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ОБЗОРЫ
REVIEWS

A SYSTEMATIC REVIEW OF POINT-OF-CARE ULTRASOUND (POCUS) OF MULTIORGAN ASSESSMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract. Background: Systemic lupus erythematosus (SLE) can affect multiple organs, presenting a diverse array of clinical symptoms. In recent years, Point-of-Care Ultrasound (POCUS) has become increasingly accessible, supported by robust evidence. POCUS can be particularly beneficial for evaluating SLE patients improving diagnostic accuracy and reducing time-to-decision. **Purpose:** To systematically identify the assessment of SLE patients through the use of POCUS. **Methods:** The data sources MEDLINE, EMBASE, LILACS, Google Scholar and ProQuest One Academic were used, English and Spanish languages were included, no limits regarding publication date or age, and review articles were excluded. Articles screening and data extraction were performed by two authors independently. Disagreements were resolved through a third author. Organ or system evaluations using POCUS were collected. **Results:** A total of 52 articles met the inclusion criteria. Assessment using POCUS detected various acute and chronic complications arising from SLE, particularly articular and cardiac compromise. Synovitis and pericardial effusion were the most frequently reported complications. Most of the reports (92%) did not specify whether they evaluated other organs with POCUS. **Limitation:** Most of the studies were case reports. **Conclusion:** Multiorgan POCUS assessment in patients with SLE, especially those suspected of disease activity, holds the potential to offer improved evaluation of SLE complications and activity. Studies are needed to develop a standardized multiorgan assessment protocol for SLE using POCUS to improve diagnosis and treatment.

Key words: early diagnosis, lupus erythematosus, systemic, point-of-care ultrasound, POCUS, systematic review, ultrasound

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease, characterized by the production of autoantibodies with a heterogeneous systemic affection [1]. The global incidence of SLE is between 1.4 and 15.3 cases per 100,000 person-year [2]. This disease presents numerous complications affecting multiple systems and organs. There are global registries including GLADEL from Latin America [3], Euro-Lupus from Europe [4], RELESSER from Spain [5], CSTAR from China [6], and the Hopkins Cohort from the United States [7] that provide valuable insights in SLE characteristics (Table 1).

In recent years, the use of Point of Care Ultrasound (POCUS) as a diagnostic tool for physicians

has gained prominence. The integration between the clinician (excluding radiologist or cardiologist) and the ultrasound at the bedside of the patient leads to diagnosis or treatment response follow up [8]. This diagnostic tool has shown potential to increase diagnostic accuracy, appropriate treatment and decrease time-to-decision or time-to-treatment [9].

Currently, there is a limited literature on the use of POCUS as a physical exam extension in SLE patients. Incorporating POCUS to identify and evaluate various organs or systems involvements in SLE could enhance diagnostic accuracy and efficiency. There is no protocol, data, or systematic review published until the date this study is conducted regarding the use of POCUS as a multiorgan assessment for patients with SLE in any clinical scenario. There-

Table 1. Different global cohort comparison of cumulative organ involvement of lupus manifestation

Characteristic/Cohort	GLADEL 1	EuroLupus 2	RELESSER 3	CSTAR 4	Hopkins Lupus Cohort 5
Publication Year	2004	2009	2015	2013	2014
Country/s	Argentina, Brazil, Colombia, Cuba, Chile, Guatemala, Mexico, Peru and Venezuela	Spain, United Kingdom, Italy, Poland, Turkey, Norway and Belgium	Spain	China	United States
Number of patients	1214	1000	4024	2104	1354
Sjögren Syndrome	-	-	14.4%	-	-
Serositis	Pericarditis: 17.2% Pleuritis: 22.1%	16%	28.1%	16.4%	-
Respiratory/Pulmonary	6.1%	-	30.6%	5.5%	17.1%
Cardiovascular	42.9%	-	28.2%	3.5%	16%
Vascular / Vascular Thrombosis	5.6%	9.2%	37.6%	-	7.4%
Renal (Total)	51.7%	27.9%	32.1%	47.4%	10.3%
End-Stage renal disease	1.7%	-	2.8%	-	-
Musculoskeletal (Total)	-	-	80.1%	-	40.6%
Arthritis	93.2%	48.1%	77.9%	53.5%	-
Weight Loss (nutritional)	26.6%	-	9.9%	-	-

fore, there is a gap in the knowledge of the usage of POCUS for this specific population. To address this gap, we conducted a systematic review of the literature on the use of POCUS to evaluate both acute and chronic complications in SLE patients and to know the actual situation of the usage of POCUS for SLE in any clinical scenario.

METHODS

This systematic review of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10]. Studies included addressed the assessment outcome of any SLE complication identified by POCUS. It was registered in PROSPERO (CRD42024529087).

Data Sources and Searches

The search was done using the following databases: MEDLINE via PubMed, EMBASE, LILACS via Virtual Health Library, Google Scholar, and ProQuest One Academic. To include clinical trials, meeting abstracts, thesis, and gray literature it was also used: ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), Cochrane Central Register of Controlled Trials, The Kings Fund (England), The New York Academy of Medicine (United States), doctoral thesis: TESEO (Spain) and LARreferencia (Latin America) (URL exposed in appendix). The en-

try terms and webpage for each database are shown in the Appendix.

Study Selection

Studies in English and Spanish were included. No limits regarding publication date, age, or geographical location were used. Eligible studies were those utilizing POCUS or bedside ultrasound to detect any lupus complication. This encompasses the use of POCUS as an adjunctive tool in the clinical assessment of lupus-related complications or differential diagnoses. Studies that solely utilize ultrasound as a diagnostic test separated from clinical assessment or guidance or presented as echocardiography by a cardiologist or ultrasound by a radiologist were excluded. Additionally, studies lacking explicit specifications of the use of bedside ultrasound, POCUS, or clinical ultrasound in the context of lupus-related assessments were excluded. Studies with insufficient information about the use and findings of POCUS were also excluded. Clinical cases, randomized control trials, case and control studies or cohort studies could have been included if found. It excluded reviews or any document that does not contain original data. Also, references cited in study reports included in the systematic review were explored and incorporated if considered. The study selection was done by two reviewers (SGJ and SJ). In case a disagreement appeared, a third reviewer made a deci-

sion (JAN). The records screened were exported to Rayyan, where decisions were recorded.

Data Extraction and Quality Assessment

Extracting data from reports using titles and abstracts was done by two independent reviewers (YA and SJ) and if a disagreement appeared a third reviewer made a decision (JAN). If there is unreported data, investigators tried to contact the study author. Biases were evaluated according to the type of studies by one author (SGJ or SJ). In case series or case reports, the criteria of Murad MH, et al. [11] were followed; in observational studies the The Risk Of Bias In Non-randomized Studies (ROBINS-I) scale [12] was used and for randomized studies the Cochrane risk-of-bias tool was used.

Data Synthesis

From the selected studies the following were extracted: number of patients, patient age, country of study/case, complication observed using POCUS, operator's specialty, presence of lupus activity and setting where the POCUS was used. Information was synthesized and proportion and distribution trends were calculated.

Role of the Funding Source

There was no funding source for this research.

RESULTS

The literature search returned 1036 records, after deleting duplicates 880 were screened, and finally, 736 were ruled out following exclusion criteria. From the reports assessed for eligibility 96 were excluded. Additionally, 34 records were included by other methods. A PRISMA flow diagram was created (Figure 1).

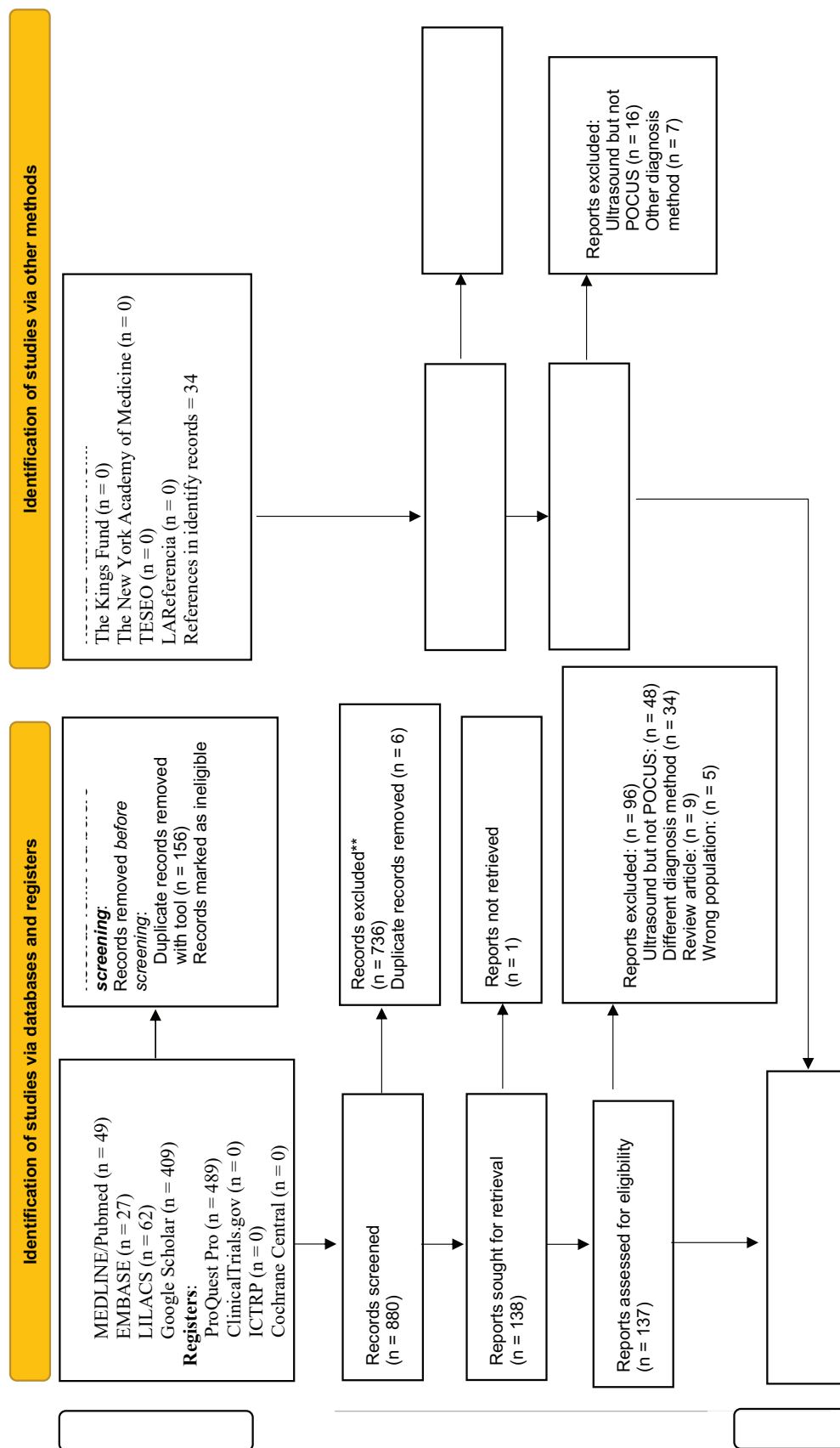
Finally, in this systematic review 52 reports regarding the use of POCUS while assessing a patient with SLE were included (Table 2). The total number of patients from all reports was 1262 subjects. Most of the reports came from Europe representing 44%; primarily from Italy (27%), followed by North America with 37%; mainly from the United States (33%), Asia with 15%, and Latin America with 4%. There were no reports from Oceania or Africa (Fig. 2). The most common types of studies were clinical cases representing 54% ($n = 28$), followed by cross-sectional studies 40% ($n = 21$) and prospective studies just 6% ($n = 3$). It must be noted that 92% of the reports from the USA were case reports. All the reports from Italy addressed the musculo-skeletal system involvement and had a cross-sectional or prospective methodology.

Musculoskeletal affection was present in 44%, serosal in 35%, cardiac in 15%, veins in 10%, and pulmonary in 6% of the studies. The musculoskeletal system accounted for most of the total of 1262 patients, representing 96.2% of patients (1214 patients); serositis represented 2.7% of patients and all the remaining represented just 1.6% of the patients. This is mainly affected by the method used in musculoskeletal reports and the high frequency of serositis. Regarding the number of systems evaluated, 92% of the reports POCUS only assessed one system and 8% of reports describe its use in more than one system. If used for other complications, the most reported was serositis or cardiac abnormality. However, there was no protocol established for multiorgan assessment, and only the cross-sectional or prospective studies used an established one-system protocol.

Rheumatologists performed the POCUS in 38% of the reports, but only to evaluate musculoskeletal pathology. It was followed by emergency physicians in 12% of reports, but only to evaluate pericardial or cardiac abnormality. The primary location where POCUS was used was the emergency room (45%), followed by the rheumatology unit (20%), and it was not mentioned in 22% of reports.

There were 23 reports (44%) that evaluated musculoskeletal compromise. These studies assessed synovitis, bone erosions, enthesitis, and tenosynovitis [13-34]. Regarding synovitis, it was the most common finding, reported in 19 of the 23 reports. Upper limbs synovitis was present in 31% of musculoskeletal reports ($n = 16$) and lower limbs synovitis in 17% ($n = 9$). The most common joint involvement was the wrist and metacarpophalangeal (MCP) joints, followed by proximal interphalangeal (PIP), knee, and ankle, and less reported the metatarsophalangeal (MTP), elbow, shoulders, and hips, represented in figure 4. The highest incidence of synovitis was 87% in a population of 67 patients in one of the reports [23]. The relationship between synovitis identification by POCUS and the disease activity usually defined by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was identified in nine reports; three of them were found a statistically significant relationship ($p < 0,05$) [19, 20, 22] and 6 of them no relationship ($p > 0,05$) [23-25, 27, 29, 31]. In two reports, it was found a relationship with serological markers such as erythrocyte sedimentation rate or anti-dsDNA antibodies ($p < 0,05$) [24, 27]. From prospective studies, one demonstrated that baseline power Doppler

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Fig. 1. PRISMA 2020 flow diagram for systematic reviews

Table 2. Systematic review data

#	Author	Year	Country	Type of research	Number of patients (n)	Complication or differential diagnostic observed	Other organs evaluated or ruled-out with POCUS	Lupus status (Active or non active)	Operator	POCUS Setting
1	Yu M. et al. 41	2023	China	Case report	1	Pericardial tamponade	NR	Active	NR	Emergency room
2	Li W. et al. 42	2017	USA	Case report	1	Pericardial effusion and plethoric inferior vena cava	NR	Active	NR	Emergency room
3	Walsh BM. et al 71	2015	USA	Case report	1	Right ventricle: dilated, with akinesis of the free wall, McConnell's sign, augmented end-diastolic diameter. Septal bowing during systole.	Left ventricular function, no pericardial effusion, no aortic root dilatation.	Non-active	Emergency physician	Emergency room
4	Palkar A. et al. 43	2017	USA	Case report	1	Bilateral B-lines, mitral jet of mitral regurgitation in long-axis and 4-chamber, pericardial effusion	Normal smooth pleural line, normal left ventricular function, normal right/left size ratio, normal aortic and mitral valves,	Non-active	NR	NR
5	Shokoochi H. et al. 44	2016	USA	Case report	1	Rupture of a left ventricular apical pseudoaneurys	NR	Not-reported	Emergency physician	Emergency room
6	Nunes G. et al. 45	2016	Brazil	Case report	1	Pericardial effusion, reduced ejection fraction and hypocontractility of the left ventricle.	NR	Active	NR	Emergency room
7	Ayat P. et al. X cita	2023	USA	Case report	1	Pericardial effusion	NR	Active	NR	Emergency room
8	Botros M. et al. 46	2022	USA	Case report	1	Inferior vena cava larger than 2 cm, ratio E/e' of 15.6 (elevated filling pressure).	NR	Non-active	NR	Emergency room
9	Lee H.J. et al. 70	2019	USA	Case report	1	Pleural effusion and pericardial effusion.	Normal cardiac contractility. The leg ventricular ejection fraction.	Active	NR	Emergency room
10	Argaiz E. Et al. 47	2022	Mexico	Case report	1 of 2	Dilated inferior vena cava, portal vein pulsatility of 77% (severe) and decreased to 33% after compressing arterio-venous fistula.	NR	NR	NR	NR
11	Zhao Y. et al. 101	2021	China	Case report	1	Left perirenal fluid collection.	NR	Active	Not reported	Nephrology Unit
12	Kahl N. et al. 90	2021	USA	Case report	1	D sign, Right ventricular dilation. Flattening of the septum indicating decreased left ventricular systolic function. Non compressive right femoral vein	NR	NR	NR	Emergency room
13	Larson N. et al. 48	2018	USA	Case report	1	Large pericardial effusion with evidence of right ventricular collapse.	NR	Active	NR	Emergency room
14	Noorvash D. et al. 113	2018	USA	Case report	1 of 2	Free fluid in the peritoneum	NR	NR	NR	Emergency room

#	Author	Year	Country	Type of research	Number of patients (n)	Complication or differential diagnostic observed	Other organs evaluated or ruled-out with POCUS	Lupus status (Active or non active)	Operator	POCUS Setting
15	Gomez-Casanovas J. et al. 49	2023	USA	Case report	1	Pericardial effusion, bilateral pleural effusions, and hyperdynamic heart with enlarged right ventricle	showed a normal left ventricular cavity with ejection fraction of around 55%	Active	NR	NR
16	Buda N. et al. 85	2017	Poland	Case report	2	hypochoic sub-pleural consolidation and bilateral B-lines (alveolar hemorrhage)	NR	Active	NR	Emergency room
17	Goswami RP. 84	2016	Switzerland	Case report	1	Shrinking lung syndrome	NR	Active	NR	Emergency room
18	Ma Z. et al. 50	2013	USA	Case report	1	Cardiac Tamponade	NR	Active	NR	Emergency room
19	Aljasmí R. et al. 51	2023	United Arab Emirates	Case report	1	Cardiac Tamponade	NR	Active	NR	Emergency room
20	Jimenez W. et al. 52	2023	Colombia	Case report	1	Cardiac Tamponade, Bilateral pleural effusion, ascites	NR	Active	Emergency physician	Emergency room
21	Tio M. et al. 53	2022	Indonesia	Case report	1	Pericardial effusion, and ascites	NR	Active	NR	Emergency room
22	Farkouh F. Et al. 54 (Abstract)	2023	USA	Case report	1	Pericardial effusion	NR	Active	NR	NR
23	Ch Rahul. et al. 109	2021	India	Case report	1	Hepatic portal venous gas (HPVG) suggestive of necrotizing enterocolitis (NEC)	NR	Active	NR	NR
24	Cho G. et al 77	2022	USA	Case report	1	Pleural effusion	NR	NR	Untrained physician and expert physician	NR
25.	Mantovani Cardoso et al. 55	2020	USA	Case report	1	Pericardial effusion	NR	Active	NR	Emergency room
26.	Yousif P. et al. 56	2022	USA	Case report	1	Pericardial effusion	NR	Active	Emergency physician	Emergency room
27	Puticiu M (Conference Abstract) 57	2012	Romania	Case report	1	Pleural and pericardial effusion, free abdominal fluid. Optic nerve evaluation.	Pleural and pericardial effusion, free abdominal fluid	Active	NR	Emergency room
28	Mandavia et al. 58	2001	USA	Prospective cohort study	19 of 478	Pericardial effusion: 42% (n = 8)	NR	Active	Emergency physician	Emergency room
29.	Hans P et al. 114	2020	Canada	Case report	1	Rhabdomyolysis (hypochoic areas of muscle, disorganization of the fascicular architecture, irregularity of the muscle fibers, and some hyperchogenicity in the muscle)	NR	Active	Emergency physician	Emergency room
30.	Marozzi et al. 82	2024	Italy	Cross-sectional	1 of 33	Interstitial lung disease (B-lines)	NR	Active	NR	NR

#	Author	Year	Country	Type of research	Number of patients (n)	Complication or differential diagnostic observed	Other organs evaluated or ruled-out with POCUS	Lupus status (Active or non active)	Operator	POCUS Setting
31.	Ogura T. et al. 80	2016	Japon	Cross-Sectional	15 of 55	Synovitis: 80%. In: wrist, MCP, PIP, thumb IP Tenosynovitis: 93%	NR	Both	Rheumatologist	Rheumatology Unit
32.	Ceccarelli F. et al. 16	2017	Italy	Cross-Sectional	17	Synovitis: effusion: 88.2%, synovial hypertrophy: 76.5%, PD: 29.4%. In: wrist, MCP, PIP Bone erosions: 58.8%	NR	Both	Rheumatologist	Inpatient clinic
33.	Di Matteo A. et al. 17	2017	Italy	Cross-Sectional	25	Synovitis: effusion: 9.5%, synovial hypertrophy: 11.5%, both: 14%. PD: 30% of 85 joints. In: wrist, MCP, PIP, knees, feet, ankles, elbows, shoulders, hips. Tenosynovitis: 17.7%. Enthesitis: 24.2% entheses. Bone erosion: 2.1%.	NR	Both	Rheumatologist	Rheumatology Unit
34.	Piga M. et al. 18	2022	Italy	Cross sectional	26	Bone erosions: 5.9% areas	NR	Both	Rheumatologist	NR
35.	Fagni et al. 19	2023	Italy	Cross-sectional	106 of 400	Enthesitis: 29.2%. In: Shoulder, DIP, Elbow, greater trochanter, knee, ankle, plantar fascia and achilles tendon	NR	Active	Rheumatologist	NR
36.	Di Matteo A. et al. 20	2018	Italy and Czech Republic	Cross-Sectional	65	Enthesitis: 67.7%. In: patella, Achilles, quadriceps and plantar fascia	NR	Both	Rheumatologist	Inpatient clinic
37.	Ceccarelli et al. 21	2019	Italy	Cross-sectional	106	Synovitis. In: wrist, MCP, PIP and knees	NR	Both	Rheumatologist	NR
38.	Smiljanic Tomicevic L. et al. 22	2022	Croatia	Cross-Sectional	60	Synovitis: 53.3%. In: ankle. Tendinitis or enthesitis: 21.7% Bone erosion: 1.6%	NR	Both	Rheumatologist	Rheumatology Unit
39.	Gabba A. et al. 23	2012	Italy	Cross - sectional	108	Synovitis: 25%. PD: 12%. In: wrist and MCP. Tendon abnormality: 40%. Bone erosions: 25.9%	NR	Both	Rheumatologist	Rheumatology Unit
40.	Torrent-Segarra V. et al. 24	2012	Spain	Cross-sectional	58	Synovitis: hypertrophy or effusion: 25%, wrist synovitis: 14.2%. In: wrist, MCP, PIP. Tenosynovitis: 39.2%	NR	Both	Rheumatologist	Rheumatology Unit
41.	Lagnocco A. et al. 25	2014	Italy	Cross-Sectional	62	Synovitis: 87.1%. In: wrist, MCP, PIP, MTP,	NR	Both	Rheumatologist	Rheumatology Unit
42.	Ho-Shung Y. et al. 26	2014	South Korea	Cross-Sectional	48	Synovitis: 58.3%. In: wrist, MCP. Tenosynovitis: 4.2%	NR	Both	Rheumatologist	Rheumatology Unit
43.	Ossandon A. et al. 27	2009	Italy	Cross Sectional	26 of 66	Synovitis: 58%. PD: 10%. In: knee	NR	Non-active	Rheumatologist	Rheumatology Unit

#	Author	Year	Country	Type of research	Number of patients (n)	Complication or differential diagnostic observed	Other organs evaluated or ruled-out with POCUS	Lupus status (Active or non active)	Operator	POCUS Setting
44.	Delle-Sedie A et al. 28	2009	Italy	Cross Sectional	50 of 100	Synovitis: wrist: 80%, MCP/PIP: 50%. In: wrist, MCP, PIP. Tenosynovitis: 22%. Bone erosion: 0.5%.	NR	Non-active	Rheumatologist	Rheumatology Unit
45.	Mosca M. et al. 29	2015	Italy	Cross Sectional	102	Synovitis: 42.2% PD: 10.7%. In: wrist, MCP, PIP Tenosynovitis: 38.2%. Bone erosion: 31.4%.	NR	Non-active	Rheumatologist	NR
46.	Demirkaya E. et al. 30	2009	Turkey	Cross-sectional	30	Synovitis: 60% (knee) – 10.3% (elbow). In: wrist, MCP, elbow, knee, ankle Tenosynovitis: 23.3%	NR	Active	Physiatrist	Rheumatology unit
47.	Morales-Lozano R. et al. 31	2016	Spain	Cross-Sectional	54 of 114	Synovitis. In: MTP, ankle.	NR	Both	Podologist	Outpatient clinic
48.	Dreyer L et al. 32	2014	Denmark	Cross-Sectional	33	Synovitis: 48% (wrist) and 21% (MCP). Tenosynovitis: 18%. Bone erosion: 6%.	NR	Both	Rheumatologist	Not reported
49.	Iagnocco A. et al. 36	2004	Italy	Cross-Sectional	26	Synovitis: 42.3%. PD: 9.6%. In: wrist. Bone erosion: 3.8%. Tenosynovitis: 3.8%	NR	Both	Rheumatologist	Rheumatology unit
50.	Mukherjee S. et al. 34	2016	England	Cross-Sectional	20	Synovitis: 80% (MTP) - 60% (MCP).	NR	Both	Rheumatologist	Rheumatology unit
51.	Piga M. et al. 35	2016	Italy	Prospective (5-year)	80	Baseline: effusion or hypertrophy: 18.8%, PD: 10% In: wrist, MCP, PIP, elbows, knee, ankle, MTP Bone erosions: Baseline = 5%. Final visit = 16.3%. Tenosynovitis: baseline = 37%.	NR	Both	Rheumatologist	Outpatient clinic
52.	Guillén-Astete et al. 36	2024	Spain	Longitudinal prospective 10-year	96	Synovitis: baseline = 74.9%. In: wrist, MCP, PIP.	NR	NR	Rheumatologist	Inpatient clinic

Unless otherwise indicated, percentage values are patients. In synovitis data, unless otherwise indicated, it represents the total percentage of synovitis presented.

JE: Joint Effusion, MCP: Metacarpo-phalangeal, MTP: Metatarso-phalangeal, NR: Not Reported, PIP: proximal interphalangeal, PD: Power-Doppler, ST: subtalar, TT: Tibio talar,

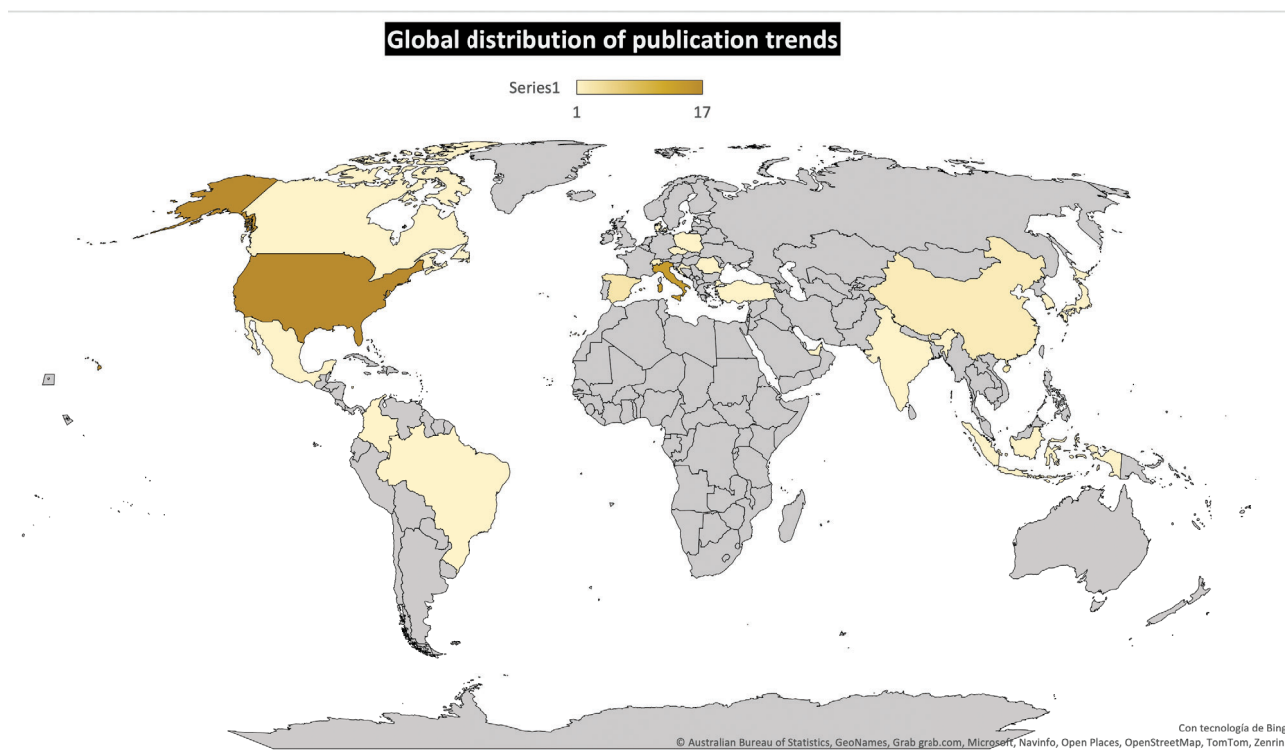


Fig. 2. Global distribution of publication trends of POCUS utilization in SLE patients included in the systematic review (Graphic created using Microsoft Excel)

synovitis was an independent predictor factor for a 2-year SLE flare ($p < 0,05$) [33]. Baseline subclinical synovitis is associated with joint compromise progression in less time than patients without this baseline abnormality [34].

Other musculoskeletal findings included one report of rhabdomyolysis evaluation using POCUS [35]. Also, enthesitis was reported in four studies, with a frequency between 5.9% to 67.7% [15, 17, 18, 20]. Bone erosions were described in 19% ($n = 10$) of reports with frequencies between 0.5% and 24.1% [15, 16, 21, 26, 33]. It must be noted that regarding the musculoskeletal system, there was no evaluation by internal or emergency medicine, and no reports from North or South America were identified.

Concerning serosal involvement, pericardial affection was reported in 33% of reports, making it the most common report of extra-articular SLE complication [36-52]. Frequently, pericardial involvement was described at the same time as pleural effusion or ascites. Pleural effusion was present in 10% of reports [41, 43, 46, 51, 53]. Ascites were described in 4% of reports [47, 52].

There were six studies evaluating the cardiovascular system. In two reports the authors exposed

any abnormality in the left ventricle (LV), reporting hypocontractility with reduced ejection fraction, and abnormal E wave/e' wave ratio (E/e') [39, 54]. It must be highlighted that in another 8% of reports, there was a description of normal ventricular function evaluation through POCUS [41, 43, 54, 55]. Evaluation of the right ventricle for pulmonary hypertension signs was described in 4% of reports and with thromboembolic disease final diagnosis in only one of those [55, 56].

Lung findings were present only in 6% of reports describing interstitial lung disease, alveolar hemorrhage, and shrinking lung syndrome respectively [57-59]. In three reports, fluid overload was evaluated through inferior vena cava diameter dilatation and in one of the hepatic vein [37, 60, 61]. As for abdominal findings, intra-abdominal bleeding was documented in two reports, and in one report necrotizing enterocolitis was described [62-64]. Finally, in one report the optic nerve was evaluated, but the findings were ruled out to be pathological [51].

The risk of bias was evaluated using the proposed tools (Table 3, appendix).

Appendix. Table 3. Risk of Bias of Included Studies**Case reports Studies. Murad et al. tool**

	Selection	Ascertainment	Causality				Reporting	Overall Risk of Bias (1-8)
Yu M. et al. 36	1	1	1	1	0	1	1	7
Li W. et al. 37	1	1	1	1	0	1	1	7
Walsh BM. et al 55	1	1	1	1	0	1	1	7
Palkar A. et al. 54	1	1	1	0	0	1	0	5
Shokoohi H. et al. 38	1	1	1	0	0	1	1	6
Nunes G. et al. 39	1	1	1	0	1	1	1	7
Ayat P. et al. 40	1	1	1	1	0	1	0	6
Botros M. et al. 60	1	1	1	0	0	1	1	5
Lee HJ. et al. 41	1	1	1	1	0	1	1	7
Argaiz E. et al. 61	1	1	1	0	0	1	0	5
Zhao Y. et al. 62	1	1	1	1	0	1	1	7
Kahl N. et al. 56	1	1	1	1	0	1	0	6
Larson N. et al. 42	1	1	1	1	0	1	1	7
Noorvash D. et al. 63	1	1	1	1	0	1	1	7
Gomez-Casanovas J. et al. 43	1	1	1	1	0	1	1	7
Buda N. et al. 59	1	1	1	1	0	1	1	7
Goswami RP. 58	1	1	1	0	0	1	1	6
Ma Z. et al. 44	1	1	1	1	0	1	1	7
Aljasmi R. et al. 45	1	1	1	1	0	1	1	7
Jimenez W. et al.46	1	1	1	1	0	1	1	7
Tio M. et al. 47	1	1	1	1	0	1	1	7
Farkouh F. Et al 48	1	1	1	1	0	1	1	7
Ch Rahul. et al. 64	1	1	1	1	0	0	1	6
Cho G. et al. 53	1	1	1	1	0	1	1	7
Mantovani Cardoso et al. 49	1	1	1	1	0	1	1	7
Yousif P. et al. 50	1	1	1	1	0	1	1	7
Puticiu M 51	1	1	1	0	0	1	1	5
Hans P et al. 35	1	1	1	1	0	1	1	7

As the study evaluated the use of POCUS; the original question included in the Murad et al. tool "Was there a challenge/rechallenge phenomenon?" was not taken into account. The scores of 4 or less points indicate high risk of bias.

[illegible]

DISCUSSION

In this systematic review, we found 52 studies where POCUS had been used to evaluate systems such as the musculoskeletal or cardiovascular systems in patients with SLE (Table 2). There were cross-sectional studies for musculo-skeletal system, one prospective study for the respiratory system, one for pericardial involvement, and various case reports of isolated organ or system evaluation. These findings highlight that the use of POCUS for a structured multiorgan assessment of patients with SLE is none.

Systemic lupus erythematosus (SLE) complications may affect broad systems and organs, including joints, muscles, lungs, heart, pleura, pericardium, peritoneum, maxillary glands, kidneys, aorta, pancreas, liver, intestines, skin, and nervous system. Epidemiology exhibits a globally heterogeneous distribution shaped by regional differences [2] (Table 1). POCUS may improve the evaluation of the multiorgan involvement associated with SLE.

Musculoskeletal

Regarding the musculoskeletal system, joint involvement can be seen between 48% in the European cohort and 93% in the Latin American cohort [3, 4] (Table 1). A linear transducer can be used to assess joints as exposed by the European League Against Rheumatism (EULAR) procedure basis and wrist, hands, elbow, shoulder, hip, knee, ankle, and foot can be evaluated [65]. All of these joints were reported, although the elbow, shoulder, and hips were exposed only in one report [15]. As documented in this systematic review, POCUS can evaluate most joints, although its capabilities may be limited depending on the type of transducer used.

Most of the reports evaluated joint effusion, synovial hypertrophy, and power Doppler signal to evaluate joint synovitis (Table 2). In the OMERACT definition of 2005, the Doppler signal was not necessary, and this was used in ten studies [19-21, 23, 24, 26, 27, 29, 30, 33]. However, the OMERACT definition was revised in 2019, as a significant number of healthy individuals were found to have similar ultrasound abnormalities [66]. The presence of joint effusion which is now excluded in the new definition, and Doppler signal activity is now mandatory for defining synovitis [66]. Only one study refers to this new definition [34]. This may be mainly affected by the year of each report. Statistically significant relationships between synovitis and SLE activity or laboratory market were identified in some of the records. Consequently, it demonstrates the potential utility of POCUS on therapeutic and prognosis

Regarding the relationship between synovitis identification by POCUS and the disease activity usually defined by Systemic Lupus Erythematosus disease activity index 2000 (SLEDAI-2K) was identified in nine reports; three of them found a statistically significant relationship ($p < 0,05$) [19, 20, 22] and 6 of them no relationship ($p > 0,05$) [23-25, 27, 29, 31]. In two reports it was found a relationship with serological markers such as erythrocyte sedimentation rate or anti-dsDNA antibodies ($p < 0,05$) [24, 27]. From prospective studies, one demonstrated that baseline power Doppler synovitis was an independent predictor factor for a two-year SLE flare ($p < 0,05$) [33]. The other is that baseline subclinical synovitis is associated with joint compromise progression in a lesser time than patients without baseline abnormality [34].

Regarding bone erosions, it has been described that in autoimmune diseases such as rheumatoid arthritis, the presence of early bone erosions during the disease is a poor prognostic factor [67]. Clinical importance in patients with SLE has not been clearly studied, but in one report it appears their presence does not affect the patient's quality of life [33]. There was only one muscular assessment, reporting rhabdomyolysis [35].

Serosal: pericardial and pleural

Serositis was the most common diagnosis after synovitis. With an incidence of between 16 to 28% in the Latin America, Europe, China, and Spain cohorts [3-6] (Table 1). Approximately 25% of all patients with SLE develop symptomatic pericarditis at some point through the course of the disease [68]. The effusion can be identified in a parasternal of a four-chamber view, and additional related findings may consist of diastolic collapse of the right ventricle, systolic collapse of the right atrium, and plethoric inferior vena cava with respiratory variation [69]. In three reports was described hypocontractility of the left ventricle [39], right ventricular collapse [42], and enlarged right ventricle [43].

Pleural effusion has been reported in up to 22% of SLE patients [3]. The diagnosis using ultrasound, compared to radiography for pleural effusion, demonstrates a sensitivity of 94% and a specificity of 98% in a meta-analysis [70]. Moreover, it performs well when conducted by novices-to-POCUS residents after training [71].

Cardiovascular

Cardiovascular complications may account for as much as 42% as reported in the GLADEL cohort, and as low as 3.5% in China's CSTAR cohort (Table 1). Affection of this system includes valvular involve-

ment, Libman-Sacks endocarditis, left or right ventricular dysfunction and aortic aneurysm.

Mitral valve prolapse appears to occur more frequently in patients with SLE, estimated to occur in 21% of SLE cases versus 5.5% of controls in one study [72]. Long-axis, short-axis, and apical four-chamber, two-chamber, three-chamber, and five-chamber views could be obtained, allowing for a qualitative assessment of valvular appearance, calcification, and degree of dysfunction [73]. Studies report that POCUS has a sensitivity and specificity between 48 to 100% for valvular heart disease [74]. Only 1 study reported mitral regurgitation [54].

Libman-Sacks endocarditis has a prevalence between 6 and 11% in patients with SLE. An autopsy study reported the presence of this condition in 50% of lupus cases [75]. Initial evaluation by POCUS could include the presence of any mobile densities on the valves or valvular insufficiency [76], although reports in this systematic review did not identify this complication.

Left ventricular dysfunction in SLE can be multifactorial, including the presence of lupus myocarditis (prevalence of 8 to 25%) [77], ischemic heart disease (incidence 9.6 events per 1,000 person-years) [78], or antimalarial-induced cardiomyopathy, which may present as congestive heart failure in 77% of cases [79]. Evaluation includes assessing symmetric endocardial movement, myocardial thickening, and the movement of the mitral valve's maximal opening point (E-Point) [80]. Quantitative measures such as E-point Septal Separation (EPSS) could be employed; a measurement of less than 2 mm indicates a high level of certainty for normal left ventricular ejection fraction [81, 82]. In one report they report hypocontractility and reduced ejection fraction, but there is no information on the quantification method used [39]. Right ventricle evaluation is discussed in the pulmonary complications section.

Aortic aneurysms may also be identified using POCUS, although it is uncommon [83]. The POCUS examination could include exploration of the aorta from the epigastrium to the distal bifurcation, including differentiation of its shape and caliber, thrombus in the lumen or signs of dissection [84]. There was not a report exploring this.

Respiratory

Respiratory or lung findings in SLE are among the most affected system/organs and can vary sig-

nificantly. The distribution of lung abnormalities includes interstitial lung disease, pulmonary embolism, and pulmonary hypertension reported in order of incidence [85]. Additional possible findings include infectious pneumonia, shrinking lung syndrome, and diffuse alveolar hemorrhage. Evaluating dyspnea assessment, POCUS reduces the-to-diagnosis by 63 minutes, and the time-to-treatment by 27 minutes and has a higher likelihood of receiving appropriate treatment compared to those cases not using POCUS [9].

Interstitial lung disease in SLE has a prevalence of 6% [86]. This complication may be observed in the POCUS assessment by the presence of irregular, fragmented, thickening, blurred, or coarse pleural line, bilateral or unilateral B-lines, and consolidations less than 5 mm [87, 88]. Even more, in connective tissue lung disease the diagnosis performance of B-lines, compared to high-resolution computer tomography scan, found a pooled sensitivity of 91,5% and specificity of 81,3% [89]. POCUS examination for this disease takes five to seven minutes and an additional three minutes for record registration using protocol [87]. There was a report evaluating interstitial lung and it showed a non-inferiority of the inclusion of the artificial intelligence algorithm: SenseUS Lung compared to expert-ultrasonography [57].

In shrinking lung syndrome, ultrasound provides real-time dynamic information and quantification of diaphragmatic contraction velocity, duration of the diaphragmatic cycle, and inspiratory time through M-mode [90]. In the only report included, it was suspected on the basis of reduced diaphragmatic movement compared to the patient's healthy sister [58]. Unfortunately, it was not used for follow-up after treatment with rituximab [58]. Diffuse alveolar hemorrhage can present as a hypoechoic subpleural consolidation along with B-lines as were described in one report identified [59].

Pulmonary hypertension has a prevalence of 8% among the SLE population and may progress to heart failure, often manifesting with right ventricular findings observed on POCUS [91]. Evaluating the tricuspid annular plane systolic excursion (TAPSE) which is a marker of right ventricle function. Although, most of the right ventricular evaluations are related to lung complications [92]. Studies suggest that visual TAPSE estimation is easy to learn and it may be a viable substitute for measurements by emergency physicians.

As a main cause, pulmonary thromboembolic disease has a prevalence in SLE of 1.29% [93]. Es-

pecially when antiphospholipid syndrome increases this risk. For detecting the presence of deep vein thrombosis in legs, compression ultrasonography must be performed, as the vein wall is weaker than the arterial wall, it will collapse in the absence of solid content in its interior, and when no solid content is present (thrombus) [94]. It offers high sensitivity (95%) and specificity (96%), a shorter examination time (<4 min), and a shorter learning period [95]. In one study, the presence of right heart findings with the POCUS that are commonly found in pulmonary embolism did not lead to that diagnosis, as the patient had normal angiotomography [55]. On the other hand, the other report that found this abnormality along with deep vein thrombosis POCUS's findings did lead to pulmonary embolism diagnosis [56].

Kidneys and overload

Highlighting that end-stage kidney disease may develop in 1.7-2.8% of cases [3-5]. POCUS can assess kidney size, echogenicity, and cortical thickness in cases of chronic disease [96]. Although two reports presented lupus nephritis, they did not describe kidney evaluation, and there was not a report of any acute kidney injury [60, 61]. Using this tool can also rule out hydronephrosis or any other anatomical urinary tract alteration in cases of hematuria or acute kidney injury [97]. Compared to tomography, POCUS has a sensitivity of 72% and specificity of 73% for hydronephrosis detection, and depending on the experience of the operator sensitivity can increase to 92 % [98]. As it may be necessary before adding some points to the SLEDAI 2K score. In patients with lupus nephritis, who are undergoing hemodialysis, POCUS plays an important role in evaluating fistula diameter, depth, maturity, and facilitating cannulation [96]. In one report for the evaluation of an arterio-venous fistula, they evaluated the portal vein pulsatility change after compression of the fistula [61].

Additionally, it is important to note that POCUS is useful for evaluating fluid overload. This includes chronic complications leading to congestion, such as lupus nephritis that could need renal replacement therapy. It may have increased utility in acute situations that require high-volume administration, such as sepsis or acute pancreatitis. Congestion can be assessed using the Venous Excess Ultrasound Score (VExUS). Evaluation utilizing power Doppler of the suprahepatic, portal, and renal veins highly correlated to venous congestion [99]. Although in the reports when evaluating the inferior

vena cava, even if it was dilated, they did not describe the VExUS score to quantify congestion [37, 60, 61].

Gastrointestinal and Hepatobiliary

Manifestations of the gastrointestinal and hepatobiliary tract may be broad, it may include lupus enteritis, pancreatitis, intestinal pseudo-obstruction, vasculitis of small or large intestines, hepatitis, and acalculous cholecystitis [100, 101]. Intra-abdominal bleeding can also be detected, as the report of perirenal hemorrhage and abdominal aortic aneurysm rupture is included in this systematic review [62, 63]. Also, there was a rare case report of necrotizing enterocolitis identified by the presence of hepatic vein gas presence POCUS [64]. POCUS may have an important role in the right clinical scenario, especially in SLE patients with acute abdominal pain.

Activity: SLEDAI-2K score

The SLEDAI 2K is a score that evaluates clinical and paraclinical activity manifestation, and a mean score of ten points is associated with all-cause mortality [102]. For 24 different variables, POCUS may be used to assess pleural and pericardial effusion and arthritis by joint effusion, summing it may provide up to eight points. POCUS may provide faster calculation of the SLEDAI score. From most of the records, this score was reported to expose the activity, although none of them linked with the usage of POCUS to calculate it.

It must be remarked that POCUS may be used to evaluate many other possible systemic complications that may arise in SLE patients: for example, secondary Sjögren syndrome, cutaneous lesions, malnutrition, or central and peripheral nerve system affections. Alternatively, it could be used to document the improvement or worsening of affected organs after treatment initiation. Multiorgan Ultrasound Lupus Assessment possibilities are represented (Fig. 3).

Limitation

The main limitation of the study was that a considerable number of reports were case reports. This takes a higher amount of bias and less reproducible information. It is also important to note that in many reports the authors did not report who performed the POCUS, where it was done, if they evaluated other organs or if they used a protocol for assessment.

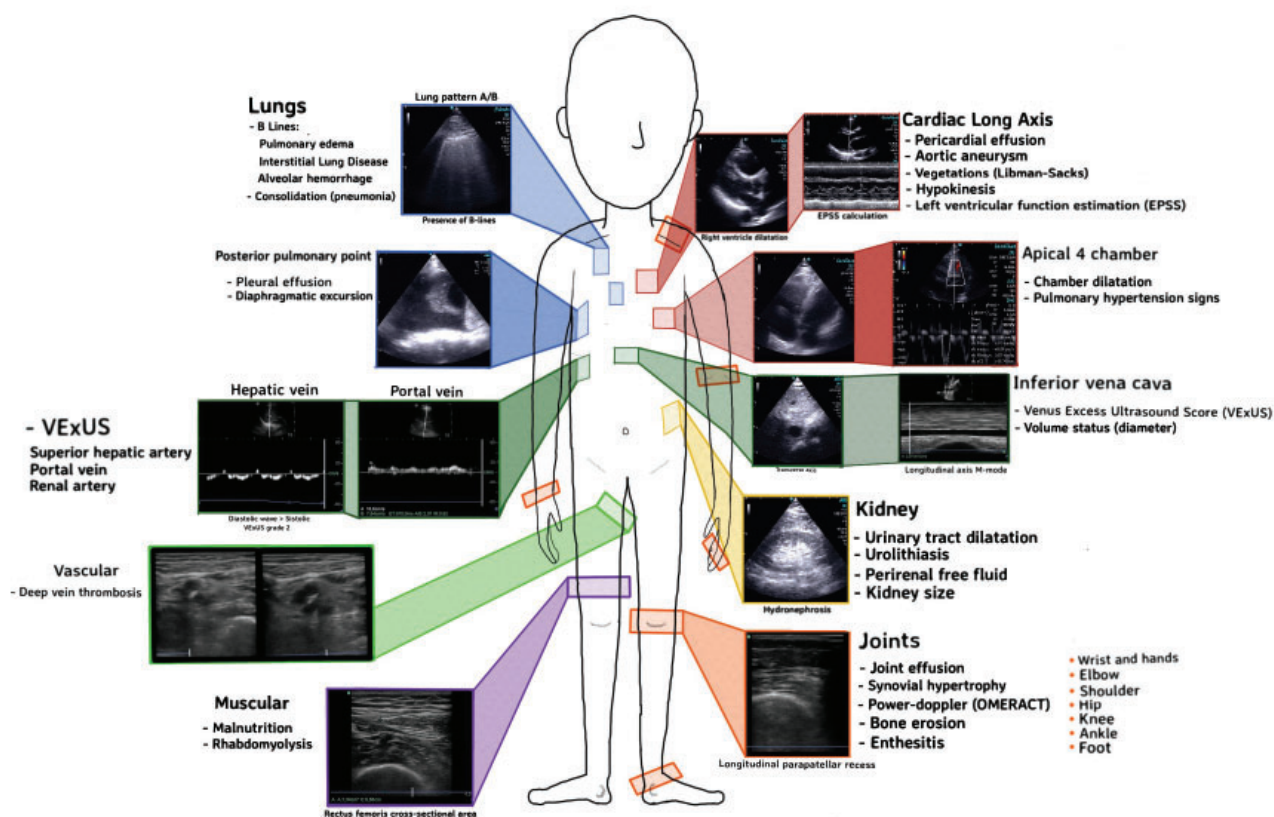


Fig. 3. Multiorgan Ultrasound Lupus Assessment (Image created using Takayasu Sketches)

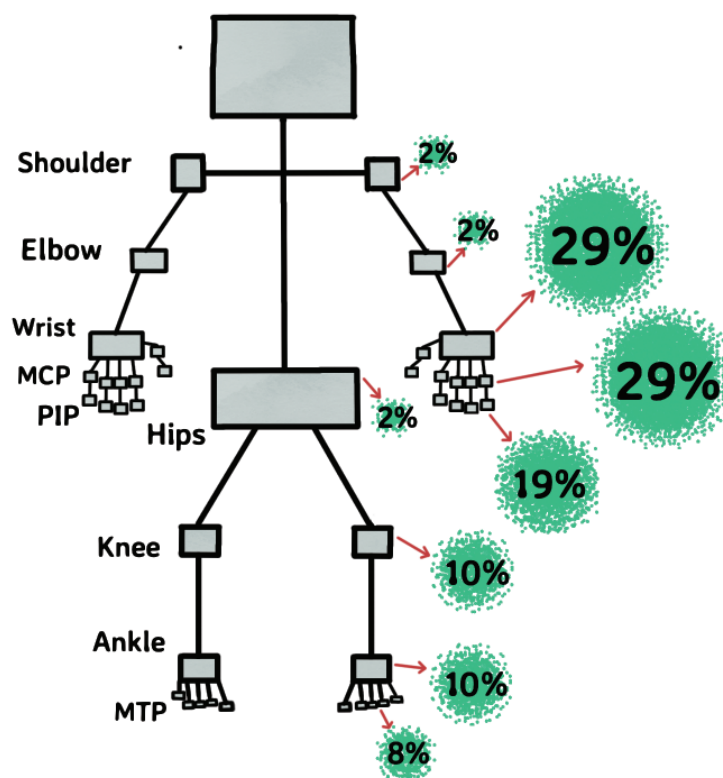


Fig. 4. Joint involvement distribution among the 23 records regarding the musculoskeletal system. (Image created using Takayasu Sketches)

CONCLUSIONS

This systematic review revealed that POCUS remains underutilized in evaluating SLE complications. These reports showed that POCUS was primarily used for the evaluation of one system or one organ. Notably, POCUS assessments mainly occur in emergency rooms under the purview of emergency physicians to evaluate the cardiovascular system or, in a rheumatology unit, to evaluate musculo-skeletal affection, overlooking other clinical settings and specialties. Addressing these gaps requires robust research to establish standardized protocols and explore their application.

Furthermore, taking into account the performance capacity and impact in diagnosis, follow-up, and treatment decisions in acute and chronic complications of POCUS in SLE, thus it may be more emphasized in practice. It is necessary to promote training and application of multiorgan assessment by POCUS in all clinical scenarios to systematically evaluate patients with SLE.

Author contributions: All authors approve the final version of the manuscript, and all agree to be accountable for all aspects of the work.

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EFFICACY OF CONNECTED DEVICES IN PROMOTING PHYSICAL ACTIVITY AND REHABILITATION AMONG PATIENTS WITH RHEUMATOID ARTHRITIS AND SPONDYLOARTHRITIS: A SYSTEMATIC REVIEW

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Abstract. Objective: The main objective of the study was to evaluate the efficacy of connected devices in promoting physical activity and rehabilitation among patients with IRD. Secondary outcomes were to assess their effects on disease activity, fatigue, and quality of life. **Data sources:** Key words related to connected devices, physical activity, rehabilitation, and inflammatory rheumatic diseases (IRD) (rheumatoid arthritis, spondyloarthritis, psoriatic arthritis) were used to search for intervention trials published as articles and abstracts in the databases MEDLINE, Web of Science, Scopus, American College of Rheumatology (ACR) abstract archive and European Alliance of Associations for Rheumatology (EULAR) abstract archive. No restrictions were applied in terms of publication date. **Study selection:** Interventions consisting of connected devices used for promoting physical activity and rehabilitation were included. Studies reporting the following primary or secondary outcomes were included: physical activity measurements, function of a limb region, and performance-based physical function tests. Studies reporting only disease activity outcomes or only evaluating feasibility of connected programs were excluded. **Data Extraction:** Data from each report were extracted by two researchers independently. The obtained data were narratively summarized. **Data Synthesis:** The search identified 584 studies and 15 met the inclusion criteria. The study designs were: randomized controlled trials ($n = 9$), non-randomized intervention trials ($n = 3$), cross-sectional study ($n = 1$), prospective observational study ($n = 1$), and a case-control study ($n = 1$). Promoting physical activity using a wearable device was improved significantly in one study. Among 9 studies assessing rehabilitation, a significant improvement was found in four studies for hand strength, in 2 studies for cardiorespiratory fitness, and in 2 studies for muscle endurance. Two of the 3 studies focusing mobility showed a significant increase for intervention groups. **Conclusion:** The present study indicates that connected devices are simple and safe tools to improve mainly performance-based physical function in patients with IRD. However, further studies with larger population sizes and a longer follow-up period are needed to make reliable conclusions.

Key words: telerehabilitation, wearable electronic devices, connected healthcare, rheumatoid arthritis, spondyloarthritis

INTRODUCTION

The burden of inflammatory rheumatic diseases (IRD) especially Rheumatoid arthritis (RA) and Spondyloarthritis (SpA) increased significantly, affecting millions of patients worldwide [1, 2]. They are responsible of chronic pain, joint damages with osteoarticular destructions, and deterioration of physical functioning which may reduce the health related quality of life (HRQoL) (less autonomy and dependence) and decreasing the work productivity [3]. In association with musculoskeletal diseases, IRD are estimated to be the second cause of functional disability [4]. This impairment reduces physical activity and increases sedentariness.

Physical activity is defined as “any bodily movement produced by skeletal muscles which results in

energy expenditure. Exercise is a subset of physical activity in that it is planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective” [5]. The World Health Organization (WHO) recommends “at least 150-300 minutes of moderate-intensity aerobic physical activity or at least 75-150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week” [6]. It is commonly recommended as non-pharmaceutical intervention. Physical activity plays a crucial role in general population and especially in patients with IRD. In this context, the European League Against Rheumatism (EULAR) recommends physical activity for patients with IRD [7].

For that, health care professionals should actively promote physical activity at diagnosis of inflammatory arthritis and throughout the disease course [8]. However, authors estimate that 60% of patients with IRD are away from those recommendations [9].

Physical activity may have an important preventive effect, as well as therapeutic and rehabilitative ones. It is associated with a decrease in cardiovascular risk, pain, and inflammation [10, 11]. A meta-analysis published by Billet et al. emphasizes that exercise improved HRQoL, function, and pain among patients with RA [12]. Moreover, sedentary behavior is associated with poor HRQoL in patients with SpA [13].

In fact, the promotion of physical activity and rehabilitation function for patients with IRD is a key challenge faced by medical professionals. Those interventions can be performed individually or in groups and should include behavioral change techniques in order to promote long-term adherence [14]. However, in addition to the lack of motivation, there is a lack of access to supervised community-based centers because of the important number of patients suffering from disability. This matter was raised during the COVID-19 pandemic because of restricted access to health care services, self-isolation and home quarantine [15]. Therefore, the need to develop other methods providing home-exercises and rehabilitation programs was identified to improve patient's adherence and motivation. It was necessary to found accessible tools to reduce sedentary behavior at home, to encourage patients to be more active in their daily life, continue their rehabilitation programs, and self-manage their disease [16]. Recently, modern technologies have revolutionized the health field worldwide. Connected devices such as Smartphone applications, web-interventions, and wearable devices have been widely used for health care promotion especially in cardiovascular diseases and recently in IRD [17-19]. Activity trackers were used to promote or to monitor physical activity, performance-based physical and rehabilitation. Recently EULAR published guidance on important aspects that should be considered for the development, evaluation and implementation of applications for self-management of IRD [20].

In fact, many studies including a meta-analysis have shown that home-based physical activity interventions and telerehabilitation were as efficient as specialized center interventions and conventional rehabilitation [21-23].

However, scarce information and limited evidence about the effectiveness of wearable devices

in promoting physical activity and rehabilitation among IRD patients are available. Therefore, there is a better need to summarize information about devices, different protocols, and their outcomes for this specific population. To the best of authors' knowledge, there is no systematic review assessing the effect of wearable devices on physical activity and rehabilitation among patients with IRD.

Therefore, the aim of the current study was to perform a systematic review on the efficacy of wearable devices on promoting physical activity and rehabilitation among patients with IRD. Secondary outcomes were to assess their effects on disease activity, fatigue, and quality of life.

METHODS

The updated version of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was used for the structure of this systematic review [24]. Ethical approval was not required, since this research was a systematic review of published articles.

Eligibility criteria

Intervention trials published as articles and abstracts involving rheumatic disease patients (RA, SpA, psoriatic arthritis) were included. Scientific texts published in a different language than English and French were excluded. No restrictions were applied in terms of publication date.

Interventions consisting of connected devices (games, smartphone applications, websites ...) used for promoting physical activity and rehabilitation were included.

Studies reporting outcomes regarding physical activity measurements (steps per day, physical activity questionnaires...) and rehabilitation evaluation: function of a limb region (mobility indexes, range of motion, muscular strength...), and performance-based physical function tests were included. Studies reporting only disease activity outcomes or only evaluating feasibility of connected programs were excluded.

Information sources

A research on MEDLINE, Web of Science, Scopus, American College of Rheumatology (ACR) abstract archive and EULAR abstract archive for relevant studies was performed. These databases were last searched on January 31st, 2024.

Search strategy

The search strategy consisted in intersecting key words related to the concepts of interest: con-

nected elements, physical activity and rehabilitation, and rheumatic disease. The search terms were chosen after discussion within the research team. A MeSH search in MEDLINE and a manual search in all the previously mentioned databases were performed. The following search terms were used for the identification of studies including the use of connected elements: Mobile Applications [MeSH], Software [MeSH], Smartphone [MeSH], Exergaming [MeSH], Virtual Reality Exposure Therapy [MeSH], Virtual Reality [MeSH], Telerehabilitation [MeSH], Telemedicine [MeSH], Wearable Electronic Devices [MeSH], Wearable technology, Telehealth, smart healthcare, and Connected healthcare. To identify studies targeting physical activity and rehabilitation, we used the search terms Exercise [MeSH], Warm-Up Exercise [MeSH], Physical Conditioning, Exercise Therapy [MeSH], Physical Fitness [MeSH], and physical activity questionnaire. Studies targeting rheumatic disease population were identified using the following search terms: Spondylarthritis [MeSH], Spondylitis, Ankylosing [MeSH], Spondyloarthropathies [MeSH], Arthritis, Psoriatic [MeSH], Arthritis, Rheumatoid [MeSH], and spondyloarthritis. Afterwards, reference lists of the included studies were screened for relevant publications.

Selection process

Search results were extracted into a Microsoft Excel spreadsheet. Study selection was performed by two independent researchers (HE, BDS). If there was a disagreement, the record was assessed by a third investigator (BTA). After removing duplicate articles, the first step of the selection process was title screening, followed by abstract screening, and finally full-text screening. Abstracts derived from the same study as a selected article and reporting similar results were excluded in favour of the article.

Data collection process and data items

Data from each report were extracted by two researchers independently. The following data were extracted from the included studies: authors, country of the study, year of publication, study design, inclusion and exclusion criteria, population, numbers of IRD patients and control groups, age, and sex of participants. As for rehabilitation, the following were collected: target, type of intervention, frequency, setting, duration of the intervention, follow-up, outcomes, and findings. The device of connected intervention was described.

Study risk of bias assessment

Quality assessment of included studies was performed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [25]. This tool evaluates 6 different domains: Selection bias, Study design, Confounders, Blinding, Data collection methods, and Withdrawals and drop-outs. Each domain is rated as strong, moderate, or weak. Based on the rating of each domain, an overall study quality was assigned to each study (strong, moderate, weak). The rating "Strong" was assigned to studies having no weak-rated domain. Studies having one weak-rated domain were rated as "Moderate." Studies were rated as "Weak" if they had two or more weak ratings. Each study was rated by two authors independently. In case of disagreement, consensus was reached through discussion within the research group.

Synthesis methods

A meta-analysis was not conceivable because of the disparity of the included studies in terms of intervention characteristics, and outcome measures. As a result, the obtained data were narratively summarized.

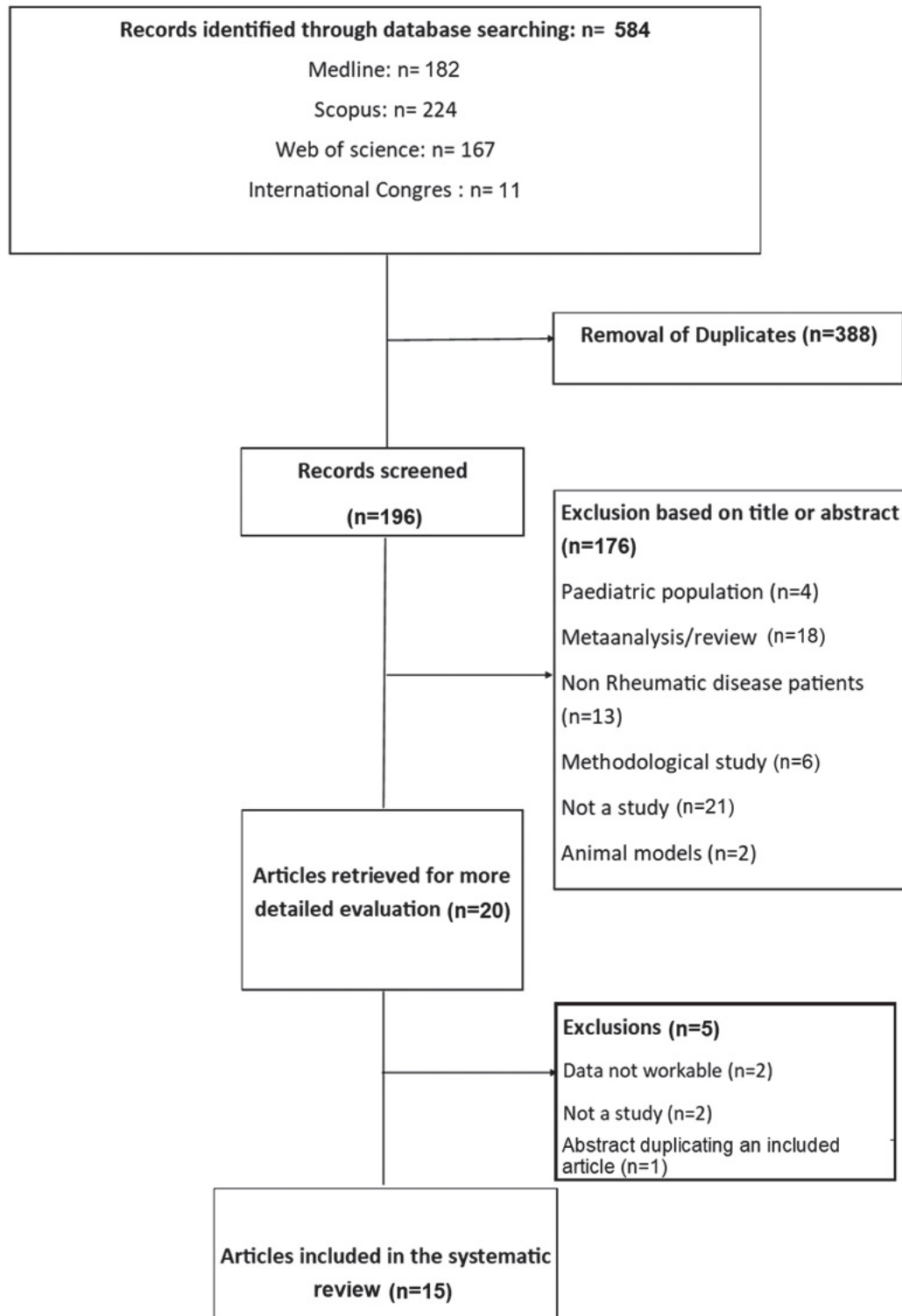
RESULTS

Study selection

The initial electronic search yielded 584 articles through the following databases: MEDLINE, Scopus, Web of science, and the international congresses. After removing duplicates from the initial search, a total of 196 articles were screened by two independent medical doctors. Screening based on title and abstract excluded 176 articles and left 19 articles to be screened in full text. Of those 19 articles, 15 studies that met the inclusion criteria of this systematic review were identified. Reasons for exclusion are shown in the flow diagram (Figure 1). The list of eligible studies was sent to an expert in the field for verification.

Risk of bias in studies

Two studies were rated as "strong," eight as moderate, and five as "weak". The highest number of weak ratings was found in the "selection bias" and the "blinding" domains. The "Study design," "confounders" and "data collection methods" domains had the highest number of strong ratings. The details of the methodologic assessment of included studies are described in Table 1.



Flow diagram for systematic review

Figure 1. Flow diagram for systematic review

Table 1. Methodologic quality assessment with EPHP tool for quantitative studies

Study	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Global rating
Pani D et al. (2014) Italy [19]	Weak	Moderate	Not applicable	Moderate	Weak	Strong	Weak
Zernicke J et al. (2016) Germany [17]	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong
Wang Y et al. (2022) China [26]	Weak	Strong	Strong	Weak	Strong	Strong	Weak
Rodríguez Sánchez-Laulhé P et al. (2022) Spain [27]	Moderate	Strong	Strong	Moderate	Strong	Moderate	Strong
Tierney M et al. (2015) Ireland [28]	Weak	Moderate	Not applicable	Weak	Weak	Strong	Weak
Li LC et al. (2020) Canada [16]	Weak	Strong	Moderate	Weak	Strong	Strong	Weak
Jacquemin C et al. (2018) France [29]	Moderate	Moderate	Strong	Moderate	Weak	Strong	Moderate
Katz P et al. (2018) USA [30]	Moderate	Strong	Strong	Weak	Strong	Strong	Moderate
Haglo H et al. (2021) Norway [31]	Weak	Strong	Strong	Moderate	Strong	Moderate	Moderate
Piga M et al. (2014) Italy [32]	Weak	Strong	Strong	Weak	Strong	Moderate	Weak
Allam A et al. (2015) Switzerland [33]	Strong	Strong	Strong	Weak	Strong	Strong	Moderate
Lorig KR et al. (2008) USA [34]	Weak	Strong	Strong	Moderate	Strong	Moderate	Moderate
Tada et al. (2022) Japan [35]	Strong	Moderate	Not applicable	Weak	Strong	Strong	Moderate
Labat et al. (2022) France [36]	Moderate	Strong	Strong	Weak	Moderate	Moderate	Moderate
Paul et al. (2024) UK [37]	Strong	Moderate	Not applicable	Weak	Moderate	Moderate	Moderate

Study characteristics

The included studies were published between 2008 and 2024. Ten of them were conducted in Europe (France, Spain, Italy, Germany, Norway, Ireland, and United Kingdom) [17, 19, 27-29, 31-33, 36, 37], two in USA [30,34], one in China [26], one in Japan [35], and one in Canada [16]. Of the included studies, nine were randomized controlled trials (RCT), three were non-randomized intervention trials, one was a cross-sectional study, one was a prospective observational study, and one was a case control study.

At the end of follow-up, the total study population size was 1769. The mean age was specified in 11 articles and ranged from 31.20 to 61.86 years [16, 17, 19, 26, 27, 29, 30, 32, 33, 36, 37]. One study specified the median age that was 66 years (Inter-Quartile Range (IQR) : 59-74) [35]. The mean disease duration was specified in 8 articles and ranged between 6.7 and 14.8 years [17, 26, 29-33, 37]. One study specified the median disease duration that was 5.3 years (IQR: 1.1-11.5) [35].

Twelve studies included RA patients with a population size of 900, a mean/median age ranging from 53 to 66 years, and a mean/median disease duration ranging from 5.3 to 14.8 years [16, 17, 19, 27-35]. Five studies included SpA patients (n = 308) of which two studies included axial SpA (axSpA) patients (n = 124) [29, 37], two studies included ankylosing spondylitis (AS) patients (n = 163) [26, 36], and one study included 21 SpA patients with no precision of the disease subtype [31]. The mean age and disease dura-

tion of SpA patients ranged from 31.2 to 52.3 years and from 10.1 to 16.2 years, respectively. Three studies represented outcome results of a combined population regardless of the diagnosis;

Lorig et al. included 866 patients with at least one of the following diagnoses: RA, fibromyalgia (FM) and osteoarthritis (OA) [34], Jacquemin et al. included 157 patients with RA (n = 83) and axSpA (n = 74) [29], and Haglo et al. included 40 patients with RA (n = 12), SpA (n = 21), and systemic lupus erythematosus (SLE) (n = 7) [31].

Physical activity was targeted by 8 studies [16, 28-30, 33, 35-37] while 10 studies focused on performance-based physical function [17, 19, 26-28, 31-35] and 4 studies targeted mobility [19, 26, 32, 37]. Two studies targeted both physical activity and performance-based physical function [28, 35] and one study targeted both physical activity and mobility [37].

The used connected elements were smartphone applications in 4 studies [26, 27, 29, 31], a web-based intervention in 3 studies [33, 34, 37], a sense-wear armband (SWA) device in 2 studies associated with a web application [16, 28], an activity tracker in two studies [29, 36], a Fitbit and a Fitbiz in one study [16], a novel telemonitoring device in 2 studies [19, 32], a Wii console in one study [17], a wearable triaxial accelerometer in one study [35], and a pedometer with a brochure in one study [30]. The intervention period lasted from one week to 12 months.

Characteristics of the included studies and the description of the wearable devices were detailed in Table 2.

Table 2. General information and study characteristics

Authors (Year)/ Country	Population (n =)	Mean age (years)	Inclusion criteria	Exclusion criteria	Target	Devise	Frequency/ Intervention period	Monitoring	Follow-up period
Li LC et al. (2020) Canada [16]	RA (n = 86) Immediate group (n = 43) Delay group (after 10 weeks) (n = 43)	53 54	- A confirmed diagnosis of RA - Having an email address and daily access to internet - Able to attend an in-person session	- Previous use of physical activity wearable Devices - To consider unsafety to be physically active without health professional supervision	The upper and lower bound of intensity and duration and mean of MVPA (min/day)	- A Fibit Flex2 and a FIViz, a new web-based application - SenseWear Mini for 7 days at each assessment, a multi-sensor monitor worn over the triceps 24 hours a day	Week 1-8 (immediate group) Week 10-17 (delay group)	Bi-weekly phone calls by PT	27 weeks
Katz P et al. (2018) USA [30]	RA (n = 120) 120 completed the study - Education only group - Pedometer group - Pedometer + step targets group	54	English-Spanish speaking, able to attend 3 in-person research visit	BMI < 20 kg/m ² , currently engaging in regular exercise, nonambulatory or presence of a condition limiting the ability to walk	Increase activity	An educational brochure and a guided discussion -Pedometer (Jawbone up)	NS	Contact patients Every 2 weeks (by phone or email)	21 weeks
Heglo H et al. (2021) Norway [31]	RA, SpA, SLE (n = 40; 12 RA, 21 SpA, 7 SLE) AG: self-administered HIIT guided by an application (n = 19; 4 RA, 11 SpA, 4 SLE) SG: standard supervised HIIT group (n = 21; 8 RA, 10 SpA, 3 SLE)	NS	NS	Unstable cardio-vascular disease, pulmonary disease, diabetes type I, pregnancy, not owning a smartphone, planned surgeries influencing the training or testing.	Cardiorespiratory fitness, commonly assessed as maximal oxygen uptake ($\dot{V}O_{2max}$)	Smartphone application with written and standardized preprogrammed audio instructions, automated email halfway in the training period	2 training sessions per week on nonconsecutive days, 34 min per session	NS	10 weeks
Piga M et al. (2014) Italy [32]	RA (n = 20) - Experimental arm (n = 10) - Control arm (n = 10)	56	Dreiser's index score ≥ 6 with stable medications for 3 months.	Irreversible anatomical damage, active arthritis, and digital ulcers. DAS28 > 2.6	Home rehabilitation exercises for the hand: hand strength, the maximum hand abduction and the ROM of MCP joints.	Recovery of Movement and Telenmonitoring portable device monitoring software interface, Calls + booklet *control arm: only booklet	5 days per week for 12 weeks, each session lasting a maximum of 50 min (45 min for control arm).	Calls for experimental arm	12 weeks
Allam A et al. (2015) Switzerland [33]	RA (n = 155) *Experimental groups: G1 (n = 30): access to informational sections only, G2 (n = 29): plus access to social support sections G3 (n = 28): access to only the gaming G4 (n = 28); access to everything *Control group (n = 40): no website access	57	No participation in another experiment or research study before Sufficient competence to use the website and internet access, No other major chronic illness), speaking Italian	NS	Physical activity	ONESELF website with Gamification	Freely access	NS	4 months

Authors (Year)/ Country	Population (n =)	Mean age (years)	Inclusion criteria	Exclusion criteria	Target	Device	Frequency/ Intervention period	Monitoring	Follow-up period
Lorig KR et al. (2008) USA [34]	RA, OA, FM patients 441 patients randomized to intervention (28.3% RA) 425 patients randomized to usual care (26.6% RA)	NS	≥ 18 years of age; a diagnosis of OA, RA, or fibromyalgia; could not have been in active treatment for cancer for 1 year; no previous participation, had access to a computer	NS	Coping with RA especially in one's everyday life	Internet-based Arthritis Self- Management Program	For each of 6 weeks, participants (approximately 25 per workshop) were asked to log on at least 3 times for a total of 1-2 hours and to participate in the weekly activities.	NS	12 months
Jacquemin C et al. (2018) France [29]	RA (n = 83), axSpA (n = 74) Healthy controls (n = 20)	45	> 18 years; Internet access; mobile phone or tablet compatible with the mobile activity tracker.	NS	Physical activity: number of steps per day, proportion of morning steps over a day	Wearing an activity tracker (Withings Activity Pop connected by Bluetooth, at least every 2 days, to a mobile phone application) every day for 3 months.	NS	NS	90 days
Pani D et al. (2016) Italy [19]	10 RA patients (10 systemic sclerosis patients were also included)	55.5 [39-74]	NS	NS	Hand rehabilitation	A novel telerehabilitation device with remote monitoring capabilities	5 sessions per week	NS	12 weeks
Zernicke J et al. (2016) Germany [17]	RA (n = 30) G1: starting with a conventional home-based physical exercise program, 15 RA patients, 100% females G2: starting with a predefined animated exercise program by using the Wii game console, 15 RA patients, 67% females	G1: 59 ± 9 [45-69] G2: 52 ± 8 [34-65]	Patients' global assessment <30 mm under therapy with a bDMARD	Patients only on cDMARD therapy	Physical activity	Wii game console	3 sessions per week, 30 minutes per session, 12 weeks for each treatment arm	Semi-structured face to face interviews	12 weeks
Wang Y et al. (2022) China [26]	AS (n = 55) G1: Controle group, receiving usual AS care, 28 patients, 77% males G2: Intervention groups, 26 patients, 75% males	G1: 31.2 ± 6.3 G2: 33.2 ± 6.2	Fulfillment of the criteria for AS (1984 Modified New York criteria) Age between 18 and 60 years stable drug treatment in the preceding month ASDAS between 1.3 and 3.5	– cardiovascular disease at high risk – Cervical vertebral bridges Surgery within the preceding 6 months – bDMARDs used in the preceding 3 months – Regular exercise in the preceding 3 months Factors leading to the inability to receive regular exercise rehabilitation	Physical activity	Smartphone application	2. 30 min/day, 5 days/ week 3. 60 min/day, 3 days/ week	Uploading pictures taken after each session by the patient.	16 weeks

Authors (Year)/ Country	Population (n =)	Mean age (years)	Inclusion criteria	Exclusion criteria	Target	Device	Frequency/ Intervention period	Monitoring	Follow-up period
Rodríguez Sánchez- Laulhé P et al. (2022) Spain [27]	36 RA patients (58 hands) G1: control group, 22 (41 hands), 59% females G2: intervention group, 14 (28 hands), 64% females	G1: 61.86 ± 10.76 G2: 57.64 ± 7.25	- age ≥ 18 years - RA of the hands, wrists, or fingers, based on the ACR guidelines - Disease duration of at least two years - report current pain and disability in the hands or wrists - possessing a smartphone with internet access	- previous hand fracture or surgery - waiting for upper limb surgery - steroid injection in the month before recruitment - pregnancy - cognitive problems that may preclude the completion of the study protocol	Hand and wrist rehabilitation	Smartphone application	15-20 min/day, 4 days/week	Adherence charts were sent via the application to a cloud database	3 months
Tierney M. et al. (2013) Ireland [28]	RA (n = 25)	NS	Fulfilling ACR criteria for RA diagnosis	NS	Physical activity	senswear armband IPAQ	7 days	NS	7 days
Tada et al. (2022) Japan [35]	RA (n = 85)	Median (IQR) 66 (59,74)	Age ≥ 20 years Fulfilling ACR criteria for RA diagnosis	Severe renal dysfunction, heart failure, neurological diseases, malignancy, other collagen diseases, myogenic disease, or surgically implanted metal	Physical activity, Muscle function	a wearable triaxial accelerometer	7 days	NS	7 days
Labat et al. (2022) France [36]	AS (n = 108) NTG: non-tracker group, n = 53, 67.9% females TG: tracker group, n = 55, 72.7% females	NTG : 50.7 ± 14 TG : 52.3 ± 13.6	Age > 18 years Understanding the objectives and constraints of the study SpA according to the ASAS criteria Lived in Nice or in a 20- km area Certified as having no contraindication to perform physical activities such as swimming or Nordic walking.	coronary artery disease moderate-to-severe heart failure uncontrolled hypertension myocarditis pericarditis endocarditis lung disease any contraindication to PA inability to go to the activity venue undergoing supervised PA in a club or with a sports coach, pregnancy or breastfeeding	Physical activity	wearable activity tracker (Garmin Vivofit 4)	Twice a week with an additional weekly coach-supervised PA session after 24th week	NS	36 weeks

Authors (Year)/ Country	Population (n =)	Mean age (years)	Inclusion criteria	Exclusion criteria	Target	Device	Frequency/ Intervention period	Monitoring	Follow-up period
Paul et al. (2024) UK [37]	axSpA (n = 50) 54% females	50 ± 12	confirmed axSpA for more than one year access to the internet at home	already exercising regularly (three or more times per week) joint replacement within the last six months comorbidities that may interfere with taking part in a regular exercise programme currently participating in another clinical trial	Physical activity, mobility	website	30 minutes 5 days per week	Data recorded on the website	12 months

AS: Ankylosing Spondylitis, SpA: Spondyloarthritis, axSpA: axial SpA, RA: Rheumatoid Arthritis, OA: Osteoarthritis, FM: Fibromyalgia, SLE: Systemic Lupus Erythematosus, ASDAS: Ankylosing Spondylitis Disease Activity Score, DAS28: Disease Activity Score, bDMARD/cDMARD: biologic/conventional disease modifying antirheumatic drug, MVPA: moderate/vigorous physical activity, HIIT: aerobic high-intensity interval training, PT: physiotherapist, ROM: range of movement, BMI: Body mass index, AG: application group, SG: standard supervised group, G1-2: group 1-2, MCP: metacarpophalangeal, NS: not specified

Results of individual studies and synthesis of results

Results of the intervention studies on primary and secondary outcomes are summarized in Table 3.

Primary outcomes

Primary outcomes consisted of the physical activity outcomes and rehabilitation outcomes, which included mobility, physical function, and performance.

Physical activity

All the 8 studies targeting physical activity focused on overall physical activity. The study populations included patients with RA in 4 studies, AS in two studies, axSpA in one study, and RA and axSpA in one study. Assessment tools to evaluate the effectiveness of wearable devices in promoting physical activity were: number of daily steps, intensity and daily time of activity, gait speed, duration of moderate/vigorous physical activity (MVPA), and the International Physical Activity Questionnaire (IPAQ). Connected elements were: Fit Bit Flex and SWA, Withings Activity Pop, wearable activity tracker (Garmin Vivofit 4), a wearable triaxial accelerometer, Pedometer, and a web-based intervention.

Wearable devices revealed positive outcome in the study of Katz et al. [30]. These researchers reported significantly step increased counts in RA patients using pedometer (PED)-based intervention compared with RA patients receiving therapeutic education.

Li LC et al. showed significantly higher mean time spent in MVPA and daily steps at week 9 in RA patients using Fitbit Flex2 and a SWA device compared to control group but not significantly higher at weeks 17 and 26 [16]. Likewise, Jacquemin et al. demonstrated similar number of steps per day in RA and axSpA patients using an activity tracker compared to healthy controls at 3 months [29]. Alam et al. found an increase in mean minutes spent on exercise over time for RA patients with access to the social support sections and gaming using a web-based intervention [33]. However, Tierney et al. did not identify correlations between all items of the short form IPAQ after 7 days of ordinary daily activity of RA patients monitored by a SWA armband [28].

Rehabilitation

There were 9 studies interested in rehabilitation for improving performance-based physical function via wearable devices among rheumatic disease patients. Different studied fields were: hand strength, cardiorespiratory fitness, and muscle endurance.

Table 3. Study outcome measures and their results

Authors/ Year	Study design	Intervention	Primary Outcome measures		Other secondary measures	Results
			Assessment tools	Findings		
Li LC et al. (2020) [16]	RCT	In-person session to plan: *Immediate Group: Education and counseling by a PT, used a Fitbit and a web-application with 4 follow-up calls from the PT. *Delay Group: same intervention (weeks 10-17) Assessment: Baseline, Week 9, 18 and 27. — Individual physical activity plan on FitViz	— The upper and lower bound of intensity, duration and mean of MVPA (min/day) — Mean daily time in purposeful activity — Average daily steps	— At 9 weeks: A significant higher mean time spent in MVPA for the Immediate Group — At weeks 17 and 26: a larger but statistically non-significant intervention effects — A trend favoring the Immediate Group was found in time spent in purposeful activity and daily steps	— Mean daily time in sedentary behavior. — Self-Reported Habit Index	— Time spent in sedentary behaviours: A trend favoring the Immediate Group — Pain and self-reported walking habit: statistically significant difference for Immediate group
Katz P et al. (2018) [30]	RCT	Weekly average number of daily steps Other activities (swimming, cycling, walking, Pilates)	Weekly average number of daily steps	Intervention groups significantly increased step counts from baseline to Week 21 The proportions of PED and PED+ groups achieved a doubled health activity with no significant differences with EDUC.	Promis Fatigue Short form, PHQ-8 HAQ RADAI	Fatigue: a reduction trending for the PED+ group by 21 weeks. PROMIS and PHQ-8: general improvement for all groups with a statistically significant improvements for the PED and PED+ groups. — HAQ: improved significantly within the PED and PED+ groups — RADAI: relatively stable between baseline and week 10, and then decreased significantly between week 10 and week 21 for PED and PED+ groups
Haglo H et al. (2021) [31]	RCT	HIIT	Cardiorespiratory fitness assessed as maximal oxygen uptake (VO_{2max}) percentage of VO_{2max} : Oxygen uptake (VO_2) from the first 3 and last 3 HIIT sessions	— AG and SG performed sessions with an intensity of 85%-90% of VO_{2max} with no difference between the groups. — No difference in improvement of VO_{2max} was apparent between the groups.	HRQoL	— Three HRQoL dimensions improved in both groups with no significant difference. — Dimensions of general health, physical functioning, and emotional well-being increased in the SG with no differences.
Piga M et al. (2014) [32]	RCT	*Experimental group: 4 strengthening and 3 mobility exercises *Control arm: 3 strengthening and 3 mobility exercises	Hand strength (grip and pinch) measured through a sphygmomanometer. The maximum hand abduction and the ROM of MCP joints for both hands measured through a goniometer.	— Experimental arm: statistically significant results on both grip and pinch strength. — Patients in experimental and control arms obtained good results on MCP ROM for both hands.	HAQ, FIHOA — VAS — DAS28	— FIHAO and HAQ: a statistically significant improvement over time in the experimental group with no significant difference between groups — VAS decrease in experimental arm without a significant difference with controls. — DAS28: a reduction of for the experimental arm patients.

Authors/ Year	Study design	Intervention	Primary Outcome measures		Other secondary measures	Results
			Assessment tools	Findings		
Allam A et al. (2015) [33]	RCT	Time spent on physical activity during a week	The time spent on physical activity in the last week on a scale from 0 = never to 5 = more than 3 hours per week. The number of minutes spent on exercise from 0 to 180 minutes.	Mean minutes spent on exercise increased over time for patients with access to the social support sections and gaming.	Health care utilization	Health care utilization: a significant decrease for patients in the social support group and patients in the social support plus gaming group
Lorig KR et al. (2008) [34]	RCT	Aerobic exercise	Aerobic exercise (minutes/week) Stretching and strength exercise (minutes/week)	No significantly difference between groups	Health status Self-efficacy Health care utilization	At 1 year, the intervention group significantly improved in 4 of 6 health status measures and self-efficacy. No significant differences in health care utilization.
Jacquemin C et al. (2018) [29]	Case control study	No intervention	Physical activity was assessed by the number of steps per day.	Controls tended to be more active than patients. There was no statistically significant difference between patients with RA and axSpA in physical activity levels or patterns.	-	-
Pani D et al. (2016) [19]	non-randomized, single arm, intervention trial	Isometric exercises: hand pinch, hand grip, finger pinch (opposition to the thumb), rotation (screwing with the fingers) Dynamic exercises: hand extension, rotation (fast manipulation), finger tapping (piano-like)	Hand algo-functional Dreiser Index ROMf ROMw Grip strength CTorque ATorque	Significant sustained improvement of all outcome measures.	Hands' acral temperature	Significant increase in acral temperature after exercise
Zernicke J et al. (2016) [17]	Non-randomized, two-arm, crossover pilot study	Wii-group: At least 12 Yoga exercises, 11 muscle-strength exercises, 7 balance games and 6 aerobic exercises Conventional home-based physical exercise group: strength training (10 exercises), coordination (2), joint mobility (10) and relaxation (9)	muscles strength* 6-MWT respiratory tests (peak expiratory flow)	12-week evaluation: Significant improvement of muscle strength in both groups Significant improvement of the mean 6-MWT in both groups No significant effects on respiratory tests -> No significant difference between both groups on all outcomes	HAQ-DI SF36 PtGA (using a 100 mm visual analogue scale)	No statistically significant difference at week 12 and 24 in and between both groups in the mean changes of HAQ-DI, SF36 and PtGA results
Wang Y et al. (2022) [26]	Randomized, two-arm pilot controlled trial	1. In-person counseling sessions and supervised training sessions 2. Home-based aerobic exercises: brisk walking or running 3. Functional home-based exercise: posture, range of motion, resistance, stability, and stretching exercises	Cardiorespiratory fitness: HRmax, the VO_{2max} Body composition: lean body mass, percentage of body fat, and visceral fat area; evaluated using a non-invasive bioelectrical impedance analysis method range of motion of the cervical spine and hip joints measured with a smartphone app lumbar muscle endurance assessed with back extensor and flexor endurance tests	Between-group differences were significant favoring the intervention group for all outcomes.	ASDAS(CRP), BASDAI, PtGA, PhGA, BASFI, BASMI, ASAS HI, SF-36.	Between-group differences for change from baseline were significant favoring the intervention in ASDAS(CRP), BASDAI, PtGA, PhGA, BASFI, and BASMI. SF-36: significant beneficial effects were detected in physical function, bodily pain, general health, and vitality in the intervention group.

Authors/ Year	Study design	Intervention	Primary Outcome measures		Other secondary measures	Results
			Assessment tools	Findings		
Rodríguez Sánchez-Lauhé P et al. (2022) [27]	single-blinded randomized controlled trial	warm-up routine, mobility, stretching, and strengthening exercises	- Michigan Hand Outcome Questionnaire (MHQ) - Grip strength (dynamometer) - pinch strength (pinch gauge) - Upper limb function (shortened version of the Disabilities of the Arm, Shoulder, and Hand questionnaire)	Significant time-group effect for the total MHQ score and subscales overall hand function, work performance, pain, and satisfaction. No significant effect for the subscales activity of daily living and aesthetic. No significant effect on grip and pinch strength and on upper limb function.	- Pain and stiffness intensity - No significant effect on pain and stiffness intensity	
Tierney M. et al. (2013) [28]	Cross-sectional study	Ordinary daily activity of patients	- Physical activity: IPAQ-SF - total energy expenditure measuring via SWA output - MET-minutes per week and Sitting Time.	No large correlations between any aspect of the SWA and any aspect of the short form IPAQ	-	-
Tada et al. (2022) Japan [35]	non-randomized, single arm, prospective observational study	Ordinary daily activity of patients	- Daily calories expended for walking and for housework - Exercise for walking and for housework (MET-minutes per week) - Number of steps 3 minutes walk test - Grip strength - Power, speed, and stabilizing time of lower limbs and trunks	Walking, housework, and total exercise were positively correlated with grip strength, walking speed, power, and speed. Walking speed (except for house work exercise), and power were independently related to exercise.	mHAQ, DAS28-ESR locomotive syndrome (5-question Geriatric Locomotive Function Scale), frailty	Walking, housework, and total exercise were negatively correlated with age, mHAQ, DAS28-ESR, locomotive syndrome, and frailty. Locomotive syndrome, frailty, and mHAQ (except for housework exercise for the two last factors) were independently related to exercise. Total daily exercise and number of steps were significantly lower in the moderate and high disease activity group. Lower number of steps was associated with a higher risk of frailty and locomotive syndrome
Labat et al. (2022) France [36]	RCT	2 weekly physical activity sessions of the participant's choice with Nordic walking encouraged and a training to avoid positions or activities that could aggravate the disease Weekly activity SMS reminders A supplementary 1 hour of coach-supervised PA after week 24	6-MWT - IPAQ-SF (rejected for missing data)	Significant increase in 6-MWT between W0 and W12, W24, and W36 without significant difference between the 2 groups	Number of flares, BASDAI SF-36	No difference between groups in number of moderate and persistent flares between W0 and W12, W24, or W36. Significant decrease in number of flares in both groups between W0 and W12 Nonsignificant decrease in BASDAI in both groups between W0 and W12, W24, and W36 SF-36: Significant increase in role limitation (physical) domain between W0 and W24 in TG Significant increase in role limitation (emotional) domain between W0 and W12 in TG

Authors/ Year	Study design	Intervention	Primary Outcome measures		Other secondary measures	Results
			Assessment tools	Findings		
Paul et al. (2023) UK [37]	Single arm, prospective, interventional cohort study	Specific exercise goals were agreed between the participant and the physiotherapist. Participants were encouraged to undertake an exercise program up to five days per week for 30 min per day	– 6-MWT, PA assessed by an accelerometer (steps/day, walking time, sitting/lying time), EQA-18, EMI-2	Significant improvements in 6-MWT at M6 and M12 No significant difference in PA, EQA-18 or EMI-2	BASDAI, BASFI, ASQoL, WPAI:SpA, EQ5D, BASMI,	Significant increase in mental health domain between W0 and W24 in TG and W0 and W36 in NTG Significant increase in general health domain between W0 and W12 in NTG Significant increase in bodily pain domain between W0 and W12 in both groups Significant improvements of BASDAI, BASMI, EQ5D-VAS, ASQoL at M6 and M12 Significant improvements of EQ5D index (quality of life) and WPAI activity impairment subscale at M6

MVPA: moderate/vigorous physical activity, MET: Metabolic Equivalent of Task, PED +: Pedometer + step targets group, EDUC: Educational group, PHQ-8: Questionnaire depression scale, HAQ: Health Assessment Questionnaire, HAQ-DI: Health Assessment Questionnaire Disability Index, RADA: Rheumatoid Arthritis Disease Activity Index, ROM: range of movement finger flexo-extension; ROMw: ROM wrist flexo-extension, C Torque: clockwise rotation torque, A Torque: anticlockwise rotation torque, 6-MWT: 6-min walk test, SF36: Short Form 36-Item questionnaire, PtGA: patient's global assessment, HRmax: maximal heart rate, VO2 max: maximal oxygen uptake, ASDAD(CRP): Ankylosing Spondylitis Disease Activity Score using C Reactive Protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, PhGA: physician global assessment, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath Ankylosing Spondylitis Metrology Index, ASAS HI: Spondyloarthritis International Society Health Index, MHQ: Michigan Hand Outcome Questionnaire, IPAQ: international physical activity questionnaire, IPAQ-SF: IPAQ short form, SWA: sensewear armband, HILT: aerobic high-intensity interval training, AG: application group, SG: standard supervised group, HRQoL: Health-related quality of life, μ : Bodily pain, vitality, social functioning), ROM: range of movement, MCP: metacarpophalangeal, FHOA: Functional Index of Hand OA, mHAQ: modified HAQ, axSpA: axial spondyloarthritis, p: significance level, *: muscle groups were neck extensors, neck flexors, shoulder abductors, elbow extensors, elbow flexors, 3-point grip strength, hip flexors, knee extensors and knee flexors, RCT: Randomized controlled trials, VAS: pain visual analog scale, PT: physiotherapist

– Muscle Strength

There were 4 studies targeting muscle strength performance among patients with IRD. There were 3 case-controlled studies, and one was a single arm intervention. Three studies focused on hand strength and one study targeted nine groups of muscles of the neck, shoulders, elbows, grips, hips, and knees. Wearable devices used were: care hand application available on smartphones, sphygmomanometer, telerehabilitation device with remote monitoring capabilities, and Wii console. There were 2 studies that have employed performance-based physical function questionnaires assessing hand strength [19, 27].

A significantly increase in muscle strength was noted in all studies [19, 27, 32]. Indeed, Piga et al. reported a significant increase in grip and pinch strength measured through a sphygmomanometer in experimental group than controls [32]. As for the single arm study, Hand algofunctional Dreiser's index of patients with RA and grip strength have shown a significant improvement after a 12-week of hand rehabilitation program [19].

In the study conducted by Zernicke J et al., there was a significant improvement of strength in nine groups of muscles (neck, shoulder, elbow, grip, hip, knee) at 12-week with no significant difference between both RA groups receiving home-based animated physical activity program using a Wii console versus conventional home-based physical exercise program [17].

Similarly, Rodríguez Sánchez-Laulhé et al. noted a significant time-group effect for the total Michigan Hand Outcome Questionnaire (MHQ) score ($p = < 0.01$) and especially for his following subscales: overall hand function ($p = 0.04$), work performance ($p = 0.006$), pain ($p < 0.001$), and satisfaction ($p = 0.06$) [27]. However, there was no significant time-group effect for pinch strength and grip strength after 3 months of hand rehabilitation programs with no significant effect for the shortened version of the Disabilities of the Arm, Shoulder, and Hand questionnaire (QuickDASH) [27].

– *Cardiorespiratory fitness*

Cardiorespiratory fitness among IRD patients was investigated in 3 papers. Assessment tools were maximal oxygen uptake (VO₂max), respiratory tests, and 6-minute walk test (6-MWT).

Following home-based programs targeted by mobile applications resulted in a significant improvement of respiratory tests and VO₂max in 2 studies [26, 31]. In fact, Wang et al. found a significant between-group differences for change from baseline of VO₂max favoring the intervention group of Ankylosing Spondylitis (AS) after 16 weeks [26]. However, after 6 supervised high-intensity interval training (HIIT) sessions guided by an application for RA and SpA patients, the increase of VO₂max from baseline was not significant compared to control groups [31].

Walk tests were also improved in a RA group using a home-based animated physical activity program via a Wii console without a significant difference between experimental and control group [17].

– *Muscle endurance*

Improving muscle endurance has been researched in 4 studies. Connected devices were: web-based interventions (two studies), smartphone application (one study), and a SWA armband (one study). The effectiveness of a connected program was proven in two studies.

Wang et al. found significant improvement in back extensor endurance test favoring the intervention group of AS patients undergoing a home-based physical activity program guided by a smartphone application for 16 weeks [26]. The same result was concluded by Allam et al. [33] who showed that the mean time spent on self-training was higher for RA patients with access to social support and gaming ($p = 0.02$) compared to control group with no website access.

However, Kate et al. did not find a significant difference between exposed and non-exposed RA patients on time spent on aerobic, stretching, and strength exercises monitored by internet self-management program for exposed patients [34]. Tierney et al. published closed negative findings in RA patients regarding the total energy exposures assessed by a SWA armband during ordinary daily activities for a week [28].

– *Mobility*

Mobility was assessed in 3 studies including range of motion (ROM) of cervical spine, hip joints, ROM of the hand, the fingers, and the wrist. In the following study, there were significant differences for the ROM of cervical lateral flexion and hip abduction between-group, favouring the intervention group of AS patients undergoing a home-based physical activity

program guided by a smartphone application for 16 weeks [26]. Similarly, there was a significant improvement in ROM of fingers and wrist of patients with RA, after a 12-week hand rehabilitation program using a novel telerehabilitation device with remote monitoring capabilities [19]. However, in the study conducted by Piga et al, there was an improvement in hand ROM for RA patients monitored by portable device without a significant difference with controls [32].

Secondary outcomes

An overview of the studies examining secondary outcomes such as disease activity, fatigue, and functional impairment is presented in Table 2.

Disease activity

Six studies were interested in searching the impact of wearable devices on disease activity among rheumatic disease patients: RA ($n = 3$), AS ($n = 2$) [26, 30, 32, 35, 36]. Different wearable devices were Pedometer, triaxial accelerometer, a wearable activity tracker, telemonitoring portable device, and a smartphone application. The follow-up duration ranged from 12 weeks to 36 weeks. The used disease activity scales were the Disease Activity Scale 28 (DAS 28), and the Rheumatoid Arthritis Disease Activity Index (RADAI) for RA patients and the Ankylosing Spondylitis Disease Activity Score using C Reactive Protein (ASDAS-CRP), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and number of flares for SpA patients.

In RA, the use of wearable devices improved the disease activity in two studies. Devices were a Pedometer and a telemonitoring portable device. In fact, Katz et al. showed that the RADAI improved in Pedometer group and Pedometer + step targets group after 10 and 21 weeks of intervention [30]. In the other study, authors noted a reduction in the DAS 28 in RA patients using telemonitoring portable device for hand rehabilitation (1.8 at baseline to 1.4 at week 12) [32]. However, authors did not find a significant difference with controls.

Regarding AS, the use of a wearable device improved disease activity parameters in one study without a significant difference with controls. Indeed, disease activity parameters decreased significantly for patients with AS undergoing wearable assisted home based exercises from baseline to 16-week follow-up ($p = 0.03$ for ASDAS, $p = 0.004$ for BASDAI) [26]. Labat et al. found a significant decrease in number of flares after a 12-week physical activity program assisted by a wearable activity tracker [36]. However, there was no significant difference compared to the non-tracker group.

Health-related quality of life, fatigue, and pain

Five studies were interested in assessing the impact of wearable devices on health-related quality of life for patients with RA. In fact, in the study conducted by Katz et al., the Health Assessment Questionnaire (HAQ) improved significantly in the experimental group compared to controls after 21 weeks of physical activity program monitored by a pedometer [30]. Similarly, there was a statistically significant improvement of the HAQ after 12 weeks of home rehabilitation exercises for the hand using a telemonitoring portable device but without a significant difference with control group [32]. Unlike Zernicke et al. who have not found a significant change after 24 weeks of physical activity targeted by a Wii console [17]. In axSpA patients, Paul et al. found a significant improvement of quality of life indexes 6 and 12 months after an exercise program guided by a website [37].

According to fatigue, there was a statistical trend for the Pedometer group to reduce fatigue scores more than the Educational group by 21 weeks in the study conducted by Katz et al. [30]. For Li LC et al., there was not a significant improvement between both RA groups (delayed and immediate group) after the use of a SWA [16].

As for pain, there were 3 studies assessing the improvement of pain via wearable devices using the Visual Analogue Scale (VAS). There was a statistically significant adjusted mean difference in the VAS in one study [16]. However, pain decreased in experimental arm without a significant difference with controls in one study [32], and there was no significant effect on pain and stiffness intensity in another [27].

DISCUSSION

Our systematic review investigated whether wearable devices could promote physical activity and rehabilitation in patients with IRD. There are few studies in the literature investigating the effect of those tools on IRD patients. For that, in this paper, we tried to summarize different studies in order to draw a conclusion.

The findings showed the increase of physical activity parameters with a significant difference between interventional and non-interventional groups in only one study. Regarding performance-based physical function, there were improvements of hand strength, cardiorespiratory fitness, and muscle endurance for most exposed groups to wearable devices. As for mobility, joints motions were also improved after the exposed period. Wearable devices had also

positive outcomes on disease activity, pain, fatigue, and on health-related quality of life.

Disability and functional impairment are frequent among patients with IRD [38, 39]. They are caused by pain and limitation of joint mobility [40, 41]. They lead to alteration of work productivity and to dependence [42]. Physical therapy and exercises are recommended for patients with IRD except flares and are often prescribed in order to improve the physical function [43]. However, following a well-defined physical therapy intervention program and adhering to physiotherapist sessions are not always obvious [44].

In this context, wearable devices were developed to promote physical function and to encourage patients with rheumatic diseases to apply to at-home exercises in order to enhance their quality of life. There are some controversies regarding the gain obtained from these interventions.

Indeed, a recent review showed significant efficacy of eHealth-supported home exercise interventions on improvements of pain, physical activity, and quality of life in patients with osteoarthritis of the knee [45]. Another one showed the efficacy of physical therapy given by telerehabilitation on shoulder pain and disability [46].

Telematic behavioral modification techniques were also effective options for the management of anxiety and depressive symptoms in patients with chronic musculoskeletal pain [47].

However, a meta-analysis of Randomized Controlled Trials conducted by Xie et al. did not find evidence of internet-based rehabilitation to improve physical function among patients with osteoarthritis [22].

The application of those devices has certain limitations, which can reduce their effect. There are different conditions related to the patient such as comorbidities or to the device himself. In fact, in a recent Systematic Review and Meta-Analysis, telematic behavioral modification techniques did not seem to be effective on reducing the stress among patients with chronic musculoskeletal pain [47]. As for adherence, a recent systematic review with meta-analyses showed that digital rehabilitation programs were effective at improving therapeutic exercise adherence for patients with musculoskeletal conditions at intermediate follow-up, but not at short- and long-term follow-up [48]. Patient satisfaction is also an important condition that may influence patients' adherence to wearable devices. Indeed, Amin et al. provided in their systematic review some evidence of satisfaction with Telerehabilitation among patients with musculoskeletal disorders [49]. The cost is considered as another condition related to the use of wearable

devices. In fact, home-based exercises using wearable devices may be expensive for some ones. However, some studies showed cost saving per patient of £38.57 related to telehealth and telerehabilitation services for physical therapy for people with musculoskeletal conditions [50, 51]. But those results were not linked to long-term cost-benefit. However, the application of wearable devices use in physical activity and rehabilitation of IRD patients should be a part of a multidisciplinary management for these patients, including sports medicine and physical medicine and rehabilitation specialists. This helps set up adequate protocols and choose the appropriate evaluation tools and questionnaires to improve the uniformity of outcome evaluation.

Limitations

There are several potential limitations related to our study that should be considered. First, the number of studies regarding this topic is limited. This can be explained by the novelty of this area of focus. However, we included only English and French papers; there are possibly interesting studies in other languages. Besides, most of randomized controlled trials included a little number of participants which may influence results. Furthermore, the follow-up duration was not long enough. There was only one study, which has been extended at 12 months. There was a lack of assessment on the prolonged effect of wearable devices in promoting physical function. Finally, even though our systematic review showed positive results, it is important to keep in mind that the selected studies included a heterogeneous population in terms of disease duration as exercise can be more difficult in patients with longstanding IRD.

CONCLUSION

Physical activity and rehabilitation via wearable devices are a promising method for patients with IRD to enhance their physical function at home. The main purpose of this review is to identify the efficacy of wearables that provide rehabilitation programs for this vulnerable population that still exposed to disability. The results of this study indicate that there is always a benefit of wearables tools. Their utilization is simple and safe. They could improve physical activity and different fields of rehabilitation, performance-based physical function, and mobility without harming patients' health. However, further studies with large population sizes and long-term follow-up are needed to make reliable conclusions.

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ОБЗОРИ
REVIEWS

СЪВРЕМЕННИ ПОДХОДИ ЗА ОЦЕНКА НА СВЪРЗАНОТО СЪС ЗДРАВЕТО КАЧЕСТВО НА ЖИВОТ ПРИ СИСТЕМЕН ЛУПУС ЕРИТЕМАТОЗУС

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Резюме. Системният лупус еритематозус (СЛЕ) е хронично аутоимунно заболяване с разнообразни клинични прояви. Навременната диагноза и оценката на болестната активност са основополагащи за определяне на оптимална терапевтична стратегия за всеки пациент. През последните десетилетия прогнозата на пациентите със СЛЕ се подобри значително. Въпреки това дори при правилно лечение и постигната ремисия качеството на живот (QoL) остава чувствително понижено. Това подчертава важността на оценката на свързаното със здравето качество на живот (HRQoL) в комплексния подход към пациентите със СЛЕ. Цялостната представа за общото състояние на пациентите обхваща не само физическото, но и психическото и социалното им благополучие. През последните години множество въпросници за QoL се използват все по-широко в ревматологичната практика. Генеричните въпросници, като Short Form-36 (SF-36), позволяват сравнение между различни заболявания, но не винаги са достатъчно чувствителни към специфични клинични симптоми при СЛЕ. От своя страна лупус-специфични въпросници, като LupusQoL, SLEQoL, LupusPRO и L-QoL, предоставят по-прецизна информация, оценявайки множество аспекти на заболяването и психосоциалните преживявания на пациентите. Съвременните препоръки подчертават значението на интегрирането на оценката на HRQoL в рутинната клинична практика и научните изследвания. Литературният обзор подчертава нарастващата роля на лупус-специфичните въпросници в клиничните изпитвания и поставя критичния въпрос за тяхната ефективност и приложимост в ежедневната практика с цел подобряване на медицинската грижа.

Ключови думи: системен лупус еритематозус, качество на живот, лупус-специфични въпросници

ВЪВЕДЕНИЕ

Системният лупус еритематозус (СЛЕ) е хронично аутоимунно заболяване, което оказва значително въздействие върху свързаното със здравето качество на живот (HRQoL). Заболяването се характеризира с широк спектър от клинични прояви, включително астено-адинамичен синдром, артрит, бъбречно и неврологично засягане, както и кожни промени, съпроводени с лабораторни и серологични отклонения. Допълнителни усложнения, като спонтанни аборти и мъртви раждания, артериална или венозна тромбоза (особено при наличие на антифосфолипиден синдром) и повишен риск от сърдечно-съдови заболявания, допринасят за дългосрочната за-

боляемост и натрупването на увреждания. Хроничната употреба на кортикостероиди – макар и жизненоважни за лечението, често води до значителни нежелани събития, които допълнително влошават качеството на живот на пациентите [1]. Въпреки регистрирането на нови молекули от класа на биологичните болестопроменящи антиревматични лекарства (бБМАРЛ) и значителния им принос за понижаването на болестната активност, СЛЕ продължава да оказва сериозно въздействие чрез персистиращи симптоми като умора и депресия [2, 3]. Тези симптоми често показват слаба корелация с активността на заболяването, но значително влошават HRQoL. Съвременните модели разделят симптомите на СЛЕ на две категории: Тип 1 – симптоми, предизвикани

от възпаление и обикновено подлежащи на лечение с имunosупресанти, и Тип 2 – симптоми като умора и депресия, които често персистират дори при ниска активност на заболяването [4]. Това разграничение може да обясни слабата връзка между HRQoL и традиционните маркери за активност на заболяването, като подчертава необходимостта от интегриране на оценките на HRQoL в цялостната грижа за пациентите със СЛЕ.

СЪВРЕМЕННИ ПРЕПОРЪКИ И ЗНАЧИМОСТ НА ОЦЕНКАТА НА HRQoL

Оптималните терапевтични цели при СЛЕ включват постигане и поддържане на ремисия, дефинирана според консенсуса за определение на ремисия при СЛЕ (DORIS), или състояние на ниска активност на заболяването (LLDAS) [5, 6]. Паралелно с това, оценката на HRQoL заема все по-значимо място в съвременните клинични препоръки. Препоръките на Европейския алианс на асоциациите по ревматология (EULAR) насърчават рутинната оценка на HRQoL при всяко клинично посещение [7]. Стратегията “лекувай до постигане на целта” (treat-to-target, T2T) поставя акцент върху оптимизирането на HRQoL, наред с контрола на активността на заболяването [8]. Освен традиционните клинични показатели оценката на HRQoL предоставя холистично разбиране за тежестта на заболяването и ефективността на терапевтичните интервенции.

ОЦЕНКА НА КАЧЕСТВОТО НА ЖИВОТ (QoL)

Оценката на качеството на живот (QoL) при пациенти със СЛЕ се извършва чрез генерични и специфични за заболяването въпросници. Генеричните инструменти, като SF-36, са приложими в различни популации и позволяват сравнение между СЛЕ и други заболявания. Лупус-специфичните въпросници, като LupusQoL, SLEQoL и LupusPRO, са по-чувствителни към специфичните характеристики на заболяването и промените в неговата активност, улавяйки множеството предизвикателства, с които се сблъскват пациентите със СЛЕ. Важно е да се направи разграничение между QoL и HRQoL, тъй като фокусът на HRQoL е върху влиянието на СЛЕ и провежданото лечение върху клиничните резултати, включително симптоми и функционални ограничения. Инструменти като L-QoL обхващат различни измерения на живота със СЛЕ и осигуряват по-добро разбиране на въздействието на заболяването. Интегрирането на тези въпросници в клиничната практика

и изследванията е от съществено значение за оптимизиране на терапевтичните стратегии [9, 10].

ПСИХОМЕТРИЧНИ СВОЙСТВА НА ВЪПРОСНИЦИТЕ

При оценката на HRQoL е от съществено значение да се познават психометричните свойства на използвания въпросник, а именно надеждност, валидност и чувствителност. Надеждността измерва последователността на въпросника чрез вътрешна съгласуваност (Кронбах $\alpha > 0,70$) и повторното използване на теста (коефициент на корелация на Пирсън, r). Валидността определя дали въпросникът измерва целта си и включва различни видове валидност (на съдържанието, критериална, конвергентна и дискриминантна). Чувствителността се отнася до способността на скалата да открива промени в състоянието на пациента през времето. Накрая, floor и ceiling ефектите описват участниците, които получават най-ниските или най-високите възможни резултати, което може да ограничи възможността на въпросника да улавя вариации. Разбирането и приложението на тези психометрични принципи гарантират правилния избор и интерпретация на въпросниците [11].

Целта на този преглед е да синтезира съществуващата литература, за да осигури цялостно разбиране на характеристиките, предимствата и ограниченията на различните инструменти за оценка на качеството на живот (QoL), използвани при системен лупус еритематозус (СЛЕ).

СТРАТЕГИЯ НА ИЗСЛЕДВАНЕТО

Извършено беше систематично търсене в електронни бази данни (PubMed, Scopus) на публикувани методики за оценка на качеството на живот (QoL) при пациенти със системен лупус еритематозус (СЛЕ). Търсенията включват термините „системен лупус еритематозус“, „качество на живот“ и „въпросници“. Идентифицирани са 1076 статии, от които след премахване на дублираните ($n = 237$) остават 839. Статиите са изключвани, ако липсват първични данни или не са на английски език ($n = 226$). Допуснати са само оригинални изследвания, обзори и метаанализи, които разглеждат използването на валидирани инструменти за оценка на QoL, като 437 статии, които не отговарят на това изискване, са изключени. В крайна сметка, в анализа са включени 72 статии, фокусирани върху генерични въпросници (например SF-36, EuroQol-5D) и лупус-специфич-

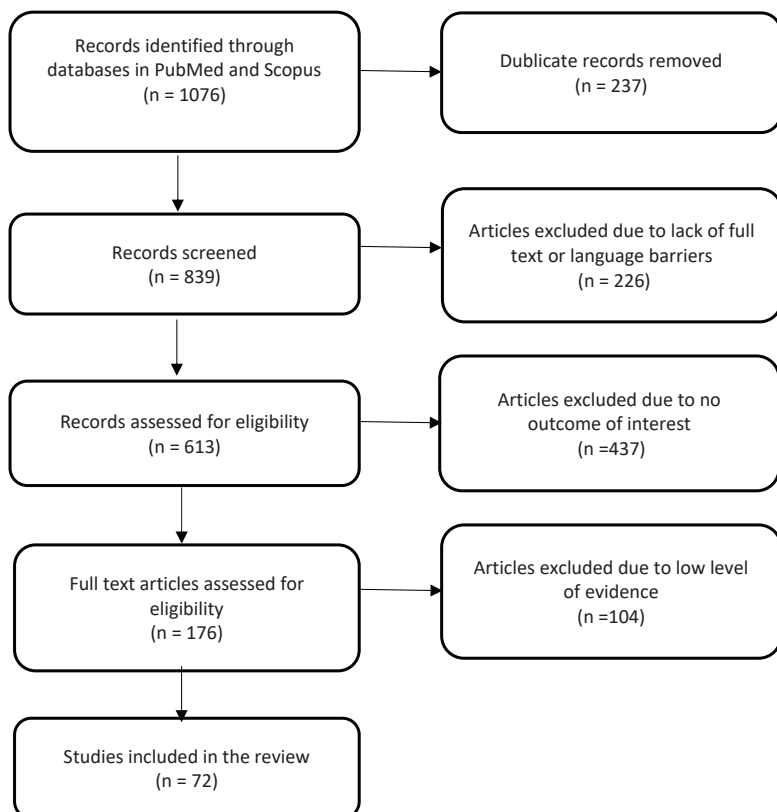
ни въпросници (например LupusQoL, SLEQoL, LupusPRO, L-QoL), като на финалния етап 104 статии са изключени поради незадоволително ниво на данните в публикациите. Извършен е анализ спрямо характеристиките на въпросниците, оценяваните домейни, психометричните свойства и посочените силни и слаби страни (фиг. 1).

ГЕНЕРИЧНИ ВЪПРОСНИЦИ

Сред най-често използваните генерични въпросници са SF-36v2 (The Short Form Health Survey Version 2), EU-Q5-D5 (EuroQoL 5 dimensions), PROMIS, скалите за умора FACIT и FSS.

The Short Form Health Survey Version 2 (SF-36v2) е разработен през 1998 г. Въпросникът SF-36v2 се състои от 36 въпроса, оценяващи качеството на живот в 8 домейна: 1) Physical functioning (PF): Физическо функциониране, 2) Role physical (RP): Ограничения в дейностите, дължащи се на физически проблеми, 3) Bodily pain (BP): Физическа болка, 4) General health (GH): Общо здраве, 5) Vitality (VT): Жизненост, 6) Social functioning (SF): Социално функциониране, 7) Role emotional (RE): Ограничения в дейностите, дължащи се на емоционални проблеми, 8) Mental health (MH): Ментално здраве. Въпросите в инструмента оценяват състоянието през предходните 4 седми-

ци. Има допълнителен въпрос относно промените в здравословното състояние през последните 12 месеца. Всеки въпрос се оценява по скала от 0 до 100, като по-нисък резултат означава по-лошо качество на живот, а по-висок – по-добро качество на живот. Резултат 0 съответства на максимално нарушение, докато резултат 100 показва липса на засягане. Освен това се отчитат два компонента: Physical Component Summary (PCS) и Mental Component Summary (MCS). PCS обобщава резултатите от сферите, свързани с ограничения, произтичащи от физическата функция (PF, RP, BP, GH), докато MCS обобщава резултатите от сферите, свързани с менталното здраве (VT, SF, RE, MH) [12]. SF-36v2 е валидиран за оценка на HRQoL при пациенти със СЛЕ и е препоръчан от British Rheumatology Society [13]. Въпреки това съществуват съображения относно чувствителността му към промени в здравословното състояние, особено при по-дълги периоди. В лонгитудинални проучвания SF-36 не показва значителна чувствителност при годишна оценка на HRQoL, тъй като въпросникът отразява само състоянието през предходните 4 седмици. Друг недостатък на SF-36 са множеството въпроси, които налагат по-голяма продължителност при попълване [14, 15]. В проучване от SLICC кохортата (Systemic Lupus International Collaborating Clinics) SF-36 показва подобрене във всички 8 домейна и в обобщените резултати за физическо (PCS) и ментално здраве (MCS) през първите 2 години, последвано от стабилни резултати през следващите 3 години. Това предполага чувствителност на SF-36 в началните етапи след диагностициране на СЛЕ, но не и при дългосрочно заболяване [16]. В проучването TULIP-1 на 365-ия ден пациентите, лекувани с Анифролумаб 300 мг, показват подобрене по отношение на физическия и менталния компонент на SF-36, съответно с 3.1 (OR CI 1.51, 0.94-2.44) и 3.8 точки (OR CI 1.00-2.79), като тези разлики не са статистически значими [17]. Следователно употребата на SF-36 за оценка на HRQoL е подходяща за краткосрочни проучвания или при новодиагностицирани пациенти с малка давност на заболяването [18]. Допълнително, SF-36 се използва като инструмент за сравнение при етапите на валидиране



Фиг. 1. Селекция на публикациите

на нови въпросници, включително лупус-специфични [19, 20].

Short Form-12 Health Survey (SF-12) е базиран на въпросника SF-36 и предоставя сходни данни, включително обобщените скорове за физическо (PCS) и ментално здраве (MCS). Значително по-малкият брой въпроси към пациентите осигурява по-лесно попълване на въпросника и приложение в ежедневната практика. SF-12 е използван за оценка на предиктори за HRQoL в кохорта от 580 пациенти със СЛЕ в проучването LuLa (Lupus-erythematoses-Langzeit-Studie), като по-доброто ниво на медицинска грижа е свързано с по-високи резултати за физическото здраве PCS [21].

Short Form-20 Health Survey (SF-20) е съкратената версия на SF-36. Тя включва 20 въпроса, обединени в 6 домейна: физическо функциониране (PF), ограничения в дейностите поради физически проблеми (RP), социално функциониране (SF), ментално здраве (MH), възприятие за здраве (HP) и физическа болка (BP). Резултатите се оценяват по скала от 0 до 10 и след това се умножават по 100 [22].

Short Form-6D (SF-6D) включва 6 домейна, базирани на избрани компоненти от SF-36, използвайки стандартна методология. Осемте домейна на SF-36 са редуцирани до 6, като домейнът за общото здраве е пропуснат, а тези, които оценяват ограничения в дейностите, дължащи се на физически и емоционални проблеми, са обединени в един общ домейн. Крайният индекс предоставя единична цифрова стойност, която може да е по-лесна за интерпретация от изследователи и клиницисти в сравнение с обобщените скорове на SF-36 [23]. SF-6D е валидиран и надежден инструмент за оценка на HRQoL в мултиетническа група пациенти със СЛЕ в САЩ, като между крайните резултати от EQ-5D и SF-6D има силна корелация [24]. В проучването LUMINA (Lupus in Minorities, Nature versus Nurture) се подчертава способността на SF-6D да предсказва натрупване на увреждания през хода на болестта [25].

EQ-5D-5L (EuroQoL 5 dimensions) е генеричен въпросник, разработен от интернационална група от изследователи EuroQoL, оценяващ 5 домейна: 1) Подвижност, 2) Самообслужване, 3) Обичайни дейности (напр.: работа, учене, домакинска работа, дейности, свързани със семейството или с прекарване на свободното време), 4) Болки/неразположения, 5) Тревожност/депресия [26]. Налични са 3 версии на EQ-5D. Оригиналният въпросник предлага 3 нива на отговор за всеки

домейн. По-новата версия на EQ-5D включва 5 нива на отговор, което позволява по-добро откриване на разлики в здравословното състояние: от никакви затруднения, леки затруднения, умерени затруднения, големи затруднения до невъзможност за извършване на определена дейност. Съществува и адаптирана версия за деца, EQ-5D-Y. В допълнение, пациентите оценяват текущото си здравословно състояние с визуална аналогова скала (EQ-5D-VAS) в диапазона от 0 до 100, като 100 означава най-доброто здраве, което можете да си представите, а 0 – най-лошото здраве, което можете да си представите. Сходните на EQ-5D и SF-36 домейни демонстрират силна корелация. Тъй като EQ-5D предоставя по-малко информация в сравнение с мултидомейновите инструменти като SF-36, той има тенденция да бъде кратък и лесен за употреба, тъй като EQ-5D се състои само от 5 компонента с VAS скала и отнема около 2 минути за попълване [24]. EQ-5D е преведен на множество езици и се използва при широк спектър от заболявания, включително СЛЕ. EQ-5D показва задоволителни психометрични свойства при група пациенти със СЛЕ в САЩ, потвърждайки валидността и надеждността на инструмента при СЛЕ, с възможност да отчита несъответствията между HRQoL, от една страна, и болестната активност и увредата – от друга [27].

Patient-Reported Outcomes Measurement Information System (PROMIS) е инструмент за самооценка на здравния статус при възрастни и деца, оценяващ различни аспекти като умора, болка, нарушения на съня, физическо функциониране, тревожност, депресия и удовлетвореност от социалната роля. Той е разработен по инициатива на Националния здравен институт на САЩ (National Institutes of Health, NIH) [28]. Като генеричен въпросник, PROMIS позволява сравнение с други болестни състояния и с популации от здрави индивиди. Отделните домейни на PROMIS могат да бъдат адаптирани към конкретно здравословно състояние чрез използване на компютризиранни адаптивни тестове (computerized adaptive tests, CATs) или чрез кратки формати, като например PROMIS10, който се състои от 10 домейна, оценяващи физическото и менталното здраве при редица хронични заболявания. Въпросите в него са до голяма степен адаптации на класически въпросници като SF-36 и EQ-5D. Психометричните свойства на PROMIS-CATs и PROMIS10 са оценени при 238 амбулаторни пациенти с лупус в САЩ, като и двата въпросника демонстрират силна корелация както с

генеричния SF-36, така и с лупус-специфичния LupusQoL [29]. В допълнение, PROMIS10 е валидиран и при деца с лупус, което позволява оценка и проследяване на педиатрични пациенти при преминаване в зряла възраст. Това е предимство на PROMIS10 пред добре утвърдените въпросници, които са само адаптирани за тази възрастова група [30].

Functional Assessment of Chronic Illness Therapy Scale (FACIT Fatigue Scale) е един от най-често използваните инструменти за измерване на умора при хронични заболявания, като е валидиран както за употреба при СЛЕ, така и при лупусен нефрит [31, 32]. Кратката версия на FACIT Fatigue Scale се състои от 13 въпроса, измерващи нивото на умора, докладвано от пациентите, както и нейното въздействие върху ежедневните дейности и функционалния капацитет през последните 7 дни. Нивото на умора се оценява по четиристепенна скала на Ликерт (4 = никаква умора до 0 = много умора). Колкото по-висок е общият резултат, толкова по-ниско е нивото на умора, следователно по-добро е качеството на живот. В post-hoc анализите на проучванията BLISS-52 и BLISS-76 незадоволителни резултати по отношение на качеството на живот се дефинират като резултат от FACIT-F < 30 [33]. FACIT-F е използван като един от инструментите за оценка на умората в проучването LEAF [34].

Fatigue Severity Scale (FSS) е инструмент за оценка на умората. Оригиналният FSS се състои от 9 въпроса и е разработен от Krupp, LaRocca, Muir-Nash и Steinberg през 1989 г. [35]. Всеки от въпросите се оценява по 7-точкова Ликерт скала, като 1 означава „категорично не се съгласявам“, а 7 – „силно се съгласявам“. Съществуват различни cut-off стойности в различните проучвания, като най-общо резултат FSS < 4 се счита за лека умора; FSS ≥ 4 и < 5 – умерена/гранична умора; FSS ≥ 5 – тежка умора. FSS е валидиран успешно при пациенти със СЛЕ (Krupp et al., 1989). FSS е използван за оценка на умората в ретроспективно проучване при 332 амбулаторни пациенти със СЛЕ в Поликлиниката по ревматология в Дюселдорф, Германия [36].

СЛЕ-СПЕЦИФИЧНИ ВЪПРОСНИЦИ

Няколко СЛЕ-специфични инструмента са предназначени за оценка на HRQoL. Към тях спадат Lupus QoL (LupusQoL), SLE-Specific QoL Questionnaire (SLEQOL), SLE QoL Questionnaire (L-QoL), както и Lupus PRO. Всички тези

въпросници са преминали през процес на валидиране, включително и на български (таблица 1).

Lupus QoL (LupusQoL) е най-широко разпространеният лупус-специфичен въпросник за оценка на качеството на живот, свързано със здравето (HRQoL). Разработен е от McElhone и съавтори през 2007 г. за оценка на качеството на живот при пациенти със системен лупус еритематозус (СЛЕ) в Обединеното кралство [19]. Оттогава въпросникът е валидиран в Съединените щати, а също така е създадена испанска версия [37, 38]. LupusQoL е преведен на 77 езика и се използва в 51 държави [39]. Въпросникът съдържа 34 въпроса, организирани в 8 домейна: 1) Физическо здраве, 2) Болка, 3) Планиране, 4) Интимни отношения, 5) Тежест за околните, 6) Емоционално здраве, 7) Външен вид, 8) Умора. Въпросите обхващат последните 4 седмици и се оценяват чрез 5-точкова скала на Ликерт, варираща от „през цялото време“ до „никога“. Средните резултати от домейните се преобразуват в стойности от 0 до 100, като по-високите стойности отразяват по-добро качество на живот. Попълването на въпросника отнема средно 4.6 минути. Оригиналната британска версия на LupusQoL демонстрира отлични психометрични свойства. Валидността по критерий е оценена чрез сравнение на домейните със сходни домейни на SF-36, като подобни резултати са наблюдавани при валидирането на американската и испанската версия. LupusQoL притежава дискриминантна валидност, което позволява разпознаване на пациенти с различна активност на заболяването и степен на органна увреда. В оригиналното проучване във Великобритания пациентите с по-висока активност на заболяването според BILAG (British Isles Lupus Assessment Group) демонстрират по-ниски стойности за HRQoL във всички домейни, с изключение на умората. При някои домейни, като емоционално здраве, външен вид и умора, не са наблюдавани значителни разлики между пациенти със или без органна увреда, определена според SLICC/SDI [19].

LupusPRO е създаден през 2012 г. въз основа на обратната връзка от етнически хетерогенни групи пациенти със системен лупус еритематозус (СЛЕ) в Съединените щати. Въпросникът включва 43 въпроса, разделени на два основни домейна: свързани със здравето (HRQoL) и несвързани със здравето (non-HRQoL). Домейните, свързани със здравето, обхващат симптоми на лупус, физическо здраве, болка-жизненост, емоционално здраве, представа за външния вид, когнитивни

способности, репродуктивни планове и терапия при лупус. Несвързаните със здравето домейни включват социална подкрепа и справяне, желаниа и цели, както и удовлетвореност от медицинските грижи. Въпросникът оценява състоянието на пациентите през последните 4 седмици, като използва 5-точкова скала на Ликерт. Общите резултати варират от 0 до 100, като по-високите стойности отразяват по-добро качество на живот. При прилагането на LupusPRO в първоначалната кохорта, инструментът демонстрира добра вътрешна съгласуваност и надеждност за всички домейни, с изключение на домейна, свързан с терапията при лупус [40, 41]. Сходните домейни на LupusPRO и SF-36 показват силна корелация. LupusPRO също така демонстрира силна корелация с болестната активност, оценена чрез BILAG (British Isles Lupus Assessment Group) и SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index). Впоследствие LupusPRO е преведен и валидиран на различни езици за употреба в различни културни и демографски популации [42, 43]. Психометричен анализ на LupusPRO позволи извличането на 10 въпроса, които най-добре представят въздействието на лупус върху ежедневието на пациентите. Този съкратен инструмент, наречен **Lupus Impact Tracker (LIT)**, предоставя единичен резултат и демонстрира отлични психометрични свойства, като същевременно предлага предимството да бъде кратък и лесен за използване [44].

SLE-Specific QoL Questionnaire (SLEQoL) е разработен през 2005 г. от Leong et al. в Сингапур за англоезични пациенти със СЛЕ. Въпросникът съдържа 40 въпроса, разпределени в шест домейна: физическо функциониране, ежедневни дейности, симптоми, лечение, настроение и самооценка. Компонентите на въпросника са създадени от ревматолози и медицински сестри, а не от самите пациенти. Въпросите се отнасят за състоянието през последната седмица и отговорите се дават чрез 7-точкова скала на Ликерт. Общият резултат е сума от всички точки, варираща от 40 до 280, като по-високите резултати индикират по-лошо качество на живот. Времето за попълване на въпросника е под 5 минути. Психометричните свойства на SLEQoL показват слаба корелация с SF-36, както и с болестната активност и органната увреда. Въпреки това SLEQoL демонстрира по-добра чувствителност към промените в състоянието на пациентите в сравнение със SF-36. Липсата на висока корелация

между двата инструмента се обяснява с различния им фокус: докато SF-36 оценява общото здравословно състояние, SLEQoL е насочен към специфични аспекти, засегнати от лупус [45].

L-QoL е лупус-специфичен въпросник за оценка на качеството на живот, разработен на основата на модел за определяне на потребностите (needs-based), според който благополучието, в контекста на качество на живот, е резултат от способността на индивидите да удовлетворяват своите нужди. Въпросникът е преведен на пет езика (български, естонски, руски, турски и унгарски) и е валидиран както при пациенти със системен лупус еритематозус (СЛЕ) в Обединеното кралство, така и в България [20, 46]. L-QoL включва 25 въпроса, които дават обобщена оценка за ефектите на СЛЕ и провежданото лечение върху качеството на живот. Въпросникът е създаден чрез събеседвания с пациенти със СЛЕ за въздействието на болестта върху живота им. На всеки въпрос се отговаря с "вярно" или "невярно", като резултатите варират от 0 до 25, като по-високият резултат показва по-влошено качество на живот. L-QoL е лесен за попълване и отнема по-малко от 5 минути. Инструментът има отлична вътрешна съгласуваност и надеждност при повторно използване на един и същ тест, което го прави подходящ за употреба при отделни индивиди. Валидността по критерий, оценена чрез докладваните от пациентите данни за болестната активност и тежестта на заболяването, също е адекватна – пациентите, които възприемат състоянието си като по-тежко, с по-висока болестна активност, докладват статистически значимо по-лошо общо здравословно състояние. За разлика от други въпросници, които оценяват качеството на живот чрез сложни мултидомейни подходи, L-QoL предоставя единичен резултат, отразяващ цялостното влияние на СЛЕ и провежданото лечение.

В обобщение, наличните въпросници предоставят ценна възможност да се извърши цялостна оценка на качеството на живот и да се подчертае значението му за разбирането на генералното въздействие на системния лупус еритематозус и перспективата пред пациентите. Задълбоченият анализ на физическото, емоционалното и социалното благосъстояние предлага по-прецизен поглед върху тежестта на заболяването. Този персонализиран подход, насочен към пациента, помага за създаването на индивидуални грижи, които подобряват клиничните резултати и оптимизират стратегиите за лечение на пациенти със системния лупус еритематозус.

Таблица 1. СЛЕ-специфични въпросници

СЛЕ-специфични въпросници	Брой въпроси	Домейни	Интерпретация на резултатите	Време за попълване	Времеви период	Психометрични свойства	Валидирана българска версия
LupusQoL	34	Физическо здраве, Болка, Планиране, Интимни отношения, Тежест за околните, Емоционално здраве, Представа за външния вид, Умора	0-100 По-висок резултат, по-добро HRQOL	< 5 мин	4 седмици	✓	✓
LupusPRO	43	HRQoL въпроси: Симптоми на лупуса, Физическо здраве, Болка-жизненост, Емоционално здраве, Представа за външен вид, Познавателни способности, Репродуктивни планове, Терапия при лупус Несвързани с HRQoL въпроси: Социална подкрепа и справяне, Желания и цели, Удовлетвореност от медицинските грижи	0-100 По-висок резултат, по-добро HRQOL	< 10 мин	4 седмици	✓	Преведен
SLEQOL	40	Физическо функциониране, Активност, Симптоми, Лечение, Настроение, Себевъзприемане	40-280 По-висок резултат, по-лошо HRQOL	< 5 мин	1 седмица	✓	–
L-QoL	25	Списък с въпроси, оценяващи цялостното влияние на СЛЕ и прилаганото лечение върху пациентите	0-25 По-висок резултат, по-лошо QOL	< 5 мин	В момента	✓	✓

EVALUATING QUALITY OF LIFE IN SYSTEMIC LUPUS ERYTHEMATOSUS: MODERN APPROACHES AND PERSPECTIVES

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Abstract. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse clinical manifestations. Timely diagnosis and accurate assessment of disease activity are essential for determining optimal therapeutic strategies for each patient. Over recent decades, the prognosis for SLE patients has significantly improved. However, even with proper treatment and remission, quality of life (QoL) remains substantially impaired. This underscores the importance of evaluating health-related quality of life (HRQoL) as part of a comprehensive approach to managing SLE patients. A holistic understanding of a patient's overall condition involves not only physical health but also psychological and social well-being. In recent years, numerous QoL questionnaires have been increasingly utilized in rheumatological practice. Generic questionnaires, such as the Short Form-36 (SF-36), facilitate comparisons across different diseases but may lack sensitivity to the specific clinical symptoms of SLE. Conversely, lupus-specific questionnaires, including LupusQoL, SLEQOL, LupusPRO, and L-QoL, offer more precise insights by capturing multiple aspects of the disease from the patient's perspective. Current guidelines emphasize the need to integrate HRQoL assessments into routine clinical practice and research. The literature review highlights the growing role of lupus-specific questionnaires in clinical trials and raises the critical question of their effectiveness and applicability in daily practice to improve medical care.

Key words: systemic lupus erythematosus, quality of Life, lupus-specific questionnaires

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that significantly impacts health-related quality of life (HRQoL). The disease is characterized by a wide range of clinical manifestations, including fatigue, arthritis, renal and neurological involvement, as well as skin changes, accompanied by laboratory and serological abnormalities. Additional complications, such as spontaneous miscarriages and stillbirths, arterial or venous thrombosis (particularly in the presence of antiphospholipid syndrome), and an increased risk of cardiovascular diseases, contribute to long-term morbidity and cumulative damage. Chronic use of corticosteroids, while often essential for treatment, frequently leads to significant adverse effects that further deteriorate patients' quality of life [1]. Despite the introduction of new molecules from the class of biologic disease-modifying antirheumatic drugs (bDMARDs) and their significant contribution to reducing disease activity, SLE continues to have a serious impact through persistent symptoms such as fatigue and depression [2, 3]. These symptoms often show weak correlation with disease activity but substantially impair HRQoL. Modern models categorize SLE symptoms

into two types: Type 1 – symptoms caused by inflammation that typically respond to immunosuppressive therapy, and Type 2 – symptoms such as fatigue and depression that often persist even when disease activity is low [4]. This distinction may explain the weak association between HRQoL and traditional markers of disease activity, underscoring the need to integrate HRQoL assessments into the comprehensive care of patients with SLE.

CURRENT RECOMMENDATIONS AND RELEVANCE OF HRQoL ASSESSMENTS

The optimal therapeutic goals in SLE include achieving and maintaining remission, as defined by the consensus on the Definition of Remission in SLE (DORIS), or attaining a state of low disease activity (LLDAS) [5, 6]. Alongside these goals, the assessment of HRQoL is becoming increasingly significant in modern clinical recommendations. The guidelines of the European Alliance of Associations for Rheumatology (EULAR) encourage routine HRQoL evaluation at every clinical visit [7]. The "treat-to-target" (T2T) strategy emphasizes optimizing HRQoL

alongside controlling disease activity [8]. In addition to traditional clinical indicators, HRQoL assessment provides a holistic understanding of disease burden and the effectiveness of therapeutic interventions.

QoL EVALUATION

QoL assessments in patients with SLE is conducted using both generic and disease-specific questionnaires. Generic tools, such as the SF-36, are applicable to various populations and allow comparisons between SLE and other diseases. Lupus-specific questionnaires, such as LupusQoL, SLEQoL, and LupusPRO, demonstrate greater sensitivity to the unique characteristics of the disease and changes in its activity, capturing the numerous challenges faced by SLE patients. It is important to distinguish between QoL and HRQoL, as HRQoL focuses on the impact of SLE and its treatment on clinical outcomes, including symptoms and functional limitations. Questionnaires like L-QoL encompass various dimensions of living with SLE and provide a deeper understanding of the disease impact. Integrating these questionnaires into clinical practice and research is essential for optimizing therapeutic strategies [9, 10].

PSYCHOMETRIC PROPERTIES OF QUESTIONNAIRES

When assessing HRQoL, it is essential to understand the psychometric properties of the questionnaire used, namely reliability, validity, and sensitivity. Reliability measures the consistency of the questionnaire through internal consistency (Cronbach's $\alpha > 0.70$) and test-retest reliability (Pearson correlation coefficient, r). Validity determines whether the questionnaire measures its intended purpose and includes various types of validity (content, criterion, convergent, and discriminant validity). Sensitivity refers to the scale's ability to detect changes in the patient's condition over time. Finally, floor and ceiling effects describe participants who achieve the lowest or highest possible scores, which may limit the questionnaire's ability to capture variations. Understanding and applying these psychometric principles ensures the appropriate selection and interpretation of HRQoL assessment tools in clinical and research settings.

The aim of this review is to synthesize existing literature to provide a com-

prehensive understanding of the characteristics, advantages, and limitations of various QoL assessment tools used in SLE.

RESEARCH STRATEGY

A systematic search was conducted in electronic databases (PubMed, Scopus) for published methodologies for assessing quality of life (QoL) in patients with systemic lupus erythematosus (SLE). The search included the terms "systemic lupus erythematosus," "quality of life," and "questionnaires." A total of 1,076 articles were identified, of which 237 duplicates were removed, leaving 839. Articles were excluded if they lacked primary data or were not in English ($n = 226$). Only original research, reviews, and meta-analyses that examined the use of validated QoL assessment tools were included, resulting in the exclusion of 437 articles that did not meet this criterion. In the end, 72 articles were included in the analysis, focusing on generic questionnaires (e.g., SF-36, EuroQol-5D) and lupus-specific questionnaires (e.g., LupusQoL, SLEQoL, LupusPRO, L-QoL). Finally, 104 articles were excluded due to inadequate data quality. An analysis was performed based on the characteristics of the questionnaires, the domains assessed, psychometric properties, and the identified strengths and weaknesses (Figure 1).

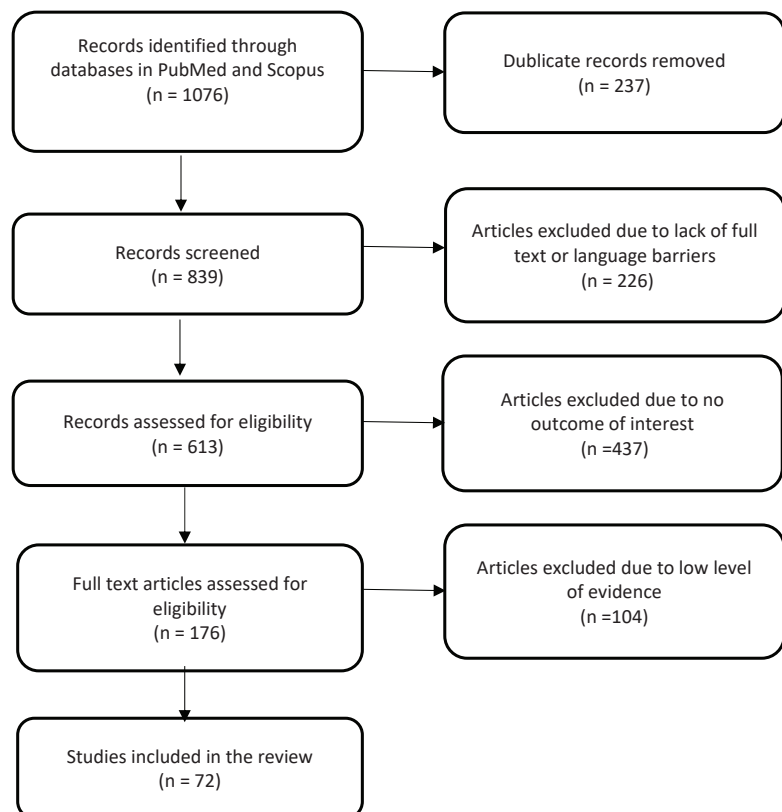


Fig. 1. Selection of included publications

GENERIC QUESTIONNAIRES

Among the most commonly used generic questionnaires are the SF-36v2 (The Short Form Health Survey Version 2), the EQ-5D (EuroQoL 5 Dimensions), PROMIS, and fatigue scales such as FACIT and FSS.

The Short Form Health Survey Version 2 (The SF-36v2) was developed in 1998. It comprises 36 questions assessing quality of life across 8 domains: 1) Physical Functioning (PF), 2) Role Physical (RP): Limitations in activities due to physical health problems, 3) Bodily Pain (BP), 4) General Health (GH), 5) Vitality (VT), 6) Social Functioning (SF), 7) Role Emotional (RE): Limitations in activities due to emotional health problems, 8) Mental Health (MH). The questionnaire evaluates the patient's health status over the preceding 4 weeks, with an additional question assessing changes in health over the past 12 months. Each question is scored on a scale from 0 to 100, where a lower score indicates poorer quality of life, and a higher score reflects better quality of life. A score of 0 corresponds to maximum impairment, whereas 100 indicates no impairment. The SF-36v2 also summarizes results into two components: Physical Component Summary (PCS): Derived from domains related to physical function (PF, RP, BP, GH); Mental Component Summary (MCS): Derived from domains associated with mental health (VT, SF, RE, MH) [12]. The SF-36v2 has been validated for assessing health-related quality of life (HRQoL) in patients with systemic lupus erythematosus (SLE) and is recommended by the British Society for Rheumatology [13]. However, there are concerns about its sensitivity to changes in health status, especially over longer periods. In longitudinal studies, SF-36 does not show significant sensitivity when assessing HRQoL on an annual basis, as the questionnaire reflects only the condition of the previous 4 weeks. Another drawback of SF-36 is the numerous questions, which take more time to complete [14, 15]. In the SLICC (Systemic Lupus International Collaborating Clinics) cohort study, the SF-36 demonstrated improvements across all 8 domains, as well as in PCS and MCS scores, during the first two years after diagnosis, followed by stable results over the subsequent three years. This suggests that the SF-36 is sensitive during the early stages of SLE but not for long-term disease assessment [16].

In the TULIP-1 trial, on day 365, patients treated with Anifrolumab 300 mg showed improvements in PCS and MCS scores by 3.1 (OR CI 1.51 (0.94-2.44)) and 3.8 points (OR CI 1.00-2.79), respectively.

However, these differences were not statistically significant [17]. Thus, the SF-36 is appropriate for short-term studies or newly diagnosed patients with early-stage disease [18]. Additionally, the SF-36 serves as a reference tool for validating new questionnaires, including lupus-specific instruments [19, 20].

Short Form-12 Health Survey (SF-12) is derived from the SF-36 questionnaire and provides comparable data, including summary scores for physical health (PCS) and mental health (MCS). The significantly smaller number of questions for patients ensures easier completion of the questionnaire and its application in daily practice. The SF-12 was used to evaluate predictors of HRQoL in a cohort of 580 patients with systemic lupus erythematosus (SLE) in the LuLa (Lupus-Erythematoses Long-Term Study). Better levels of medical care were associated with higher PCS in the SF-12 [21].

Short Form-20 Health Survey (SF-20) is a condensed version of the SF-36. It comprises 20 questions grouped into six domains: physical functioning (PF), role limitations due to physical problems (RP), social functioning (SF), mental health (MH), health perception (HP), and bodily pain (BP). Scores are assessed on a scale of 0 to 10 and then multiplied by 100 [22].

Short Form-6D (SF-6D) includes 6 domains, based on selected components of the SF-36, using standard methodology. The eight domains of SF-36 are reduced to 6, with the general health domain omitted, and those assessing limitations in activities due to physical and emotional problems combined into one common domain. The final index provides a single numerical value, which may be easier for researchers and clinicians to interpret compared to the summary scores of SF-36 [23]. SF-6D is a validated and reliable tool for assessing HRQoL in a multi-ethnic group of SLE patients in the U.S., with a strong correlation between the final results of EQ-5D and SF-6D [24]. The LUMINA study (Lupus in Minorities, Nature versus Nurture) highlights the ability of SF-6D to predict the accumulation of damage throughout the course of the disease [25].

EQ-5D-5L (EuroQoL 5 Dimensions) is a generic questionnaire developed by the international EuroQoL research group to assess health across five domains: 1) Mobility, 2) Self-care, 3) Usual activities (e.g., work, study, household tasks, family or leisure activities), 4) Pain/discomfort, 5) Anxiety/depression [26]. There are 3 versions of EQ-5D available. The original questionnaire offers 3 levels of response for each domain. The newer version of EQ-5D includes 5 response levels, allowing for better detection of dif-

ferences in health status: no problems, slight problems, moderate problems, severe problems, and unable to perform a specific activity. An adapted version for children, EQ-5D-Y, is also available. In addition, patients assess their current health status with a visual analogue scale (EQ-5D-VAS) ranging from 0 to 100, where 100 represents the best health you can imagine and 0 represents the worst health you can imagine. The similar domains of EQ-5D and SF-36 show strong correlation. Since EQ-5D provides less information compared to multi-domain tools like SF-36, it tends to be shorter and easier to use as EQ-5D consists of only 5 components with a VAS scale and takes about 2 minutes to complete [24]. EQ-5D has been translated into multiple languages and is used in a wide range of diseases, including SLE. EQ-5D shows satisfactory psychometric properties in a group of SLE patients in the U.S., confirming the validity and reliability of the tool in SLE, with the ability to capture discrepancies between HRQoL on one hand and disease activity and damage on the other [27].

Patient-Reported Outcomes Measurement Information System (PROMIS) is a self-assessment tool for health status in adults and children, evaluating various aspects such as fatigue, pain, sleep disturbances, physical functioning, anxiety, depression, and social role satisfaction. It was developed under the initiative of the National Institutes of Health (NIH) [28]. As a generic questionnaire, PROMIS allows for comparison with other disease conditions and with populations of healthy individuals. The individual domains of PROMIS can be adapted to specific health conditions through the use of computerized adaptive tests (CATs) or short formats, such as PROMIS10, which consists of 10 domains assessing physical and mental health in a variety of chronic diseases. The questions in PROMIS are largely adapted from classic questionnaires such as SF-36 and EQ-5D. The psychometric properties of PROMIS-CATs and PROMIS10 have been evaluated in 238 outpatient lupus patients in the U.S., with both questionnaires showing strong correlations with both the generic SF-36 and the lupus-specific LupusQoL [29]. In addition, PROMIS10 has been validated in children with lupus, allowing for assessment and tracking of pediatric patients as they transition into adulthood. This is an advantage of PROMIS10 over well-established questionnaires that are only adapted for this age group [30].

Functional Assessment of Chronic Illness Therapy Scale (FACIT Fatigue Scale/FACIT-F) is one of the most widely used tools for measuring

fatigue in chronic illnesses and has been validated for use in Systemic Lupus Erythematosus (SLE) and lupus nephritis [31, 32]. The short version of the FACIT-F consists of 13 questions that assess patient-reported levels of fatigue and its impact on daily activities and functional capacity over the past 7 days. Fatigue is evaluated using a 4-point Likert scale (4 = no fatigue to 0 = severe fatigue). Higher total scores indicate lower levels of fatigue and, therefore, better quality of life. In post-hoc analyses of the BLISS-52 and BLISS-76 trials, poor quality-of-life outcomes were defined as FACIT-F scores < 30 [32]. The FACIT-F was also employed as one of the tools for assessing fatigue in the LEAF study [33].

Fatigue Severity Scale (FSS) is another instrument used to evaluate fatigue. Originally developed by Krupp, LaRocca, Muir-Nash, and Steinberg in 1989, the FSS consists of 9 items scored on a 7-point Likert scale, where 1 signifies “strongly disagree” and 7 indicates “strongly agree” (35). Different studies have proposed various cut-off values: FSS < 4: Mild fatigue; FSS ≥ 4 and < 5: Moderate/borderline fatigue; FSS ≥ 5: Severe fatigue. The FSS has been successfully validated in SLE populations. It was utilized to assess fatigue in a retrospective study of 332 outpatient SLE patients at the Rheumatology Clinic in Düsseldorf, Germany [36].

SLE-SPECIFIC QUESTIONNAIRES

Several Systemic Lupus Erythematosus (SLE) – specific instruments have been developed to assess health-related quality of life (HRQoL). These include the LupusQoL (Lupus Quality of Life), the SLE-Specific QoL Questionnaire (SLEQoL), the SLE QoL Questionnaire (L-QoL), and Lupus PRO. All these questionnaires have undergone validation processes (Table 1).

Lupus Quality of Life (LupusQoL) questionnaire is the most widely used lupus-specific tool for assessing HRQoL. It was developed by McElhone et al. in 2007 to evaluate the quality of life in SLE patients in the United Kingdom [19]. Since its development, it has been validated in patient cohorts from the United States and adapted into a Spanish version. To date, LupusQoL has been translated into 77 languages and is utilized in 51 countries [37, 38]. The questionnaire consists of 34 items divided into 8 domains: 1) Physical Health, 2) Pain, 3) Planning, 4) Intimate Relationships, 5) Burden to Others, 6) Emotional Health, 7) Body Image, 8) Fatigue. The questions cover the past 4 weeks and are evaluated using a 5-point Likert scale, ranging from “all the time” to “nev-

Table 1. SLE-Specific Questionnaires

SLE-Specific Questionnaires	Number of Questions	Content	Interpretation of Results	Time to Complete	Time Period	Psychometric Properties	Validation in Bulgarian
LupusQoL	34	Physical Health, Pain, Planning, Intimate Relationships, Burden to Others, Emotional Health, Body Image, Fatigue	0-100 Higher score indicates better HRQoL	< 5 min	4 weeks	✓	✓
LupusPRO	43	HRQoL domains: Lupus symptoms, Physical health, Pain-vitality, Emotional health, Body image, Cognitive function, Reproductive health plans, and Lupus treatments. Non-HRQoL domains: Social support and Coping, Desires and Goals, and Satisfaction with medical care.	0-100 Higher score indicates better HRQoL	< 10 min	4 weeks	✓	Translated
SLEQOL	40	Physical functioning, Activities, Symptoms, Treatment, Mood, and Self-image.	40-280 Higher score indicates worse HRQoL	< 5 min	1 week	✓	–
L-QoL	25	A list of questions assessing the overall impact of SLE and its treatment on patients.	0-25 Higher score indicates worse QoL	< 5 min	At the moment	✓	✓

er". The mean scores of the domains are converted into values from 0 to 100, with higher values reflecting better quality of life. Completing the questionnaire takes an average of 4.6 minutes. The original British version of LupusQoL demonstrates excellent psychometric properties. Criterion validity was assessed by comparing the domains with similar domains of the SF-36, with similar results observed in the validation of the American and Spanish versions. LupusQoL has discriminant validity, which allows for the recognition of patients with different disease activity and degrees of organ damage. In the original study in the UK, patients with higher disease activity according to BILAG (British Isles Lupus Assessment Group) demonstrated lower HRQoL values in all domains except for fatigue. In some domains, such as emotional health, appearance, and fatigue, no significant differences were observed between patients with or without organ damage, as defined by SLICC/SDI [19].

LupusPRO is a patient-reported outcome instrument developed in 2012 based on feedback from ethnically diverse groups of SLE patients in the United States. The questionnaire consists of 43 items divided into two domains: health-related quality of life (HRQoL) and non-HRQoL domains. HRQoL domains include lupus symptoms, physical health, pain-vitality, emotional health, body image, cognitive function, reproductive health plans, and lupus treatments. Non-HRQoL domains encompass social support and coping, desires and goals, and satisfaction with medical care. The instrument assesses the patient's condition over the preceding four weeks using a 5-point Likert scale. Scores range from 0 to 100, with higher scores indicating better QoL. In its initial validation cohort,

LupusPRO demonstrated good internal consistency, reliability, and coherence across all domains except the lupus treatment domain [40, 41]. Similar domains within LupusPRO and the SF-36 questionnaire showed strong correlations, supporting the criterion validity of LupusPRO. The instrument also correlated well with disease activity as measured by the British Isles Lupus Assessment Group (BILAG) index and the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI). LupusPRO has been translated and validated in multiple languages, confirming its applicability across diverse cultures and patient populations with SLE [42, 43]. A psychometric analysis of LupusPRO enabled the extraction of 10 items most representative of lupus' impact on patients' daily lives. This new tool, the Lupus Impact Tracker (LIT), provides a single score and demonstrates strong psychometric properties. Its brevity and ease of use make it a practical option for assessing the impact of lupus on quality of life [44].

SLE-Specific QoL Questionnaire (SLEQoL) was originally developed for English-speaking SLE patients in Singapore by Leong et al. in 2005. The questionnaire consists of 40 items grouped into six domains: physical functioning, activities, symptoms, treatment, mood, and self-image. These components were generated by rheumatologists and nurses rather than by patients. The questions refer to the preceding week, and responses are rated on a 7-point Likert scale. The total score is the sum of all item scores, ranging from 40 to 280. Higher scores indicate poorer quality of life. The questionnaire can be completed in under five minutes. In terms of psy-

chometric properties, SLEQoL demonstrates weak correlations with the SF-36, lupus disease activity, and damage indices. However, it is more sensitive to changes in patient status compared to SF-36. The poor correlation between SLEQoL and SF-36 is attributed to differences in their domains and focus. While SF-36 assesses general health, SLEQoL specifically targets areas affected by lupus [45].

L-QoL is a lupus-specific quality of life (QoL) assessment questionnaire developed based on a needs-based model, which posits that well-being, in the context of QoL, is determined by an individual's ability to meet their needs. The questionnaire has been translated into five languages (Bulgarian, Estonian, Russian, Turkish, and Hungarian) and validated in SLE patient populations in the United Kingdom and, more recently, in Bulgaria [20, 46]. The L-QoL consists of 25 items providing a single, overall measure of the impact of SLE and its treatment on QoL. It was developed through interviews with SLE patients about how the disease affects their lives. Responses are dichotomic ("true" or "false"), yielding a score range of 0 to 25, with higher scores indicating worse QoL. The questionnaire is simple to complete and takes less than 5 minutes. The tool demonstrates excellent internal consistency and test-retest reliability, making it suitable for individual-level assessments. Criterion validity, assessed via patient-reported disease activity and severity, is adequate; patients who perceive their condition as more severe or have higher disease activity report significantly worse overall health status. Unlike other QoL instruments that assess multiple domains, L-QoL provides a single composite score, reflecting the overall impact of SLE and its treatment. This streamlined approach offers a straightforward measure of QoL in SLE patients.

CONCLUSIONS

In summary, the available questionnaires provide a valuable opportunity to conduct a comprehensive assessment of quality of life and highlight its significance in understanding the overall impact of systemic lupus erythematosus and the patients' perspective. A deeper analysis of physical, emotional, and social well-being offers a more precise view of the severity of the disease. This personalized, patient-centered approach helps create individualized care that improves clinical outcomes and optimizes treatment strategies for patients with systemic lupus erythematosus.

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ГЛОБАЛНИ ТЕНДЕНЦИИ И ПРОБЛЕМИ НА ИНФЕКЦИОЗНИТЕ ЗАБОЛЯВАНИЯ – COVID-19, HIV/AIDS, ТУБЕРКУЛОЗА

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Резюме. Глобализацията и взаимовръзките между страните в съвременния свят поставят нови предизвикателства в областта на общественото здраве. През вековете инфекциозните заболявания доказват, че са едни от основните заплахи за глобалното здраве. В исторически план няколко пандемии и епидемии променят и отнемат живота на милиони хора по света. Множество инфекциозни причинители продължават да представляват сериозен проблем въпреки напредъка в медицината, кампаниите за здравна осведоменост на населението и ваксинапрофилактиката. Целта на настоящия обзор е да се разгледат глобалните епидемиологични тенденции и проблеми, свързани с три ключови инфекциозни заболявания: COVID-19, HIV/AIDS и туберкулоза. Пандемията от COVID-19, заедно с дългогодишните заплахи от HIV/AIDS и туберкулоза, представлява сериозно изпитание за здравните системи и социално-икономическите структури в много държави. COVID-19, причинен от SARS-CoV-2, бързо се разпространи по целия свят, довеждайки до значителен брой заболели, смъртни случаи, както и до дългосрочни здравни проблеми. Последствията от инфекцията, „long“ COVID-19 и пост-COVID-19 отключените синдроми се превърнаха в една от основните причини за намалена работоспособност и влошено качество на живот през последните години. В същото време HIV/AIDS остава глобален здравен проблем, особено в определени региони, а туберкулозата продължава да представлява сериозна заплаха, най-вече в условия на ограничен достъп до здравни услуги. Всеки от тези здравни проблеми поставя специфични изисквания за лечение и превенция, като същевременно води до сериозни здравни, социални и икономически последици въпреки глобалните инициативи и стратегии за справяне с тях.

Ключови думи: глобални тенденции, проблеми, стратегии, COVID-19, HIV/AIDS, туберкулоза

ВЪВЕДЕНИЕ

Пандемията от COVID-19, причинена от коронавирус SARS-CoV-2, беше доказателство за глобалните здравно-икономическо-социални предизвикателствата и последици, свързани с инфекциозните заболявания. Наред с множеството отнети човешки животи, усложненията на заболяването, причинено от вируса, доведоха до влошено качество на живот на пациентите. От изключително значение за овладяването на болестта се оказаха бързото въвеждане на множество противоепидемичи мерки и разработването на ваксини. Адаптацията от страна на медицинските специалисти (включително в насока дигитализация на здравеопазването), обществото и бизнеса бяха необходимост. На глобално ниво финансовата подкрепа за възстановя-

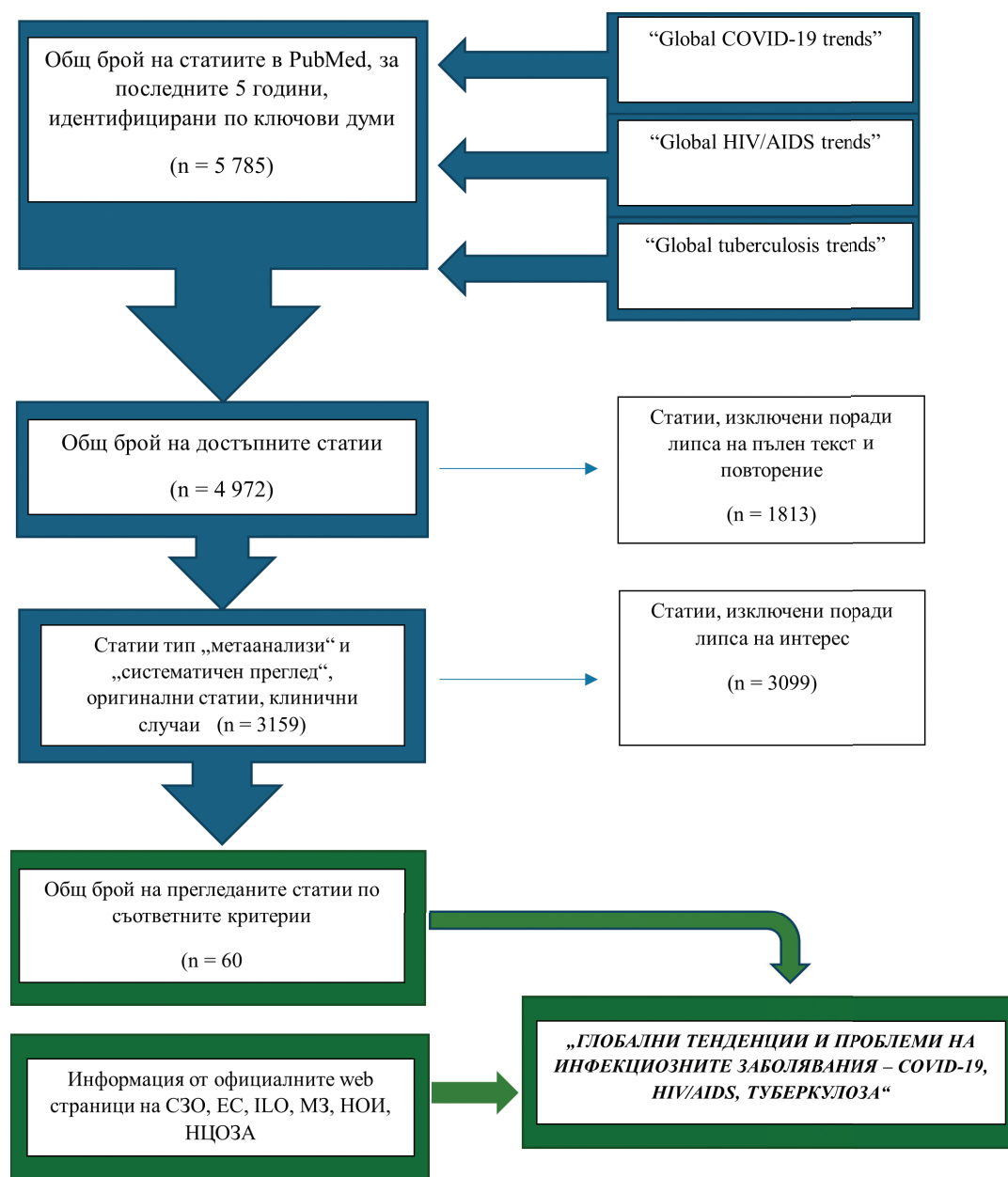
ване беше осигурена чрез различни инициативи и финансови пакети от Европейския съюз (ЕС) и Съединените американски щати (САЩ). Паралелно с разпространението на вируса беше налице забавяне в диагностиката и лечението на много други инфекциозни (например туберкулоза и HIV) и хронични заболявания. Вирусът на човешкия имунен дефицит (HIV), причинител на синдрома на придобита имунна недостатъчност (СПИН), продължава да бъде значим глобален здравен проблем. Въпреки кампаниите за информираност, преекспозиционната профилактика (PrEP) и наличието на антиретровирусно лечение (АРТ), СПИН остава основна причина за смъртност, особено в региони като Африка на юг от Сахара, поради социално-икономическите бариери пред ефективната превенция и лечение. Туберкулозата (ТБ) е още едно инфек-

циозно заболяване, което въпреки усилията за контрол и лечение продължава да бъде водеща причина за смъртност по света. В допълнение, инфекцията с HIV, силикозата (специфично професионално заболяване) и мултирезистентната туберкулоза (MDR-TB) усложняват не само лечението, но и превенцията на ТБ. Към тези глобални проблеми се добавят и професионалните болести, причинени от биологични агенти в работната среда, които също водят до стотици хиляди смъртни случаи годишно. В настоящия обзор разглеждаме глобалните тенденции и част от проблемите, свързани с тези ключови инфекциозни заболявания, и правим анализ на

съществуващите стратегии за справяне с бъдещи пандемии

Методи

Бяха прегледани публикации със свободен достъп в PubMed, както и официалните web страници на Световната здравна организация (СЗО), ЕС, Международната организация на труда (МОТ; ILO, International Labour Organization), Министерство на здравеопазването на Република България (МЗ), Националния осигурителен институт (НОИ), Националния център по обществено здраве и анализи (НЦОЗА). На фиг. 1 е



Фиг. 1. Селекция на публикациите въз основа на включващите и изключващите критерии

представена селекцията на публикациите, спрямо включващите и изключващи критерии.

COVID-19: Епидемиология, предизвикателства и глобални усилия за контрол

През декември 2019 г. в град Ухан (провинция Хубей, Източен Китай) са регистрирани множество пациенти със симптоми на неизвестна досега инфекция, протичаща с широк спектър от клинични прояви. Изключително тревожната тенденция за полиорганно и полисистемно ангажиране, високата честота на смъртност и сериозните усложнения наложиха обявяването на епидемия, която впоследствие се разрасна в глобален мащаб и се превърна в пандемия. Усложненията на болестта доведоха до влошено качество на живот и неработоспособност, а при някои – до силно ограничена работоспособност с месеци след инфекцията [1-12]. По данни на СЗО пандемията от COVID-19 изключително бързо достигна глобални мащаби, като към края на 2024 г. е засегнала над 776 млн. души и е довела до над 7 млн. смъртни случаи [13]. Симптомите могат да продължат седмици или месеци след началото на инфекцията (т.нар. дълъг COVID, пост-COVID синдром, (PCS), което доведе до значимо увеличение на отсъствията от работното място поради временна нетрудоспособност, както и до намиране на алтернативни варианти за дистанционна работа и обучение. Болестта и izolацията причиниха не само здравословни, но и социално-икономически проблеми [14-22].

Основните предизвикателства, особено в началото на пандемията, бяха липсата и/или неравномерното разпределение на ресурси (медицински, финансови, логистични, организационни и др.) [23]. Засегнатите страни се опитаха да изравнят епидемиологичната крива и да избегнат претоварване на системите за здравеопазване чрез налагане на специфични хигиенни мерки, ограничаване на социалните контакти, носене на маска, физическо дистанциране, повишаване информираността на населението, ограничения за пътуване, затваряне на граници, национални блокирания и задължителна карантина за заразените и техните контактни лица [1, 22]. За кратък период бяха разработени множество ваксини (Pfizer-BioNTech, Moderna, AstraZeneca) с висока ефективност, повечето с леки странични ефекти след приложението [1, 11, 22, 24-27]. Бедните и развиващите се страни получиха подкрепа чрез международни фондове и инициативи като COVAX [28]. COVAX беше съвместна инициатива

на Световния алианс за ваксини (Gavi), Коалицията за иновации за готовност за епидемии (CEPI), СЗО и УНИЦЕФ от 2020 г. до 2023 г., която имаше за цел да ускори разработването на ваксини срещу COVID-19 и да гарантира равен и справедлив достъп до тях за всички [28].

На 21 юли 2020 г. лидерите от ЕС сключиха споразумение за общ бюджет от 1824 млрд. евро за периода 2021-2027 г. Като съчетава многогодишната финансова рамка (МФР) и извънредни усилия за възстановяване в размер на над 750 млрд. евро, пакетът спомага за възстановяването на ЕС след пандемията от COVID-19 и подкрепя инвестициите в екологичния и цифровия преход. Тези елементи допълват трите предпазни механизма в размер на 540 млрд. евро, които ЕС вече е въвел в подкрепа на работниците, предприятията и държавите (от 9 април 2020). През 2024 г. ЕС е отпуснал пакет от стимули на стойност 2018 млрд. евро за насърчване възстановяването на различни ресурси [29, 30]. През 2021 г. САЩ са осигурили \$3 500 000 000 по проект ARPA (American Rescue Plan Act) [31]. Федералното финансиране е в подкрепа на системите за обществен транспорт на нацията, докато те продължават да реагират на пандемията от COVID-19 и подкрепят призива на президента за ваксиниране на населението на САЩ [32]. Законът за американския спасителен план подкрепя работниците чрез: усъвършенстване на системата за осигуряване при безработица (модернизиране на осигурителната система, за да помогне на работниците да получат обезщетенията, които заслужават), осигуряване безопасността на работниците (чрез осигуряване на допълнително финансиране за подпомагане на уязвимите работници да бъдат здрави и защитени от COVID-19) и съдействие за здравноосигурителни премии (помага на работниците, които са загубили работата си или са имали намалено работно време по време на пандемията да плащат за здравно осигуряване чрез пълен субсидиране на премиите) [33].

Основен проблем в прилагането на тези глобални мерки за контрол се оказа съпротивата от страна на част от населението относно социалната дистанция и ваксинацията. Въпреки това съвместните усилия на множество институции постигнаха своята цел да намалят заболяемостта и смъртността в световен мащаб [34].

Пандемията COVID-19 оказва значително въздействие върху здравния туризъм, като доведе до рязко намаляване на международните пътувания и прекъсване на много медицински услуги.

Голяма част от здравните институции и туристическите оператори бяха принудени да адаптират своите услуги, като въведат нови изисквания, за да осигурят безопасността и здравето на пътуващите [29]. Въпреки тези трудности пандемията също така предизвика нов интерес към медицинския туризъм в постпандемичния период, с фокус върху безопасни дестинации и иновации в дистанционното здравеопазване и виртуалните консултации. Тези тенденции подчертават необходимостта от адаптиране на индустрията към новите изисквания на потребителите и регулиращите органи [35]. В допълнение, пандемията COVID-19 отложи и възпрепятства прегледите при различни специалисти с месеци. Особено потърпевши бяха и пациентите с ревматични заболявания, които нямаша достъп до ревматолог с месеци. По литературни данни в повечето страни от Централна и Западна Европа консултацията с ревматолог отнема около 30 седмици [36]. Fuchs и кол., както и други източници съобщават, че в Р. Германия са необходими повече от 6 месеца от появата на първия симптом на възпалителна ставна болест до реализирането на консултация със специалист [37]. Тази тенденция е актуална и за други държави извън ЕС. Widdiefield и колектив публикуват данни, според които в Канада са необходими средно 74 дни за осъществяване на подобна консултация, което значително влошава качеството на здравните грижи за пациентите с ревматични заболявания [37, 38].

HIV/СПИН: Глобална пандемия и борба с вируса

Към 2024 г. СПИН, причинен от HIV, продължава да бъде предизвикателство и глобален здравен проблем. Въпреки значителния напредък в диагностицирането и лечението през последните десетилетия, болестта остава един от основните фактори за смъртност в някои региони, особено в Африка (на юг от Сахара) [39-41]. По данни на Съвместна програма на ООН за HIV и СПИН (Joint United Nations Programme on HIV and AIDS, UNAIDS) и C3O към края на 2023 г. около 1,3 млн. души са новозаразени, около 40 млн. живеят с HIV, а смъртните случаи са около 630 000 [39]. Около 28 млн. души по света получават антиретровирусно лечение, което значително подобрява качеството на живот и намалява вирусния товар. [39, 40].

Създадени са множество международни кампании за повишаване на информираността и намаляване на стигмата около заболяването. PrEP

(профилактика преди излагане) – прием на лекарства за предпазване от заразяване – е една от основните програми за превенция. Това е особено ефективно в определени рискови групи (хора с множество сексуални партньори, лица със зависимости или хомосексуалисти) [39, 41]. Основните компоненти на таблетката са тенофовир (TDF) и емтрицитабин (FTC). Най-известното патентовано име за тази комбинация е Truvada®, но вече има генерични версии на PrEP. У нас е достъпен медикаментът под наименованието Tenofovir Disoproxil Emtricitabine [42]. Съществуват активни усилия в изследванията на ваксини и нови терапии, които да могат да излекуват СПИН, но към момента те са с ограничено клинично приложение. [40, 43]. Програмата на ООН за борба с HIV/СПИН, известна като UNAIDS, работи за постигане на целта за премахване на HIV като глобален здравен проблем до 2030 г. [39]. Съществуват няколко вида лекарства срещу HIV инфекцията, насочени срещу различни фази на процеса на размножаване на вируса. Тъй като вирусът мутира бързо и става резистентен спрямо всяко отделно взето лекарство, пациентите трябва да приемат комбинирана анти-HIV терапия (антиретровирусна терапия, АРТ). За съжаление, АРТ не може да премахне инфекцията напълно [44]. Лечението се поема от МЗ, без оглед на здравноосигурителния статус на пациента [46].

Основните предизвикателства, които стоят на дневен ред, са социално-икономическите бариери пред профилактиката и лечението (липса на информираност и достъп до здравни услуги, нисък социален статус и образование). Друг основен проблем е дългосрочното непридържане към терапията и липсата на здравна инфраструктура в държавите с нисък брутен вътрешен продукт (БВП) [40, 41].

Туберкулоза: Древно заболяване в съвременния свят

Туберкулозата (ТБ), причинена от *Mycobacterium tuberculosis* (MTB), е хронично протичащо, системно инфекциозно заболяване, което обичайно засяга белите дробове, но може да се развие във всички органи и системи на организма. Разпространява се предимно по въздушно-капков път от болните с белодробна ТБ (БТБ). Независимо от наличието на етиологично лечение и от усилията в глобален мащаб за ефективен контрол, ТБ все още представлява заплаха пред общественото здраве поради задържане нивото на разпространението ѝ и на броя на смъртните

случаи [46, 47]. Силикозата (специфично професионално заболяване) и инфекцията с HIV са най-значимите рискови фактори за развитие на ТБ и взаимно се допълват, особено в страните с нисък БВП [47-50]. Инфекцията с HIV повишава заболяемостта от ТБ чрез увеличаване на риска от реактивиране на латентната ТБ инфекция (ЛТБИ) с МТВ и бързото прогресиране към активна ТБ [47]. Проблемът с БЦЖ (BCG, Bacillus Calmette-Guerin) ваксинацията, въпреки задължителния ѝ характер според имунизационния календар на Р. България, става все по-популярен.

По данни на СЗО през 2021 г. ТБ е второто най-смъртоносно инфекциозно заболяване в света след COVID-19, като всяка година причинява около 1,5 млн. смъртни случаи [46]. През 2023 г. по изчисления на СЗО около 10,8 млн. души са новозаболяли от ТБ, а приблизително 1,25 млн. са починали от заболяването. От тях 6,1% са лица, живеещи с HIV. Повечето случаи са в страните от Югоизточна Азия (45%), Африка (24%) и западното Тихоокеанско крайбрежие (17%). В 8 страни са съсредоточени над 2/3 от случаите: Индия (26%), Индонезия (10%), Китай (6,8%), Филипините (6,8%), Пакистан (6,3%), Нигерия (4,6%), Бангладеш (3,5%) и Демократична република Конго (3,1%). Жените, засегнати от заболяването, са 3,6 млн. (33% от всички прогнозирани случаи), а децата от 0 до 14 години са 1,3 млн. (12%) [46]. Разпространението на мултирезистентната туберкулоза (MDR-TB) и екстензивно резистентната туберкулоза (XDR-TB) усложняват борбата срещу заболяването. Други предизвикателства са недостатъчният достъп до диагностика и лечение в бедни и отдалечени страни/региони, влиянието на HIV върху възприемчивостта към туберкулозата и продължителността на лечението с комбинация от противотуберкулозни лекарствени продукти минимум 6 месеца при чувствителна ТБ, вкл. 2 месеца с 4 лекарства и 4 месеца с 2 лекарства [46]. Пандемията от COVID-19 оказва сериозно влияние върху контрола на ТБ, като забави достъпа до диагностика и лечение. Според СЗО в резултат на пандемията през 2020 и 2021 г. се наблюдава увеличение на смъртността и броя на недиагностицираните случаи на ТБ (скрита заболяемост) [46].

В стремеж за контрол и превенция на заболяването са организирани инициативи за информираност, подобряване на имунизационния обхват (БЦЖ ваксината остава основната ваксина за превенция на ТБ), ранно диагностициране, лечение с нови терапии и програми за подобряване

на достъпа до лечение в развиващите се страни. Партньорството за спиране на ТБ (Stop TB Partnership) е основано през 2001 г. и е част от Организацията на обединените нации (ООН), администрирано от службата на ООН за проектни услуги (United Nations Office for Project Services, UNOPS) със седалище в Женева (Швейцария) [51]. Stop TB Partnership обединява усилията на различни международни организации с цел елиминиране на туберкулозата. Целите на настоящата Стратегия „Край на туберкулозата“ на СЗО са намаляване с 90% на заболяемостта и с 95% на смъртните случаи до 2035 г. в сравнение с нивата от 2015 г. и дори елиминирането на туберкулозата до 2050 г. (по-малко от 1 новооткрит случай на 1 млн. население годишно) [46, 47, 51.]

Около 1/4 от населението по света е с ЛТБИ, т.е. тези лица са инфектирани с МТВ, но (все още) не са болни и не могат да разпространяват тази инфекция. ЛТБИ е вероятно най-важният фактор за липсата на желания напредък в контрола на ТБ. Дефинира се като състояние на персистиращ имунен отговор към стимулация от антигени на МТВ без клинични данни за активна болест. Тя представлява огромен резервоар за развитието на ТБ епидемия, тъй като около 1/10 от инфектираните лица развиват активна туберкулоза по време на живота си. Имунокомпрометираните лица са особено изложени на риск от активиране на ЛТБИ, което е тясно свързано със способността на имунитета на гостоприемника да осигури адекватен отговор. Лицата, инфектирани с HIV, лицата с имуномедирирани възпалителни заболявания, приемащи лечение със системни кортикостероиди и антагонисти на туморнекротизиращия фактор – алфа (TNF- α), пациентите на хемодиализа, кандидатите за трансплантация и реципиентите са с повишен риск от реактивиране на ТБ.

Препоръчаните от СЗО тестове за установяване на ЛТБИ са: туберкулинов кожен тест (ТКТ) на Mantoux и тестове, основани на отделяне на интерферон-гама (IGRAs; Interferon-Gamma Release Assays) – имунологични методи, основани на отделянето на интерферон-гама (IFN- γ) от сенсibiliзираните Т-клетки на инфектирани с ТБ лица при повторен контакт с антигени на МТВ. Понастоящем на разположение са два вида IGRA тестове, които използват различни имунологични методи: QuantiFERON-TB Gold Plus (QFT-Plus) и T-SPOT.TB.

Изключително важно е да се подчертае, че диагнозата „ЛТБИ“ не се основава само на ТКТ или IGRAs, а се поставя винаги след изключване на активна ТБ със съответната медицинска оценка

(анамнеза и физикално изследване, микробиологично изследване на хранка и други биологични проби за наличието на МТВ, рентгенография на гръден кош, патоморфологични и други изследвания). При изключване на активна болест, особено при имunosупресирани лица, малки деца и контактни в тесен семеен кръг, превантивното лечение на ЛТБИ, причинена от МТВ щамове, за които се предполага, че са с лекарствена чувствителност, бива: монотерапия с изониазид (H) за поне 6 месеца и лечение със схеми, съдържащи рифамицинов антибиотик: рифампицин (R) или рифапентин (P).

В допълнение на проблема се явяват и професионалните болести, причинени от биологични фактори [52]. През 2005 г. биологичните рискове на работното място са били причина за около 320 000 смъртни случая годишно в световен мащаб и около 5000 смъртни случая в ЕС. По данни на Cogroa и сътр. професионалните болести, дължащи се на инфекции, са около 0,8% от всички починали, предимно в сферата на здравеопазването и социалните услуги (65,21%) [52, 53]. Според Европейско проучване на условията на труд от 2015 г. делът на работещите в Европейския съюз, изложени на инфекциозни агенти по време на работа, е 13%, което е 1,5 пъти повече в сравнение със ситуацията преди 10 години [54]. По експертна оценка през 2021 г. по света има 550 000 смъртни случая поради излагане на биологични агенти в работната среда. Най-голям дял през 2021 г. се пада на COVID-19 като причина за смърт, свързана с работата при 230 000 души [55]. Според проучване на UN Global Union само 98 държави в света са признали COVID-19 като професионална болест, което покрива едва 2% от населението [56]. Към днешна дата COVID-19 и дългият COVID-19 не са включени в списъците на професионалните заболявания, предоставени от международни организации (МОТ, СЗО, ЕС) и не са признати за професионално заболяване в България и в повечето държави [22, 57]. Несигурното финансово състояние на много работещи намалява тяхната способност да си позволят разходите за здравеопазване. Това от своя страна води до персонални икономически загуби, но също така се отразява на техните семейства, работодатели и държавата [14-22].

Ситуацията в България

В „Националната здравна стратегия 2020“ на Република България особено внимание е

отделено на дейността по надзора на заразителните болести, опазването на страната от внос и разпространение на тези инфекции, ограничаване възникването на епидемични взривове и епидемии, осигуряване на висок имунизационен обхват на населението от ваксинапредотвратими инфекции и организирането на бърз отговор при възникване на ситуации, заплашващи общественото здраве (в т.ч. и използването на биологични агенти с терористична цел) [58]. Приоритетна задача е ограничаването на вътрешболничните инфекции (ВБИ) и антимикробната резистентност (AMP), които са критерии за оценка на качеството на медицинските услуги и безопасността на пациентите. Посочено е, че ВБИ са сред първите десет водещи причини за повишена смъртност при пациентите, въпреки че в голяма част са предотвратими. Появата на полирезистентност води до трайно ограничаване на възможностите за лечение и профилактика на бактериалните инфекции [58].

По данни на НЦОЗА за 2022 г. в страната са регистрирани 563 079 случая с COVID-19 и 38 106 души починали, като все пак се отчита намаляване на леталитета спрямо предходната година. От 1 юли 2024 г. е преустановено функционирането на Националната система за борба с COVID-19, както и на Единния информационен портал – cogonavirus.bg. Информация за регистрираните в страната случаи се публикува веднъж седмично на сайтовете на Министерството на здравеопазването и Националния център по заразни и паразитни болести [59-61].

По отношение на останалите две инфекции към края на 2022 г. са регистрирани общо 4048 лица с HIV инфекция, като за съответната година броят на новорегистрираните случаи е 327. При 9% от диагностицираните със СПИН, диагнозата е поставена при наличие на туберкулоза като опортюнистична инфекция [59]. В периода 2004-2017 г. с изпълнението на Програма „Превенция и контрол на ХИВ/СПИН“, финансирана от Глобалния фонд за борба със СПИН, туберкулоза и малария, в страната бяха въведени превантивни услуги сред най-уязвимите групи чрез изграждане на ниско-прагови центрове и мрежи от обучени екипи на неправителствени организации [59]. Националните програми отговарят на изискванията и ангажиментите, поети от страната в изпълнение на международните препоръки и редица политически документи като: Цели за устойчиво развитие на ООН (Sustainable Development Goals), Декларацията

за ангажираност с проблема HIV (Дъблинска декларация); Третата програма за действие на Съюза в областта на здравето (2014-2020), проект на Глобалната стратегия срещу HIV на Обединената програма на ООН за борба с HIV/СПИН (2021-2026) [39, 62, 63]. В рамките на Националната програма за превенция и контрол на HIV и сексуално предавани инфекции в Република България 2021-2025 г. продължават да се провеждат 4 ежегодни АНТИСПИН кампании: по повод 14 февруари, Международния ден за съпричастност със засегнатите от HIV/СПИН (третата неделя от м. май), лятната АНТИСПИН кампания (м. август) и по повод 1 декември – Световния ден за борба срещу СПИН. Програмите за превенция на СПИН се фокусират върху образованието на младите хора, рисковите групи и увеличаване на информираността относно начините за предотвратяване на заразяване с HIV, включително използването на презервативи и ПрЕП [64].

България заема междинно ниво в сравнение с високата заболяемост от ТБ в държавите от Източна Европа и Централна Азия, и ниското ѝ разпространение в страните от Западна Европа. В съответствие с предприетите мерки в световен мащаб у нас от 1951 г. са разработени собствени програми за контрол на това социално значимо заболяване, с прилагане на утвърдените модели и практики с цел намаляване на общественото бреме на ТБ. Благодарение на усилията, предприети в изпълнение на „Националната програма за превенция и контрол на туберкулозата в Република България“ у нас се наблюдава тенденция за намаляване на заболяемостта – от 48,8 на 100 000 през 2001 г. до 13,5 на 100 000 през 2023 г.

През последните 4 години и в страната ни се отчитат същите тенденции поради пандемията с COVID-19, както и в световен мащаб – намаляване на регистрираните случаи с туберкулоза вследствие реструктуриране и нарушени функции на специализираните лечебни заведения за контрол на туберкулозата по области, невявяване на suspectните и пациентите за туберкулоза в здравните структури от въведения локдаун и стигма поради сходните симптоми на двете заболявания; персистиращ контакт в домашни условия и повишен риск от предаване на инфекцията сред членовете на семействата на пациентите. Общият брой на регистрираните у нас лица с туберкулоза по данни на НЦОЗА през 2023 г. е 869, което съответства на 13,5 на 100

000 население. Броят на мъжете със заболяването обичайно е два пъти по-голям от този на жените. Най-засегнати са възрастовите групи от 45-54 г., над 65 г. и 55-64 г. Административните области със заболяемост над средната за страната през 2023 г. са: София област – 32,2; Враца – 22,9; Монтана – 24,3; Перник – 18,9; Ямбол – 18,7 на 100 000 [65].

По данни на НОИ за периода 2009-2022 г. са признати общо 13 случая на професионални болести, причинени от биологични агенти, като 7 случая са на ТБ – по 1 докладван случай за 2009 г., 2013 г. и 2014 г., и 4 случая за 2015 г. От данните, предоставени от НОИ, не може да се направи връзка между докладваните случаи и разпределението им по пол, възрастови групи, професия/дейност на заболялите, категория на труд, особености на работа, продължителност на експозицията и тежест на болестта [66, 67]. Основните трудности при оценката на професионалния риск са свързани с липсата на систематизирана информация за биологичните агенти в много трудови дейности, недостатъчната осведоменост и неадекватното обучение на работещите по здравословни и безопасни условия на труд, липса на стандартизирани критерии за професионална експозиция на биологични агенти във въздуха. Познаването на биологичните агенти е от изключително значение за превенцията на свързаните с тях заболявания и смъртност.

Съвременни стратегии за справяне с предизвикателствата от социалнозначимите инфекциозни заболявания

1. В основата на стратегиите за борба с инфекциозните заболявания стоят глобалното сътрудничество, разработването на международни инициативи, свързани с обмен на информация, образование по здравни въпроси, както и финансова и материална подкрепа (дарения/закупуване на ваксини) за държавите с нисък БВП.

2. Достъпността до медицински услуги, лечебни заведения, съвременна медицинска апаратура, лекарствени продукти и ваксини е основополагаща за намаляването на заболяемостта, профилактиката и превенцията.

3. Финансирането и разработването на нови молекули за лечение на трите инфекции е ключов механизъм за намаляването и предотвратяването на последствията им.

4. Международни кампании за намаляване на стигмата и предразсъдъците, съвместно със соци-

ални програми за подкрепа на болелите, могат да намалят социалната изолация и да подобрят психосоциалното здраве на засегнатите индивиди.

5. Изработването на стриктни стандарти за безопасност в работната среда (с приоритет в здравеопазването), както и на ефективни протоколи за защита и обучение на персонала са основен приоритет за ограничаване на разпространението на инфекциите.

6. Разработване на специални програми и здравни застраховки, които да облекчат икономическите последици от инфекциозните заболявания.

ЗАКЛЮЧЕНИЕ

Пандемията от COVID-19 подчерта уязвимостта на глобалната обществена система пред

нововъзникващи здравни кризи. Инфекциозните заболявания (COVID-9, HIV/СПИН и туберкулоза) остават сериозни глобални проблеми, които изискват координирани усилия на глобално, национално и локално ниво. Въпреки напредъка в диагностицирането и лечението, както и международните усилия за превенция и контрол, остават множество предизвикателства, включително социално-икономическите бариери и недостигът на здравни услуги в много региони. Много от проблемите се крият в неравномерния достъп до здравни услуги, стигмата и недостига на ресурси в бедните и развиващите се страни. Успехът в борбата срещу тези заболявания зависи от глобалната солидарност, научни иновации и ефективни здравни политики.

GLOBAL TRENDS AND PROBLEMS OF INFECTIOUS DISEASES – COVID-19, HIV/AIDS, TUBERCULOSIS

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Abstract. Globalization and the interconnectedness of countries in the modern world pose new challenges to public health. Over the centuries, infectious diseases have proven to be one of the major threats to global health. Historically, several pandemics and epidemics have changed and claimed the lives of millions of people around the world. Many infectious agents continue to pose a serious problem despite advances in medicine, public health awareness campaigns and vaccination. The aim of this review is to present the global epidemiological trends and challenges related to three key infectious diseases: COVID-19, HIV/AIDS, and tuberculosis. The COVID-19 pandemic, along with the long-standing threats of HIV/AIDS and tuberculosis, is posing a serious challenge to health systems and socio-economic structures in many countries. COVID-19, caused by SARS-CoV-2, has spread rapidly around the world, resulting in significant numbers of cases, deaths, and long-term health problems. The consequences of long COVID-19 and “post-COVID-19 syndrome” have become one of the main causes of reduced work capacity and impaired quality of life in recent years. At the same time, HIV/AIDS remains a global health problem, especially in certain regions, and tuberculosis continues to constitute a serious threat, especially in conditions of limited access to health services. Each of these health problems creates specific requirements for treatment and prevention, while leading to serious health, social and economic consequences, despite global initiatives and strategies to address them.

Key words: global trends, issues, strategies, COVID-19, HIV/AIDS, tuberculosis

INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has demonstrated the global health, economic, and social challenges and consequences of infectious diseases. In addition to the numerous deaths, the complications of the disease caused by the virus have led to a deterioration in the quality of life of patients. The rapid introduction of numerous anti-epidemic measures and the development of vaccines proved to be of utmost importance for controlling the disease. Adaptation by medical professionals (including in the direction of digitalization of healthcare), society and business was a necessity. At the global level, financial support for recovery was provided through various initiatives and financial packages from the European Union (EU) and the United States of America (USA). In parallel with the spread of the virus, there was a delay in the diagnosis and treatment of many other infectious (e.g. tuberculosis and HIV) and chronic diseases. Human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS), continues to be a significant global health problem. Despite awareness campaigns, pre-exposure prophylaxis (PrEP) and the availability of antiretroviral treatment (ART), AIDS remains a major cause of mortality, especially in regions

such as sub-Saharan Africa, due to socio-economic barriers to effective prevention and treatment. Tuberculosis (TB) is another infectious disease that, despite efforts to control and treat it, remains a leading cause of death worldwide. In addition, HIV infection, silicosis (a specific occupational disease), and multidrug-resistant tuberculosis (MDR-TB) complicate not only the treatment but also the prevention of TB. Added to these global problems are occupational diseases caused by biological agents in the workplace, which also lead to hundreds of thousands of deaths annually. In this review, we examine global trends and some of the problems associated with these key infectious diseases, and analyze existing strategies to address future pandemics.

METHODS

Open access publications in PubMed were reviewed, as well as the official websites of the World Health Organization (WHO), the European Union (EU), the International Labour Organization (ILO), Ministry of Health of the Republic of Bulgaria (MoH), National Social Security Institute (NSI), National Center for Public Health and Analysis (NCPHA). Figure 1 presents the selection of publications according to the inclusion and exclusion criteria.

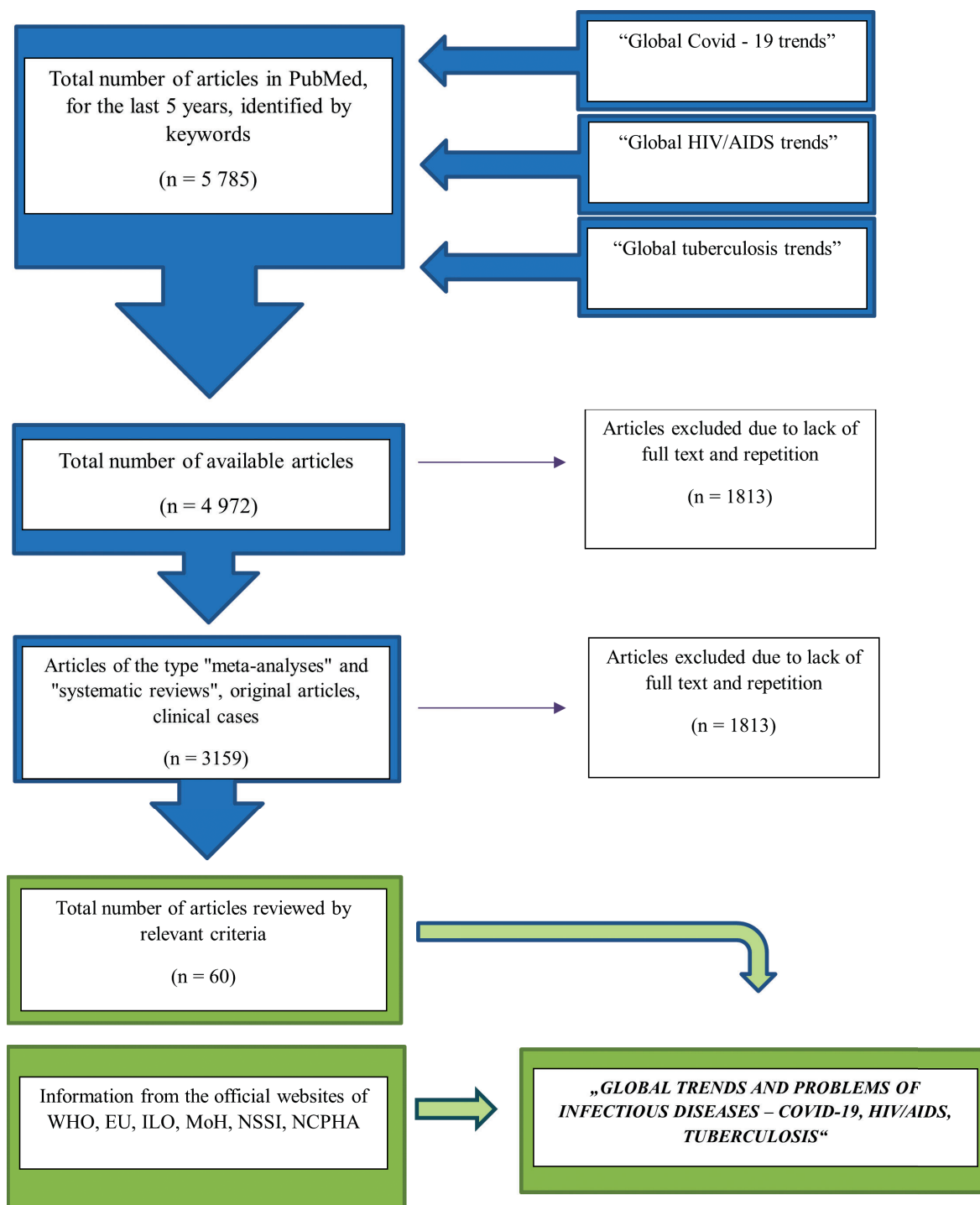


Fig. 1. Selection of publications based on inclusion and exclusion criteria

COVID-19: Epidemiology, challenges and global control efforts

In December 2019, numerous patients with symptoms of a previously unknown infection with a wide spectrum of clinical manifestations were registered in the city of Wuhan (Hubei province, eastern China). The extremely worrying trend of multi-organ and multi-system involvement, the high mortality rate

and serious complications necessitated the declaration of an epidemic, which subsequently expanded globally and became a pandemic. Complications of the disease have led to a reduced quality of life and disability, and in some cases to severely limited work capacity for months after infection [1-12]. According to WHO data, the COVID-19 pandemic has rapidly reached global proportions, affecting over 776 mil-

lion people by the end of 2024 and causing over 7 million deaths[13]. Symptoms can persist for weeks or months after the onset of infection (so-called “long COVID”, post-COVID syndrome (PCS)), which has led to a significant increase in absenteeism from work due to temporary disability, as well as to the search for alternative options for remote work and learning. Illness and isolation have caused not only health but also socio-economic problems [14-22]. The main challenges, especially at the beginning of the pandemic, were the lack and/or uneven distribution of resources (medical, financial, logistical, organizational, etc.) [23]. Affected countries have tried to flatten the epidemiological curve and avoid overburdening health systems by imposing specific hygiene measures, restricting social contact, wearing a mask, keeping physical distance, raising public awareness, impose travel restrictions, border closures, and mandatory quarantine for infected people and their contacts [1, 22]. Multiple vaccines (Pfizer-BioNTech, Moderna, AstraZeneca) have been developed in a short period of time with high efficacy, most with mild side effects after administration [1, 11, 22, 24-27]. Poor and developing countries have received support through international funds and initiatives such as COVAX [28]. COVAX was a joint initiative of the Global Alliance for Vaccines (Gavi), the Coalition for Epidemic Preparedness Innovation (CEPI), WHO and UNICEF from 2020 to 2023, which aimed to accelerate the development of COVID-19 vaccines and ensure equal and equitable access to them for all [28].

On 21 July 2020, EU leaders agreed on a total budget of €1.824 billion for the period 2021-2027. Combining the Multiannual Financial Framework (MFF) and an emergency recovery effort of over €750 billion, the package helps the EU recover from the COVID-19 pandemic and supports investment in the environmental and digital transition. These elements complement the three €540 billion backstops the EU has already put in place to support workers, businesses and countries (from 9 April 2020). In 2024, the EU has allocated an incentive package worth €2,018 billion to promote recovery in various sectors [29, 30]. In 2021 The United States has provided \$3,500,000,000 under the American Rescue Plan Act (ARPA) [31]. Federal funding supports the nation's public transportation systems as they continue to respond to the COVID-19 pandemic and support the President's call to vaccinate the U.S. population [32]. ARPA supports workers by: improving the unemployment insurance system (modernizing the insurance system to help workers get the benefits they deserve), ensuring worker safety

(by providing additional funding to help vulnerable workers be healthy and protected by COVID-19), and assisting with health insurance premiums (helping workers who lost their jobs or had their hours reduced during the pandemic to pay for health insurance by fully subsidising premiums) [33].

A major problem in the implementation of these global control measures has been the resistance of a segment of the population to social distance and vaccination. However, the collaborative efforts of multiple institutions have achieved their goal of reducing morbidity and mortality worldwide [34].

The COVID-19 pandemic has had a significant impact on health tourism, leading to a sharp reduction in international travel and disruption of many medical services. Many healthcare institutions and tourism operators have been forced to adapt their services, introducing new requirements to ensure the safety and health of travelers [29]. Despite these difficulties, the pandemic has also sparked new interest in medical tourism in the post-pandemic period, with a focus on safe destinations and innovations in telehealth and virtual consultations. These trends highlight the need for the industry to adapt to new consumer and regulatory demands [35]. In addition, the COVID-19 pandemic delayed and prevented examinations with various specialists for months. Patients with rheumatic diseases were particularly affected, as they could not access a rheumatologist for months. According to the literature, in most Central and Western European countries, consultation with a rheumatologist takes about 30 weeks [36]. Fuchs et al. and other sources reported that in Germany, it takes more than 6 months from the onset of the first symptom of inflammatory joint disease until a consultation with a specialist is scheduled [37]. This trend is also relevant for other non-EU countries. Widdiefield et al. published data showing that in Canada it takes an average of 74 days to appoint such a consultation, which significantly worsens the quality of health care to patients with rheumatic diseases [37, 38].

HIV/AIDS: Global pandemic and the fight against the virus

By 2024, AIDS (AIDS) caused by HIV continues to be a challenge and a global health problem. Despite significant advances in diagnosis and treatment in recent decades, the disease remains one of the major contributors to mortality in some regions, particularly in Africa (sub-Saharan Africa) [39-41]. According to the Joint United Nations Programme on HIV and AIDS (UNAIDS) and WHO, by the end

of 2023 about 1.3 million people are newly infected, about 40 million are living with HIV, and there are about 630,000 deaths [39]. About 28 million people worldwide are receiving antiretroviral treatment, which significantly improves quality of life and reduces viral load [39, 40].

Numerous international campaigns have been created to raise awareness and reduce the stigma surrounding the disease. PrEP (pre-exposure prophylaxis) - taking medication to prevent infection - is one of the main prevention programmes. This is particularly effective in certain at-risk groups (people with multiple sexual partners, people with addictions or homosexuals) [39, 41]. The main components of the tablet are Tenofovir (TDF) and Emtricitabine (FTC). The best known patented name for this combination is Truvada®, but generic versions of PrEP are now available. In Bulgaria, the drug is available under the name Tenofovir Disoproxil Emtricitabine [42]. There are active efforts in researching vaccines and new therapies that can cure AIDS, but they are currently of limited clinical use [40, 43]. The United Nations Programme to Fight HIV/AIDS, known as UNAIDS, is working towards the goal of eliminating HIV as a global health problem by 2030 [39]. There are several types of drugs against HIV, the infection that targets different phases of the virus' replication process. Because the virus mutates rapidly and becomes resistant to any single drug taken, patients must take combination anti-HIV therapy (antiretroviral therapy, ART). Unfortunately, ART cannot completely eliminate the infection [44]. The treatment is covered by the Ministry of Health, regardless of the patient's health insurance status [45].

The main challenges on the agenda are socio-economic barriers to prevention and treatment (lack of awareness and access to health services, low social status and education). Another major problem is long-term non-adherence to treatment and lack of health infrastructure in countries with low gross domestic product (GDP) [40, 41].

Tuberculosis: An Ancient Disease in the Modern World

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), is a chronic, systemic infectious disease that usually affects the lungs but can develop in all organs and systems of the body. It is usually spread by the airborne route by patients with pulmonary TB (PTB). Despite the availability of an aetiological treatment and global efforts to effectively control it, TB still poses a public health threat due to the persistence of its prevalence and the number

of deaths [46, 47]. Silicosis (a specific occupational disease) and HIV infection are the most significant risk factors for TB and complement each other, especially in low GDP countries [47-50]. HIV infection increases the incidence of TB by increasing the risk of reactivation of latent TB infection (LTBI) with MTB and rapid progression to active TB [47]. The problem with BCG (*Bacillus Calmette-Guerin*) vaccination, despite its compulsory nature according to the immunization calendar of R. Bulgaria, is becoming increasingly popular. According to the WHO, in 2021, TB is the second deadliest infectious disease in the world after COVID-19, causing an estimated 1.5 million deaths each year [46]. In 2023, WHO estimates that about 10.8 million people were newly infected with TB, and approximately 1.25 million deceased from the disease. Of these, 6.1% are persons living with HIV. The majority of cases are in Southeast Asian countries (45%), Africa (24%) and the Western Pacific (17%). More than two-thirds of cases are concentrated in 8 countries: India (26%), Indonesia (10%), China (6.8%), Philippines (6.8%), Pakistan (6.3%), Nigeria (4.6%), Bangladesh (3.5%), and Democratic Republic of Congo (3.1%). Women affected by the disease account for 3.6 million (33% of all estimated cases) and children aged 0-14 years account for 1.3 million (12%) [46]. The spread of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) complicates the fight against the disease. Other challenges include inadequate access to diagnosis and treatment in poor and remote countries/regions, the impact of HIV on TB susceptibility, and the duration of treatment with a combination of anti-TB drugs – a minimum of 6 months for susceptible TB, including 2 months with 4 drugs and 4 months with 2 drugs [46]. The COVID-19 pandemic has had a major impact on TB control by delaying access to diagnosis and treatment. According to the WHO, there is an increase in mortality and the number of undiagnosed TB cases (hidden morbidity) in 2020 and 2021 as a result of the pandemic [46].

In an effort to control and prevent the disease, initiatives have been organized to raise awareness, improve immunization coverage (the BCG vaccine remains the main vaccine for TB prevention), early diagnosis, treatment with new therapies, and programs to improve access to treatment in developing countries. The Stop TB Partnership was founded in 2001 and is part of the United Nations (UN), administered by the United Nations Office for Project Services (UNOPS) based in Geneva, Switzerland [51]. Stop TB Partnership brings together the efforts of

various international organizations with the goal of eliminating TB. The goals of the current WHO End TB Strategy are to reduce TB incidence by 90% and deaths by 95% by 2035 compared to 2015 levels, and even to eliminate TB by 2050 (less than 1 new case per 1 million population per year) [46, 47, 51].

About 1/4 of the world's population has latent tuberculosis infection (LTBI), i.e. these individuals are infected with MTB but are not (yet) sick and cannot spread this infection. LTBI is probably the most important factor in the lack of desired progress in TB control. It is defined as a state of persistent immune response to stimulation by MTB antigens without clinical evidence of active disease. It represents a huge reservoir for the development of a TB epidemic, as about 1/10 of infected persons develop active TB during their lifetime. Immunocompromised individuals are particularly at risk of LTBI activation, which is closely linked to the ability of host immunity to provide an adequate response. Persons infected with HIV, persons with immune-mediated inflammatory diseases, those receiving treatment with systemic corticosteroids and tumor necrosis factor- α (TNF- α) antagonists, hemodialysis patients, transplant candidates, and recipients are at increased risk of TB reactivation.

The WHO-recommended tests to detect LTBI are the Mantoux tuberculin skin test (TST) and interferon-gamma release assays (IGRAs), immunological methods based on the release of interferon-gamma (IFN- γ) from sensitized T cells of TB-infected individuals upon repeated exposure to MTB antigens. Two types of IGRAs are currently available that use different immunological methods: the QuantiFERON-TB Gold Plus (QFT-Plus) and the T-SPOT.TB.

It is extremely important to emphasize that the diagnosis of LTBI is not based on TFTs or IGRAs alone, but is always made after exclusion of active TB with appropriate medical evaluation (history and physical examination, microbiological examination of sputum and other biological samples for the presence of MTB, chest radiography, pathomorphological and other examinations). In the exclusion of active disease, especially in immunosuppressed persons, young children and close family contacts, the preventive treatment of LTBI caused by MTB strains presumed to be drug-susceptible would be: monotherapy with isoniazid (H) for at least 6 months and treatment with regimens containing the rifamycin antibiotic: rifampicin (R) or rifapentine (P).

Adding to the problem are occupational diseases caused by biological agents [52]. In 2005, biological hazards at work were responsible for around 320 000 deaths per year worldwide and around 5 000

deaths in the EU. According to Corrao CR et al. occupational diseases due to infections accounted for about 0.8% of all deaths, mainly in health and social services (65.21%) [52, 53]. According to the European Working Conditions Survey 2015, the proportion of workers in the European Union exposed to infectious agents at work was 13%, which is 1.5 times higher than the situation 10 years ago [54]. Experts estimate that there were 550 000 deaths worldwide in 2021 due to exposure to biological agents in the work environment. COVID-19 accounts for the largest share in 2021 as a cause of work-related death in 230,000 people [55]. According to a UNI Global Union study, only 98 countries in the world have recognized COVID-19 as an occupational disease, covering only 2% of the population. [56] o date, COVID-19 and long COVID-19 are not included in the lists of occupational diseases provided by international organizations (ILO, WHO, EU) and are not recognized as an occupational disease in Bulgaria and in most countries [22, 57]. The precarious financial situation of many workers reduces their ability to afford health care costs. This in turn leads to personal economic losses, but also affects their families, employers and the state [14-22].

The situation in Bulgaria:

The National Health Strategy 2020 of the Republic of Bulgaria pays particular attention to the surveillance of communicable diseases, the protection of the country from the import and spread of these infections, the containment of outbreaks and epidemics, the provision of high immunisation coverage of the population against vaccine-preventable infections and the organisation of a rapid response to situations threatening public health (including the use of biological agents for terrorist purposes) [58]. A priority task is the reduction of hospital-acquired infections (HAIs) and antimicrobial resistance (AMR), which are criteria for assessing the quality of medical services and patient safety. It has been pointed out that HAIs are among the top ten leading causes of increased patient mortality, although they are largely preventable. The emergence of polyresistance leads to a permanent limitation of treatment and prevention options for bacterial infections [58].

According to the NCDC, there were 563,079 cases of COVID-19 and 38,106 deaths in the country in 2022, yet a decrease in lethality from the previous year was reported. As of 1 July 2024, the National COVID-19 System has been discontinued, as well as the Single Information Portal – coronavirus. bg. Information on cases registered in the country is

published once a week on the websites of the Ministry of Health and the National Centre for Infectious and Parasitic Diseases [59-61].

In terms of the other two infections, a total of 4048 persons with HIV infection have been registered by the end of 2022, with 327 new cases registered in the corresponding year. In 9% of those diagnosed with AIDS, the diagnosis was made in the presence of tuberculosis as an opportunistic infection [59]. In the period 2004-2017, the implementation of the "HIV/AIDS Prevention and Control Programme", funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria, introduced prevention services among the most vulnerable groups in the country through the establishment of low-threshold centres and networks of trained non government organization teams [59]. The national programmes respond to the requirements and commitments made by the country in implementation of international recommendations and a number of policy documents such as: the UN Sustainable Development Goals, the Declaration of Commitment on HIV (Dublin Declaration); the Third Union Programme of Action on Health (2014-2020), the draft Global HIV Strategy of the Joint United Nations Programme on HIV/AIDS (2021-2026) [39, 62, 63]. Within the framework of the National Programme for the Prevention and Control of HIV and Sexually Transmitted Infections in the Republic of Bulgaria 2021-2025, four annual Anti-AIDS campaigns continue to be held: on the 14th of February, the International Day of Compassion for those Affected by HIV/AIDS (the third Sunday in May), the summer Anti-AIDS campaign (August) and on the 1st of December – World AIDS Day. AIDS prevention programs focus on educating young people, at-risk groups, and increasing awareness about ways to prevent HIV infection, including condom use and PrEP [64].

Bulgaria occupies an intermediate level compared to the high prevalence of TB in the countries of Eastern Europe and Central Asia, and its low prevalence in the countries of Western Europe. In line with measures taken worldwide, our country has developed its own programmes for the control of this socially important disease since 1951, applying established models and practices to reduce the societal burden of TB. Thanks to the efforts undertaken in the implementation of the „National Programme for Prevention and Control of Tuberculosis in the Republic of Bulgaria“, the country is witnessing a downward trend in the incidence of TB from 48.8 per 100 000 in 2001 to 13.5 per 100 000 in 2023. Over the last 4 years, the same trends have been reported

in our country due to the COVID-19 pandemic as globally – a decrease in registered TB cases due to restructuring and disrupted functions of specialized TB control facilities by districts, non-appearance of TB cases and patients in health facilities since the introduction of lockdown and stigma due to similar symptoms of the two diseases; persistent household contact and increased risk of transmission among family members. The total number of people registered with TB in the country according to the National Center for Public Health and Analysis in 2023 is 869, which corresponds to 13.5 per 100,000 population. The number of men with the disease is usually twice the number of women. The most affected age groups are 45-54, 65+ and 55-64. The administrative districts with incidence rates above the national average in 2023 are: Sofia District – 32.2; Vratsa – 22.9; Montana – 24.3; Pernik – 18.9; Yambol – 18.7 per 100 000 [65].

According to the National Social Insurance Institute (NSI), for the period 2009-2022, a total of 13 cases of occupational diseases caused by biological agents have been recognized, with 7 cases of TB – 1 case each reported for 2009, 2013 and 2014, and 4 cases for 2015. From the data provided by the NSI, no correlation can be made between the reported cases and their distribution by sex, age groups, occupation/activity of the patient, category of work, work characteristics, duration of exposure and severity of the illness [66, 67]. The main difficulties in occupational risk assessment are related to the lack of systematic information on biological agents in many work activities, insufficient awareness and inadequate training of workers on occupational health and safety, lack of standardized criteria for occupational exposure to airborne biological agents. Awareness of biological agents is critical for the prevention of related diseases and mortality.

Modern strategies for addressing the challenges of socially significant infectious diseases

1. The basis of strategies to combat infectious diseases is global cooperation, the development of international initiatives related to information exchange, health education, as well as financial and material support (donations/purchase of vaccines) for countries with low GDP.

2. Accessibility to medical services, medical facilities, modern medical equipment, medicinal products and vaccines is fundamental to reducing morbidity, prophylaxis and prevention.

3. Funding and development of new molecules to treat the three infections is a key mechanism for reducing and preventing their consequences.

4. International campaigns to fight stigma and prejudice, together with social support programs for those affected, can reduce social isolation and improve the psychosocial health of affected individuals.

5. The development of strict standards for safety in the work environment (with priority in healthcare), as well as effective protocols for the protection and training of personnel are a top priority for limiting the spread of infections.

6. Development of special programs and health insurance to alleviate the economic consequences of infectious diseases.

CONCLUSION

The COVID-19 pandemic highlighted the vulnerability of the global public system to emerging health crises. Infectious diseases (COVID-19, HIV/AIDS and tuberculosis) remain serious global problems that require coordinated efforts at global, national and local levels. Despite advances in diagnosis and treatment, and international prevention and control efforts, many challenges remain, including socioeconomic barriers and shortages of health services in many regions. Many of the problems lie in unequal access to health services, stigma and resource scarcity in poor and developing countries. Success in the fight against these diseases depends on global solidarity, scientific innovation and effective health policies.

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КЛИНИЧНИ СЛУЧАИ
CASE REPORTS**ЛЕЧЕНИЕ ДО ПОСТИГАНЕ НА ЦЕЛТА – КЛИНИЧНИ СЛУЧАИ НА ПАЦИЕНТИ
С РЕВМАТОИДЕН АРТРИТ И ЛИПСА НА РЕНТГЕНОГРАФСКА ПРОГРЕСИЯ
ПРИ ПРОДЪЛЖИТЕЛНО ПРОСЛЕДЯВАНЕ****С. Емин¹, Вл. Бояджиева¹, Н. Стоилов¹, Д. Лазаров², М. Иванова¹, Р. Стоилов³**¹Клиника по ревматология, УМБАЛ „Св. Ив. Рилски“, Медицински университет – София²Клиника по образна диагностика, УМБАЛ „Софиямед“ – София³Клиника по ревматология, УМБАЛ „Софиямед“ – София

Резюме. Ревматоидният артрит е хронично аутоимунно възпалително-ставно заболяване, което се характеризира с болка, скованост и симетричен полиартрит, водещо до деструкция на засегнатите стави в дългосрочен план. Целта на treat-to-target стратегията при лечение на заболяването е постигане на ремисия или ниска болестна активност. Днес съществуват различни конвенционални, биологични и таргет-синтетични болестмодифициращи антиревматични лекарства (БМАРЛ), които са широкозастъпени в ревматологичната практика с оглед персонализиране на терапевтичната стратегия спрямо всеки един пациент. Една от основните цели на лечението е потискане и забавяне на рентгенографската прогресия на болестта, която води до инвалидизация, влошено качество на живот и намалена работоспособност на пациентите. Съществуват различни скали за оценка на ставната деструкция, базиращи се на рентгенографско изследване на малки и големи стави на ръцете и краката, благодарение на които можем да оценим структурните промени в динамика. Представяме три клинични случая на пациенти с дългогодишен сероположителен ревматоиден артрит, провеждащи лечение с различни конвенционални и/или биологични БМАРЛ, при които е постигната дългосрочна ремисия и се наблюдава минимална рентгенографска прогресия на болестта.

Ключови думи: ревматоиден артрит, ремисия, рентгенографска прогресия, лечение до постигане на целта

ВЪВЕДЕНИЕ

Ревматоидният артрит е хронично аутоимунно възпалително-ставно заболяване, което се характеризира с болка, продължителна сутрешна скованост и симетричен ерозивен полиартрит на ставите на горните и долните крайници. Според Световната здравна организация (СЗО) към 2019 г. броят на страдащите от ревматоиден артрит в световен мащаб е 18 милиона души [1].

По данни на European Federation of Pharmaceutical Industries and Associations (EFPIA) от 2008 година пациентите с РА в България са 29 711 [2, 3]. Характерни прояви на болестта са възпалението и последващата деструкция на костите и хрущяла в засегнатите стави [4]. Въпреки по-високата чувствителност на ядрено-магнитния резонанс и ставната ултрасонография [5], най-често използваният метод, утвърдил се

като “златен стандарт” през годините за оценка на структурните промени и прогресията на заболяването, остава конвенционалната рентгенография [6, 7]. Типичните рентгенографски белези на РА са: юкстаартикуларна остеопороза, субхондрални кисти, маргинални ерозии, намаление на ставните междини, сублуксации и в крайните стадии анкилоза [8]. С цел определяне степента на структурните увреди и проследяване ефекта от терапията, още преди десетилетия са създадени първите скали за оценка на рентгенографските белези при пациенти с ревматоиден артрит. През 1949 г. Steinbrocker et al. създават първата система за оценка, която е качествена и класифицира ставните промени в четири стадия [9]. Недостатъкът на тази система е, че е твърде обща и не предоставя количествена оценка на уврежданията. През следващите години се раз-

работват и други скали – количествени и полу-количествени, доста по-прецизни, например тази на Larsen, Sharp, Genant и други, които във времето претърпяват модификации [10, 11, 12, 13]. Тези инструменти оценяват характерните белези при РА на различен брой стави от рентгенография на ръцете и краката. През последните години в рутинната клинична практика и в клинични изпитвания се наложи употребата на Sharp/Van der Heijde score поради проявената прецизност [14]. Недостатъкът на този метод е, че изисква опит и повече време за оценяване. Разработена е и по-опростена оценка на – Simplified erosion narrowing score (SENS), която чрез дихотомен метод оценява ерозии на 32 стави на ръцете и 12 на краката, както и стеснение на ставните междини на 30 стави на ръцете и 12 стави на краката. Тя е удобна за рутинната клинична практика и е с еквивалентна прецизност в сравнение с по-сложната и времеемка система на Sharp/Van der Heijde score [15].

Литературните данни показват, че първите структурни увреди се визуализират най-често на втора и трета метакарпофалангеална става, както и трета проксимална интерфалангеална става на ръцете [16], докато ерозивните промени по малките стави на краката, основно метатарзофалангеални и проксимални интерфалангеални стави, могат да предшества тези на ръцете [17].

Представяме три клинични случая на пациенти с дългогодишен сероположителен ревматоиден артрит на лечение с различни конвенционални и/или биологични БМАРЛ, при които е постигната дългосрочна ремисия и се наблюдава минимална рентгенографска прогресия на болестта.

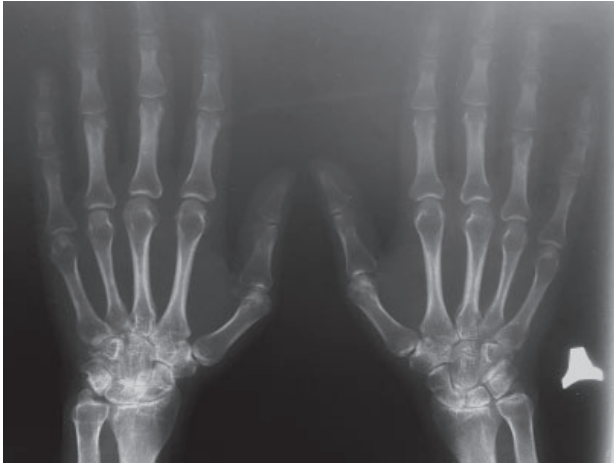
Клинични случаи

Представяме клиничен случай на жена на 56 г., бяла раса, с поставена диагноза сероположителен ревматоиден артрит през 2004 г. Пациентката е била с полиставно ангажиране на МКФС двустранно, болка в глезенни стави, завишени острофазови показатели. Лекувана е с Chloroquine и нестероидни противовъзпалителни средства (НСПВС) до 2009 г., след което е започнато лечение с метотрексат 20 мг седмично. Дозата е редуцирана на 15 мг/сед. след постигане на клинична и лабораторна ремисия, като терапията продължава и до днес. През 2020 г. поради висока болестна активност на заболяването (DAS28 >

5.1) към терапията е добавен и адалимумаб. При сравнителна оценка на рентгенографските образи на длани и пръсти през годините (2009 г., 2011 г., 2013 г. и 2022 г.) не се установява съществена динамика (SENS 7 à SENS 9).

Вторият клиничен случай, който представяме, е на жена на 67 г., бяла раса, с поставена през 2007 г. диагноза сероположителен ревматоиден артрит по повод артрит в МКФС и МТФС II, III, IV двустранно. От проведения клиничен преглед, оценка на ставния статус и ехографска оценка на опорно-двигателния апарат се визуализират синовит в изброените стави, завишени стойности на острофазовите показатели, положителни ревматоидни фактори. Болната е лекувана 12 месеца с НСПВС, салазопирин 2 г дн., кортикостероид 8 мг дн. в стабилна доза перорално. След незадоволителен ефект 2009 г. е започнато лечение с метотрексат който е преустановен през 2011 г. поради НЛР от гастроинтестиналния тракт (гадене и повръщане). Персистиращата висока болестна активност налага лечение с тоцилизумаб 8 мг/кг месечно интравенозно. Една година по-късно при пациентката е постигната пълна клинична и лабораторна ремисия. Лечението с анти-IL-6 продължава и към настоящия момент. При сравнителна рентгенография на ръцете и дланите от 2013 г. и 2022 г. прави впечатление липса на рентгенографска прогресия на болестта (SENS 10).

Представяме и клиничния случай на мъж на 32 г., бяла раса, с поставена диагноза ЮХА през 2007 г. по повод рецидивиращ артрит на лява колянна става, лекуван с НСПВС, салазопирин, арава, медрол 2 т. сутрин. През 2010 г. след оплаквания от болка и оток в лява колянна става, двете глезенни и гривнени стави, сутрешна скованост около 1 час и положителен ревматоиден фактор пациентът е диагностициран със сероположителен ревматоиден артрит и е започнато лечение с метотрексат 15 мг седмично и адалимумаб 40 мг с.к. през 14 дни, на фона на които е постигната ремисия. През 04.2014 г. терапията с адалимумаб е преустановена по собствено желание. Шест месеца по-късно се наблюдава обостряне на болестта със засягане на коленни и глезенни стави, поради което биологичното лечение с адалимумаб отново е подновено. При сравнителна рентгенография от 2010 г. и 2022 г. на длани и пръсти не се наблюдава съществена динамика в образите (SENS 4 à SENS 6).

РЕНТГЕНОГРАФИЯ

Фиг. 1. Рентгенография на длани и пръсти в предно-задна проекция, 07.2011 (Случай 1)



Фиг. 4. Рентгенография на длани и пръсти в предно-задна проекция, 08.2022 (Случай 2)



Фиг. 2. Рентгенография на длани и пръсти в предно-задна проекция, 12.2022 (Случай 1)



Фиг. 5. Рентгенография на длани и пръсти в предно-задна проекция, 07.2010 (Случай 3)



Фиг. 3. Рентгенография на длани и пръсти в предно-задна проекция, 01.2013 (Случай 2)



Фиг. 6. Рентгенография на длани и пръсти в предно-задна проекция, 08.2023 (Случай 3)

ОБСЪЖДАНЕ

Стратегията *treat-to-target* се използва от десетилетия в медицината, но за първи път в областта на ендокринологията при лечението на захарен диабет тип 2 [18]. Това е стратегия на лечение, при която се поставят ясни терапевтични цели, които да доведат до по-добри дългосрочни резултати за пациентите. През 2010 г. методът *treat-to-target* е въведен и в ревматологията чрез дефиниране на десет препоръки за лечение на ревматоиден артрит. Основните принципи на лечение са поставяне на терапевтична цел. В ревматологията този измерител е ремисия или ниска болестна активност, стриктно мониториране на пациента и адаптиране на терапията при невъзможност за постигане на целта [19]. Множество инструменти за измерване на болестната активност са въведени в ревматологичната практика. Най-често използваните са Disease activity score – 28 (DAS-28), Clinical disease activity index (CDAI) и Simplified disease activity score (SDAI) [20, 21, 22]. Въпреки широкото им приложение и опита за прецизиране на обективната оценка на активността на болестта, те не могат да отразят инвалидизацията на пациентите за сметка на настъпилите рентгенографски изменения. Това е и една от причините мултифакторната оценка да се превърне във водеща при стадиране на заболяването.

При представените пациенти, които са с дългогодишна давност на болестта и на различна терапия – с конвенционално и/или биологично БМАРЛ, беше оценена рентгенографската прогресия на ръцете по метода SENS. Прави впечатление, че на фона на лечение характерните деструктивни промени за ревматоидния артрит не се проявяват за периода на проследяване на болните. По същество, не се наблюдава съществена рентгенографска прогресия спрямо изходните образи.

През годините, особено след навлизането на биологичните БМАРЛ, е натрупан голям опит и са проведени голям брой клинични изпитвания по отношение на тяхната ефективност и безопасност [23, 24, 25, 26]. Безспорно, тяхното приложение

при пациентите с РА подобрява качеството на живот, функционалния капацитет и намалява развитието на структурните увреди [23, 24, 25, 26].

Според едно клинично проучване през 1997 г. на Drosos et al., при което е изследвана динамиката на рентгенографските образи на 30 пациенти с ревматоиден артрит на лечение с метотрексат и 30 пациенти на лечение с Д-пенициламин, се оказва, че в групата с метотрексат има значително по-бавна рентгенографска прогресия на заболяването. Дори при 15 от пациентите не се регистрира никаква прогресия [27]. Нашите клинични наблюдения потвърждават данните, публикувани в международната литература. През последните години данните от все повече клинични изпитвания също потвърждават липсата на сигнификантна рентгенографска прогресия при пациенти, лекувани с биологична терапия [23, 24, 25]. Множество клинични изпитвания са проведени по отношение ползите на комбинираната терапия пред монотерапията при лечението на РА. В изследването PREMIER са включени 799 пациенти с РА. Резултатите потвърждават, че комбинираната терапия на метотрексат с адалимумаб превъзхожда монотерапията и с двата медикамента както по отношение на бързина на ефекта, ниска болестна активност и ремисия, така и по отношение на рентгенографската прогресия [28].

Въпреки че тоцилизумаб е показан за приложение като монотерапия, в литературата има данни, че комбинираната терапия на тоцилизумаб с метотрексат е по-ефективна по отношение потискане на рентгенографската прогресия [29].

ЗАКЛЮЧЕНИЕ

Рано поставената диагноза, придържането към терапията, стриктният контрол на пациента и своевременното преминаване от една към друга лекарствена стратегия са основни фактори за постигането на продължителна ремисия, съхраняване функционалния капацитет и работоспособността и за предотвратяване инвалидизацията на пациентите с РА.

TREAT TO TARGET – CASE SERIES OF PATIENTS WITH RHEUMATOID ARTHRITIS AND NO RADIOGRAPHIC PROGRESSION AT LONG-TERM FOLLOW UP

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Abstract. Rheumatoid arthritis is a chronic autoimmune inflammatory joint disease characterized by pain, morning stiffness and symmetrical polyarthritis, leading to destruction of the affected joints in long term. The goal of the treat-to-target strategy in treating the disease is to achieve remission or low disease activity. Today, there are various conventional, biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), which are widely used in rheumatological practice in order to personalize the therapeutic strategy for each patient. One of the main goals of treatment is to suppress and slow the radiographic progression of the disease, which leads to disability, impaired quality of life and reduced work capacity of patients. There are different scales for assessing joint destruction, based on radiographic examination of small and large joints of the hands and feet, due to which we can assess structural changes in dynamics. We present three clinical cases of patients with long-standing seropositive rheumatoid arthritis, treated with conventional and/or biologic DMARDs, who achieved long-term remission and minimal radiographic progression of the disease.

Key words: rheumatoid arthritis, remission, radiographic progression, treat to target

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory joint disease characterized by pain, prolonged morning stiffness, and symmetrical erosive polyarthritis of the joints of the upper and lower extremities. According to the World Health Organization (WHO), as of 2019, the number of people suffering from rheumatoid arthritis worldwide amounted to 18 million people [1].

According to data from the European Federation of Pharmaceutical Industries and Associations (EFPIA) from 2008, there were 29,711 patients with RA in Bulgaria [2, 3]. Characteristic manifestations of the disease are inflammation and subsequent bone and cartilage destruction in the affected joints [4]. Despite the higher sensitivity of magnetic resonance tomography (MRT) and joint ultrasonography [5], the most commonly used method, which has established itself as the “gold standard” over the years for assessing structural changes and assessing disease progression, remains conventional radiography [6, 7]. Typical radiographic features of RA are: juxtaarticular osteoporosis, subchondral cysts, marginal erosions, joint space narrowing, subluxations and, in the end-stages, ankylosis [8]. In order to determine the degree of structural damage and monitor the effect of therapy, the first scales for assessing radiographic features in patients with rheumatoid arthritis were

created many decades ago. In 1949, Steinbrocker et al. created the first qualitative scoring system that classified joint changes into four stages [9]. The disadvantage of this method is that it is too general and does not provide a quantitative assessment of the structural changes. In the following years, other scales were developed that are quantitative and semi-quantitative and are much more precise, such as those of Larsen, Sharp, Genant and others, which have undergone modifications over time [10, 11, 12, 13]. These tools assess the characteristic features of RA on a different number of joints from radiographs of the hands and feet. In recent years, the Sharp/van der Heijde score has become the standard in routine clinical practice and clinical trials due to its accuracy. [14]. The disadvantage of this method is that it requires experience and more time for assessment. A simpler system has been developed by van der Heijde et al. – Simplified erosion narrowing score (SENS), which uses a dichotomous method to assess erosions in 32 joints of the hands and 12 of the feet, as well as joint space narrowing in 30 joints of the hands and 12 of the feet. It is convenient for routine clinical practice and has equivalent accuracy compared to the more complex and time-consuming Sharp/van der Heijde score system [15].

Literature data show that the first structural damage is most often visualized in the second and third metacarpophalangeal joints, as well as the third

proximal interphalangeal joint of the hands [16], while erosive changes in the small joints of the feet, mainly metatarsophalangeal and proximal interphalangeal joints, may precede those in the hands [17].

We present three clinical cases of patients with long-standing seropositive rheumatoid arthritis, who are treated with conventional and/or biological DMARDs, in whom long-term remission was achieved and minimal radiographic progression of the disease was observed.

CLINICAL CASE DESCRIPTIONS

The first case is a 56-year-old Caucasian woman diagnosed with seropositive RA in 2004. The patient had bilateral polyarticular involvement of the metacarpophalangeal (MCP) joints, ankle joint pain, and elevated acute phase reactants. She was treated with Chloroquine and Nonsteroidal anti-inflammatory drugs (NSAIDs) until 2009, when she started treatment with Methotrexate 20 mg weekly. The dose was reduced to 15 mg/week after achieving clinical and laboratory remission and the therapy continues to this day. In 2020, due to high disease activity (DAS-28 > 5.1), Adalimumab was added to the therapy. In a comparative assessment of the radiographic images of the palms and fingers over the years (2009, 2011, 2013 and 2022) no significant changes were detected (SENS 7 -> SENS 9).

The second clinical case that we present is of a 67-year-old Caucasian woman, diagnosed with seropositive RA in 2007. She has had arthritis in MCP and metatarsophalangeal (MTPS) joints II, III, IV bilaterally. Musculoskeletal ultrasound confirmed the synovitis in the listed joints. The patient had elevated values of acute phase reactants and positive rheumatoid factor. The patient was treated for 12 months with NSAIDs, Sulfasalazine 2 g/daily, Methylprednisolone 8 mg/daily per oral. Due to unsatisfactory effect, treatment with Methotrexate was started in 2009, which was discontinued in 2011 due to adverse drug reaction (ADR) from the gastrointestinal tract (nausea and vomiting). Due to persistent high disease activity, treatment with Tocilizumab 8 mg/kg monthly intravenously was started. One year later, the patient achieved complete clinical and laboratory remission. Treatment with anti-interleukin-6 continues to the present. Comparative radiography of the hands and palms from 2013 and 2022 shows lack of radiographic progression of the disease (SENS 10).

The third case is a 32-year-old man, Caucasian, diagnosed with Juvenile idiopathic arthritis in 2007 due to recurrent arthritis of the left knee joint, who

was treated with NSAIDs, Sulfasalazine, Leflunomide, Methylprednisolone 8 mg daily. In 2010 the patient's had complaints of pain and swelling in the left knee joint, both ankle and wrist joints, morning stiffness for about 1 hour. He had positive Rheumatoid factor. The patient was diagnosed with seropositive RA and treatment with Methotrexate 15 mg/week and Adalimumab 40 mg/subcutaneously every 14 days was started and remission was achieved. In April 2014 the therapy with Adalimumab was discontinued at patient's own request. Six months later, an exacerbation of the disease was observed, where the knee and the ankle joints were inflamed, and then biological treatment with Adalimumab was resumed again. In comparative radiography from 2010 and 2022 of the hand, no significant radiographic structural damage were observed in the radiographic images (SENS 4 -> SENS 6).

RADIOGRAPHY



Fig. 1. Radiography – anterior-posterior of the hands – July 2011 (Case 1)



Fig. 2. Radiography – anterior-posterior of the hands – December 2022 (Case 1)



Fig. 3. Radiography – anterior-posterior of the hands – January 2013 (Case 2)



Fig. 6. Radiography anterior-posterior of the hands – August 2023 (Case 3)



Fig. 4. Radiography – anterior-posterior of the hands – August 2022 (Case 2)



Fig. 5. Radiography – anterior-posterior of the hands – July 2010 (Case 3)

DISCUSSION

Treat-to-target strategy has been used for decades in medicine, but it was introduced in the field of endocrinology in the treatment of type 2 diabetes [18]. It is a treatment strategy that sets clear therapeutic goals that will lead to better long-term outcomes for patients. In 2010, the treat-to-target approach was introduced in rheumatology by defining ten recommendations for the treatment of Rheumatoid arthritis. The main principle of treatment is setting a therapeutic goal. In rheumatology, this measure is remission or low disease activity, close monitoring of the patient, and adaptation of the therapy if the goal cannot be achieved [19]. Many tools for measuring disease activity have been introduced in rheumatology practice. The most commonly used are the Disease activity score – 28 (DAS-28), Clinical disease activity index (CDAI), and Simplified disease activity score (SDAI) [20, 21, 22]. Despite their widespread use and the attempt to refine the objective assessment of disease activity, they cannot reflect the disability of patients in term of radiographic changes. This is one of the reasons why multifactorial assessment has become the leading one in disease staging.

In the presented patients, who have had the disease for many years and are on different therapies – with conventional and/or biological DMARDs, the radiographic progression of the hands was assessed using the SENS method. It is noteworthy that against the background of treatment, the characteristic destructive changes of rheumatoid arthritis do not oc-

cur during the period of follow-up of the patients. In essence, no significant radiographic progression compared to the baseline images is observed.

Over the years, especially after the introduction of biological DMARDs, a great deal of experience has been gained and a large number of clinical trials have been conducted regarding their effectiveness and safety [23, 24, 25, 26]. Undoubtedly, their use in patients with RA improves the quality of life, functional capacity and reduces the development of structural damage [23, 24, 25, 26].

According to a clinical study in 1997 by Drosos et al., in which radiographic changes of 30 patients with rheumatoid arthritis treated with Methotrexate and 30 patients treated with D-penicillamine were studied, it turns out that in the Methotrexate group there is a significantly slower radiographic progression of the disease. Even in 15 of the patients no progression was registered [27]. Our clinical observations confirm the data published in the international literature. In recent years, data from an increasing number of clinical trials also confirm the lack of significant radiographic progression in patients treated with biological therapy [23, 24, 25]. Numerous clinical trials have been conducted regarding the benefits of combination therapy over monotherapy in the treatment of RA. The PREMIER study included 799 patients with RA. The results confirmed that the combination therapy of Methotrexate with Adalimumab was superior to monotherapy with either drug, both in terms of rapidity of effect, low disease activity and remission, and in terms of radiographic progression [28].

Although Tocilizumab is indicated for use as monotherapy, there is evidence in the literature that the combination therapy of Tocilizumab with Methotrexate is more effective in suppressing radiographic progression [29].

CONCLUSION

Early diagnosis, compliance to the therapy, strict patient monitoring, and switching from one drug strategy to another on time are key factors in achieving sustained remission, preserving functional and work capacity, and preventing disability in patients with RA.

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ТЕЖКИ КОСТНИ ДЕФОРМАЦИИ ПРИ ПЪРВИЧЕН ХИПЕРПАРАТИРЕОИДИЗЪМ

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Резюме. *Класическото описание на първичния хиперпаратиреоидизъм (ПХПТ) е като заболяване с бъбречни камъни и на костите. Въпреки това клиничната картина на osteitis fibrosa cystica с тежки костни изменения е рядкост в съвременната медицина. Представяме клиничен случай на 30-годишен мъж с тежки костни деформации на дългите кости, сколиоза, кафяви тумори и тежка остеопороза. При диагностициране заболяването е с класическа биохимична и хормонална картина на първичен хиперпаратиреоидизъм: високостепенна хиперкалциемия, хипофосфатемия и значително повишени стойности на паратхормон. Промените се повлияват временно след оперативно лечение на паратиреоидния аденом. След четиригодишна загуба от проследяване пациентът е с влошаване на симптоматиката и хиперкалциемията, вероятно на фона на непълно отстраняване на туморната формация. Костните изменения са инвалидизиращи и предполагат непълно обратно развитие, имайки предвид тяхната тежест и давност. Направени са паралели с други сходни случаи в литературата.*

Ключови думи: хиперпаратиреоидизъм, костни деформации, osteitis fibrosa cystica

ВЪВЕДЕНИЕ

От края на 19 век костното засягане при тежък и персистиращ хиперпаратиреоидизъм е с класическо описание „osteitis fibrosa cystica“ (OFC) [1]. Понятието включва изразена субпериостална костна резорбция, водеща до формиране на кистоподобни кухини и кафяви тумори, повишен фрактурен риск, скелетни деформитети и нарушения в калциево-фосфорната обмяна. OFC може да се развие при постоянно повишени нива на паратхормон (ПТХ) в условията на първичен, вторичен и третичен хиперпаратиреоидизъм [2].

Първичният хиперпаратиреоидизъм (ПХПТ) е заболяване на паратиреоидните жлези с повишено образуване на ПТХ (автономна хиперсекреция) и висока или високо нормална калциемия [3]. Най-чести са спорадичните форми, дължащи се в 85-90% от случаите на аденом на една от паращитовидните жлези [4]. По-редки са множествените аденоми, паратиреоидният карцином, както и фамилните форми в рамките на синдромите на множествена ендокринна неоплазия (MEN I и MEN IIA) и др.

Първичният хиперпаратиреоидизъм е чест при жените и във възрастта над 50 години.

През последните десетилетия се бележи промяна в клиничната манифестация на първичния хиперпаратиреоидизъм с превес на асимптоматичните форми, включително и нормокалциемични и нормохормонални. Счита се, че включването на серумния калций в рутинния биохимичен панел е основна причина за промяната в разпространението на ПХПТ от симптоматични към асимптоматични (ранни) форми. В Дания например за периода от 1977 г. до 1990 г. се отчита сравнително постоянна заболяемост от ПХПТ, след което има 3-кратно нарастване при мъжете и 5-кратно при жените до 2010 г. [5]. Шотландско проучване, включващо популация от 400 000 лица (Тейсайдска кохорта), показва стабилно покачваща се честота на ПХПТ от 0.71% през 2007 г. до 1.02% през 2018 г. [6]. Друг фактор за нарастващото разпространение е по-честото изследване на ПТХ, витамин D, калций и фосфор при лица с остеопороза. Нерядко така се откриват нормокалциемичните форми с високи нива на паратхормон и нормален калций [7]. Тези тенденции водят до много по-ранно откриване и лечение на хиперпаратиреоидизма в страните с развито здравеопазване. Именно затова тежки форми на osteitis fibrosa cystica със скелетни деформитети представляват казуистика в наше време.

Клиничен случай

В настоящия клиничен случай представяме мъж на 30-годишна възраст, който през 2020 г. постъпва в УМБАЛ “Св. Марина” – Варна, с оплаквания от поява на туморовидна формация в дясна шийна област, изхождаща от мандибулата, и костни деформации. При щателно сваляне на анамнезата се оказва, че болките в гръбнака и появата на сколиоза датират от 15-годишна възраст, когато преживява и фрактура на лява тибия. На 25-годишна възраст е регистрирано и снижаване в ръста.

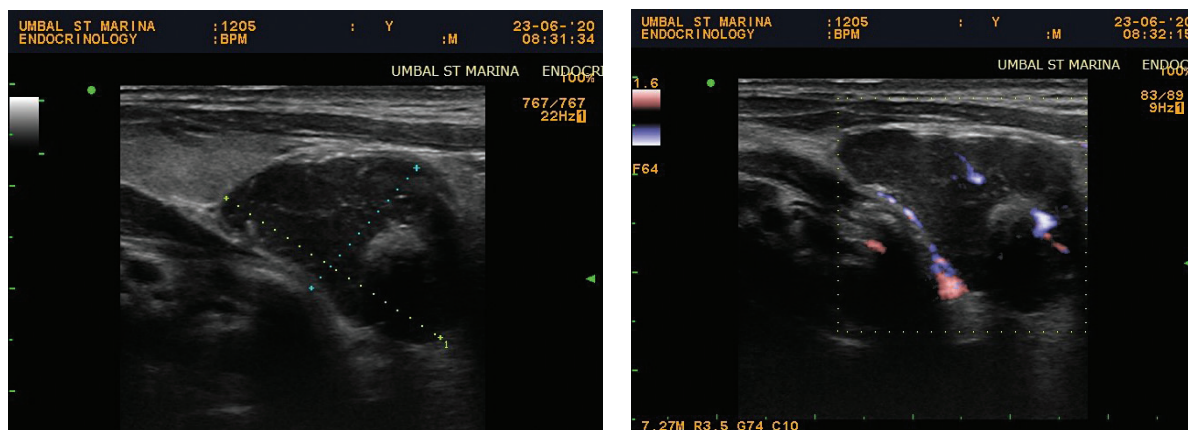
Пациентът съобщава за ставни болки от 13-годишна възраст в малки и големи стави на горни и долни крайници, наложили прием на нестероидни противовъзпалителни медикаменти за период от 6 месеца. Вследствие на това е бил с кръвоизлив от стомашна язва, за която е опериран през същата година.

При постъпване в Клиниката по ендокринология от физикалния статус прави впечатление изразената лицево-челюстна деформация вдясно с костна твърдост, неболезнена при палпа-

ция. Видима е сколиоза на гръбнака със силно изразен гйбус, деформирани коленни и лакътни стави, задебелени гривнени стави. Наблюдава се ограничен обем на движенията. Фалангите са деформирани, особено дисталните – скъсени и разширени двустранно – тип „барабанни пръсти“.

От лабораторните изследвания е с констелация, характерна за първичен хиперпаратиреоидизъм (табл. 1), а шийната ехография демонстрира видима лезия с типичен образ на паратиреоиден аденом с размери 15/24 mm, най-вероятно на долна дясна паращитовидна жлеза (фиг. 1). Паралелно с това пациентът е с данни за нефрокалциноза и хронично бъбречно заболяване стадий II по KDIGO. С оглед поставената диагноза, потвърдена и с радиоизотопно изследване (^{99m}Tc SESTAMIBI), е насочен за паратиреоидектомия.

Постоперативно се регистрира значимо понижаване на стойностите на паратхормон (ПТХ), на общия и йонизиращия калций, представени на таблица 1, отговарящо на т.нар. „синдром на гладните кости“, или криза на рекалцификация, предполагащо успешно лечение.



Фиг. 1. Ехография на шия. Видима е хипоехогенна, васкуляризирана формация с размери 15/24 mm, с неправилна форма и хетерогенна структура, локализирана под долен полюс на десен дял, на типичното място на долна дясна паращитовидна жлеза

Таблица 1. Лабораторни резултати в хода на проследяването

Параметър	2020 г. при диагностициране	2020 г. пост-оперативно	2024 г.	Референтна граница и мерна единица
ПТХ	2049	71	2376	pg/ml (0-87)
β -cross laps	3.63	-	> 6.00	ng/ml (0.093-0.580)
Алкална фосфатаза	1246	1117	682	U/l (< 150)
25-ОН-Витамин D	12.3	12.27	27.9	ng / ml
Йонизиран Ca^{2+}	1.9	1.08	2.19	mmol/l (1.12-1.23)
Общ калций	3.57	2.03	4.06	mmol/l (2.12-2.62)
Фосфор	0.93	0.56	0.7	mmol/l (0.77-1.56)
Калциурия	6.10	-	8.62	mmol/24 ч (2.5-7.5)
Фосфатурия	15.2	-	21.11	mmol/24 ч (13-32)
Креатинин	137	141	250	mcml/l
eGFR (CKD-EPI)	61	56	29	ml/min/1.73 m ²
Пикочна киселина	496	408	777	mcml/L

Първоначалното подобрене в биохимичните показатели би предположило пълно коригиране на хиперпаратиреоидизма, с регресия на биохимичните отклонения. След операцията пациентът се изгубва от проследяване за период от четири години. През 2024 г. отново постъпва в Клиниката по ендокринология с прогресия на оплакванията и по-изразени скелетните деформации спрямо 2020 г., с влошаваща се бъбречна функция с eGFR 29 ml/min/1.73 m² (стадий IV по KDIGO). Като нова находка се установява и податлива тофа на първи пръст на дясна ръка без съпътстваща ставна криза (фиг. 2). Проведените рентгенови изследвания демонстрират тежките промени в костната анатомия (фиг. 3, фиг. 4).

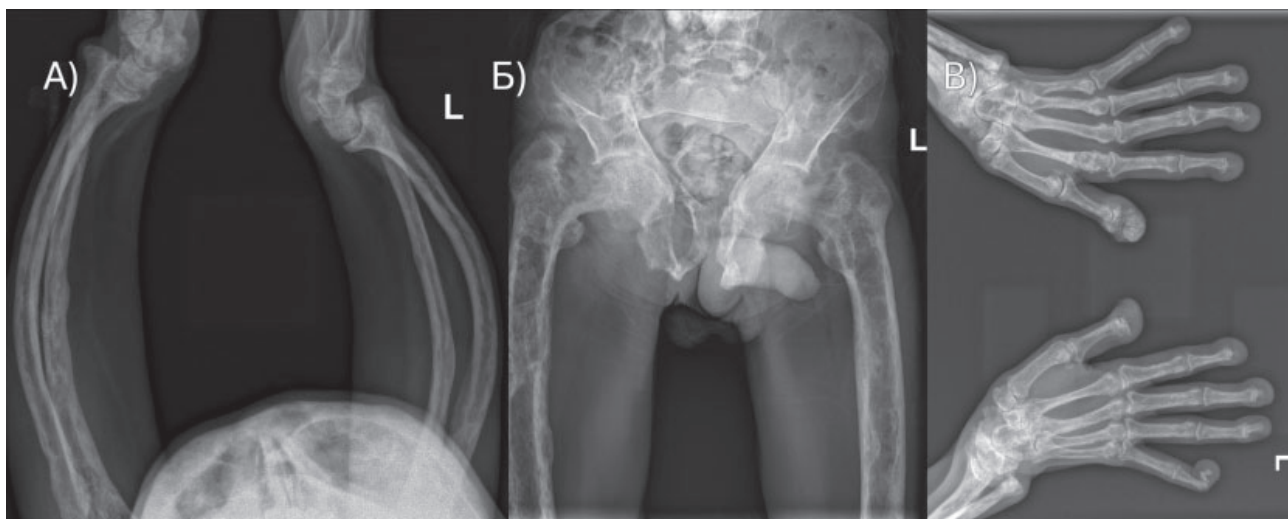
Рентгенографиите показват остеолитични лезии във всички дълги кости по модела на Браунови тумори (фигура 2А и Б). Радиусът и улната са с валгусен деформитет в дисталния си край и варусен – в проксималния (фигура 2А). От рентгенографията на длани се виждат акроостеолиза и сублуксации на дисталните фаланги (фигура

2В). Проведена е и остеометрия със затруднена интерпретация поради силно изразени деформации на гръбнака и дългите кости. Видима е изразена остеопороза с предимно засягане за кортикална кост: Z-score L1-L4 (-1.2); L2 (-1.6); бедрена шийка: Z-score total hip: (-2.2); Z-score femoral neck (-2.2); Z-score дистален радиус: (-4.2).

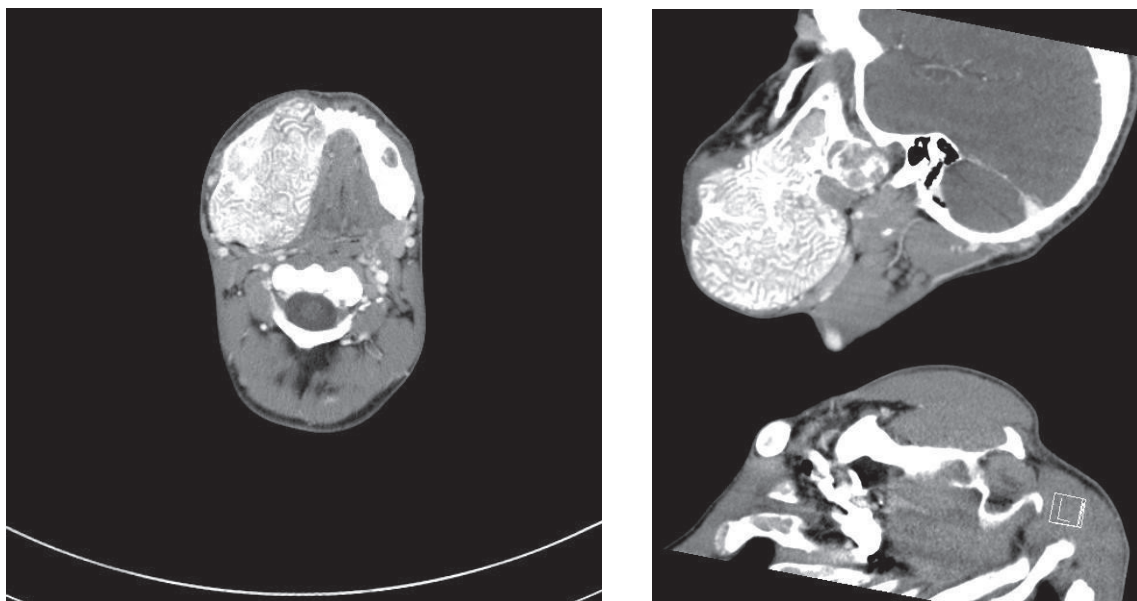
От биохимичните и хормоналните показатели е налице перисистираща хиперкалциемия с повишени стойности на ПТХ, хипофосфатемия и ехографски данни за персистираща/рецидивирала паратиреоидна формация под долен полюс на десен тиреоиден дял. Направен бе опит за повлияване на високостепенната хиперкалциемия с рехидратация, форсирана диуреза, приложение на деносумаб и калцимитетика синакалцет като подготовка за реоперация. Резултатът е краткотрайно и недостатъчно подобрене – на пети ден след приложението на деносумаб е отчетен спад на йонизирания калций до 1.52 mmol/l от изходен 2.19 mmol/l. Допълнително е включен урикоинхибитор (алопуринол) заедно с краткосрочен ниско-



Фиг. 2. Множество скелетни деформации при физикалния преглед



Фиг. 3. Рентгенография на: А) радиус и улна; Б) бедрени кости и таз; В) китки и длани



Фиг. 4. КТ образ на костна формация, произлизаща от дясната половина на мандибулата. Впечатление прави костната ѝ структура. Видими са и остеолитични лезии по типа на *osteitis fibrosa cystica* контралателно в мандибулата

дозиран колхицин (0.5 mg през ден за 10-дневен период).

ОБСЪЖДАНЕ

Представеният от нас пациент е с класическо за далечното минало протичане на първичен хиперпаратиреоидизъм, с много тежки костни и ставни изменения, несрещани в съвременето ни. Въпреки че случаят не представлява диагностичен проблем, е интересен за клинициста поради големия спектър на патологичните изменения и неочаквания рецидив след първоначалната паратиреоидектомия.

Костите, наред с бъбреците и стомашно-чревния тракт са основните прицелни органи, засегнати при ПХПТ и обуславящи клиничната симптоматика. Пораженията от ПХПТ в таргетните органи и тъкани се опосредстват от свързването на ПТХ със специфичния му рецептор РТН рецептор тип 1 (PTHr1), експресиран върху клетъчната повърхност на голям брой клетки. Катаболните ефекти на ПТХ в костта са явни при пациентите с класически ХПТ и са доказани с постоянна инфузия на ПТХ при гризачи [8]. Обратно, интермитентното приложение на ПТХ (1-34) има анаболно действие и се използва през т.нар. „анаболен прозорец“ в лечението на остеопорозата [9].

Интерес представлява фактът, че въпреки основната експанзия на остеокластите при ПХПТ, водеща до костна резорбция, фрактури, деформации и образуването на кафяви тумори, самите

остеокласти не експресират рецептори за ПТХ (PTH). Последният оказва своето действие, опосредстван от остеобластите, по чиято повърхност има PTHR1. Свързването на PTH-PTHr1 в костта води до повишена остеобластна експресия на RANKL (рецепторен активатор на лиганда на ядрения фактор карпа-В). RANKL се свързва с рецептора си RANK върху прекурсорите на остеокластите, стимулирайки фузията, диференциацията и активацията им, водещи до костна резорбция [8, 10].

Заболяването при представения случай започва още в юношеска възраст със сколиоза, костни болки и фрактури. Подобни тежки скелетни деформации при случаи, стартирали в детството и юношеството, докладват и други автори [11, 12]. Неспецифичната първоначална изява и симптомите, припокриващи се с рахит при ниски нива на 25-ОН-витамин D, биха могли да забавят поставянето на правилната диагноза.

Обичайно, към момента на диагностициране на първичния хиперпаратиреоидизъм той е с безсимптомно или олигосимптомно протичане. Това важи най-вече за Европа и САЩ [13]. За разлика от това симптоматичните форми с изразени костни промени и деформитети са по-характерни за здравните системи с по-лошо покритие, при които липсва повсеместен скрининг със серумен калций [14].

В общия случай наличието на таргетно органично засягане (кост или бъбрек) и ранната възраст на изява изискват хирургично лечение

и отстраняване на паратиреоидния аденом. В представения случай са налице всички показания за извършването му [15]. След отстраняване на свръхпродуциращия паратхормон тумор се очаква подобрене в костната плътност и костните изменения, вкл. и на "кафявите тумори". В серия от случаи Agarwal и сътрудници [16] проследяват 51 пациенти след паратиреоидектомия. Техните резултати демонстрират реминерализация още на първата седмица постоперативно и подобрене в костната плътност през първите 3 месеца. При серийни рентгенографии авторите показват първоначално абнормно повишаване на плътността на кафявите тумори през първите 3 месеца, с последващо „изсветляване“ и частична регресия в размера на костните лезии. Това е съпроводено от корекция на костните деформитети при 6 от 27 пациенти (22%).

Имайки предвид изключително тежките костни и ставни изменения при представения от нас случай, вероятно би могло да се очаква значимо подобрене в костната плътност. От друга страна, обратно развитие на гибуса, костните деформации и голямата челюстна лезия изглежда малко вероятно с оглед тежестта и давността им.

Друг важен момент в описания случай е постоперативната криза на рекалцификация, която би следвало да настъпи след успешно отстраняване на паратиреоидния аденом. В случая е отчетен такъв рязък спад в калциемията, както и в нивата на ПТХ постоперативно. Бързото снижаване на серумния калций е резултат от функционалната инхибция на останалите здрави паращитовидни жлези. В случаи на те-

жък хиперпаратиреоидизъм може да се очаква развитието на „синдрома на гладните кости“. По тази причина заместването с активен витамин D и калций са от съществена важност [17]. Тези първоначални промени предполагат пълното излекуване на тумора, но последващата еволюция на заболяването при нашия пациент подсказва непълното му отстраняване.

Предприемането на повторна операция изисква определена подготовка на пациента. Същественото в случая е, че високостепенната хиперкалциемия ($> 4 \text{ mmol/l}$) е рисков фактор за развитие на сърдечни аритмии и съответно за по-висок оперативен риск. Предприетата стратегия за снижаване на калциевите нива с оводняване, бримков диуретик, калцимиметик и денозумаб може да бъде само частично ефективна до постигане на пълно излекуване чрез хирургия.

ЗАКЛЮЧЕНИЕ

Съвременните и широкоразпространени методи за диагностика на състоянията, свързани с хиперкалциемия, предполагат лесното и навременно диагностициране на първичния хиперпаратиреоидизъм. Въпреки това единични случаи с тежки костни и ставни изменения се срещат в клиничната практика. Настоящият случай подчертава важността на костните симптоми като първа, макар и понякога неспецифична, изява на заболяването. Първичният хиперпаратиреоидизъм би следвало да е част от диференциалната диагноза при рентгенографски данни за остеолитични и кистозни костни лезии.

SEVERE BONE DEFORMITIES IN PRIMARY HYPERPARATHYROIDISM

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Abstract. *The classic description of primary hyperparathyroidism (PHPT) is as a disease of kidney stones and bones. However, the clinical manifestation of osteitis fibrosa cystica with severe bone changes is rare in modern medicine. We present a clinical case of a 30-year-old man with severe bone deformities of the long bones, scoliosis, brown tumors and severe osteoporosis. At the time of the diagnosis, he has the classic biochemical and hormonal picture of primary hyperparathyroidism: severe hypercalcemia, hypophosphatemia, and significantly elevated parathyroid hormone values. The changes were temporarily affected after surgical treatment of the parathyroid adenoma. After a four-year loss to follow-up, the patient presented with worsening symptoms and hypercalcemia, possibly due to incomplete tumor removal. The bone changes are debilitating and imply incomplete reverse development, considering their severity and duration. Comparison is made with other similar cases in the literature.*

Key words: hyperparathyroidism, bone deformities, osteitis fibrosa cystica

INTRODUCTION

Bone involvement in severe and persistent hyperparathyroidism was classically described as osteitis fibrosa cystica (OFC) in the late 19th century [1]. It includes pronounced subperiosteal bone resorption leading to the formation of cyst-like cavities and brown tumors, increased fracture risk, skeletal deformities, and disturbances in calcium-phosphate metabolism. OFC can develop with persistently elevated parathyroid hormone (PTH) levels in the settings of primary, secondary, and tertiary hyperparathyroidism [2].

Primary hyperparathyroidism (PHPT) is a disease of the parathyroid glands with increased production of PTH (autonomic hypersecretion) and high or high-normal calcium [3]. The most common are the sporadic forms, due to an adenoma of one of the parathyroid glands in 85-90% [4]. Multiple adenomas, parathyroid carcinoma, as well as familial forms within the syndromes of multiple endocrine neoplasia (MEN I and MEN IIA), etc., are rarer causes.

Primary hyperparathyroidism is more common in women and over the age of 50. In recent decades, there has been a change in the clinical manifestation of primary hyperparathyroidism with predominance of asymptomatic forms, including normocalcemic and normohormonal forms. The inclusion of serum calcium in the routine biochemical panel is thought to be a major reason for the shift in prevalence of PHPT from symptomatic to asymptomatic (early) forms. In Denmark, for example, for the period from 1977 until

1990 a relatively constant incidence of PHPT was reported, after which there was a 3-fold increase in men and a 5-fold increase in women by 2010 [5]. A Scottish study involving a population of 400,000 individuals (Tayside Cohort) showed a steadily increasing incidence of PHPT from 0.71% in 2007 to 1.02% in 2018 [6]. Another factor for the increasing prevalence is the more frequent testing of PTH, vitamin D, calcium and phosphorus in individuals with osteoporosis. Thus, normocalcemic forms with high levels of parathyroid hormone and normal calcium are often discovered [7]. These trends lead to much earlier detection and treatment of hyperparathyroidism in countries with developed health care. That is why severe forms of osteitis fibrosa cystica with skeletal deformities are an extremely rare finding nowadays.

CLINICAL CASE DESCRIPTION

In the present clinical case, we present a 30-year-old man who was admitted to the University Hospital "Sv. Marina" Varna in 2020, with complaints of the appearance of a tumor-like formation in the right neck region, originating from the mandible and bone deformities. After a careful history taking, it turns out that the pain in the spine and the appearance of scoliosis dated back to the age of 15, when he also experienced a fracture of the left tibia. At the age of 25, a decrease in height was also recorded.

The patient reported joint pain since the age of 13 involving small and large joints of the upper and lower extremities, which necessitated the use

of non-steroidal anti-inflammatory drugs for a period of 6 months during adolescence. As a result, he had a hemorrhage from a gastric ulcer, for which he was operated in the same year.

On admission into the clinic of endocrinology, the physical status was striking, with a pronounced right maxillofacial deformity with bone hardness, painless on palpation. Scoliosis of the spine was evident with a pronounced gibbus, deformed knee and elbow joints, thickened wrist joints. A limited mobility was observed. The phalanges of both hands were deformed, the distal phalanges being shortened and thickened, with pseudoclubbing.

Laboratory tests showed a constellation characteristic of primary hyperparathyroidism (Table 1), and neck ultrasound demonstrated a visible lesion with a typical appearance of a parathyroid adenoma, 15/24 mm in size, most likely of the lower right parathyroid gland. (Figure 1). Additionally, the patient had evidence of nephrocalcinosis and chronic kid-

ney disease stage II according to KDIGO. In view of the established diagnosis, confirmed also by a TC^{99m} SESTAMIBI scan, he was referred for surgical parathyroidectomy.

Postoperatively, there was a significant decrease in the values of parathyroid hormone (PTH), total and ionized calcium, presented in table 1, corresponding to the so-called “hungry bone syndrome” or recalcification crisis, suggesting successful treatment.

Initial improvement in biochemical parameters would suggest complete cure and correction of hyperparathyroidism with regression of biochemical abnormalities. After surgery, the patient was lost to follow-up for a period of four years. In 2024 he was admitted again to the endocrinology clinic with progression of complaints and skeletal deformities in comparison to those from 2020, worsening renal function with eGFR 29 ml/min/1.73 m² (stage IV according to KDIGO).

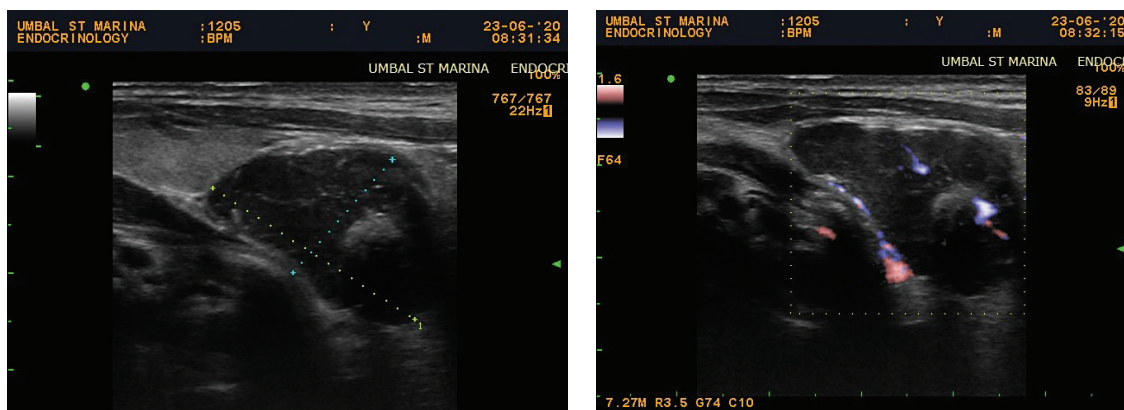


Fig. 1. Neck ultrasonography. A hypoechoic vascularized formation is visible, 15/24 mm in size, with an irregular shape and heterogeneous structure, localized below the lower pole of the right thyroid lobe, in the typical location of the right inferior parathyroid gland

Table 1. Laboratory results during follow-up

Parameter	In 2020 At diagnosis	In 2020 Postoperatively	In 2024	Unit of measurement/ reference range
PTH	2049	71	2376	pg/ml (0-87)
β-cross laps	3.63	-	> 6	ng/ml (0.093-0.580)
alkaline phosphatase	1246	1117	682	U/l (< 150)
25-OH-Vitamin D	12.3	12.27	27.9	ng / ml
Ionized Ca ²⁺	1.9	1.08	2.19	mmol/l (1.12-1.23)
Total calcium	3.57	2.03	4.06	mmol/l (2.12-2.62)
Phosphate	0.93	0.56	0.7	mmol/l (0.77-1.56)
Calciuria	6.10	-	8.62	mmol/24 h (2.5-7.5)
Phosphaturia	15.2	-	21.11	mmol/24 h (13-32)
Creatinine	137	141	250	mcmol/l
eGFR (CKD-EPI)	61	56	29	ml/min/1.73 m ²
Uric acid	496	408	777	mcmol/L

As a new finding, a gouty tophus on the first finger of the right hand was also established without accompanying joint crisis (Figure 2). The X-ray studies performed demonstrate the severe changes in the bone anatomy (Figure 3, Figure 4).

Radiographs showed osteolytic lesions in all long bones corresponding to brown tumors (Figure 2). The radius and ulna have a valgus deformity at their distal end and a varus deformity at the proximal end. X-rays of the hands show acroosteolysis and subluxations of the distal phalanges. DEXA bone mineral measurement was also performed, although it was difficult to interpret due to severe deformations of the spine and long bones. Pronounced osteoporosis is visible with dominant involvement for cortical bone: Z-score L1-L4 (-1.2); L2 (-1.6); femoral neck: Z-score total: (-2.2); Z-score femoral neck (-2.2); Z-score distal radius: (-4.2).

From the biochemical and hormonal indicators, there is persistent hypercalcemia with increased PTH

values, hypophosphatemia and ultrasound data of a persistent/recurrent parathyroid formation under the lower pole of the right thyroid lobe. A therapeutic attempt was made to influence the high-grade hypercalcemia with rehydration, forced diuresis, administration of denosumab and the calcimimetic cinacalcet in preparation for reoperation. The result was a short-term and insufficient improvement – on the fifth day after the application of denosumab, a drop in ionized calcium to 1.52 mmol/l from the initial 2.19 mmol/l was registered. Additionally, a uric acid inhibitor (allopurinol) was initiated along with short-term low-dose colchicine (0.5 mg every other day for a 10-day period).

DISCUSSION

The patient presented by us has a classical for the distant past course of primary hyperparathyroidism, with severe bone and joint changes, exceptional for our time. Although the case does not present a di-

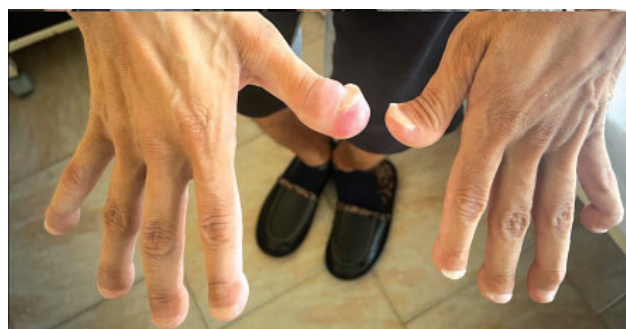


Fig. 2. Multiple skeletal deformities on physical examination

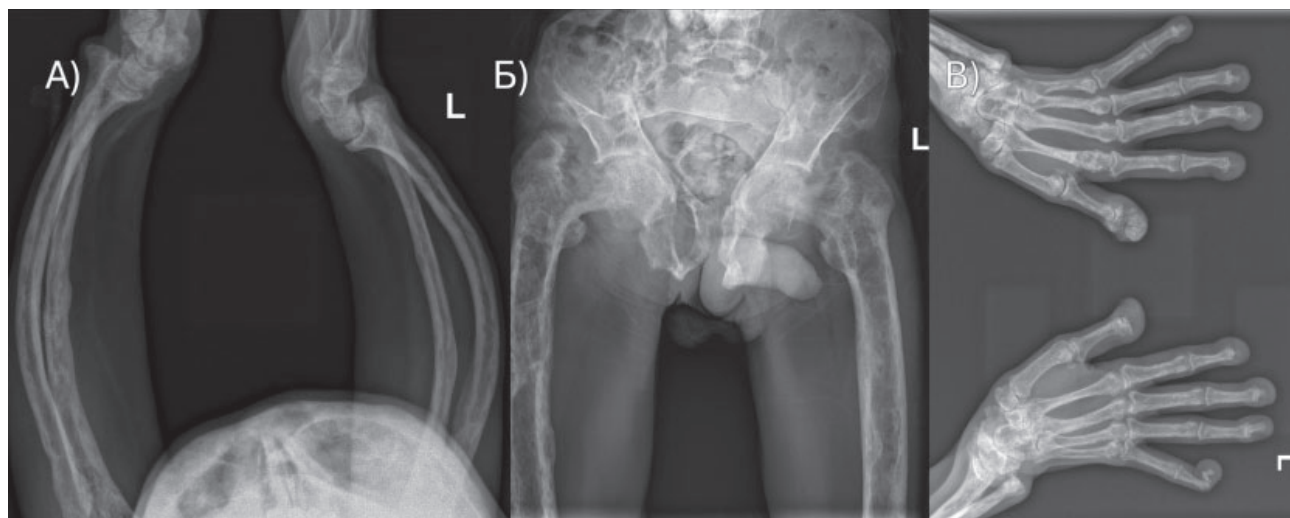


Fig. 3. X-Ray of A) radius and ulna bilaterally; B) femoral bones and pelvis; C) wrists and hands

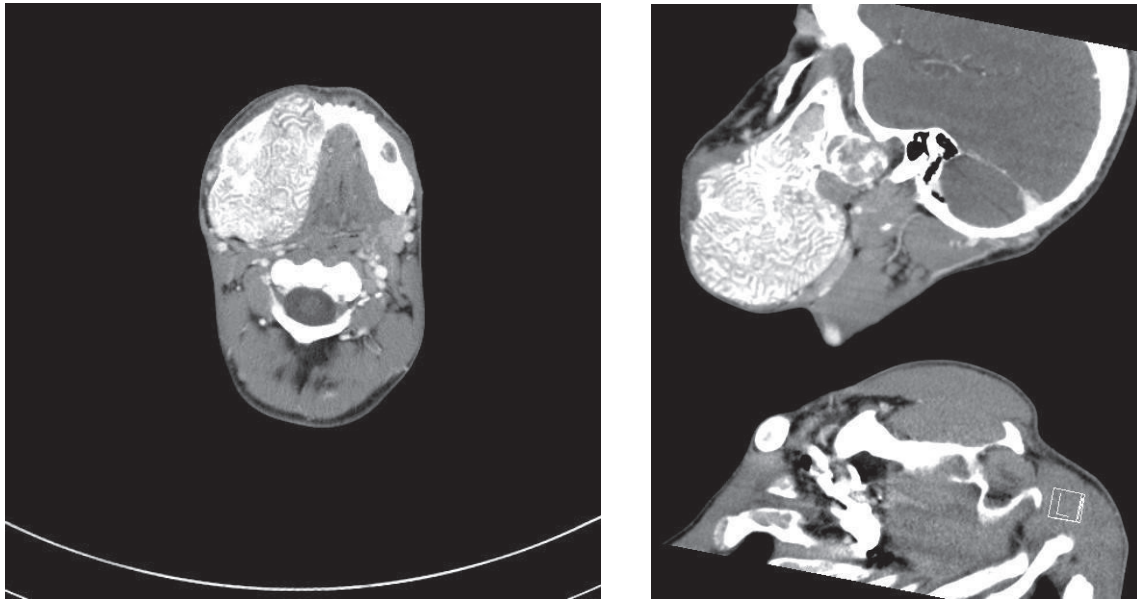


Fig. 4. CT imaging of a bone formation, originating from the right half of the lower jaw. Its bone structure is a point of interest. Osteolytic lesions of the type of osteitis fibrosa cystica are also visible contralaterally in the mandible

agnostic problem, it is of interest to the clinician due to the wide spectrum of pathologic changes and the unexpected recurrence after initial parathyroidectomy.

Bones, along with the kidneys and the gastrointestinal tract, are the main target organs affected in PHPT and leading to the clinical symptoms. PTH damage in target organs and tissues is mediated by the binding of PTH to its specific receptor PTH receptor type 1 (PTHr1), expressed on the cell surface of a large number of cells. The catabolic effect of PTH in bone is evident in patients with classical PHPT and have been demonstrated with continuous infusion of PTH in rodents⁸. Conversely, intermittent administration of PTH (1-34) has an anabolic effect and is used during the so-called “anabolic window” for osteoporosis treatment [9].

Of interest is the fact that despite the major expansion of osteoclasts in PHPT, leading to bone resorption, fractures, deformities and the formation of brown tumors, osteoclasts themselves do not express a receptor for PTH. The latter exerts its action mediated by osteoblasts on the surface of which there is PTHr1. PTH-PTHr1 binding in bone results in increased osteoblastic expression of RANKL (receptor activator of nuclear factor kappa-B ligand). RANKL binds to its receptor RANK on osteoclast precursors, stimulating their fusion, differentiation and activation resulting in bone resorption [8, 10].

The disease in the presented case had started already in adolescence with scoliosis, bone pain and fractures. Other authors also report similar severe skeletal deformities in cases with onset during

childhood and adolescence [11, 12]. The nonspecific initial presentation and symptoms overlapping with rickets with low 25-OH-vitamin D levels could delay the correct diagnosis.

Usually, at the time of diagnosis of primary hyperparathyroidism, it is an asymptomatic or oligosymptomatic disease. This applies mostly to Europe and the USA [13]. In contrast, symptomatic forms with marked bone changes and deformities are more typical of health systems with poorer coverage, which lack universal serum calcium screening [14].

In general, the presence of target organ involvement (bone or kidney) and the early age of presentation require surgical treatment and removal of the parathyroid adenoma. In the presented case, there are all indications for operation [15]. After removal of the overproducing parathyroid tumor, an improvement in bone density and bone changes is expected, including reversal of “brown tumors”. In a case series, Agarwal et al. [16] followed 51 patients after parathyroidectomy. Their results demonstrated remineralization as early as the first week postoperatively, and an improvement in bone density during the first 3 months. In serial radiographs, the authors show an initial abnormal increase in the density of the brown tumors during the first 3 months, with subsequent “lightening” and partial regression in the size of the bone formations. This was accompanied by correction of bony deformities in 6 of 27 patients (22%).

Considering the extremely severe bone and joint changes in the case presented by us, a significant

improvement in bone density could probably be expected. On the other hand, reverse development of the gibbus, bony deformities and large jaw lesion seems unlikely in view of their severity and duration.

Another important point in the described case is the postoperative recalcification crisis, which should occur after successful removal of the parathyroid adenoma. In our clinical case, such a sharp drop in calcemia as well as in PTH levels postoperatively was reported. The rapid decrease in serum calcium is the result of the functional inhibition of the remaining healthy parathyroid glands. In cases of severe hyperparathyroidism, the development of this "hungry bone syndrome" can be expected. For this reason, replacement with active vitamin D and calcium is essential [17]. These initial changes suggest complete cure of the tumor, but the subsequent evolution of the disease in our patient points to incomplete removal.

Undertaking reoperation requires a certain preparation of the patient. It is essential that severe (in our case > 4 mmol/l) and even moderate hypercalcemia is a risk factor for the development of cardiac arrhythmias and a correspondingly higher operative risk. The calcium-lowering strategy undertaken with rehydration, loop diuretic, calcimimetic, and denosumab may be only partially effective until complete cure is achieved by surgery.

CONCLUSION

Modern and widespread diagnostic methods of conditions associated with hypercalcemia suggest easy and timely diagnosis of primary hyperparathyroidism. However, isolated cases with severe bone and joint changes occur in clinical practice. The present case highlights the importance of bone symptoms as the first, although sometimes nonspecific, manifestation of the disease. Primary hyperparathyroidism should be part of the differential diagnosis in radiographic evidence of osteolytic and cystic bone lesions.

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**ПИСМО ДО РЕДАКТОРА
LETTER TO THE EDITOR**

**FIRST BULGARIAN EULAR-ENDORSED COURSE ON CAPILLAROSCOPY
AND MICROCIRCULATION IN RHEUMATIC DISEASES**

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Nailfold capillaroscopy is a unique method with the advantages of safe noninvasiveness, easy and rapid performance. Moreover, it is the only technique for morphological evaluation of the nailfold capillaries. Its major role in rheumatology is to facilitate the differential diagnosis of Raynaud's phenomenon. In systemic sclerosis, capillaroscopic findings are included in the current classification criteria [1, 2]. Microvasculopathy is also observed in a number of other rheumatic diseases with peripheral vascular syndrome [3, 4].

Recently, the EULAR (European Alliance of Associations for Rheumatology) Study Group on Microcirculation in Rheumatic Diseases has approved a fast-track algorithm for differentiation of a scleroderma from a non-scleroderma pattern [5] and is part of the 2013 ACR/EULAR classification criteria for systemic sclerosis. As there is a wide variety of nonscleroderma patterns, the categorisation of capillaroscopic images as nonscleroderma patterns may be a challenge to the capillaroscopist. Objectives: This study was designed to propose a simple fast track algorithm to differentiate scleroderma patterns from non-scleroderma patterns and to assess its interobserver reliability. Methods: During the 8th EULAR course on capillaroscopy

held in Genoa, September 2018, a lecture on teaching the fast track algorithm to categorise an image as non-scleroderma (category 1), a consensus on minimum reporting standards in capillaroscopy [6] and the standardisation of capillaroscopic image acquisition and analysis [7]. The evolving knowledge about microcirculation in rheumatic diseases requires continuing education of the specialists involved in capillaroscopy diagnostics.

In Europe, the great interest shown by rheumatologists during the capillaroscopy seminars organized since 2003 at the annual EULAR congresses, stimulated the idea of organizing a course in capillaroscopy. The first EULAR course "Capillaroscopy in Rheumatic Diseases" was held in 2004 in Genoa, Italy. Since then, the course has been held every two years in Genoa until 2018. The course organizer at the beginning was Prof. Dr. Maurizio Cutolo – Professor of Rheumatology and Head of the Department of Clinical Rheumatology at the University of Genoa, Italy. Shortly thereafter, Prof. Dr. Vanessa Smith, Professor of Rheumatology, and Head of Clinics at the University Hospital of Ghent, Belgium joined the steering team of the course [8, 9]. Since 2020, the EULAR course in capillaroscopy takes place during the annual EULAR Rheumatology congress.

In four consecutive years (from 2020 to 2023), the Bulgarian Rheumatology Society also started organizing workshops in capillaroscopy held by the Bulgarian rheumatologists Prof Dr. Sevdalina Lambova and Dr. Vladimira Boyadzhieva. In 2021, a national consensus on capillaroscopy was published by the Bulgarian Rheumatology Society [10]. As a continuation of these initiatives, the first Bulgarian EULAR-endorsed Course on Capillaroscopy and Microcirculation in Rheumatic Diseases was planned and took place from 27 to 29 September 2024 in Saints Constantine and Helena, Varna, Bulgaria. A total number of 36 rheumatologists and trainees attended the course from different Bulgarian centers in the country, i.e. Sofia, Plovdiv, Pleven, Ruse, Varna, Stara Zagora, etc., including a physician from Romania (Fig. 1).



Fig. 1. Lecturers and attendees in the first Bulgarian EULAR-endorsed Course on Capillaroscopy and Microcirculation in Rheumatic Diseases (2024)

Members of the scientific committee and lecturers were three international guests – Prof. Dr. Maurizio Cutolo (founder of modern capillaroscopy training in Europe; President of EULAR for the period 2011- 2015), Prof. Dr. Vanessa Smith (Chair of the EULAR study group for the study of microcirculation in rheumatic diseases) and Prof. Dr Ulf Müller-Lad-

ner (Head of the Department in Rheumatology and Internal Medicine at the University of Giessen, Bad Nauheim, Germany; President of EUSTAR/EULAR Scleroderma Trials and Research from 2010 to 2013, of the Scientific Society of Rheumatology in Germany for the period 2015-2016 and of the German Society of Internal Medicine 2022-2023). Bulgarian organizers and lecturers were Prof. Dr. Rumen Stoilov (President of the Bulgarian Rheumatology Society), Prof. Dr. Sevdalina Lambova, Dr. Vladimira Boyadzhieva, Prof. Dr. Hristo Dobrev and Dr. Nikolay Stoilov. Prof Dr. Sevdalina Lambova is Professor of Rheumatology in the Department of Propaedeutics of Internal Diseases “Prof. Dr. Anton Mitov”, Medical University of Plovdiv. She is leading expert in capillaroscopy and the author of the first two monographs in Bulgaria about the application of capillaroscopy in rheumatology (“Capillaroscopy in rheumatology – norm and pathology”, 2021 [11], and “Capillaroscopy in rheumatology – what else do we need to know?”, 2024) [12]. Prof. Dr. Hristo Dobrev (Head of the Section of Dermatology and Venereology at the Medical University of Plovdiv, Bulgaria) is leading expert in the field of capillaroscopy education for the country and organizer of the first basic course in capillaroscopy at the Medical University of Plovdiv in 2012. Dr. Vladimira Boyadzhieva and Dr. Nikolay Stoilov are specialists in rheumatology from the Medical University of Sofia.

The aim of the course was to present the proper technique of capillaroscopy, analysis of capillaroscopic images, interpretation of the results, differentiation between normal and pathological findings in rheumatic diseases. The full immersion 3-day-course provided a summary of the most recent advances in the field of microvascular pathology in rheumatic diseases from leading experts in the field. The course covered both basic theoretical and practical principles in performing and interpretation of capillaroscopic examination, as well as innovative aspects regarding microvasculopathy in rheumatic diseases based on the contemporary knowledge and the considerable practical experience of the experts [12]. Capillaroscopic findings in Raynaud’s phenomenon as well as in other less frequent peripheral vasculopathies, for which only scant data are existing, were presented. With the improvement of modern knowledge in the field of capillaroscopy, expanding indications for performing capillaroscopy should be taken into account that was also extensively discussed during the course.

Altogether, the course included 4 sessions in 3 days with 19 lectures and 3 practical sessions with patients. The training provided the participants with the opportunity to acquire new knowledge and skills, as well as to share valuable experiences during the practical sessions with examination of patients with different rheumatic diseases and with discussion of the findings in complex clinical cases (Fig. 2). In-depth and inspiring discussions were held within the course, which encouraged the exchange of expertise and posed questions for future research.

Tests were conducted at the beginning and at the end of the training to evaluate the acquired knowledge. Analysis of the results showed an increase in success rates, which illustrates the value of the training process and the overall goal of the course.



Fig. 2. Image from the practical session

The first Bulgarian EULAR-endorsed Course on Capillaroscopy and Microcirculation in rheumatic diseases (2024) was a logic consequence of the

increasing need of international education in capillaroscopy in Bulgaria and reflects also the intensive collaboration between European experts in the field of capillaroscopy.

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