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TITLE

Identifying Domains for CNO and SAPHO: A scoping review to create domains from existing outcome measures by the OMERACT CNO and SAPHO working group

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ABSTRACT

Introduction: Chronic nonbacterial osteomyelitis (CNO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome are autoinflammatory bone diseases of unknown etiology that present with bone pain and varying degrees of extraosseous manifestations such as skin, intestinal and joint involvement. Currently, there are no validated outcome measurement sets that represent the input from all collaborating groups.

Methods: The OMERACT CNO & SAPHO working group performed a scoping review to identify domains previously used in CNO and SAPHO clinical studies. The list of potential domains was narrowed through a process of binning and winnowing.

Results: A scoping review included 260 observational studies published from 1978 -2020 and 220 domains were initially identified. Domains were reduced to 25 through a binning and winnowing process. Domains cover each of the OMERACT core with most domains mapped to life impact and pathophysiological manifestations.

Conclusion: We identified 25 potential domains covering health concepts of function, disease manifestations, pain, and impact on mental health and societal participation to be included in the final Core Domain Set. The next step will be to reach a consensus on the final CNO & SAPHO Core Domain Set and begin instrument selection.

KEYWORDS

Chronic nonbacterial osteomyelitis
Autoinflammatory Disease
Core Domain Set
Scoping Review
OMERACT

BACKGROUND

Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disease of unknown etiology that presents with bone pain with or without swelling. It is difficult to diagnose as there is no diagnostic test, and labs can be normal or only show mildly elevated inflammatory markers. Radiographic abnormalities include osteolytic bone lesions. Extraosseous manifestations can be present and can consist of skin, intestinal and joint involvement. The severity of the disease can vary from mild to severe with complications that can include bone overgrowth, disfigurement, vertebral compression fractures, as well as limb size and length discrepancy. CNO is most frequently diagnosed in children and adolescents but can extend into or newly present in adulthood (1). CNO is an umbrella term, which spans a spectrum from unifocal CNO to chronic recurrent multifocal osteomyelitis (CRMO), and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome (1). SAPHO syndrome is the diagnostic term primarily utilized in adults who present with similar manifestations to CNO in children and adolescents. SAPHO and CRMO are thought to be part of CNO's disease spectrum across the age span (2).

CNO has a significant impact on the patient's and family's quality of life (3,4). Most patients experience chronically active or recurrent disease affecting multiple bones (5). Recent outcome studies show most families and patients are limited in their activities due to pain and physical limitations from their disease (4,6). Treatment for CNO is usually empiric, based on personal experience or case series (7,8). There are consensus treatment plans (CTPs) for children with CNO refractory to NSAIDs (9). To evaluate the effectiveness of these CTPs, there is a need for validated disease monitoring scoring tools to determine proposed treatment criteria (9). Additionally, there are no treatment guidelines in adults with CNO and SAPHO, and no regulatory authority-approved therapies (10). The lack of standardized treatment guidelines in CNO and SAPHO may contribute to delays in initiating effective treatment with the sequelae of poorer clinical outcomes.

In CNO, there are no randomized controlled trials (RCTs) that are considered to be the gold standard in evaluating treatment efficacy (9). Prior to the development of a randomized control trial (RCT), core domains are urgently needed to measure disease outcomes in response to interventions. Notably, clinical trials and the development of outcome measures for CNO are some of the highest priorities agreed upon among patients and clinicians (11). While a proposed framework for clinical trials has been recently suggested, this work only included consensus by 15 experts, 1 former patient who is now a clinician and another family representative (12).

While several candidate serum proteins have been suggested in the literature (13, 14), there are currently no validated clinical or laboratory markers that reliably measure disease activity in response to treatment (8). The PedsCNO was developed as a potential outcome measure, scoring the percentage of improvement as an analogy to ACR scores (15). The PedCNO items include the erythrocyte sedimentation rate (ESR), number of radiological lesions, severity of disease estimated by the physician, severity of disease estimated by patient or parent, and the childhood health assessment questionnaire (CHAQ). However, the outcomes used may be selectively reported or may not reflect all the relevant aspects to patients and clinicians, limiting the utility of study findings in clinical practice. A recent publication suggested the clinical disease activity score (CDAS) to measure treatment response and activity in pediatric CNO, but more work is needed to establish its validity and role in future pediatric RCTs (16).

Thus, both a Core Domain Set (CDS) reflecting decisions about *what* is essential to measure and report, and a Core Outcome Measurement Set representing decisions about *how* to measure each of the chosen domains in future clinical trials for CNO and SAPHO, are needed to study the success of treatments. This will allow for consistency and broad applicability across trials. Through a rigorous, data-driven, iterative consensus process defined by OMERACT (Outcome Measures in Rheumatology), we are working with relevant collaborator groups (e.g. patients, caregivers, providers, researchers, and policy makers) across the globe to develop this Core Outcome set. This current study aims first to identify the key health areas, i.e., the domains, reported in prior research studies for patients with CNO and SAPHO.

METHODS

This scoping review was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (17).

Search strategy and eligibility criteria

The protocol was developed by the international OMERACT CNO/SAPHO working group (https://omeract.org/working-groups/cno/), including patient research partners, clinicians, and representatives from OMERACT (methodologist and technical advisor) to identify outcome measures previously used in CNO and SAPHO clinical studies. (Supplement A). A literature search in OVID, PubMed and Google Scholar databases was designed and implemented on October 24, 2019, to identify relevant studies. Selected Population, Intervention, Control, Outcome, Context (PICOC) criteria included patients of any age with physician-diagnosed CNO/SAPHO and any intervention (i.e., medications, complementary and alternative therapies, physical therapy, exercise, pain management, psychosocial support), with 'standard of care' as the control. All observational study designs and case series with 3 or more patients were included. Languages other than English were excluded.

Study Selection

Title and abstract screening and full-text screening were performed by working group members in independent reviewer pairs (MO, YZ, CA, FN, MR, MH, GS, EF, AJ, SS, AL, AA, EW). Duplicates and studies not meeting eligibility criteria were excluded. Full-text manuscripts were obtained for all titles that fit the eligibility criteria and screened by new reviewers. Any conflicts were resolved by a third reviewer. All steps of the article selection process were documented using Covidence online platform (https://www.covidence.org/). The scoping review search results after identification, screening and full-text review and reasons for exclusion are summarized in the PRISMA flow diagram (Figure 1).

Data extraction and reporting

Data was extracted by two reviewers, one who independently extracted and a second who reviewed. As with study selection, any conflicts were resolved by a third reviewer. Extracted data included first author, study publication year, the aim of the study, study design, population characteristics, all reported disease-related manifestations and impacts and their definition, any outcome measurement instrument used, and adverse events.

Synthesis

Thematic analysis was conducted by the OMERACT CNO/SAPHO working group consisting of examining the data extracted from the journal text to identify candidate domains. The initial list of candidate

domains generated was reviewed and reduced by the working group through a process of binning and winnowing (18) at bi-monthly virtual meetings, the 2023 OMERACT CNO/SAPHO Special Interest Group session and multiple smaller subgroup meetings of working members over the course of four years. All potential domains identified for the core set were categorized according to one of four core areas: Pathophysiological manifestation, Life impact, Resource Use, and Death/Longevity, as defined by the OMERACT 2.2 Filter (19).

RESULTS

Search results/PRISMA

An initial search identified 4821 articles. After removing duplicates, 3002 articles were screened at the title and abstract level. Of these, 2420 articles were excluded due to not fulfilling eligibility criteria. The remaining 578 articles underwent full-text review. Of those, 326 were excluded because of study design did not meet inclusion criteria (127) such as case reports with less than 3 or review articles, non-English text (112), non-CNO or SAPHO patient population (83), and duplicate study (4). A total of 252 articles were included in the final data extraction (Fig. 1).

Characteristics of studies

Publication dates ranged from 1972-2020. Most studies were observational, including 117 retrospective cohort studies, 21 prospective studies, 86 case series (62 with N<=10 and 24 with N>10), 16 case-control studies, 7 cross-sectional studies, 3 basic science studies, and 2 mixed method studies. The sample sizes ranged from 3, which was the minimum set by the inclusion criteria, to 486 from the Eurofever observational registry study by Girschick and colleagues (22).

Figure 2 shows the global span of studies, covering 5 continents (North America, Europe, Asia, South America, and Australia) and 34 countries. The largest number originated in Germany (18%, N=46), followed by USA (11%, N=28) and Japan (9%, N=23). Eleven countries had one article included.
Of the 251 studies, 88 (35.1%) included patients with CNO, 140 (55.8%) patients with SAPHO and 23 (9.1%) included patients with either (subtypes defined by the original authors of the publication). Age was specified in 246 studies. Of those, 107 (43.5%) were pediatric studies, 86 (35.0%) were adult, and 53 (21.5%) had both adult and pediatric populations.

Domains reported

The total number of domains identified from this scoping review was 220 (supplement table?). Through the process of binning and winnowing (i.e. reviewing the domains, removing duplicates, and grouping like domains) at the working group's bi-monthly virtual meetings, the list was reduced to 42. The final 25 domains from the scoping review were established during the discussion at the 2023 OMERACT CNO/SAPHO Special Interest Group (SIG) session in Colorado Springs, CO, USA.

Domains identified by scoping review mapped to the four OMERACT Core Areas which are also listed in Table 1. Most domains identified fell under the Core Areas "Life Impact" (N=11) and "Pathophysiology Manifestations" (N=12). Domains mapped to Life Impact included education impact, health-related QOL, fatigue, physical impact, severity of disease, pain interference, anxiety, depression, psychological burden/impact, sleep, and social impact. The 12 domains mapped to pathophysiological manifestation cover pain intensity, clinical musculoskeletal symptoms, skin manifestation, growth disturbance,

damage, and fever. For the core area "Resource Use" the domain identified was economic impact and for "Death/Longevity" adverse events or side effects were identified.

DISCUSSION

This is the first study exploring the domains reported in the current literature for adults and children with CNO and SAPHO. We conducted an extensive review of nearly 50 years of research into a rare disease and a wide range of countries spanning over 5 continents.

This extensive scoping review covering almost 50 years of CNO/SAPHO research identified over 200 domains across the four OMERACT Core Areas. Through a process of binning and winnowing, we were able to narrow down the list to 25 domains covering health concepts of function, disease manifestations, pain, and impact on mental health and societal participation. Over 90% of the domains mapped to core areas of Life Impact and Pathophysiological Manifestations with a nearly even split between these two core areas, emphasizing the importance of the impact CNO and SAPHO have on a person's life in addition to more objective disease manifestations. The scoping review also identified the potential economic impacts of the disease. However, very few studies mapped to the core areas of Societal/Resource Use and Death/Longevity, highlighting a significant gap in the literature for CNO and SAPHO.

There is no standardized outcome measure set for CNO and SAPHO. Only a few disease-specific outcome measures for CNO and SAPHO have been reported in the literature, including the PedCNO score (15), the CNO CTP for treatment failure (9), a SAPHO osteitis and skin score (20), and most recently the CNO CDAS developed for disease activity monitoring and assessment of treatment effectiveness (16). However, the two CNO-specific scores lack measures for commonly observed extraosseous disease manifestations including skin manifestations, which were identified in our scoping review as a potential domain (21). These scores also do not include many of the domains identified in this exercise falling under Life Impact domain, such as fatigue, health-related QOL measures, sleep, depression, anxiety, educational impact, or social impact. Further work is needed to evaluate the psychometric properties of current instruments and their performance in prospective observational and interventional studies.

We acknowledge several limitations of this study. There is a potential for publication bias due to the evaluation of English-only articles, use of only 3 databases, representation mostly from North America and Europe, and the field of pediatric rheumatology itself being very small, limiting access and outcomes reporting in some parts of the world. Many of the included studies were also case series or had small sample sizes, potentially limiting generalizability.

CONCLUSION

Following this scoping review, the OMERACT CNO working group performed qualitative work to generate candidate domains. This included virtual focus groups and online discussion boards with all collaborators to identify additional domains to complement the work from this scoping review. The next step will be to conduct a series of Delphi surveys to reach a consensus on the final CNO & SAPHO Core Domain Set. This Core Domain Set will be the foundation for the next step in the development of the outcome measurement set, which is instrument selection. A standardized core outcome measurement

set will facilitate conducting well-designed trials essential to the care of our patients with CNO and SAPHO.

ABBREVIATIONS

CDS: Core Domain Set
CNO: Chronic Nonbacterial Osteomyelitis
CRMO: Chronic Recurrent Multifocal Osteomyelitis
OMERACT: Outcome Measures in Rheumatology
SAPHO: Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis

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Table 1: Reported domains from scoping review mapped to OMERACT Core Areas

Core Areas			
Pathophysiological manifestation	**Life impact**	**Death/Longevity**	**Resource Use**
Pain Intensity	Education impact	Adverse/Side effect	Economic impact
Growth disturbance	Health related QOL		
Damage	Fatigue		
Headache	Physical impact		
Clinical bone disease	Severity of disease		
Clinical Arthritis	Pain Interference		
Clinical Enthesitis	Anxiety		
Morning stiffness	Depression		
Skin disease	Psychological burden/impact		
Myalgia	Sleep		
Trismus	Social impact or Participation		
Fever			

QOL: quality of life