Fibromyalgia syndrome – a risk factor for poor outcomes following orthopaedic surgery: A systematic review

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ABSTRACT

BACKGROUND

Fibromyalgia (FM) is a complex syndrome incorporating many features associated with poor outcome in orthopaedic surgery. Aim of the present review was to comprehensively characterize the available evidence on the consequences of pre-existent FM on the outcomes of orthopaedic surgery.

METHODS

We performed a systematic search in MedLine and Web of Science (WOS) to identify studies evaluating the effect of FM on patient-centred outcomes, opioids consumption and postoperative complications.

RESULTS

The search strategy identified 519 records in PubMed and 507 in WOS. A total of 27 articles were deemed eligible for inclusion in qualitative synthesis. Based on quality assessment, 10 studies were rated as good quality, 10 as fair quality and 7 as poor quality. Studies reporting the prevalence of FM in consecutive patients undergoing orthopaedic surgery (n = 19) were included in quantitative synthesis. The pooled prevalence of FM in patients undergoing orthopaedic surgery was 4.1% (95% CI: 2.4–6.8) in those receiving hip or knee surgery, 10.1% (95% CI: 5.7–17.2) in those receiving shoulder or elbow surgery and 21.0% (95% CI: 18.5–23.7) in those receiving spinal surgery. The results of our systematic review consistently report FM as a significant risk factor for less satisfaction, higher pain, worse functional outcome, increased risk for postoperative opioids prescription and higher rate of medical and surgical complications following orthopaedic surgery.

CONCLUSION

Identifying pre-existing FM in patients scheduled for elective orthopaedic surgery may help to better assess the benefit/risk ratio, improve patients' awareness and minimize any discrepancy between expectancy and results.

KEYWORDS

Fibromyalgia; widespread pain; orthopaedic surgery; knee arthroplasty; hip arthroplasty; spinal surgery

1. INTRODUCTION

Fibromyalgia (FM) is a rheumatic disorder characterized by chronic widespread musculoskeletal pain, sleep disorders, fatigue and cognitive disturbances [1, 2]. Additional symptoms commonly include exercise intolerance, morning stiffness, irritable bowel syndrome, headache, paraesthesia, and psychological dysfunction such as depression and anxiety [3, 4]. It is not surprising that FM has a substantial impact on patient's quality of life (QoL) [5] and, consequently, on society and healthcare expenditure [6]. The diagnosis of FM historically relied on the 1990 American College of Rheumatology (ACR) criteria [1] including widespread pain of at least 3 months' duration and tenderness on pressure at 11 or more of 18 specific tender points. In 2010, the ACR proposed a new set of clinical criteria for the diagnosis of FM based on a widespread pain index (WPI) and a symptom severity (SSS) scale, however, the tender point examination was withdrawn [7]. The 2010 criteria underwent a revision in 2016 [8] that combined physician and questionnaire criteria and eliminated the previous recommendation regarding diagnostic exclusions. Furthermore, the ACR 2010 criteria have also been adapted for administration as a self-report questionnaire (*"survey criteria"*) to be used in epidemiologic studies with good reliability, convergent, and discriminant validity [9].

From an epidemiological point of view, FM is a common disorder with strong female predominance occurring in approximately 5% of the general population and accounting for 14% of rheumatology outpatient visits [10]. Comorbid FM is also common in patients with rheumatoid arthritis (18-24%), axial spondyloarthritis (14-16%), psoriatic arthritis (18%) and osteoarthritis (35%)[11, 12]. The etiopathogenesis of widespread pain in FM is still elusive, but most evidence points towards central sensitization to painful and non-painful stimuli [13] arising from periphery, as exemplified by the evidence of a high prevalence of FM in patients with other inflammatory or degenerative joint diseases[14]. Amongst these, a common association is found in clinical practice between features consistent with FM and clinic-radiological findings of osteoarthritis[15], the most common indication for joint replacement surgery.

In the last decades, the aging population[16], an increasing prevalence of osteoarthritis[17], and overall improvement in surgical techniques[18] have led to a dramatic increase in the number of orthopaedic surgical procedures, in particular knee and hip arthroplasty[19]. In the United States, 371,605 total hip arthroplasties (THA) and 680,886 total knee arthroplasties (TKA) were performed in 2014 and recent projections estimate that these numbers are likely to increase up to 1,429,000 (+284%) and 3,416,000 (+401%), respectively, by 2040[20]. Despite providing a clear improvement in patients' quality of life[21], a significant number of patients still suffer ongoing pain in the treated joint. Indeed, 44% of patients with TKA and 27% of patients with THA experience persistent postsurgical pain, with 15% of TKA patients and 6% of THA patients reporting severe to extreme persistent pain after three to four years[22]. Several presurgical factors have been demonstrated to influence the outcome of surgery, including musculoskeletal pain in other sites, catastrophizing, and depression[23]. In this regard, clinical studies have consistently demonstrated that both depression[24] and pain catastrophizing[25] contribute to the clinical course of the condition and treatment response in patients. For this reason, it is possible to hypothesize that FM, by incorporating many features associated with poor outcome in orthopaedic surgery, may represent the prototypical preoperative risk factor to be considered when planning surgery for non-urgent indications. Further, given the epidemiological trajectories and the overall high prevalence of FM in the general population, it is expected that the proportion of FM patient's candidate to orthopaedic surgery will increase.

In view of this background, the aim of the present review is to comprehensively characterize the available evidence on the consequences of pre-existent FM on the outcomes of orthopaedic surgery. This review will also clarify the relationship between FM and orthopaedic surgery, identify future directions for research and promote optimal orthopaedic care for this category of patients.

2. METHODS

2.1 Search strategy

MedLine (via PubMed) and Web of Science (WOS) databases were searched from inception until 20 November, 2020. The search in MedLine was performed using the string "((Orthop* AND Surger*) OR (Spin* AND Surger*) OR Fixation OR Fusion OR Replacement OR Repair OR Osteotom* OR Amputation OR Decompression OR Reconstruction OR Arthroscop* OR Arthrodes* OR Arthroplast* OR Discectom* OR Fracture* OR "carpal tunnel" OR Meniscectom* OR Laminectomy* OR Vertebroplast* OR Foraminotom* OR Interlaminar* OR Nucleoplast* OR Vertebroplast* OR Kyphoplast* OR Ostectomy OR Chondroplast*) AND ((fibromyalgia) OR ("chronic fatigue syndrome") OR ("Chronic Fatigue Disorder"))". The search in WOS was performed using the string "[TS=((Orthop* AND Surger*) OR (Spin* AND Surger*) OR Fixation OR Fusion OR Replacement OR Repair OR Osteotom* OR Amputation OR Decompression OR Reconstruction OR Arthroscop* OR Arthrodes* OR Arthroplast* OR Discectom* OR Fracture* OR (carpal tunnel) OR Meniscectom* OR Laminectomy* OR Vertebroplast* OR Foraminotom* OR Interlaminar* OR Nucleoplast* OR Vertebroplast* OR Kyphoplast* OR Ostectomy OR Chondroplast*) AND TS =((fibromyalgia) OR ("chronic fatigue syndrome") OR ("Chronic Fatigue Disorder"))]". Additionally, relevant keywords were used in different combinations for free-hand search and the bibliography of selected articles was reviewed.

The decision to include the keyword *"chronic fatigue syndrome"* was adopted to increase the sensitivity of the search strategy (e.g., identification of studies centred on chronic fatigue syndrome but including also individuals satisfying criteria for FM, given the clinical overlap between the two conditions) although the focus of our article was FM. The search was designed and performed by one author (MD) under supervision of a senior investigator (FU). No date restriction was applied. The protocol of the systematic review was submitted for registration to the international register PROSPERO[26] (ID# 228989). The review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[27].

2.2 Eligibility criteria

For the purpose of this study only articles written in English language were considered eligible. To be included in the final review, studies had to be published as full-text original articles in international, peer-reviewed journals. Randomized controlled trials (RCT), quasi-RCT (trials in which allocation to treatment was made by alternation, use of alternate medical records, date of birth or other expected methods), and prospective or retrospective cohort studies were deemed eligible.

The population, intervention, comparator, outcome (PICO) framework was used to build the search question. All studies meeting the following criteria were included in the final review:

- *Population:* patients undergoing orthopaedic surgery
- *Intervention:* any surgical procedure
- *Comparison:* patients with a pre-existent diagnosis of FM versus patients without FM or comparison of FM features before/after surgery or comparison between patients with different degree of FM-related symptoms
- *Outcome:*
    - Studies evaluating patient-centered outcomes of surgery, i.e., satisfaction, pain and functional status
    - Studies evaluating the need of analgesic medication (e.g., opioids) consumption following surgery

- Studies assessing postoperative complications in patients with FM.

2.3 Study selection process and data extraction

After removal of duplicate records, two reviewers (MD and JC) independently screened titles and abstracts for the first-step evaluation. Following the screening phase, the same two reviewers independently evaluated the full-text of the remaining articles to determine eligibility for inclusion in the final review. Disagreements among the reviewers were discussed with a third senior investigator (FU) until consensus was reached. A detailed flowchart of the study selection process is reported in Figure 1.

2.4 Quality assessment

The quality of included studies was evaluated using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [28].

2.5 Quantitative synthesis and statistical analysis

After identification of studies for the review and qualitative synthesis, only studies that included data on the prevalence of FM, in consecutive patients undergoing orthopaedic surgery, were included in a quantitative synthesis.

Data from relevant studies were pooled using a random-effects model that accounts for the expected high heterogeneity. Publication bias was graphically assessed by visual inspection of the funnel plot. The *“trim and fill”* method proposed by Duval and Tweedie [29] was used to calculate pooled estimates after correction for potential publication bias. Statistical analyses were performed using Comprehensive Meta-Analysis Software (CMA; Version 2.0, Englewood, US).

For qualitative synthesis, data retrieved from eligible articles were summarized by reporting p values for Students’ t test or other non-parametric tests, percentages with p values for chi-squared tests, odds ratio (OR) with 95% confidence interval (95% CI) for logistic regression analysis, or β coefficients for linear regression analysis.

3. RESULTS

3.1 RESULTS OF THE SYSTEMATIC SEARCH

The search strategy identified 519 records in PubMed and 507 in WOS. After removal of duplicates, 769 studies proceeded to review. Of these, 703 were excluded following screening of titles and abstracts, and full text evaluation was performed on 66 articles. A total of 27 articles were deemed eligible for inclusion in qualitative synthesis (Figure 1). General characteristics and main findings of studies included in qualitative synthesis are reported in Table 1. Based on quality assessment, 10 studies were rated as good quality, 10 as fair quality and 7 as poor quality (Table 2).

3.2 PREVALENCE OF FIBROMYALGIA IN PATIENTS UNDERGOING ORTHOPEDIC SURGERY

Studies reporting the prevalence of FM in consecutive patients undergoing orthopaedic surgery (n = 19) were included in quantitative synthesis. The overall prevalence of FM in patients undergoing orthopaedic surgery was 6.9% (95% CI: 4.7–10.2). Visual inspection of the funnel plot revealed potential publication bias (Figure 2). By applying the “trim and fill” method under a random-effects model, six studies were trimmed and the imputed point estimate fall to 4.3% (95% CI: 2.9–6.1). More in details, the pooled prevalence of FM was 4.1% (95% CI: 2.4–6.8) in patients receiving hip/knee surgery, 10.1% (95% CI: 5.7–17.2) in those receiving shoulder/elbow surgery and 21.0% (95% CI: 18.5–23.7) in those receiving spinal surgery (Figure 3).

3.3 FIBROMYALGIA AND OUTCOMES OF SPINAL SURGERY

Four of the included studies investigated the impact of preoperative FM on spinal surgery. Available data suggest that FM affects negatively patient’s satisfaction with surgical results, consumption of opioids and risk of complications after surgery.

3.3.1 Satisfaction, pain and functional status. Ablin et al.[30] investigated the consequences of pre-existing FM on postoperative outcomes in a prospective cohort (n = 40) of patients undergoing cervical or lumbar laminectomy or foraminectomy. After a follow-up of 10-12 weeks, those with FM (n = 11) experienced a significant improvement in WPI (6.7 ± 2.3 versus 5.4 ± 2.4, p = 0.04) but not in SSS (p = 0.76); conversely, patients without FM showed a significant reduction in both SSS (2.6 ± 2.2 versus 1.3 ± 1.2, p < 0.01) and WPI (3.8 ± 2.1 versus 2.2 ± 1.6, p < 0.001).

In 2020 Weiner et al.[31] published the results of a prospective cohort study on 193 veterans with lumbar spinal stenosis undergoing decompressive laminectomy. The main outcome was the Brigham Spinal Stenosis (BSS) questionnaire. The BSS is a disease-specific self-reported measure widely used to quantify treatment outcomes in patients with lumbar spinal stenosis and has three scales: physical function, symptom severity and satisfaction with surgical results. Bivariate logistic regression analysis revealed that patients with FM (23.3%) had a lower odd of reaching the threshold for BSS satisfaction after 12 months (OR: 0.51, 95% CI: 0.25–1.01, p = 0.05), but not for BSS physical function or symptom severity.

3.3.2 Postoperative opioid consumption. Mining the administrative database PearlDiver, Qureshi et al.[32] investigated the factors associated with prolonged opioids prescription after lumbar discectomy. PearlDiver (http://www.pearldiverinc.com/researchinfo.html) is one of the largest healthcare databases in the world, collecting claims data of over 122 million patients from government (Medicare, Medicaid) or commercial (Humana, United Healthcare) insurance plans. Records are de-identified and compliant with the Health Insurance Portability and Accountability Act (HIPAA) but can be used for longitudinal research based upon unique patient identifier codes. By interrogating PearlDiver, authors retrieved a cohort of 1,321 patients who had undergone lumbar discectomy, and stratified them in to two groups according to opioids prescription after three months. Patients in the prolonged opioid group (n = 621) had a higher prevalence of comorbid FM (24.9%) versus those not taking opioids (15.7%, p < 0.001); in a multiple logistic regression model, a past diagnosis of FM was amongst the strongest risk factors for long-term narcotics prescription (OR: 2.12, 95% CI: 1.56–2.89, p < 0.001).

3.3.3 Postoperative complications. A similar methodology was used by Donnally et al. [33] to identify the potential role of comorbid FM as a predisposing factor for postoperative complications in patients who underwent posterolateral lumbar spine fusion. A total of 9,346 patients with a documented diagnosis of FM were matched 1:1 with controls. With respect to the control group, binary analysis of 30-day postoperative complications revealed that patients with FM had higher rates of acute post haemorrhagic anaemia (0.52% versus 0.20%; OR: 2.58, 95% CI: 1.52–4.39, p < 0.001) and readmission (3.80% versus 3.08%; OR: 1.23, 95% CI: 1.05–1.43, p = 0.007). When analysing 90-day complications, patients with a concomitant diagnosis of FM showed higher risk of pneumonia (0.43% versus 0.12%; OR: 3.73, 95% CI: 1.92–7.27, p < 0.001) and postoperative anaemia (1.03% versus 0.37%; OR: 2.79, 95% CI: 1.89–4.11, p < 0.001), compared to those in the control group.

3.4. FIBROMYALGIA AND OUTCOMES OF HIP AND KNEE SURGERY

Twelve of the included studies investigated the impact of preoperative FM on hip and knee surgery. Available data consistently suggest that FM affects negatively postoperative pain, patient’s satisfaction with surgical results, consumption of opioids and risk of surgical and medical complications after joint replacement.

3.4.1 Satisfaction, pain and functional status. The first report investigating the impact of FM on outcomes of TKA was a case-control study published by Bican et al. [34] in 2011. The authors identified 59 patients with comorbid FM from their institutional joint arthroplasty database. After a mean follow-up of 3.4 years, patients with FM reported significantly less satisfaction – graded on a 4-point Likert scale – with pain relief (p = 0.0018), ability to return to daily activities (p = 0.0062), functional recovery (p = 0.0280), and overall surgery (p = 0.0124), when compared to a 1:1 matched control population.

Similarly, D’Apuzzo et al. [35] reviewed a cohort of 110 patients with FM undergoing TKA to determine the level of postoperative pain and satisfaction with the surgical outcome. After a mean follow-up of 7 years, 62 (44%) patients reported some degree of residual knee pain; despite this, 82% were satisfied with the results of surgery. Complications were common and mainly represented by arthrofibrosis (14.3%) and symptomatic instability (13.2%); eight knees (6%) underwent subsequent revision surgery.

In a prospective cohort study recruiting 464 patients, Brummet et al.[36] aimed to evaluate the effect of pre-existing FM on measures of pain obtained six months after TKA or THA. In multiple logistic regression analysis, higher preoperative FM survey score (obtained by adding WPI to SSS) was a significant predictor of failure to meet the threshold of at least 50% improvement in measures of pain such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (OR: 1.17, 95% CI: 1.08–1.29, p = 0.00032), or the Brief Pain Inventory (BPI) (OR: 1.30, 95% CI: 1.19–1.42, p < 0.00001), and in patient's global assessment of change (OR: 1.18, 95% CI: 1.05–1.31, p = 0.0038). Overall, those with FM who received TKA (41.6% of the sample) showed increased odds of poor outcome.

Skrejborg et al. [37] aimed to identify risk factors for the development of chronic postsurgical pain in a cohort of 352 patients who underwent TKA. Consistent with previous results, comorbid FM was the strongest predictor of having chronic postsurgical knee pain five years after surgery, using bivariate analysis OR: 20.66, 95% CI: 1.50–284.88. Likewise, the prevalence of FM was significantly higher in individuals who reported moderate-to-severe pain (rated on a 0-10 numerical rating scale; NRS ≥ 3) compared with those with mild-to-no pain (NRS < 3) (5.6% versus 0%, p = 0.001).

Furthermore, a retrospective study by Vina et al.[38] (n = 298) aimed to determine if widespread musculoskeletal pain, defined according to the 1990 ACR criteria for FM, was associated with an increased risk of no clinical improvement two years after TKA. These authors reported that amongst women (n = 184), having widespread pain before TKA was associated with an increased risk of no improvement in WOMAC pain score (widespread pain: 13.5%, no widespread pain: 4.6%, p = 0.02), 7-day NRS indicating pain severity versus no pain (widespread pain: 20.4%, no widespread pain: 7.8%, p = 0.02), and Knee Injury and Osteoarthritis Outcome Score (KOOS) for pain two years after TKA versus no pain (widespread pain: 16.5%, no widespread pain: 4.9%, p = 0.01). Similarly, any use of medication for pain, aching, or stiffness in the knee during the past 12 months was more frequent amongst participants satisfying criteria for widespread pain before TKA versus those who did not satisfy the criteria (74% versus 60%, p = 0.01).

In 2020, Schrepf et al.[39] explored clinical differences in 150 patients undergoing TKA or THA who had a minimum level of FM-related symptoms (defined as FM survey score ≥ 4) prior to surgery. To identify groups that showed different patterns of FM symptoms change after surgery, the author stratified patients in tertiles according to the residuals of the change in FM survey score (baseline to six months) regressed on baseline survey score values. Patients in the top two tertiles were defined as *Improve* while those in the bottom tertile were defined as *Worsen/Same*. At baseline, total FM survey scores (p = 0.045), fatigue (p = 0.014), depression (p = 0.003) and surgical site pain severity (p = 0.032) were higher in the *Worsen/Same* group compared with those who improved. Interestingly, despite the fact that there was no significant difference in the number of patients reporting surgical site pain after six months (*Improve:* 74% versus *Worsen/Same:* 69%, p = 0.54) the authors observed different trajectories of FM-related symptoms, including either non-surgical musculoskeletal pain and constitutional symptoms, when comparing patients belonging to the two groups. Although improvement occurred in both groups at the one-month time point, by month three the *Worsen/Same* group showed substantial regression in their FM-related symptoms, such that by month six they had returned to pre-surgical levels. Conversely, the *Improve* group continued to show benefits at month three and through month six.

3.4.2 Postoperative opioid consumption. In 2013 Brummet et al.[40] conducted a prospective cohort study to evaluate the interaction between FM and postoperative opioid consumption after TKA (n = 233) or THA (n = 286). Although there were no differences in hospital length of stay, total postoperative opioid consumption (from post-anaesthesia care to discharge) was greater in patients in the higher tertile of FM survey score compared to the lowest (p < 0.00001). In a multivariate regression model, the postoperative opioid consumption showed a significant, although weak association with FM survey score (β = 0.022, SE = 0.0073, p= 0.0024).

Similar results were obtained by Namba et al.[41] in a retrospective study on 23,726 patients undergoing TKA of which 381 (1.6%) had comorbid FM. In the year before surgery, 60% of the patients received opioids prescription; following TKA, this decreased to 30.4% (after 271-360 days). Multiple logistic regression analysis revealed that history of chronic pain was amongst the risk factors for prolonged opioid use; in particular, patients with FM had a 15% increase in the odds of taking opioids up to 360 days post-surgery (OR: 1.15, 95% CI: 1.06–1.25, p = 0.001).

In 2017, Kim et al.[42] investigated the risk factors for long-term opioid use after TKA or THA in a large cohort (n = 57,545; 68.5% TKA) of patients retrieved by mining the Clinformatics Data Mart Database, collecting data from a commercial health insurance (United HealthCare). Persistent opioid users were defined as patients who filled ≥ 1 opioid prescription every month during the one-year postoperative period based on group-based trajectory models. In multiple logistic regression analysis, patients who underwent TKA (OR: 1.75, 95% CI: 1.59–1.93, p < 0.05), who were discharged to an acute rehabilitation facility (OR: 1.26, 95% CI: 1.12–1.42, p < 0.05) and who had a longer length of stay (OR: 1.04 for an additional day of stay, 95% CI: 1.02–1.06, p < 0.05) were more likely to use opioids persistently after surgery. Similarly, presence of chronic back pain (OR: 1.28, 95% CI 1.17–1.40, p < 0.05), FM (OR: 1.22, 95% CI: 1.07–1.39, p < 0.05), migraine (OR: 1.19, 95% CI: 1.04–1.36, p < 0.05) and rheumatoid arthritis (OR: 1.40, 95% CI: 1.20–1.65, p < 0.05) were also significant predictors of persistent opioid use.

In 2019, Larach et al.[43] reported the results of a prospective observational study focused on acute and chronic postoperative pain (The Analgesic Outcome Study). The final cohort comprised 913 patients undergoing elective hysterectomy, thoracic surgery, and primary TKA (n = 325) or THA (n = 221). The univariate linear regression analysis performed on the overall cohort showed that higher FM survey score was associated with increased self-reported opioid consumption during the first month after surgery in both TKA (β = 16.8, SE = 8.3, p = 0.044) and THA (β = 18.6, SE = 7.2, p = 0.009), although multiple regression models failed to confirm the independence of this relationship.

In 2020 Sheth et al.[44] published the results of a prospective study on 258 patients undergoing TKA (n = 163) or THA (n = 95). Binary logistic regression analysis, revealed that comorbid FM (OR: 6.58, 95% CI: 1.56–27.58, p = 0.01) and chronic pain syndrome (OR: 21.82, 95% CI: 7.64–62.24, p < 0.0001) were associated with prolonged (> 90 days) opioid use. However, this association was not confirmed in multiple logistic regression analysis.

In a large cohort of patients who underwent primary arthroscopic meniscectomy from the PearlDiver database, Khazi et al.[45] investigated predictors of postoperative opioid prescription. A total of 88,120 patients were retrieved, of which 25.3% filled opioid prescription after 12 months. In multiple logistic regression analysis, comorbid FM was associated with a significantly increased risk of opioid refill after 12 months (OR: 1.71, 95% CI: 1.64–1.78, p < 0.0001).

3.4.3 Postoperative complications. A number of studies have been conducted using the PearlDiver database to explore the association of FM with patient outcomes. Sodhi et al.[46] and Moore et al.[47] for example, have both demonstrated that, compared to controls, FM patients had increased odds of developing any surgical complication (OR: 1.55, 95% CI: 1.51–1.60, p < 0.001) or medical complication following TKA (OR: 1.95, 95% CI: 1.86–2.04, p<0.001), such as wear (OR: 2.11, 95% CI: 1.48–3.01, p < 0.0001), periprosthetic osteolysis (OR: 1.71, 95% CI: 1.10–2.66, p = 0.018), revision of tibial insert (OR: 1.5, 95% CI: 1.14–2.05, p = 0.046), mechanical loosening (OR: 1.34, 95% CI: 1.26–1.53, p < 0.0001), infection/inflammation (OR: 1.33, 95% CI: 1.26–1.14, P < 0.0001), acute post-haemorrhagic anaemia (OR: 1.56, 95% CI: 1.41–1.73, $p < 0.001$), or shortness of breath (OR: 3.02, 95% CI: 2.60–3.51, $p < 0.001$) and other respiratory abnormalities (OR: 3.49, 95% CI: 2.87–4.24, $p < 0.001$).

Similarly, Cregar et al.[48] aimed to investigate the risk factors for undergoing lysis of adhesion (LOA) surgery for postoperative arthrofibrosis following TKA. Overall, 106,874 patients were identified from the PearlDiver database of which 0.6% received LOA within 12 months and 2.3 revision TKA within 24 months post-surgery. A diagnosis of FM was present in 18.3% of LOA patients compared to 12.7% of those not receiving LOA ($p = 0.006$). In multiple logistic regression, the presence of FM was associated with higher risk of LOA (OR: 1.30, 95% CI: 1.01–1.70, $p = 0.0484$) and revision (OR: 1.19, 95% CI: 0.93–1.52, $p = 0.0093$).

A similar methodology was applied to THA as the index surgery by Nelson et al.[49]. By matching 1:1 76,103 FM patients with controls, the authors demonstrated that, in binary logistic regression, FM was associated with a significantly higher two-years risk of implant-related complications (5.94% versus 3.79%, $p < 0.001$), such as articular bearing surface wear of prosthetic joint (OR: 3.20, 95% CI: 1.93–5.29, $p < 0.001$), broken prosthetic joint implant (OR: 2.00, 95% CI: 1.56–2.56, $p < 0.001$), THA revisions (OR: 1.85, 95% CI: 1.45–2.36, $p < 0.001$), mechanical loosening of prosthetic joint (OR: 1.71, 95% CI: 1.50–1.94, $p < 0.001$), dislocation of prosthetic joint (OR: 1.63, 95% CI: 1.51–1.75, $p < 0.001$), periprosthetic fracture around prosthetic joint (OR: 1.44, 95% CI: 1.26–1.64, $p < 0.001$), and prosthetic joint infection (OR: 1.38, 95% CI: 1.26–1.52, $p < 0.001$). In addition, FM patients had higher risk of 90-days medical complications (2.88% versus 1.43%, $p < 0.001$), including shortness of breath (OR: 3.38, 95% CI: 2.64–4.32, $p < 0.001$), cerebrovascular accidents (OR: 3.27, 95% CI: 1.66–6.43, $p < 0.001$), pneumonia (OR: 2.67, 95% CI: 1.86–3.85, $p < 0.001$), non-healing surgical wound (OR: 2.27, 95% CI: 1.11–4.62, $p < 0.001$), urinary tract infections (OR: 2.10, 95% CI: 1.82–2.43, $p < 0.001$), acute post-haemorrhagic anaemia (OR: 1.95, 95% CI: 1.70–2.25, $p < 0.001$), thrombocytopenia (OR: 1.84, 95% CI: 1.05–3.22, $p = 0.032$), requiring transfusions (OR: 1.69, 95% CI: 1.36–2.10, $p < 0.001$), and acute kidney failure (OR: 1.58, 95% CI: 1.14–2.20, $p = 0.005$).

3.5 FIBROMYALGIA AND OUTCOMES OF SHOULDER AND ELBOW SURGERY

Four of the included studies investigated the impact of preoperative FM on shoulder surgery while only one focused on elbow surgery. Available data consistently suggest that FM affects negatively consumption of opioids after surgery.

3.5.1 Satisfaction, pain and functional status. In 2019 Lopiz et al.[50] investigated the role of comorbid FM in determining outcomes of isolated arthroscopic subacromial decompression (ASD). The final study cohort included 20 FM patients matched 1:1 with non-FM controls. After a mean follow-up of 36.8 months, the postoperative Disability Arm Shoulder and Hand scale (DASH) score was significantly worse in patients with FM versus controls (38.9 ± 21.6 versus 20.7 ± 19.6; $p = 0.009$). However, no significant differences were observed for other measures of pain and function. Furthermore, a significant lower percentage of patients in the FM declared themselves satisfied with surgery (55% vs 85%, $p = 0.03$), although no significant difference was observed in failure rates.

3.5.2 Postoperative opioid consumption. In 2016 Cheng et al.[51] performed a prospective study aimed to investigate whether a preoperative history of FM could predict postoperative outcomes in a cohort of 92 patients undergoing shoulder arthroscopy. Although patients with higher FM survey score reported increased pain severity at the surgical site before surgery, survey score was not associated with short-term postoperative pain or opioid consumption; however, in multiple linear regression it was independently correlated with poorer quality of recovery scores (β: -0.185, SE: 0.056, $p = 0.001$) from baseline to second postoperative day.

In 2019 Khazi et al.[52] reported the results of a retrospective review of 12,038 patients in the PearlDiver database undergoing anatomic or reverse primary total shoulder arthroplasty (TSA) to identify risk factors associated with opioid use after 12 months. In binary logistic regression, a past diagnosis of FM, detected in 18.1% of patients, was independently associated with opioid use at 12 months after anatomic (OR: 2.00, 95% CI: 1.70–2.35, $p < 0.0001$) and reverse (OR: 1.75, 95% CI: 1.47–2.07, $p < 0.0001$) TSA. This finding was further confirmed in multiple regression model, in both anatomic (OR: 1.45, 95% CI: 1.20–1.75, $p = 0.0001$) and reverse (OR: 1.23, 95% CI: 1.00–1.50, $p = 0.0457$) TSA.

Similar results were obtained from the same group[53] when a similar methodology was applied to shoulder stabilization surgery (n = 4,802 patients): in multiple logistic regression analysis a past diagnosis of FM (7.1%) was independently associated with opioid use at 12 months after surgery (OR: 2.01, 95% CI: 1.39–2.89; $p = 0.0002$).

On the other hand, only one study investigated the consequences of comorbid FM on elbow surgery. In 2020 Rojas et al.[54] focused on patient factors associated with postoperative opioid prescription in patients underwent primary elbow arthroscopy. The retrospective review of PearlDiver database retrieved 778 patients; a previous diagnosis of FM was detected in 5.44% of the opioid naive individuals and in the 21.63% of the preoperative opioid use group ($p < 0.001$), respectively. In multiple logistic regression, a preoperative diagnosis of FM was independently associated with higher odds of postoperative opioid prescription filling, at nine (OR: 2.21, 95% CI: 1.26–3.82, $p = 0.005$) and 12 months (OR: 1.95, 95% CI: 1.10–3.39, $p = 0.020$) postoperatively, but not after six or three months.

3.6 FIBROMYALGIA AND OUTCOMES OF WRIST AND HAND SURGERY

Literature on the impact of preoperative FM on wrist and hand surgery was scarce, and only two low-quality studies focused on self-reported measures of satisfaction satisfied criteria for inclusion.

3.6.1 Satisfaction, pain and functional status. In 1999 Straub et al.[55] aimed to identify factors that could predispose to a less satisfactory outcome after endoscopic carpal tunnel release. A past diagnosis of FM was present in 23 hands out of 100 recruited; after a follow-up of 6–24 months, a significantly lower proportion of patients with FM reported satisfactory results, defined as none to mild symptoms on a qualitative scale ranging from none to severe, compared to patients without FM (74% versus 97%, $p < 0.05$).

Similar results were obtained by Munjal et al.[56] in a retrospective analysis of 51 patients treated with open carpal tunnel decompression. After a follow-up of at least two years, a significantly higher proportion of patients with FM (55%) reported poor outcome according to the classification proposed by Clarke and Stanley[57] when compared to patients without FM (55% versus 10.5%, $p = 0.001$).

4. DISCUSSION

Given the rapidly increasing number of orthopaedic procedures performed worldwide, it is expected that more patients with FM will undergo orthopaedic surgery in the coming years. Indeed, frequent indications for elective orthopaedic surgery such as spinal pain/degenerative disc disease, hip or knee osteoarthritis, shoulder pain or carpal tunnel syndrome are prevalent in those with FM[12, 58-60]. The impact of pre-existent FM on surgery may have previously been underestimated and, although many FM patients will often require orthopaedic surgery over their lifetime, awareness and knowledge about FM is low among orthopaedic surgeons[61]. It is well accepted that surgery remains the best option in many patients with severe degenerative joint diseases; however, there is still sizeable proportion of patients reporting unsatisfactory results following orthopaedic surgery. Despite robust data supporting the favourable cost-efficacy profile of TKA and THA[62], up to 44% of TKA patients and 27% of THA patients experience persistent postsurgical pain after three to four years[22]. It was for these reasons we performed a systematic review to assess the influence of preoperative FM on outcomes of orthopaedic surgery.

The pooled analysis of eligible studies suggests that FM is a frequent comorbidity in patients undergoing to orthopaedic surgery, ranging from 4.1% in patients undergoing hip or knee surgery to 21% in those receiving spinal surgery. The number of patients undergoing orthopaedic surgery emphasizes the potential relevance of disclosing FM as a negative prognostic factor. Beyond patient-centred outcomes, the increasing number of surgical procedures performed on those with FM may pose a societal burden as hypothesized in a study demonstrating that healthcare expenditure in FM patients undergoing surgery may be higher than non-FM counterparts[63], again supporting the relevance of this topic in healthcare resource planning.

The results of the current systematic review consistently report FM as a significant risk factor for less satisfaction, higher pain and worse functional outcome after orthopaedic surgery. Similar results have been reported when looking at other surgeries such as hysterectomy[64] and antireflux surgery[65]. Although FM pathophysiology is still puzzling, pain centralization has emerged as the main hypothesis, with the Central Nervous System (CNS) governing a complex network of interactions with the periphery leading to augmentation of pain perception [66]. It is somewhat intuitive therefore to speculate that patients with prevailing centralized mechanisms may experience a higher degree of pain following any nociceptive stimulus, such as surgery. Further, patients’ satisfaction following surgery seems primarily determined by patients' expectations, and not their absolute level of function[67, 68]. Patients have high expectations regarding the outcome of surgery, mainly concerning relief of pain, improvement in physical functioning and improvement in psychosocial wellbeing[69, 70]. These expectations can be sometime unrealistic and different from those of the surgeon[71]. Patients who have unfulfilled expectations are up to ten times more likely to be dissatisfied with their treatment results[72]. This phenomenon may even be more likely when dealing with FM patients. The complex pathophysiology and the heterogeneous phenotype of FM make it difficult to give patients a reasonable idea of what to expect in terms of pain relief after surgery. Consequently, FM patients who were expecting extensive pain relief and increased functionality may have been more disappointed by the outcome of the surgery.

Another result emerging from our systematic review is that FM is associated with higher opioid consumption following surgery. Strong opioids are not recommended in FM patients due to the risk of addiction[73]; only tramadol, owning to the unique serotoninergic and adrenergic effects[74, 75], is frequently used despite the conflicting evidence[76]. Furthermore, there is some concern about their efficacy[77, 78] in patients in which the pathogenesis is mediated by centralized pain as opposed to more common peripheral or nociceptive pain; in this regard, an elegant μ-opioid receptor (MOR) positron emission tomography study by Harris et al.[77] demonstrated a reduced MOR availability in brain regions involved in pain modulation and thus less binding sites for exogenous opioids. Despite this, up to 30% of patients with FM are still treated with opioids[73], a rate similar to that of osteoarthritis[79].

Even though the limitations of retrospective studies in assessing causal relationships is well known, there is consistent evidence that female sex, preoperative opioid use, anxiety, depression, and sleep disturbances are predictors of postoperative opioid use in patients undergoing orthopaedic surgery. All these factors, in turn, characterise the complex clinical phenotype of FM and therefore it is possible to speculate that the association may rely on the synergy between all those risk factors marking the “fibromyalgianess” of the patients. Alternatively, it is possible to hypothesize that, given the fact that no information is available about the specific reason for prescription, opioids may have been prescribed for background FM symptoms and not for surgery-related pain. Finally, it must also be pointed out that prescription and dispending opioids does not automatically imply active consumption especially in the setting of FM where poor adherence to treatment plan is reported in more than half of the patients[80, 81].

Finally, five studies have demonstrated that FM is associated with higher risk of medical and surgical complications. Although a causal relationship cannot be ascertained on the basis of available data, some hypotheses can be drawn. It is known that depression[82, 83], opioid consumption[84] and postoperative pain[85] are associated with increased risk of surgical complications. Therefore, the association between FM and surgical complications may be mediated by a high prevalence of these conditions. Furthermore, FM patients tend to display an increased tendency to seek medical attention and healthcare resources utilization [86], and therefore, this may lead to higher rate of reporting and overestimation of minor complications. This behaviour may be even favoured by a temporary worsening of FM symptoms following the surgical stress or post-surgical immobilization. Regarding surgical complications, it is possible that an altered gait pattern in FM[87], coupled with an increased prevalence of obesity[88] may cause an accelerated deterioration of prosthetic components leading to wear, osteolysis and need for revision[89]. When looking at medical complications and in particular postoperative anaemia, it is possible that increased bleeding risk or reduced bone marrow response to blood loss may arise from concurrent pain medications such as non-steroidal antinflammatory drugs[90] or duloxetine[91]. Lastly, it has been demonstrated that FM is frequently associated with medical comorbidities such as gastrointestinal, respiratory and cardiometabolic diseases[92] that, in turn, may represent an additional preoperative risk factor for the development of post-surgical complications[93].

Our study provides a broad overview on the available evidence for a potential role of FM as a negative prognostic factor in orthopaedic surgery. Despite the potential impact on clinical practice, some limitations must be acknowledged. A significant proportion of the included studies were retrospective cohort studies, of moderate quality, based on data from large electronic medical records (EMR) databases. Although EMRs contain rich demographic and clinical information and have been used extensively in epidemiology and health service research, they are affected by some well-recognized intrinsic limitations[94]. In the specific case, the diagnosis of FM extrapolated from EMR has not be validated against clinical diagnosis and therefore it is not possible to ascertain its sensitivity and specificity, leading to a possible risk of misclassification bias. Moreover, other sources of bias may arise when dealing with retrospective data, affecting the generalizability of the results to the whole population of patients undergoing surgery. The inclusion of patients from specific insurance plans, in example, may be a source of selection bias. Information bias may rise in case of poor registration quality or due to variables that were not registered in advance. Finally, confounding bias may be expected because of the lack/paucity of information on some potential confounders (such as psychiatric comorbidity).

5. CONCLUSIONS

Despite the above-mentioned limitations, data retrieved from our systematic review represent a hypothesis-generating basis to further address this issue in longitudinal research. Despite surgery, and joint replacement in particular, is superior to conservative treatment in knee osteoarthritis[95], the risk/benefit ratio may be blunted in the cohort of FM patient. Although being burdened by a higher risk of poor outcome, surgery may still remain the better option and, theoretically, may remove the peripheral trigger for central sensitization so improving the generalized pain in some patients. Nevertheless, our results suggest that the potential benefit of surgery versus conservative treatment in this specific cohort needs further investigation. In conclusion, results from our systematic review suggest that identifying pre-existing FM in patients scheduled for orthopaedic surgery may help to better assess the benefit/risk ratio, provide realistic expectations, improve patients' awareness and minimize any discrepancy between expectancy and results.

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7. CRediT author statement

Martina D'Onghia: *Data curation, Investigation, Writing original draft;* Jacopo Ciaffi: *Data curation, Formal analysis, Investigation, Writing - original draft;* Joseph G. McVeigh: *Investigation, Writing – review & editing;* Cesare Faldini: *Investigation, Writing – review & editing;* Jacob N. Ablin: *Investigation, Writing – review & editing;* Riccardo Meliconi: *Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft;* Francesco Ursini: *Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft.*

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Figure 1.

PRISMA-compliant study selection flow chart.

Figure 2.

Funnel plot for assessment of publication bias in studies reporting the prevalence of fibromyalgia in patients undergoing orthopaedic surgery. Observed (blue) and imputed (red) studies are plotted.

Figure 3.

Forest plot for prevalence of fibromyalgia in patients undergoing orthopaedic surgery.