently hides its secrets. Recent years have shown that despite many difficulties and gaps in the understanding of its pathomechanism, we can increasingly treat and diagnose the disease earlier and help our patients in a variety of ways.

ARTICLE INFORMATIONS AND DECLARATIONS

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CONFLICT OF INTEREST

None.