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MINIREVIEWS

Linkage of microbiota and osteoporosis: A mini literature review

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Abstract

The gut microbiota (GM) has become a recent topic of interest in the role of many disease states. Assessing patients with osteoporosis (OP), there is a strong correlation between gut microbe dysregulation and decreased bone density. Gut dysbiosis may lead to inflammation, dysregulation of nutrient and calcium transport across the intestine into circulation and systemic inflammation. Investigation of microbial profile relative to normal gut microbiomes, assessment of inflammatory markers such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha. Therapies to normalize GM in patients with OP or prevent occurrence of OP to be investigated include: High fiber prebiotic diets to promote growth of normal gut bacteria and short chain fatty acid production, *Probiotics* to encourage growth of normal gut microbes, and antibiotic treatment followed by fecal matter transplant.

Key words: Osteoporosis; Microbiota; Linkage; Bone density; Gut microbiota

Core tip: Assessing patients with osteoporosis (OP), there is a strong correlation between gut microbe dysregulation and decreased bone density. Gut dysbiosis may lead to inflammation, dysregulation of nutrient and calcium transport across the intestine into circulation and systemic inflammation. Therapies to normalize gut microbiota in patients with OP or prevent occurrence of OP to be investigated include: High fiber prebiotic diets to promote growth of normal gut bacteria and short chain fatty acid production, *Probiotics* to encourage growth of normal gut microbes, and antibiotic treatment followed by fecal matter transplant.

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GUT MICROBIOTA DYSREGULATION AND DECREASED BONE DENSITY

There exists a correlation between gut microbiota (GM) dysregulation and decreased bone density. Osteoporosis (OP) is a disease state: The loss of bone density and increased risk of bone fracture[1-3]. The most current United States data shows that 10.3% of adults in United States over 50 years of age had OP based on data collected from 2005-2010, affecting over 10 million adults with 43.9% of adults over 50 experiencing low bone mass[4]. There are two forms of OP: Primary, due to estrogen deficiency and natural aging and secondary, due to disease pathology[3,5-9]. Both forms of OP result from an imbalance of bone remodeling slated toward bone loss[1-3,5-9].

The flora of the human gastrointestinal tract has nearly one hundred trillion microbes[10,11]. For millions of years these organisms have symbiotically evolved to habituate the human gut: Converting much of what mankind consumes into nutrients that can cross the GI tract into circulation[11]. The contents of each person's gut varies; however, there are four main classes that are consistent in most normal GM: *Firmicutes*, *Bacteroides, Proteobacteria*, and *Actinobacteria*, with *Bacteroidetes* and *Firmicutes* comprising over 90% of the phylogenic categories[11-13]. The ratio of *Firmicutes* to *Bacteroidetes* GM is indicative of various dysregulation of biological processes[11-13].

Ratio of *Firmicutes/Bacteriodetes* negatively correlated with bone volume and levels of clostridia and lachnospiraceae. Abundance of *actinobacteria phylum* members: *Bifidobacteriaceae* were positively correlated with bone volume[11-13].

Osteomicrobiology: The role of microbiota in bone health may bridge the gap between bone physiology, gastroenterology, immunology, and microbiology. GM may lead to novel targets for OP and as biomarkers for future susceptibilities[7,10].

POSSIBLE MECHANISM OF GUT DYSBIOSIS LEADS TO OP

Microbiota: Normal function, dysbiosis and its role in calcium transport and inflammatory response

GM dysregulation is correlated with increased inflammatory response and bone resorption. Proposed mechanisms include impaired calcium transport, T cell response, systemic inflammation via cytokine activation: Osteoclast activation and bone resorption. Short-term colonization of germ-free mice with GM results in activation of CD4+ T cells, increased pro-inflammatory cytokines in bone and subsequent activation of Osteoclastic bone resorption[14]. Mice with normal GF demonstrated decreased frequency of CD4+ T cells and CD11b+/GR1 osteoclast precursors than those mice with dysbiosis[14]. GM is also involved in nutritional uptake and may thereby regulate overall body growth and bone sizes mediated by altered insulin-like growth factors-1 levels. Mechanism of bone degradation, in murine models, is inflammatory in nature and normalization of GM may lead to prevention or limitation of OP[14].

A diversity analysis of the GM in OP and osteopenia (ON) patients was conducted using 16s ribosomal RNA sequencing. There was an inverse correlation between diversity estimators and bone density. In OP, ON, and control groups the four dominant phyla included *Firmicutes, Bacteroidetes, Proteobacteria*, and *Actinobacteria*[11-13]. In OP samples *Firmicutes* were significantly increased and *Bacteroidetes* significantly decreased but were largest proportion in all groups. In the control group *Bacteroides*, *Faecalibacterium*, and *Prevotella* contributed more than half of the bacterial community, while in ON and OP groups five and 11 genera accounted for 50% of the bacterial community[15]. *Blautia, Parabacteroides*, and *Ruminococcaceae* genera differed significantly between OP and control group [15]. *Lachnoclostridium* and *Klebsiella* were more abundant in OP and ON than control[15]. The immune-inflammatory axis is hypothesized to be the mediator between GM and Bone metabolism.

Microbiota play an integral role in the transport and uptake of nutrients needed for bone growth and remodeling: Vitamin D[11,16,17]. Vitamin D stimulates intestinal calcium absorption, while 1,25-dihydroxyvitamin D_3 can regulate calcium homeostasis including calcium channel: TRPV6 and calbindin-D_{9K}, which mediates intracellular calcium diffusion[11,16]. Intestinal resistance of $1,25(OH)_2D_3$ and decreased calcium absorption increase in old age and are strongly correlated to gut dysbiosis[11,16,17]. Subsequently, dysbiosis can impact absorption of calcium and vitamin D contributing to OP.

Colonization of *Firmicutes* and increased biodiversity is associated with increased inflammatory response in gut. Increased inflammation is correlated with osteoclast activation at the site of the bones. Osteoclasts originate from monocytic precursors in

the bone marrow ($CD4^+/Gr1^-$)[18]. Osteoclasts carry out bone resorption and are regulated by several pathways including calcium and vitamin D, estrogen, and Inflammation[18]. Therefore gut-mediated inflammation, specifically markers: Tumor necrosis factor-α, interleukin-1 (IL-1), and IL-6 can play a role in osteoclast activation and if sustained OP[18].

How normalization of GM can decrease/prevent occurrence of OP and related disorders

Probiotics modify the microbiota composition, intestinal barrier function and immune system resulting in systemic benefits to the host: Bone health (growth, density, and structure) under conditions of dysbiosis, intestinal permeability, and inflammation[5,19,20]. *Probiotics* may be useful in postmenopausal OP[19]. Probiotic supplementation may prevent OP in healthy individuals and slow its progression in those with the disease based on testing in rodents[5]. In a rat study the probiotic (*Bacillus subtilis*) supplementation the number of osteoclasts decreased versus vehicle, while number of osteoblasts increased[21]. Additionally, *Probiotic Lactobacillus reuteri* supplementation mice studies, blocked type-1 diabetes-induced OP and postmenopausal OP: Mimicked by ovariectomized mice[22,23]. *Lactobacillis reuteri* supplementation suppressed increase in CD4+ T-Lymphocytes, and directly suppressed Osteoclastogenesis *in vitro*[23]. *Probiotics* supplemented with the isoflavone contributing red clover extract RCE, which has estrogen receptor affinity, have shown to decrease bone loss in postmenopausal osteopenic women supplemented with calcium, magnesium, and calcitriol[24]. This trial demonstrated potential benefit over hormone replacement therapy, which has increased risk of cancer[24]. Further benefits of *Probiotics* are related to intestinal permeability and inflammation, which mediates bone loss and OP)[18].

Prebiotics, non-digestible carbohydrate compounds, have also shown to increase calcium absorption in the lower gut of animals and humans and improve bone mineral density and strength in rodent models[24,25]. Non-digestible oligosaccharides have much potential to improve bone health and merit more investigation[25]. Most commonly accepted mechanism is microbial fermentation of prebiotics. This leads to increase in short-chain fatty acids and decrease in pH increasing bioavailability of calcium in the colon[24,26].

Antibiotics can vastly alter the composition of the GM. In a normal GM antibiotics used for other purposes may clear out normal flora and promote growth of resistant strains that may induce inflammation and associated symptoms[26]. Alternatively, antibiotic treatment and subsequent fecal microbiota transplants can be used to correct dysbiosis: Overgrowth of *Clostridioides difficile* and to promote growth of normal microbiota[27] (Table 1).

Short chain fatty acids such as acetate mediate anti-inflammatory conditions systemically[28,29]. These have demonstrated positive effects in preventing bone density loss and preventing OP progression in a rat model by directly feeding them to rats, which not only bolstered anti-inflammatory effects but also enabled normal GM to proliferate[25]. Exercise alters ratio of *Firmicutes/Bacteriodetes* and may be another venue of investigation into its effects on the GM and potentially as a preventative or therapeutic solution to OP[30,31].

In conclusion, the current literature shows that there may be a linkage between the GM and OP; subsequently, understanding the microbiota and how changes in diet and exercise can modify microbiota can prevent or improve OP disease pathology.

Table 1 Potential therapies of gut microbiota, proposed mechanisms of action, and subsequent immunological and metabolic effects

Proposed therapy	Mechanism of action	Effect on GM
Antibiotics supplemented by fecal transplant	Broad spectrum antibiotics clear out dysregulated GM Fecal transplant with *Bacteroides* and immunoprotective microbiota (*i.e.*, *Lactobacilli*) suppresses inflammatory response	Removal of inflammatory inducing bacteria species replaced with immunoprotective flora, normalizes GM and reduces inflammatory response
Prebiotic supplementation	Promote growth of bacterial species that induce fermentation of nondigestible carbohydrates, increases SCFAs, and decreases pH of GM and increases calcium absorption	Decreased pH promotes growth of bacteria less likely to induce inflammatory response, while SCFAs promote anti-inflammatory effects systemically Decreased pH and increased calcium absorption correlated with increased bone density
Probiotic supplementation	Supplementation by *Lactobacilli reuteri, Bacilis subtilis* and *Bacteroidetes* promote immunoprotective response in gut Reduced inflammatory response should reduce cytokine storm and active reduction in bone density	Supplementation of these bacteria to promote a normal GM, immunoprotective effects: IL-10

GM: Gut microbiota; SCFA: Short chain fatty acid; IL-1: Interleukin-1.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Short-term differences in anterior knee pain and clinical outcomes between rotating and fixed platform posterior stabilized total knee arthroplasty with a new femoral component design

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Abstract

AIM

To compare rotating versus fixed-bearing Press-Fit Condylar (PFC) Sigma posterior stabilized (PS) total knee arthroplasty (TKA) with the new "J curve" femoral design in terms of clinical outcomes and anterior knee pain.

METHODS

We retrospectively analyzed 39 patients who underwent primary total knee replacement surgery for knee osteoarthritis using the PFC Sigma PS TKA with either fixed (FP group, 20 cases) or rotating platform (RP group, 19 cases) treated between 2009 and 2013 by the same surgeon. The two groups were homogeneous for age, gender, weight, American Society of Anesthesiologists status, pre-operative clinical and functional scores, and prosthetic alignment at two years after surgery. We analyzed clinical outcomes score at two years follow-up using Knee Society Score (KSS), Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Performance Score, Short Form (SF) 36, and anterior knee pain assessed by the Hospital for Special Surgery (HSS) patellar score.

RESULTS

No differences were found in KSS, Knee Performance Score, and SF-36 outcome scores. A statistically significant difference was found in the HSS Patella score objective (FP: 22.36; RP: 28.75; $P < 0.05$), HSS Patella score total (FP: 73.68; RP:

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86.50; $P < 0.05$), and KOOS symptoms (FP: 73.49; RP: 86.44; $P < 0.05$).

CONCLUSION
Rotating platform in PFC Sigma PS TKA appears to reduce the short-term incidence of anterior knee pain compared to the fixed platform.

Key words: Total knee arthroplasty; Anterior knee pain; Rotating platform; Gonarthrosis; Fixed platform

Core tip: Rotating platform in Press-Fit Condylar Sigma posterior stabilized total knee arthroplasty reduces the short-term incidence of anterior knee pain compared to the fixed platform.

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INTRODUCTION

Total knee arthroplasty (TKA) has been shown to be a durable and successful treatment for end-stage arthritis of the knee[1]. Anterior knee pain is one of the major challenges after TKA and is one of the major causes of revision at five years follow-up[2-5]. The incidence of anterior knee pain after TKA is reported to be between 4 and 49%[6-10].

The causes of anterior knee pain are multifactorial, and can be functional (muscle imbalances, dynamic valgus[5]) or due to surgical and biomechanical aspects (patellofemoral compartment overstuffing[11], rotational alignment mistakes[12]). Additionally, the prosthetic design plays a role in the development of patellofemoral problems, primarily the design of the femoral component. Changes in the design of the femoral trochlear groove or in the femoral posterior condyle radius curvature have shown improvement in clinical outcomes. Femoral components with a posterior center of rotation have been shown to have a better outcome in terms of anterior knee pain[10]. This aspect has also been addressed in the design evolution of one of the most commonly used knee prosthesis.

The PFC-Sigma (DePuy Orthopaedics Inc., Warsaw, United States) TKA was introduced in 1996 as an improvement of the Press-Fit Condylar (PFC) implant (Johnson and Johnson, Raynham, Massachusetts, United States) and showed good mid-terms functional outcomes. Recently, some authors reported minor extensor mechanism complications following the use of this implant, such as patellar crepitation and patellar clunk syndrome, compared to other posterior stabilized (PS) models[13]. Because of these patellofemoral problems, the PFC-Sigma femoral component was re-designed, becoming available in 2009 under the name PFC Sigma PS available with a rotating platform and a fixed-bearing system. The principal modifications regarding the PS housing design included a "J curve" femoral design, a new femoral box, and smoother trochlear groove edges: these design changes provided better patellar tracking during range of motion (ROM)[14].

Is well known that geometry and kinematic patterns of different guided-motion prosthetic designs can affect the clinical-functional outcome in primary TKA[15]. Rotating platform TKA has numerous theoretical benefits, including the ability to self-align and accommodate small errors in component placement. If this is true, the improved patellar tracking might decrease the incidence of anterior knee pain[16].

Only a few studies[17,18] have investigated the clinical outcomes of the PFC-Sigma PS mobile-bearing versus fixed-bearing systems as a primary outcome measure. The short term clinical outcomes reported in the literature show different results depending on study design and prosthesis model[16,19-21]. This investigation aimed to compare the short term clinical and functional outcomes and the degree of anterior

knee pain of these two bearing types in PS TKA with a new femoral component design at two years follow-up. The hypothesis is that mobile-bearing TKA reduces anterior knee pain by improving patellar tracking.

MATERIALS AND METHODS

We considered only patients who underwent primary total knee replacement surgery for advanced degenerative knee OA, stage 3 or 4 of the Kellgren classification with limitation of daily activity, using the PFC Sigma PS TKA with either a fixed or rotating platform, treated between 2009 and 2013.

The inclusion criteria were: (1) correct prosthetic components alignment, as described by Cherian[22] (Table 1); (2) complete two years' follow-up scores and X-rays; and (3) surgery performed by the same surgeon. Exclusion criteria were: (1) inflammatory systemic disease (*e.g.*, rheumatoid arthritis); (2) impaired cognitive status; (3) body mass index > 40; and (4) conditions that could influence the clinical outcome (*e.g.*, contralateral lower limb amputation, important limitation and/or pain in other joints of the lower limbs, systemic inflammatory joint disease, patients with Charnley classification B or C[23]).

We performed in our hospital 506 TKA from 2009 to 2013 according to the previous criteria we excluded 264 patients that were implanted with different prothesis, 162 patients treated by a different surgeon and 41 patients for other reason listed in Figure 1.

Thirty-nine patients were eligible for the study criteria and we divided them in two groups: (1) DePuy Sigma Fixed Platform (FP): 20 patients; and (2) DePuy Sigma Rotating Platform (RP): 19 patients. For each patient, we retrospectively collected preoperative and postoperative data at 2 year follow-up.

The preoperative data were: demographic data, American Society of Anesthesiologists (ASA) score, functional status using the Knee Society score, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Performance Score, Short Form (36) Health Survey (SF-36), and Hospital for Special Surgery (HSS) Patellar Score.

The preoperative data were obtained during the outpatient assessment that is planned 2 wk before surgery.

At 2 years follow-up, we collected: X-ray exams (anteroposterior and lateral weight-bearing knee views, weight-bearing full length radiographs of the lower limbs, and a "Skyline" view), clinical and functional scores (subjective scores: KOOS[24] and SF-36[25]; objective scores: HSS Patella Score[26], Knee Performance Score[27], and Knee score[28]).

On the X-ray exams, we measured the anatomical axis and mechanical axis of the lower limb, the anatomic coronal and sagittal alignment of the femoral and tibial component, the angle of flexion of the femoral component with respect to the anterior cortex, and the alpha and gamma patellar angles with respect to the femoral component (Table 1)[22].

In our Hospital post-operative scores and X-rays are always requested in all the follow up outpatient visits after a TKA.

Pre-operative and follow up data were collected in 2016 retrospectively analyzing the outpatient visits.

The two groups were homogeneous for age, gender, weight, ASA status, pre-operative clinical and functional scores, and prosthetic alignment two years after surgery (Tables 1-3).

The study protocol was approved by the local research ethic committee and all procedure was in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Statistical analysis

Statistical analysis was performed using SPSS Version 16.0 software (SPSS Inc., Chicago, IL, United States). The chi-square test and the Fisher's exact test were used to evaluate categorical data, in particular, the evaluation of gender and ASA score. We verified the normality of the data of each group with the Shapiro-Wilk test. The Student *T*-test was used to compare results with a normal distribution, and the Mann-Whitney test was used to evaluate groups without a normal distribution. For all statistical analysis, the significance threshold was set at a *P*-value of less than 0.05. A statistical review of the study was performed by a Biomedical Statistician.

Surgical procedure

The surgery was performed by the same surgeon (GZ), fellowship-trained in Joint Replacement Surgery. Every procedure was performed with spinal anesthesia. A first-generation cephalosporin (Cefamezin®, Pfizer, New York City, United States) was

Table 1 Radiographic alignment at two years

Radiographic alignment at two years, mean (SD)	FP	RP	*P* value
Anatomical axis	174.7° (1.69°)	175.30° (2.32°)	0.428
Mechanical axis	179.49° (2.47°)	181.10° (2.41°)	0.838
Anatomic lateral distal femoral angle (aLDFA)	86.60° (3.5°)	85.70° (2.74°)	0.960
Medial proximal tibial-angle (MPTA)	89.84° (2.81°)	90.31° (1.37°)	0.084
Posterior femoral-prosthetic angle	90.3° (2.97°)	88.51° (2.89°)	0.753
Posterior tibial-prosthetic angle	88.9° (1.9°)	89.07° (2.12°)	0.790
Anterior femoral-prosthetic angle	8.2° (3.02°)	6.42° (2.11°)	0.262
Patellar tilt angle alpha	25.64° (7.87°)	26.81° (4.84°)	0.407
Patellar tilt angle gamma	1.32° (3.3°)	1.87° (3.5°)	0.805

FP: Fixed platform; RP: Rotating platform.

used as short-term antibiotic prophylaxis, administered 30 min preoperatively and 8 h and 16 h postoperatively, according to our institutional protocol. A tourniquet was applied before skin incision and deflated after the cemented component placement. A standard medial parapatellar approach was used, and the cruciate ligaments were removed. Distal femoral resection was done first using an intramedullary alignment guide, and then the proximal tibial resection was done with an extramedullary guide. The extension gap was then evaluated with spacer block and balanced if needed. The femoral component was externally rotated by 3°, using the posterior condyle line as a reference. Then, with the four in one cutting block in place, the flexion gap at 90° was checked using a spacer block 2 mm thinner than the extension spacer block to compensate for the thickness of the cutting block. If the extension and flexion gap were balanced, the remaining femoral cuts were performed. If the two gap were unbalanced, the flowchart described by Bottros[29] was used to balance them. The trial components were then positioned and limb alignment, range of movement, and the flexion-extension gaps were checked. The rotational alignment of the tibial component was determined using either the third part of the anterior tibial tuberosity or the dynamic flexion-extension alignment.

All patients were implanted with cemented PFC Sigma PS (DePuy Orthopaedics Inc., Warsaw, United States). The new design features included a "J curve" femoral design, three different tangential radius curves in the sagittal profile, and an increased radius in transition from anterior flange to the box to enhance patella tracking during flexion while reducing the risk of soft tissue impingement and associated patella crepitus. The blending radii around the medial and lateral edges of the femur have been increased to provide a smoother transition to reduce the risk of soft tissue impingement.

Fixed bearings with oxidatively stable cross-linked polyethylene were implanted until May 2010 and mobile bearings with super polished GVF until 2013.

The patellae were treated by denervation and patelloplasty without replacement in all patients.

A standard TKA rehabilitation protocol was performed. On the second post-operative day, physical therapy and continuous passive motion were started in all patients. After approximately 5 d in the hospital, patients were followed in a rehabilitation service for 3 wk.

RESULTS

The clinical and functional evaluation with scores 24 months after surgery demonstrated the following results (Table 4).

The average SF-36 score was 75.94 (SD: ±17.27; range: 35.87-93.75) in the FP group and 65.1 (SD: ±22.4; range 19.50-95.5) in the RP group, in favour of the FP group. Knee Performance Score in the FP group was 80.26 (SD: ±14.85; range: 45-100) and 74.75 (SD: ±10.52; range 15-100) in the RP group, in favour of the FP group. Knee Score in the FP group was 83.94 (SD: ±12.35; range: 47-100) and 87.52 (SD: ±10.08; range: 67-100) in the RP group, in favour of the RP group. Considering these scores, we did not identify a statistically significant difference between groups.

Analyzing the KOOS total score, there was no statistically significant differences between groups, but evaluation of subsections of the score demonstrated differences.

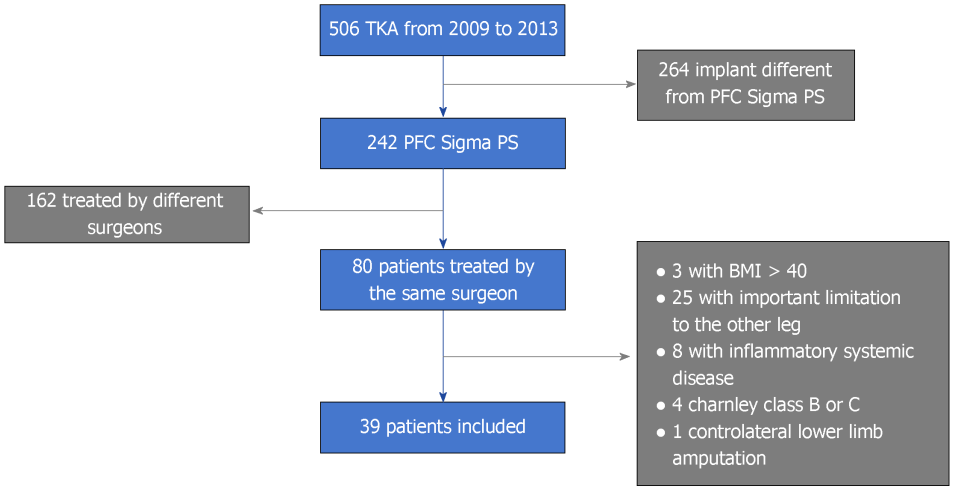

Figure 1 Patients selection. TKA: Total knee arthroplasty; PFC: Press-Fit Condylar; PS: Posterior stabilized; BMI: Body mass index.

A statistically significant difference was found in the KOOS symptoms subsection, with a mean score of 73.49 (SD: ±17.63; range 32.14-96.93) in the FP group and 86.44 (SD: ±8.39; range 67.86-100) in the RP group ($P < 0.05$), in favour of the RP.

We found a statistically significant difference in the HSS Patella total score; values were 73.68 (SD: ±16.73; range 35-95) in the FP group and 86.50 (SD: ±12.98; range 50-100) and in the RP group ($P < 0.05$) in favour of the RP group. For the HSS Patella score objective subsection, values were 22.36 (SD: ±6.74; range 15-35) in the FP group and 28.75 (SD: ±6.66; range 10-35) in the RP group ($P < 0.05$), in favour of the RP group.

We didn't found any major complication like infection, mobilization, patella dislocation or instability.

Minor complication were reported in two patients; they both developed a delayed wound healing, no surgical revision was necessary.

These two patients were heavy smoker, wound healing was achieved respectively in 4 and 6 week with weakly advanced dressing.

DISCUSSION

Mobile-bearing designs were introduced in TKA to decrease polyethylene wear by increasing the conformity of the implant in sagittal and coronal planes, without restricting the rotational freedom of the bearing. Several studied have confirmed that, in comparison to fixed-bearing designs, mobile-bearing designs result not only in decreased polyethylene wear, but also lower grade and more symmetrical wear[30-34]. Other advantage of mobile bearings were postulated, including more physiological knee kinematics and a facilitation of central patellar tracking by self-alignment[35,36].

In an intra-operative kinematic study, Sawaguchi *et al*[37] demonstrated that there was significantly improved patellar tracking with decreased patellofemoral contact stresses, because the rotating platform design, through bearing rotation, permits self-correction of component rotational mal-alignment, allowing better centralization of the extensor mechanism. This process of self-alignment might be expected to improve patellar tracking and reduce anterior knee pain, one of the major short term complaints after TKA[2-6]. The rotating platform also permits adaptation to inferior limb rotational defects, improving patello-femoral contact stresses[38].

Several studies have analyzed knee kinematics, functional outcome, and long-term survivorship of the rotating platform versus fixed platform as the primary outcome measure[39-41]. Symptoms were usually considered as secondary measures in rotating platform studies, because this component was primarily thought to increase survivorship of the implant thanks to increased implant conformity and contact area with reduced stress transmitted to the fixation interface and a lower and more symmetrical wear rate.

Recent meta-analyses[40,41] did not identify a clinical difference between mobile-bearing and fixed-bearing systems. Although a meta-analysis is advantageous compared to primary-source studies in terms of increased statistical power, it can be substantially affected by the weaknesses and heterogeneity of original studies (different implant models, different surgeons, different clinical scores). For example,

Table 2 Demographic data

Variable	FP	RP	*P* value
Age; yr, mean (SD)	71.89 (9.8)	71.70 (7.84)	0.94
Gender (% males); (M-F)	45%; (9-11)	36.8%; (7-12)	0.43
Weight; kg, mean (SD)	78.36 (10.71)	76.05 (14.32)	0.57
Pre-operative; ASA score	ASA 1: 0 (0%); ASA 2: 15 (75%); ASA 3: 5 (15%)	ASA 1: 2 (10.5%); ASA 2: 12 (63.1%); ASA 3: 5 (26.3%)	0.85

FP: Fixed platform; RP: Rotating platform; ASA: American Society of Anesthesiologists.

not all mobile-bearings designs are the same and, often, different types of mobile-bearing system were grouped together for comparison against fixed-bearing implants.

Breugem *et al*[16], in a prospective double-blind study, found less anterior knee pain with PS mobile-bearing prosthesis compared to fixed-bearing systems of the same model with a 1 year follow-up and no difference in anterior knee pain after 7.9 years in the same group[7]. The patients included in the study were treated by three different fellowship-trained surgeons and clinical evaluation was made by four orthopedic surgeons. Kim *et al*[21] found better short terms clinical outcomes (2 years follow-up) in patients with the PFC Sigma DePuy rotating platform implant compared to the fixed platform of the same model.

The specific strengths of the current study are that all patients were treated by the same fellowship-trained surgeon with the same prosthesis model and the clinical valuation was made by the same orthopedic surgeon on a strongly selected population homogeneous for age, gender, pre-operative clinical status, comorbidities, and optimal prosthesis positioning.

We also recognize limitations of our study. First, this is a limited sample study, which could lead to a lack of power to detect clinically important differences. Second, this is a retrospective study with the relative disadvantage compared to a prospective one. We recommend more structured studies with a larger number of patients to support our results.

We found a significant difference in the HSS patella objective score in favor of the RP group, mainly due to the tenderness during palpation of the patella facet section. This result could reflect the reduction of stress forces on the patella and retinaculum ligament with the mobile-bearing prosthesis. A difference in KOOS symptoms in favor of the mobile-bearing system was also observed. This outcome investigates symptoms such as clicking, grinding, or stiffness during the ROM that are frequently report in patients with anterior knee pain. In this series, patients treated with the PFC Sigma PS TKA rotating platform showed better clinical outcomes compared with patients treated with the fixed system, with two years of follow-up. We choose this timing of follow-up to avoid any influence on the clinical outcome such as operative pain and psychological and functional limitation due to the rehabilitation period.

In conclusion, our data support the concept that the rotating platform prosthesis reduces the short-term incidence of anterior knee pain compared to the fixed platform system of the PFC Sigma PS TKA with "J curve" femoral design. Longer follow-up will determine whether this difference will persist or decrease.

Table 3 Pre-operative scores

Scores before surgery, mean (SD)	FP	RP	*P* value
SF-36	66.63 (15.10)	58.41 (20.30)	> 0.05
KOOS	51.2 (3.78)	50.95 (4.07)	> 0.05
HSS Patella Score	53.15 (12.71)	58.75 (7.04)	> 0.05
Knee Performance Score	48.68 (10.52)	50.75 (22.43)	> 0.05
Knee Score	65.92 (9.44)	69.77 (8.73)	> 0.05

FP: Fixed platform; RP: Rotating platform.

Table 4 Post-operative scores

Scores two yr after surgery, mean (SD)	FP	RP	*P* value
SF-36	75.94 (17.27)	65.10 (22.40)	> 0.05
KOOS symptoms	73.49 (17.63)	86.44 (8.39)	< 0.05
HSS Patella Score; HSS Patella Score objective	73.68 (16.73); 22.36 (6.74)	86.50 (12.98); 28.75 (6.66)	< 0.05; < 0.05
Knee Performance Score	80.26 (14.85)	74.75 (10.52)	> 0.05
Knee Score	83.94 (12.35)	87.52 (10.08)	> 0.05

FP: Fixed platform; RP: Rotating platform; HSS: Hospital for Special Surgery; KOOS: Knee Injury and Osteoarthritis Outcome Score.

ARTICLE HIGHLIGHTS

Research background

Anterior knee pain is one of the most common complications after total knee arthroplasty (TKA). Several aspects can cause this problem included muscle imbalances, dynamic valgus, patellofemoral compartment overstuffing, rotational alignment mistakes and prosthetic design.

In 2009 Press-Fit Condylar (PFC) Sigma femoral component was re-designed in order to improve patellar tracking and reduce anterior knee pain.

This new knee prothesis was available with rotating or fixed platform under the name of PFC Sigma posterior stabilized (PS).

Research motivation

Only a few studies have analyzed clinical results of this new prothesis as primary outcome.

Research objectives

The aim to this study is to compare rotating versus fixed-bearing PFC Sigma PS with the new "J curve" femoral design in terms of clinical outcomes and anterior knee pain with two years of follow up.

Research methods

Retrospective study with 39 patients underwent primary TKA with PFC Sigma PS TKA.

We analyzed clinical outcomes two years after surgery with Knee Society Score Knee Society score, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Performance Score, Short Form Health Survey (SF-36), and Hospital for Special Surgery (HSS) Patellar Score.

Research results

We found better clinical results (HSS Patellar score and KOOS) in PFC Sigma PS rotating platform compared to fixed platform.

Research conclusions

PFC Sigma PS rotating platform reduce the short term incidence of anterior knee pain compared to the fixed platform model and improve clinical outcomes.

Research perspectives

Long term follow up studies will be useful to understand if this difference will be unchanged over time.

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ORIGINAL ARTICLE

Retrospective Study

Comparison of implant related complications amongst patients with opioid use disorder and non-users following total knee arthroplasty

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Abstract

BACKGROUND

The influence of opioid use disorder on implant related complications, infection and readmission rates, and total global episode-of-care costs following primary total knee arthroplasty (TKA) is limited.

AIM

To examine whether opioid abuse in patients undergoing primary TKA.

METHODS

A retrospective analysis of the Medicare dataset, using the PearlDiver database, from 2005-2014 comparing outcomes in patients with opioid abusers (OUD) to non-opioid abusers (NOU) undergoing primary TKA was performed. Patient outcomes were analyzed including implant complications, readmission rates, and day-of-surgery and 90-d cost. Statistical analysis was performed with R (University of Auckland, New Zealand) calculating odds-ratio (OR) along with their respective 95% confidence interval (95%CI) and *P*-values.

RESULTS

The OUD group was at greater odds of having implant related complications overall (20.84% *vs* 11.25%; OR: 2.07; 95%CI: 1.93-2.23; $P < 0.001$). Revision (OR: 2.07; 95%CI: 1.11-3.84; $P < 0.001$), infection (OR: 1.92; 95%CI: 1.72–2.18; $P < 0.001$), periprosthetic fractures (OR: 1.83; 95%CI: 1.16-4.79; $P < 0.001$), and 90-d

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readmission rates (OR: 1.47, 95%CI: 1.35-1.61, $P < 0.001$) were also significantly increased. OUD patients also incurred in higher day-of-surgery and total global 90-d episode-of-care costs compared to NOU.

CONCLUSION
Patients with OUD show an increased risk of complications compared to the non-opioid users group. Appropriate recognition, pre-surgical optimization, and patient education are essential to mitigate these complications and improve patient outcome.

Key words: Opioid use; Total knee arthroplasty; Medicare; Database; Cost; Readmission rates

Core tip: A retrospective analysis of the Medicare database demonstrated that patients with opioid dependence or abuse diagnosis had higher rates of implant related complications, 90-d readmission rates, and cost of care in patients undergoing primary total knee arthroplasty.

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INTRODUCTION

Patients with osteoarthritis of the knee can manifest with symptoms such as pain and reduced range of motion, negatively impacting the patient's quality of life[1]. Total knee arthroplasty (TKA) is the treatments of choice when conservative therapy has failed for patients suffering from osteoarthritis of the knee[2,3]. Recent studies have shown that there has been an increase in the number of TKA procedures performed in the United States and is expected to grow exponentially[4]. Minimizing postoperative complications and improving patient-reported outcome measurements (PROMs) is important for patients undergoing these procedures[5]. Preoperative optimization, by identifying risk factors associated with adverse events and worse clinical outcomes, has been shown to directly impact postoperative complications and PROMs[6-9].

Currently, Orthopedic Surgeons are the third highest prescriber of opioids following Internists and Dentists[10,11]. Morris *et al*[11] and Dufour *et al*[12] have illustrated an increasing trend in the number of opioids prescribed by providers and the incidence of opioid abuse or dependency diagnosis in the community. Blazer and Wu[13] reported that 1.4% of adults above the age of 50 consume opioids for recreational use. This finding was greater than the use of sedatives, tranquilizers, and stimulants, all of which were less than 1%[13]. In addition to providing an analgesic affect, opioids are known to directly impact endocrine, immune, gastrointestinal and musculoskeletal systems[14]. The influence of opioid use disorder on implant related complications, infection and readmission rates, and total global episode-of-care costs following primary TKA is limited.

The aim of the study was to analyze and compare rates of implant complications, 90-d infection rates, 90-d readmission rates, and hospitalization cost among opioid abusers (OUD) and non-opioid abusers (NOU) undergoing primary TKA. We hypothesize that following primary TKA, opioid abuse and dependency is associated with higher implant complications, infections, 90-d readmissions rates and higher episode-of-care costs compared to NOU.

MATERIALS AND METHODS

A retrospective review of the Medicare patient population from 2005–2014 within the PearlDiver (Pearl Diver Technologies, Fort Wayne, IN) claims based database was

performed. PearlDiver is a commercially available database which has been used extensively for orthopedic-related research. The database is compliant with the Health Insurance Portability and Affordability Act and holds the records of over 100 million patients. The database provides information on diagnosis, procedures, complications, and additional information such as demographics, region, discharge library, and length of stay (LOS).

Patients who underwent TKA were identified using International Classification of Disease, ninth revision (ICD-9) procedure code 81.54. Patients with a history of opioid use disorder and dependency were identified with ICD-9 diagnosis code 304.00-304.02 and 305.50-305.52. The inclusion criteria for the study group consisted of all patients in the database undergoing TKA and having a 90-d history and diagnosis of OUD on the same day of their index procedures. The control group consisted of all patients who underwent TKA and had no history of opioid abuse or dependency. Patients in the study group were randomly matched 1:1 to patients in the control group with respect to age, gender, and Elixhauser-Comorbidity Index (ECI). ECI was used as a marker to ensure that patients in the study group and control group were matched appropriately, as used in previous studies[15,16]. The authors decided to use ECI compared to the traditional Charlson-Comorbidity Index (CCI) as ECI as it includes 31 conditions, and demonstrates better predictions of mortality in patients with cardiac, pulmonary gastrointestinal, nephrology, hepatobiliary, and oncologic conditions[17]. Additionally, ECI also contains comorbidities such as hypertension, obesity, psychiatric disorders that are not found in CCI[18]. After the matching process two mutually exclusive cohorts were formed.

Implant related complications 2-years following the index procedure were analyzed and compared. ICD-9 coding was also used to determine implant and infection related complications (Table 1). Reimbursements were used as a marker for cost, as used in previous studies[16,19-21]. Ninety-days was chosen for infection related complications and readmission rates to be in accordance with the Comprehensive Care for Joint Replacement model design, stating that episode of care begins day of admission and ends 90-d following discharge[19,20].

Statistical analysis

Descriptive and statistical analysis was performed with the programming language R (University of Auckland, New Zealand) analyzing odds-ratios (OR) with their respective 95% confidence interval (95%CI), and *P*-value. Welch's t-test was utilized to determine significance in reimbursement rates between the two cohorts. An alpha value less than 0.05 was considered statistically significant.

RESULTS

After appropriately matching the study group with the control group, there were 23072 (female = 15616; males = 7230; unknown = 226) OUD (n = 11536) and NOU (n = 11536) to have undergone TKA (Table 2). Patients in the study group and control group undergoing primary TKA had an average ECI of 11.93 ± 4.31 (P = 1.00) indicated the two groups were matched appropriately and no statistical difference exists between the two groups.

Implant complications and LOS

OUD patients were found to have greater odds of implant related complications (20.84% *vs* 11.25%; OR: 2.07; 95%CI: 1.93-2.23; P < 0.001) compared to NOU within 2-years following the index procedure. Complications such as requiring a revision procedure (OR: 2.07, 95%CI: 1.11-3.84, P < 0.001), periprosthetic fracture (OR: 1.83, 95%CI: 1.16-4.479, P < 0.001), dislocation of prosthetic joint (OR: 1.68, 95%CI: 1.37-2.05, P < 0.001), and mechanical loosening (OR: 1.33, 95%CI: 1.08-1.62, P < 0.001) were greater in the OUD group compared to NOU (Table 3). Odds of developing infections within 90-d were also higher in the OUD group (OR: 1.92; 95%CI: 1.70-2.18; P < 0.001) compared to controls (Table 3). In-hospital LOS was greater in OUD (3.44 d *vs* 3.32 d; P < 0.001) compared to NOU following primary TKA.

Readmission rates and reimbursements

Readmission rates within 90 d of primary TKA were higher in OUD compared to NOU (OR: 1.47, 95%CI: 1.35-1.61, P < 0.001). Cost analysis revealed that day-of-surgery reimbursements ($14499.39 *vs* $14247.74; P < 0.001) were higher for OUD undergoing TKA compared to controls. Similarly, total global 90-d episode of care reimbursements were also higher ($18619.98 *vs* $16885.21; P < 0.001) in OUD compared to the NOU group (Table 4).

Table 1 List of ICD-9 procedure and complication codes used

ICD-9 code	Procedure and/or complication
81.54	Total knee arthroplasty
81.55; 00.80-00.84	Total knee arthroplasty revision
305.50-305.52	Opioid abuse
304.00-304.02	Opioid dependency
996.41	Mechanical loosening of prosthetic joint
996.42	Dislocation of prosthetic joint
996.43	Broken prosthetic joint implant
996.44	Peri-prosthetic fracture around prosthetic joint
996.47	Other mechanical complication of prosthetic joint implant
996.49	Other mechanical complication of other internal orthopedic device, implant, and graft
996.77	Other complications due to internal joint prosthesis
730, 996.66, 996.67, 996.69, 998.13, 998.30–998.32, 998.51, 998.59	Infection and wound

DISCUSSION

Recent studies show an alarming increase in the overall rates of opioid abuse, misuse, and dependence in the United Sates-collectively termed: Opioid Use Disorder. Meanwhile, orthopaedic surgeons were found to be the third highest prescribers of opioid prescriptions amongst all providers[20-23]. These statistics place a significant number of our orthopaedic patients at risk of the detrimental effects of narcotics and potential for abuse. In the arthroplasty patient population, there remains limited evidence in the literature linking opioid abuse to post-operative complications and implant survivorship following primary THA and TKA. Our study demonstrates that patients with opioid use disorder are at a significantly higher risk for having short-term implant related complications and failure such as periprosthetic fractures, along with increased risk of infections within 90 d of their primary procedure, longer lengths of stay, and greater odds for readmission within the first 90 d, all resulting in higher episode of care costs.

Similar to our results, Sing *et al*[24] found that 5.1% of their patients taking short-acting opioids and long-acting opioids prior to surgery subsequently went on to develop periprosthetic fractures following total hip and TKA, compared to 1.7% who were not taking opioids. Out of this population, 14.2% of patients required revision surgery. In their study, they found short and long-acting opioids to have a 4.42 and 6.15 times greater odds of developing postoperative complications following TKA, respectively[24]. Saunders *et al*[25] found similar results in elderly patients consuming opioids, where higher doses of opioids (> 50 mg/d) were associated with 2.00 increase risk of fractures.

Long term opiate use has shown to have negative effects on cognition and motor function as demonstrated by Kerr *et al*[26] who demonstrated that infusion of morphine to normal concentrations led to significant cognitive and motor impairments. The study found that the processing time of verbal instructions and ability to maintain force were increased and decreased, respectively[26]. Opioid use has shown to lead to development of dizziness and sedation affecting balance and proprioception, all leading to an increased risk for falls and therefore fractures[14]. Studies have shown that opioids impact the immune system negatively[27]. Animal studies demonstrate that opioids impair both adaptive and innate immunity, and increases susceptibility to many pathogens[27,28]. Furthermore, opioids increase production of corticosteroid production, amplifying the inflammatory state with proinflammatory cytokines[28,29]. The effects of diminished bone mineralization, increased susceptibility to falls, alterations within the immune system may explain the increased rate of periprosthetic fractures, dislocation, mechanical loosening, prosthetic joint infections, and ultimately TKA revisions in the OUD group[14,26].

This study also showed that readmission rates 90-d following surgery was also significantly higher in the OUD group. The findings were consistent with an investigation by Mosher *et al*[30], where readmission rates where compared in occasional users, OUD, and non-abusers. OUD had greater 30-d readmission rates compared to non-abusers[30]. Our data is consistent with the findings in current literature. In addition, a large database study performed by Menendez *et al*[31] found patients with a history of opioid abuse and dependency undergoing elective orthopedic surgery had greater odds of prolonged hospitalization stays (OR: 2.5,

Table 2 Demographics of patient age and gender undergoing total knee arthroplasty after matching process

Demographics	No. of patients
Age	
64 and under	16102
65–69	3616
70–74	1756
75–79	902
80–84	358
85 and over	112
Unknown	226
Gender	
Female	15616
Male	7230
Unknown	226

95%CI: 2.4–2.5). Oderda *et al*[32] quantitatively found the average LOS in OUD and dependency increased by 10.3% (95%CI: 6.5–14.2, $P < 0.001$) compared to patients without a history of opioid abuse or dependency. Azar *et al*[33] found the average increase in LOS and amongst OUD undergoing primary orthopedic procedures was 0.52 d. In our study, patients in the study group had an average LOS of 12 d longer when undergoing primary TKA.

Improving patient outcome while reducing cost has been the main focus of the value-based care initiatives put forth by Center for Medicare and Medicaid Services. Our study, however, showed that the increased complication rate associated with opioid abuse translates into poorer patient outcome and increased cost of care. For example, the OUD group was found to have significantly higher day-of-surgery costs following primary TKA when compared to the control group. One study found that the approximate increase in costs for patients with a diagnosis of OUD was approximately 6% higher and another study calculated an increase of $861.50[34,35]. Meyer *et al*[35] reported that OUD with private insurance had an average cost of care of $24193 in direct healthcare costs, in contrast to NOU who incurred only $3647 in healthcare costs. When comparing healthcare costs of OUD within the Medicaid provider, OUD incurred approximately $26724 in costs, compared to $11541 for patients in the matched control group.

While the study has its advantages of including a large sample size, database studies are not without limitations. Being a database analysis study, the validity of our analysis and results are reliant on accuracy of procedural coding within the database[36]. This translates to the fact that miscoding and noncoding by providers is a potential source of error. Currently, it is expected that 1.3% of coding errors are present within the Medicare population[37]. Secondly, only a single insurer's data was included in our analysis, and may not represent a true cross section of the OUD group in the United States[37]. Additionally, the prevalence of comorbid conditions and adverse events may be underreported[36]. A selection bias may also be present as patients in the study may enter or exit the database as a natural manifestation[36].

In conclusion, the study demonstrates that patients with opioid use disorder undergoing primary TKA are at a greater risk for implant complications such as revision, infections, and periprosthetic fractures. They were also found to have a higher 90-d readmission rates, and incur in higher episode of care costs. The results of this study may improve a providers' ability to preoperatively counsel patients regarding specific adverse events associated with opiate abuse and TKA and highlights the need to reduce narcotic prescriptions to our patients.

Table 3 Comparison of implant related complications 2-years following primary total knee arthroplasty in opioid abusers and non-opioid abusers

	OUD	NOU	OR	95%CI	*P*-value
Revision of knee replacement total (all components)	0.42%	0.20%	2.07	1.11–3.84	b
Infection and wound[1]	6.55%	3.51%	1.92	1.70–2.18	b
Peri-prosthetic fracture around prosthesis	0.72%	0.39%	1.83	1.16–4.79	b
Dislocation of prosthetic joint	2.27%	1.36%	1.68	1.37–2.05	b
Mechanical loosening	1.93%	1.46%	1.33	1.08–1.62	0.006
Broken prosthetic joint implant	0.67%	0.60%	1.11	0.81–1.54	0.509
Other complication due to other internal orthopedic device implant	2.77%	0.99%	2.83	2.28–3.51	b
Other mechanical complication of other internal orthopedic device	3.05%	1.33%	2.33	1.92–2.82	b
Other mechanical complication of prosthetic joint implant	2.46%	1.41%	1.76	1.45–2.13	b
Total	20.84%	11.25%	2.07	1.93–2.23	b

[b]$P < 0.001$;
[1]Assessed within 90 d. OUD: Opioid abusers; NUD: Non-opioid abusers; OR: Odds-ratio; 95%CI: 95% Confidence interval.

Table 4 Comparison of day of surgery and total global 90-d episode of care reimbursement amongst opioid abusers and non-opioid abusers undergoing primary total knee arthroplasty within the medicare population

	OUD	NOU	
	Day of surgery		*P*-value
Average reimbursement (SD)	$14499.39 ($10121.95)	$14247.74 ($8827.31)	< 0.001
	90 d cost		*P*-value
Average reimbursement (SD)	$18619.98 ($14718.50)	$16885.21 ($12184.91)	< 0.001

SD: Standard deviation; OUD: Opioid abusers; NUD: Non-opioid abusers.

ARTICLE HIGHLIGHTS

Research background

Opioid use has been shown to be effective method of analgesia following orthopedic surgery, and as a result, the prescribing rates of opioids have increased. Currently, orthopedic surgeons are the third highest prescribers of opioids following internists and dentists. The literature demonstrates that opioids are known to interfere with endogenous synthesis of testosterone and estrogen, which are vital for proper bone mineralization; in addition to other complications. There is no study to our knowledge which has analyzed the effects of opioid abuse and dependency on implant related complications in patients undergoing primary total knee arthroplasty (TKA).

Research motivation

As the number of prescriptions and abuse potential is increasing within the United States, its impact in orthopedics should be well understood. The study addresses the question on the implant related complications orthopedic surgeons may encounter in patients who have a history of opioid abuse and dependency following primary TKA. The study will allow for further studies on how to properly optimize opioid abusers prior to undergoing surgery.

Research objectives

The authors of this study wanted to determine the impact opioid abuse and dependency on implant related complications in patients undergoing primary TKA in patients greater than the age of 65.

Research methods

Patients who underwent primary TKA with a history of opioid abuse and dependency were identified from the Medicare claims database and were randomly matched 1:1 to a control group. Two-year implant related complications were analyzed and compared, along with 90-d reimbursement rates, along with day of surgery and total global 90-d episode of care costs.

Research results

The study found that patients who with a history of opioid abuse and dependency were at greater odds of developing implant related complications compared to controls. Implant related complications which were higher in the study group consisted of: requiring a revision

procedure, periprosthetic fractures, prosthetic joint infection, mechanical loosening, in addition to others. Similarly, 90-d readmission rates along with day of surgery and total global 90-d episode of care costs were higher in patients with a history of opioid abuse and dependency compared to controls.

Research conclusions

The findings of the study demonstrate that opioid abuse and dependency increase the odds of developing implant related complications, 90-d readmission rates, and cost within patients who are undergoing primary TKA. These findings further confirm the hypothesis that patients with a history of opioid abuse or dependency would have greater complications following surgery compared to controls. The results of the study should warrant further studies on how to offset the detrimental effects of opioid abuse on bone mineralization.

Research perspectives

Patients with a history of opioid abuse or dependency are at a significantly greater risk of implant related complications, 90-d readmission rates, and cost following primary TKA. Further research should be warranted at identifying these patients prior to surgery and adequately optimizing them prior to surgery.

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SYSTEMATIC REVIEW

Aetiology of Legg-Calvé-Perthes disease: A systematic review

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Abstract

BACKGROUND

Legg-Calvé-Perthes disease (LCPD) is a clinical condition affecting the femoral head of children during their growth. Its prevalence is set to be between 0.4/100000 to 29.0/100000 children less than 15 years of age with a peak of incidence in children aged from 4 years to 8 years. LCPD aetiology has been widely studied, but it is still poorly understood.

AIM

To analyse the available literature to document the up-to-date evidence on LCPD aetiology.

METHODS

A systematic review of the literature was performed regarding LCPD aetiology, using the following inclusion criteria: studies of any level of evidence, reporting clinical or preclinical results and dealing with the aetiology or pathogenesis of LCPD. Two reviewers searched the PubMed and Science Direct databases from their date of inception to the 20th of May 2018 in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. To achieve the maximum sensitivity of the search strategy, we combined the terms: ''Perthes disease OR LCPD OR children avascular femoral head necrosis" with "pathology OR aetiology OR biomechanics OR genetics" as either key words or MeSH terms.

RESULTS

We include 64 articles in this review. The available evidence on LCPD aetiology is still debated. Several hypotheses have been researched, but none of them was found decisive. While emerging evidence showed the role of environmental risk factors and evidence from twin studies did not support a major role for genetic factors, a congenital or acquired predisposition cannot be excluded in disease pathogenesis. One of the most supported theories involved mechanical induced

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ischemia that evolved into avascular necrosis of the femoral head in sensible patients.

CONCLUSION
The literature available on the aetiology of LCPD presents major limitations in terms of great heterogeneity and a lack of high-profile studies. Although a lot of studies focused on the genetic, biomechanical and radiological background of the disease, there is a lack of consensus on one or multiple major actors of the etiopathogenesis. More studies are needed to understand the complex and multifactorial genesis of the avascular necrosis characterizing the disease.

Key words: Legg-Calvé-Perthes disease; Aetiology; Pathogenesis; Genetics; Risk factors

Core tip: Legg-Calvé-Perthes disease is a complex disease affecting the epiphysis of the femoral head in the paediatric population. Historically considered an osteochondrosis, it is now being referred to as an idiopathic avascular necrosis of the femoral head in the paediatric population. Despite the aetiology of the disease having been widely researched, it is still not fully understood. The major hypothesis relies on a multifactorial genesis involving mechanical, genetic and systemic conditions. Further studies are necessary to understand the complex and multifactorial genesis of the avascular necrosis characterizing the disease.

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INTRODUCTION

Legg-Calvé-Perthes disease (LCPD) is a complex disease affecting the epiphysis of the femoral head in the paediatric population. Historically considered an osteochondrosis, it is now being referred to as an idiopathic avascular necrosis of the femoral head in the paediatric population. Among its prevalence there is no general agreement. It is set to be between 0.4/100000 to 29.0/100000 children < 15 years of age with a peak of incidence in children aged from 4 years to 8 years and a male/female ratio of 5:1[1,2]. A high profile epidemiological study held in 2017[3] involving 2.1 million individuals attempted to report a more accurate prevalence of this disease. An overall prevalence of 9.3 per 100000 subjects was found. The male/female ratio was 3.1:1. Even though the study was conducted in Sweden from 1973 to 1993, it is one of the most up-to-date sources of evidence of LCPD epidemiology.

Despite the aetiology of the disease having been widely researched, it is still not fully understood. While the major hypothesis relies on a multifactorial genesis, several hypotheses involving mechanical, genetic and systemic conditions have been proposed to explain the pathogenesis of the femoral head osteonecrosis. The best-supported theory involves interference with normal blood supply to epiphysis due to repetitive mechanical stress[4,5]. There is no consensus for the optimum treatment. The aim of treatment is to maintain the sphericity of the femoral head and the congruency of the femur-acetabulum relationship to prevent secondary degenerative arthritis, which eventually leads to total hip arthroplasty in 5% of cases[6]. Early diagnosis and management can help prevent the collapse of the femoral head, progressive femoral head deformity and impingement[7].

Children who have a skeletal age of 6.0 years or less at the onset of the disease do well without treatment[8]. Operative treatment should be considered in children who are 6 years old or older and have over 50% femoral head necrosis when the diagnosis is made[9].

MATERIALS AND METHODS

Literature search strategy

We conducted this systematic review according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10]. A systematic review of two medical electronic databases (PubMed and Science Direct) was performed by two independent authors from their date of inception to May 20, 2018. To achieve the maximum sensitivity of the search strategy, we combined the terms: ''Perthes disease OR LCPD OR children avascular femoral head necrosis" with "pathology OR aetiology OR biomechanics OR genetics" as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies and assessed using the inclusion and exclusion criteria.

Selection criteria

Eligible studies for the present systematic review included those dealing with the aetiology of LCPD. The initial title and abstract screening was made using the following inclusion criteria: studies of any level of evidence, written in English, reporting clinical or preclinical results, published in peer review journals and dealing with the aetiology of LCPD. Exclusion criteria were articles written in other languages or studies with a focus on secondary/LCPD-like diseases caused by systemic conditions such as sickle-cell disease, inflammatory disease, the effects of chemotherapy, radiation or prolonged steroid use. We also excluded all the remaining duplicates, articles dealing with other topics, those with poor scientific methodology or without an accessible abstract. Reference lists were also hand-searched for further relevant studies. All publications were limited to *in vivo*, *in vitro*, animal and human studies in the English language. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded.

Data extraction and criteria appraisal

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each article. Discrepancies between the two reviewers were resolved by discussion and consensus. The final results and any remaining controversy on the reviewed article were reviewed and discussed with senior investigators.

Risk of bias assessment

In this systematic review, risk of bias assessment of the *in vitro* studies was not performed as there is no accepted grading scale for such studies. Risk of bias assessment of all *in vivo* selected full-text articles was performed according to the Regional Online Brownfields Information Network I for non-randomized studies[11]. The Regional Online Brownfields Information Network I (ROBINS-I) tool consists of three stage assessment of the studies included. First stage regards the planning of the systematic review, the second stage is the assessment of the common bias possibly found in these studies and the latter is about the overall risk of bias (Table 1).

The assessments were performed by three authors independently. Any discrepancy was discussed with the senior investigator for the final decision. All the raters agreed on the final result of every stage of the assessment.

RESULTS

Included studies

A total of 1630 articles were found. After the exclusion of duplicates, 1078 articles were selected. At the end of the first screening, following the previously described selection criteria, we selected 130 articles eligible for full text reading. Ultimately, after full text reading and reference list check, we selected n = 64 articles following previous written criteria. A PRISMA[10] flowchart of the method of selection and screening is provided (Figure 1). The included articles[11-85] mainly focus on genetic research, epidemiological studies, magnetic resonance imaging analysis and histological histochemical analysis. The main findings of the included articles are summarized (Tables 1-4).

Smoking

While other environmental factors may be present, smoking seems to one of the most reported risk factor for developing LCPD[11-16]. In particular, Perry *et al*[12] recently showed how maternal smoking can affect the risk of developing the disease in a case control study. In addition to this, another four studies[13-16] report evidence of the association between environmental smoke and LCPD, both during maternal

Table 1 Main findings of the included case-control studies

Ref.	Subjects	Association/molecule studied	Results
Perry *et al*[12] (2017)	A hospital case-control study (n = 149/146)	Tobacco smoke exposure during pregnancy	The odds of Perthes' disease significantly increased with reported *in utero* exposure after adjustment for socioeconomic deprivation (maternal smoking OR = 2.06, 95%CI: 1.17-3.63; paternal smoking OR = 2.09, 95%CI: 1.26-3.46).
Daniel *et al*[13] (2012)	128 children with LCPD and 384 children attending the hospital for other orthopaedic complaints	environmental tobacco smoke, firewood smoke and socioeconomic status and the risk of LCPD	The main risk factors for LCPD were indoor use of a wood stove (adjusted OR, 2.56) and having a family member who smoked indoors (adjusted OR, 2.07).
García Mata *et al*[15] (2000)	90 patients with LCPD and 183 normal children, as controls, selected at random to determine whether the condition of passive smoking is related to the disease	LCPD and passive smoking	The association between LCPD and passive smoking, after controlling for age and gender, became significant (p = 0.0000). Thus the risk of LCPD in passive smoking children is more than five times higher than in children who are not exposed to smoke.
Bahmanyar *et al*[17] (2008)	The Swedish Inpatient Register identified 852 individuals with a diagnosis of LCPD from 1983 to 2005, individually matched by year of birth, age, sex and region of residence with 4432 randomly selected control subjects.	Maternal smoking pregnancy and LCPD	Maternal smoking during pregnancy was associated with an increased LCPD risk, and heavy smoking was associated with a risk increase of almost 100%. Very low birth weight and caesarean section were independently associated with approximately 240% and 36% increases in the risk of LCPD, respectively.
Wiig *et al*[29] (2006)	402 patients with a matched control group of non-affected children (n = 1025952) from the Norwegian Medical Birth Registry	Epidemiology and possible aetiology of LCPD	Applying Sartwell's log-normal model of incubation periods to the distribution of age at onset of Perthes' disease showed a good fit to the log-normal curve. Our findings point toward a single cause, either genetic or environmental, acting prenatally in the aetiology of Perthes' disease.
Perry *et al*[32] (2013)	146 cases of LCPD and 142 hospital controls, frequency matched by age and sex	LCPD and hyperactivity	Significant associations (P < 0.05) existed with the majority of the psychological domains captured by the Strength and Difficulties Questionnaire [OR for "high" level of difficulties-Emotion OR 3.2, Conduct OR 2.1, Inattention-Hyperactivity OR 2.7, Prosocial behaviour OR 1.9]. Hyperactivity was especially marked among individuals within 2 years of diagnosis (OR = 8.6; P < 0.001), but not so among individuals over 4 years from diagnosis.
Berman *et al*[34] (2016)	16 children with LCPD (age 9.1 ± 3.3, 75% males) were compared with their closest-aged siblings (age 9.3 ± 2.6, 30% males).	LCPD and ADHD	Our findings in a small cohort of children with LCPD and their comparably aged siblings do not support an association between LCPD and ADHD
Hailer *et al*[35] (2012)	2579 patients with LCPD in Sweden during the period 1964-2005. 13748 individuals without LCPD were randomly selected from the Swedish general population	LCPD and risk of injury	Patients with LCPD are vulnerable to injuries that could be interpreted as a marker of hyperactive behaviour.
Hailer *et al*[36] (2014)	4057 individuals with LCPD in Sweden during the period 1964-2011. 40570 individuals without LCPD were randomly selected from the Swedish general population	LCPD and ADHD	Compared to the control group, individuals with LCPD had a raised HR of 1.5 (95%CI: 1.2-1.9) for ADHD.

Türkmen *et al*[37] (2014)	The study included 3 groups of patients: Perthes patients, trauma patients and orthopaedic patients without Perthes disease or history of trauma. Each group was comprised of 56 males and 4 females.	LCPD and ADHD	ADHD was diagnosed in 7 patients in the Perthes group. The findings are not significant
Lee *et al*[39] (2013)	38 male and 3 female patients with LCPD, and an equal number of age (range was 4-12) and sex-matched control patients with healthy fractures.	LCPD and leptin	Leptin, disease severity and treatment outcomes were associated. This correlation suggests that leptin might play an important role in LCPD pathogenesis.
Srzentić *et al*[51] (2014)	37 patients with Perthes disease and 50 healthy controls	LCPD and IL-6	Our study revealed that heterozygote subjects for the IL-6 G-174C/G-597A polymorphisms were significantly overrepresented in the control group than in the Perthes patient group.
Kamiya *et al*[52] (2015)	28 patients with matched controls	LCPD and IL-6	In the synovial fluid of the affected hips, IL-6 protein levels were significantly increased (LCPD: 509±519pg/mL, non-LCPD: 19±22pg/mL; P=0.0005) on the multi-cytokine assay.
Perry *et al*[76] (2012)	149 cases and 146 controls	Vascular abnormalities in LCPD patients	Children with Perthes disease exhibit small artery calibre and reduced function, which is independent of body composition. These data imply that that Perthes disease may reflect a wider vascular phenomenon that could have long-term implications for the vascular health of affected individuals.
Kitoh *et al*[78] (2003)	125 children (105 boys, 20 girls) with unilateral LCPD	Delayed ossification in LCPD	Our findings support the hypothesis that a delay in endochondral ossification in the proximal capital femoral epiphysis may be associated with the onset of Perthes' disease.
Kocjančič *et al*[79] (2014)	135 adult hips of patients who had been treated for Perthes disease in childhood with matched controls	Hip stress distribution in LCPD	No differences were found in resultant hip force and in peak contact hip stress between the hips that were in childhood subject to Perthes disease and the control population, but a considerable (148%) and significant (P < 0.001) difference was found in the contact hip stress gradient index, expressing an unfavourable, steep decrease of contact stress at the lateral acetabular rim.
Neidel *et al*[83] (1992)	59 consecutive children with Perthes' disease and 59 matched controls	IGF-1 and LCPD	Our data may reflect an impaired synthesis or release of IGF I relative to age in Perthes' disease or changes in the affinity or metabolism of IGF binding proteins. The observed changes seem to be of a temporary nature.
Kim *et al*[82] (2009)	56 immature pigs	HIF-1α and LCPD	Acute ischemic injury to the immature femoral head induced severe hypoxia and cell death in the bony epiphysis and the deep layer of the epiphyseal cartilage. Viable chondrocytes in the superficial layer of the epiphyseal cartilage showed HIF-1α activation and VEGF upregulation with subsequent revascularization occurring in the cartilage.
Matsumoto *et al*[84] (1998)	27 children with Perthes' disease and 10 age-matched control subjects	IGF binding protein-3 and LCPD	The bone age was delayed 2 years or more compared with the chronological age in 7 of 18 patients, and all of them, except 1, showed decreased levels of IGFBP-3 on WLB.

Graseman *et al*[85] (1996)	23 children with unilateral LCPD and in 23 sex and age matched controls	IGF binding protein-3 and LCPD	Data confirm that most children with LCPD are skeletally immature. However, IGF-I measured with IGF-II-blocked IGFBP binding sites, and IGFBP-3 serum concentrations analysed with respect to bone age showed no evidence for a disturbance of the hypothalamo-pituitary-somatomedin axis in these children.
Neidel *et al*[86] (1993)	55 children with Perthes' disease and 55 age- and sex-matched controls	IGF and LCPD	Our findings indicate that low levels of circulating IGF I in Perthes' disease, as we have reported previously, are caused neither by altered concentrations of the principal IGF-binding protein, IGFBP-3, nor by an underlying growth hormone deficiency.

LCPD: Legg-Calvé-Perthes disease; OR: Odds ratio; CI: Confidence interval; ADHD: Attention deficit hyperactivity disorder; IL-6: Interleukin 6; IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding protein; HR: Hazard ratio: HIF: Hypoxia-inducible factor.

pregnancy and the childhood of the patient. Lastly, a study involving 852 patient showed how the smoking habit augmented the risk for LCPD by 100% in the examination sample[17].

Socioeconomical deprivation

Three different studies[14,18,19] involving an overall 340 LCPD patients explored the link between the disease and socioeconomic deprivation without revealing a significant association. On the contrary, Kealey *et al*[20], investigating 311 patients, found a higher prevalence among the most deprived rural category. In 2012, another study[21] analysed the incidence of LCPD between 1990 and 2008 in children between 0 years and 14 years in the United Kingdom. They reported how the incidence was coherently higher within the quintile with the highest degree of deprivation (risk ration = 1.49, 95% confidence interval (CI): 1.10–2.04) ($P < 0.01$). Five more studies[22-26] held in United Kingdom by the same research group reported similar results.

Low birth weight

Metcalfe *et al*[27] reported an increased presence of low birth weight in children affected by LCPD. Similar to the results provided by Lappin *et al*[28], Sharma *et al*[18] reported an association between low birth weight and LCPD, whereas the weight of the children at the moment of the diagnosis and follow up did not show significant alteration. This was further supported by other studies with similar results[26]. On the contrary, Bahmanyar *et al*[17] reported a possible association between low birth weight and LCPD, but that was shown to be insignificant after evaluating other risk factors like maternal smoking. Only really low birth weight (< 1500 g) seemed to be associated independently with LCPD. Another nationwide study[29] held in Norway and involving 425 patients reported similar results. Their results supported the presence of environmental or genetic factors but not low birthweight. Similar results were reported by other epidemiological studies[12-16].

Attention deficit hyperactivity disorder (ADHD) and psychological burden

Loder *et al*[30] in 1993 studied the association between ADHD and LCPD in 24 patients. He reported the presence of one third (33%) of the children with abnormally high scores in profiles associated with ADHD. Perry *et al*[31,32] investigated both general practise registry of comorbidities in LCPD patients and the incidence of behavioural disturbance. ADHD was not associated with Perthes' disease (OR = 1.01, 95%CI: 0.48-2.12) in the first study[31]; while in the second one[32], a case control study involving 146 cases of LCPD and 142 hospital controls, the presence of behavioural disturbance was reported.

In 2015, a prospective study[33] evaluated in 58 adolescents patients (11 with LCPD) undergoing hip preservation surgery the presence of psychological disturbances. A significant presence of depression and anxiety symptoms was reported. Bergman *et al*[34] investigated ADHD in LCPD patients and in siblings of the child affected. A similar incidence was reported in both the groups. Hailer *et al* investigated the prevalence of the disease in two high profile studies held in 2012[35] and in 2014[36]. The first one involved 2579 LCPD patients and 13748 controls. It investigated the risk of injury in both groups and reported a higher percentage in the LCPD group. The second one involved 4057 individuals with LCPD in Sweden during the period 1964-

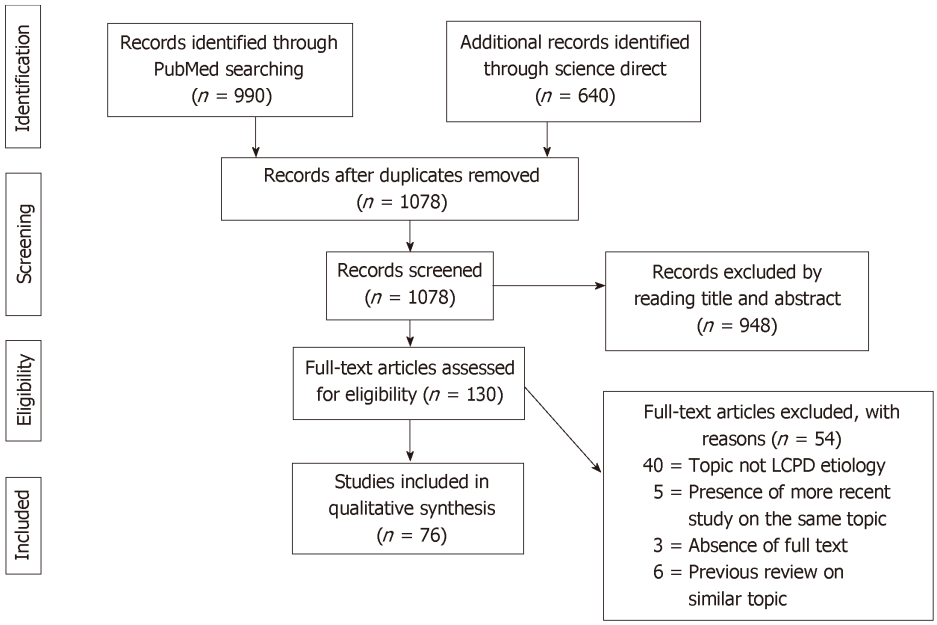

Figure 1 PRISMA flowchart of the systematic literature review. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

2011 and 40570 individuals without LCPD randomly selected from the Swedish general population and matched by year of birth, sex and region. They reported that individuals with LCPD also had a raised hazard ratio (HR) of 1.5 (95%CI: 1.2-1.9) for ADHD.

Türkmen *et al*[37], instead, did not find a significant difference in ADHD prevalence between LCPD group and control groups.

Obesity and leptin

A study held in 2016[38] reported a positive association between LCPD and obesity. Obesity was associated with a more severe clinical presentation and femoral head deformity. Lee *et al*[39] have investigated the levels of leptin in LCPD patients compared to control subjects. A significantly higher value concordant with the severity of the disease was reported.

Familiarity and genetic role

Over the years, several cases of LCPD in the same family have been reported[40,41]. This evidence suggested a genetic role in the development of the disease. In particular, Miyamoto *et al*[42] were the first to report a case of familiar LCPD associated with a mutation of the Collagen type II gene (*COL2A1*). Thus, *COL2A1* genes were proposed as potential pathogenic trigger of LCPD. Several case reports also found evidence of this association in LCPD patients[43,44]. Further studies investigated the relationship between this gene mutation and LCPD. Su *et al*[45] recruited 42 members of a five-generation family and found in 16 patients a p.Gly1170Ser mutation of *COL2A1* cosegregated with LCPD, precocious hip osteoarthritis or avascular femoral head necrosis not linked with LCPD. Li *et al*[46] in 2014 held a study, including a four-generation family, reporting the presence of the mutation in six affected family members.

Metcalfe *et al*[27] investigated the presence of genetic factors using the information derived from the Danish Twin Registry. After studying concordance with LCPD in 81 twin pairs (10 monozygotic, 51 dizygotic and 20 unclassified), they concluded that the absolute risk that a co-twin of an affected individual will develop LCPD is low, even in the case of monozygotic twin pairs. While Metcalfe *et al*[27] did not find an association between LCPD and birth weight, another twin study[28] and a case control study[17] involving an overall of 320 twin patients and 852 patients, respectively, concluded that low birth weight may play a role in developing the disease.

Coagulation disturbance

A meta-analysis[47] held in 2012 investigated factor V Leiden, prothrombin II and methylenetetrahydrofolate reductase (MTHFR) polymorphism as sources of possible genetic aetiology of LCPD. They comprised 12 case-control studies, including 824 children in the Perthes group and 2033 children in the control group. Factor V Leiden

Table 2 Main findings of included cohort studies

Ref.	Subjects	Association/molecule studied	Results
Gordon *et al*[14] (2004)	60 patients with LCPD	Smoking and socio-economic status and the severity of LCPD	A significant association was noted between living with a smoker and LCPD as well as between increasing smoke exposure and increased risk of developing LCPD. No significant association was noted between lower income and LCPD. There was no association between increased smoke exposure and increased severity of LCPD as measured by the lateral pillar classification.
Glueck *et al*[16] (1998)	39 children with Legg-Perthes disease	Second-hand smoke exposure	Second-hand smoke exposure had no significant effects on other measures of coagulation. Second-hand smoke exposure while *in utero* and during childhood appears to lower stimulated tissue plasminogen activator activity and additionally may depress heritable low stimulated tissue plasminogen activator activity, leading to hypofibrinolysis. Hypofibrinolysis may facilitate thrombotic venous occlusion in the head of the femur, leading to venous hypertension and hypoxic bone death, Legg-Perthes disease.
Sharma *et al*[18] (2005)	240 children (263 hips) who presented with Perthes' disease in Greater Glasgow	Socio economic deprivation and LCPD	There was no significant evidence of a preponderance of Perthes' disease in the most deprived groups.
Pillai *et al*[19] (2005)	40 LCPD patients and the Southwest Scotland registry	The incidence of LCPD in Southwest Scotland	The incidence of LCPD increases with deprivation and poor living standards.
Kealey *et al*[20] (2000)	313 children with LCPD and Northern Ireland registry	Socio economic deprivation and LCPD	While the incidence of Perthes' disease was found to be associated with indicators of the level of deprivation for areas, there was no evidence to suggest that there was an increased risk in urban areas; the highest rate was found in the most deprived rural category
Perry *et al*[21] (2012)	The General Practice Research database was analysed to identify incident cases between 1990 and 2008 in children aged 0-14 years	LCPD incidence in United Kingdom	The incidence was declining in the study period. The declining incidence, along with the geographic variation, suggests that a major etiologic determinant in LCPD is environmental and closely linked to childhood deprivation.
Perry *et al*[22] (2012)	Scottish Morbidity Record, based in Scotland, United Kingdom using data from 2000-2010. A total of 443 LCPD patients	Socio economic deprivation and LCPD	The occurrence of Perthes' disease within urban environments is high, yet this appears to be a reflection of higher socioeconomic deprivation exposure. Disease rates appear equivalent in similarly deprived urban and non-urban areas, suggesting that the determinant is not a consequence of the urban environment.
Perry *et al*[23] (2011)	1082 children with Perthes' disease (682 from a geographically defined area). Regional disease register in Merseyside, United Kingdom, 1976-2009	Social deprivation and the declining incidence of LCPD	There was a marked decline in disease incidence over the study period, particularly in more deprived areas. The magnitude of the association with deprivation, and the changing incidence, strongly suggest that environmental factor(s) are a major aetiological determinant in Perthes' disease.
Hall and Barker[24] (1989)	Yorkshire region registry	Perthes incidence over the region	There were large geographical differences in incidence that could not be explained by urban-rural or social class differences.

Hall *et al*[25] (1983)	Case registry in Liverpool and adjacent parts of Knowsley and Sefton during 1976-81	Incidence of LCPD in the region	The inner city of Liverpool, which has been shown to be underprivileged, had the highest yearly incidence of the disease ever reported: 21.1 cases/100000 children aged 14 years and under. The associations with poverty support the hypothesis that undernutrition is a causative factor in the disease.
Margetts *et al*[26] (2001)	Registry of Liverpool (1982-1995)	Incidence and distribution of LCPD in Liverpool	We suggest that environmental influences may come into play some years before a child presents with pain in the hip. There may be a genetic predisposition to the disease.
Metcalfe *et al*[27] (2016)	All twin pairs from the Danish Twin Registry (DTR) in which at least 1 individual had LCPD (81 twin pair)	Twin study of LCPD	This study found evidence of familial clustering in LCPD but did not show a genetic component. The absolute risk that a co-twin of an affected individual will develop LCPD is low, even in the case of monozygotic twin pairs.
Lappin *et al*[28] (2003)	320 patients on the Northern Ireland Perthes' database	Birthweight and LCPD	We observed that the low birthweight twin in each case was the affected child. It is proposed that environmental factors associated with low birthweight are involved in the aetiology of Perthes' disease.
Loder *et al*[30] (1993)	24 LCPD patients	LCPD and ADHD	One third (33%) of the children had abnormally high scores in profiles associated with ADHD (impulsive, hyperactive and psychosomatic categories), much higher than the 3%-5% incidence of ADHD in the general population.
Perry *et al*[31] (2012)	General Practise Research database in United Kingdom	LCPD comorbidities	The risk of Perthes' disease was significantly increased with the presence of congenital anomalies of the genitourinary and inguinal region, such as hypospadias (OR = 4.04, 95%CI: 1.41-11.58), undescended testis (OR = 1.83, 95%CI: 1.12-3.00) and inguinal herniae (OR = 1.79, 95%CI: 1.02-3.16). Attention deficit hyperactivity disorder was not associated with Perthes' disease (OR = 1.01, 95%CI: 0.48-2.12), although a generalised behavioural disorder was (OR = 1.55, 95%CI: 1.10-2.17). Asthma significantly increased the risk of Perthes' disease (OR = 1.44, 95%CI: 1.17-1.76), which remained after adjusting for oral/parenteral steroid use.
Podeszwa *et al*[33] (2015)	11 LCPD patients	Psychological finding in patients undergoing surgery	A significant presence of depression and anxiety symptoms was reported.
Neal *et al*[38] (2016)	150 patients (172 hips) with LCPD	LCPD and obesity	Obesity is common in patients with LCPD and is associated with a later stage of disease presentation.
Srzentić *et al*[48] (2015)	37 LCPD patients	Markers of coagulation, inflammation and apoptosis in LCPD	The results presented indicate that apoptosis could be one of the factors contributing to the lack of balanced bone remodelling process in Perthes patients.
Calver *et al*[56] (1981)	50 children with "irritable hip"	Radionuclide scanning in LCPD	Five of the 50 children seen during the one year had areas of ischemia in the capital femoral epiphysis demonstrated on the scan. All five developed radiological signs of Perthes' disease within 6 mo. The remaining 45 had radiographically normal hips at one year.

Royle and Galasko[60] (1992)	192 patients with a typical transient synovitis syndrome	Scintigraphy in LCPD patients	Fifteen patients had evidence of ischemia of the femoral head, but only four patients went on to develop the typical radiographic features of Perthes' disease. The other 11 patients are thought to represent a minor, radiographically silent form of Perthes' disease.
Lamer *et al*[61] (2002)	26 DGS MRI and bone scintigraphies of 25 hips in 23 children	Blood supply in LCPD	DGS MRI allows early detection of epiphyseal ischemia and accurate analysis of the different revascularisation patterns. These changes are directly related to the prognosis of LCPD
Atsumi *et al*[62] (2000)	28 hips in 25 patients with LCPD	Blood supply in LCPD	We suggest that in Perthes' disease the blood supply of the LEAs is impaired at their origin and that revascularisation occurs from this site by ingrowth of small vessels into the femoral epiphysis. This process may be the result of recurrent ischemic episodes.
de Camargo *et al*[63] (1984)	30 patients, including 26 aortographies and 6 selective angiographies	Blood supply in LCPD	The major angiographic alterations were: general decrease of blood flow in the affected hip, lack of a patent medial circumflex artery, an atrophic medial circumflex artery or obstruction of its branches, distended vessels in subluxations of the hip joint and almost complete absence of the obturator artery
Theron *et al*[64] (1980)	11 cases of LCPD	Blood supply in LCPD	The balance between the respective vascular territories of the dilated superior and inferior capsular arteries is variable and seems to affect the position of the sequestrum and the centering of the femoral head.
Kitoh *et al*[78] (2003)	125 children (105 boys, 20 girls) with unilateral LCPD	Delayed ossification in LCPD	Our findings support the hypothesis that a delay in endochondral ossification in the proximal capital femoral epiphysis may be associated with the onset of Perthes' disease.

LCPD: Legg-Calvé-Perthes disease; ADHD: Attention deficit hyperactivity disorder; OR: Odds ratio: CI: Confidence interval; MRI: Magnetic resonance imaging.

polymorphism (carrying the minor A allele instead of the G allele) was associated with a three times higher incidence of the disease. Prothrombin II polymorphism (A allele instead of the G allele) reported giving a 1.5-fold increase risk of disease. There was no association between MTHFR polymorphism and Perthes disease. In 2015, Srzentic *et al*[48] investigated gene expression and variants by quantitative reverse-transcriptase polymerase chain reaction and reported no difference between LCPD patients and controls for Factor V Leiden, Factor II, MTHFR and Plasminogen activator inhibitor-1.

Also, a prospective study held in 2002 did not suggest that thrombotic diatheses due to deficiency of protein C, protein S or antithrombin III or due to factor-V Leiden mutation are major causes of Legg-Perthes disease[49].

Inflammation markers

Liu *et al*[50] analysed age- and sex-matched serum samples from 10 control subjects and 10 patients with LCPD. They reported a higher presence of proteins and factors linked to complement and coagulation cascade. Increased activity of these factors may contribute to LCPD aetiology. In 2014 Srzentić *et al*[51] studied the association of frequencies of genetic variants of immune response genes with LCPD. They found significantly over-represented heterozygous subjects with an interleukin-6 (IL-6) polymorphism (G-174C/G-597A) in the LCPD group. In 2015, another studied reported a significantly increased IL-6 protein level in the synovial fluid of the hips affected by LCPD[52].

Apoptosis factors

Srzentić *et al*[48] investigated the expression of apoptosis genes by the quantitative

Table 3 Main findings of the included animal studies

Ref.	Subjects	Association/molecule studied	Results
Suehiro *et al*[49] (2005)	Mouse model	Osteonecrosis in rat model	Repetitive mechanical stress on the femoral heads from 5 wk to 9 wk of age played an important role in the aetiology of osteonecrosis
Gershuni *et al*[59] (1983)	Hip of the immature pig	Joint tamponade in LCPD animal model	The data from this experiment do not support the theory that tamponade of the femoral capital epiphysis is the cause of osteonecrosis in Legg-Calvé-Perthes syndrome
Cheon *et al*[66] (2015)	10 piglets	Quantitative MRI in piglet model of LCPD	The epiphyseal ADC values of the ischemic hip decreased immediately (1 hour) after embolization. However, they increased rapidly at 1 wk after embolization and remained elevated until 4 wk after embolization. Perfusion MRI of ischemic hips showed decreased epiphyseal perfusion with decreased Kep immediately after embolization.
Li *et al*[67] (2006)	20 femoral heads of 10 piglets	MRI in piglet model of LCPD	Gadolinium-enhanced MRI can identify early ischemia and its reversal of the capital femoral epiphysis induced by hip hyper-abduction
Babyn *et al*[68] (1998)	Piglet model	MRI in piglet model of LCPD	High resolution MRI can demonstrate changes in the CE associated with ischemic injury and may have a role in the assessment of the CE and its development after ischemic injury.
Li *et al*[69] (2008)	25 piglets models	Diffusive MRI in a model of LCPD	Histological study revealed necrosis of chondrocytes and osteocytes and abnormal thickening of the epiphyseal cartilage in the ischemic femoral head.
Levin *et al*[70] (1999)	Rat model	Epiphysis studies in a rat model	Thickening and condensation of the subchondral bone, leading to increased stiffness of the subchondral zone, result in the osteoarthritis-like disorder. Mimicking the well-known phases of human osteonecrosis, the model readily allows for preclinical studies of therapeutic regimens.
Kandzierski *et al*[71] (2004)	Calf femurs	Calf femur experimental study	The author concludes that impaired blood flow within the growth layers additionally weakens the immature bone tissue of the femoral head and neck, which may lead to mechanical damage of the bone tissue itself, as well as to the epiphyseal blood vessels entering bony epiphysis.
Suehiro *et al*[72] (2000)	Twenty femora from 10 Wistar Kyoto rats	Standing and induction of OA	Repetitive mechanical stress on the femoral heads from 5 wk to 9 wk of age played an important role in the aetiology of osteonecrosis
Naito *et al*[74] (1992)	Canine femoral head	Acute effect of traction, compression, and hip joint tamponade on blood flow of the femoral head	These experimental data may have important implications for the pathogenesis of iatrogenic avascular necrosis in the treatment of congenitally dislocated hip, Legg-Perthes disease and avascular necrosis following nondisplaced femoral neck fracture

Kim *et al*[77] (2013)	56 immature pigs	MRI in the initial stage of LCPD	Acute ischemic injury to the immature femoral head induced severe hypoxia and cell death in the bony epiphysis and the deep layer of the epiphyseal cartilage. Viable chondrocytes in the superficial layer of the epiphyseal cartilage showed HIF-1α activation and VEGF upregulation with subsequent revascularization occurring in the cartilage.
Zhang *et al*[81] (2015)	6-wk-old Sprague Dawley rats	HIF-1α and LCPD	Hypoxia might be an etiological factor for femoral head necrosis. HIF-1α, VEGF as well as apoptotic genes participated in the pathophysiological process of ischemic osteonecrosis.
Kim *et al*[83] (2009)	56 immature pigs	HIF-1α and LCPD	Acute ischemic injury to the immature femoral head induced severe hypoxia and cell death in the bony epiphysis and the deep layer of the epiphyseal cartilage. Viable chondrocytes in the superficial layer of the epiphyseal cartilage showed HIF-1α activation and VEGF upregulation with subsequent revascularization occurring in the cartilage.

LCPD: Legg-Calvé-Perthes disease; HIF-1: Hypoxia-inducible factor; VEGF: Vascular endothelial growth factor; MRI: Magnetic resonance imaging.

reverse-transcriptase polymerase chain reaction technique in 37 patients. They reported a higher presence of proapoptotic factor Bcl-2-associated X protein (Bax) along with a significantly higher Bax/Bcl-2 ratio in the patient group. Zhang *et al*[49] found in a rat model similar results, with a higher expression of the apoptotic genes Casp3, Casp8 and Casp9 in chondrocytes after hypoxia.

Mechanical stress and ischemia damage: Ischemia damage was reported in the first research documents we have on LCPD and its pathology insight[53,54]. In 1976, one of the first studies[55] about the aetiology of LCPD reported the presence of areas of infarction in 51% of hips histopathologically examined in 57 cases of femoral head biopsy. Calver *et al*[56] examined radiologically the ischemia areas in the hips of 50 children. The five with evidence of ischemia areas developed LCPD within 6 mo. The other 45 were healthy at 1 year follow up. Catteral *et al*[57] and Ponseti *et al*[58], respectively, in two different historical studies reported an area of ischemia in two children's biopsies and morpho-structural alteration possibly associated with ischemic damage. In addition, several animal studies were conducted. A study held in 1983[59] investigated how joint tamponade in pigs would provoke ischemia of the epiphyseal plate. The necessity of high and prolonged pressure, which is difficult to achieve in normal conditions, was reported. Several research studies reported evidence of ischemia damage using radiological techniques[60-64]. This provides evidence of its role in the enteropathogenesis of the LCPD. Recently, Pinheiro *et al*[65] proposed a biomechanical model that further supports a combined role of both ischemic condition, skeletal immaturity and altered biomechanics. Also, studies on hip osteonecrosis in piglets confirmed this aetiology[66-69].

Mechanical stress-induced ischemia was found to be a possible aetiology of LCPD also using several animal models[70-72] and experimental analysis models[65,73,74]. One particular study performed by Suehiro *et al*[49] involving Wistar Kyoto rats reported how repetitive mechanical stress on the femoral heads from 5 wk to 9 wk of age played an important role in the aetiology of osteonecrosis. This theory is historically and currently one of the most supported[54,61,75-77].

Delayed epiphysial growth and hip geometry alterations: In 2003, Kitoh *et al*[78] investigated the epiphyseal height (EH) and width (EW) of the unaffected hip in 125 children affected by LCPD. A positive linear correlation (R = 0.87) was observed in the EH: EW ratio in these patients. A smaller EH than expected for EW in our series indicated epiphyseal flattening of the femoral head in LCPD cases. This finding supports the hypothesis that a delay in endochondral ossification in the proximal capital femoral epiphysis may be associated with the onset of Perthes' disease.

In 2014, Kocjančič *et al*[79] investigated the resultant hip force and contact hip stress

Table 4 The main findings of the included *in vitro* human studies are reported

Ref.	Subjects	Association/molecule studied	Results
O'Sullivan *et al*[40] (1985)	A family in which Legg-Calvé-Perthes disease (LCPD) occurred in four members	Genetic factors and LCPD	This unusually high incidence in one family raises questions about the genetic versus the environmental factors in the aetiology of LCPD.
Livesey *et al*[41] (1998)	Case report of three family with three female first-degree relatives affected by LCPD	Genetic factors and LCPD	First case of three first-degree relative affected
Miyamoto *et al*[42] (2007)	A Japanese family with an autosomal dominant hip disorder manifesting as LCPD	LCPD and *COL2A1*	This is the first report of a mutation in hereditary LCPD. *COL2A1* mutations may be more common in LCPD patients than currently thought, particularly in familial and/or bilateral cases.
Al-Omran and Sadat-Ali[43] (2013)	2 generations of 4 male family members with LCPD-like features and mutation of the *COL2A1* gene of the 12q13 chromosome	LCPD and *COL2A1*	If LCPD occurs in any family member, we recommend genetic analysis and counselling as well as early radiological screening of related children.
Kannu *et al*[44] (2011)	Two children who presented with abnormal development of both hips and in whom novel mutations in the *COL2A1* gene were found	LCPD and *COL2A1*	The purpose of our report is to alert clinicians to the possibility that children who present with bilateral Perthes-like disease of the hip might have an underlying mutation in the gene encoding type II collagen.
Su *et al*[45] (2008)	Forty-two members of a 5-generation family	LCPD and *COL2A1*	The p.Gly1170Ser mutation of *COL2A1* in the family described is responsible for pathology confined to the hip joint, which presents as isolated precocious hip OA, AVN of the femoral head, or Legg-Calvé-Perthes disease.
Li *et al*[46] (2014)	Forty-five members of a four-generation family	LCPD and *COL2A1*	In our research, we identify a heterozygous mutation (c.1888 G>A, p. Gly630Ser) in exon 29 of *COL2A1* in the Gly-X-Y domain, in a Chinese family affected by LCPD and ANFH.
Woratanarat *et al*[47] (2014)	Twelve case–control studies met inclusion criteria and had sufficient data for extraction	Hypercoagulability and LCPD	The factor V Leiden mutation is significantly related to Perthes disease, and its screening in atrisk children might be useful in the future.
Srzentić *et al*[48] (2015)	37 LCPD patients	Markers of coagulation, inflammation and apoptosis in LCPD	The results presented indicate that apoptosis could be one of the factors contributing to the lack of balanced bone remodelling process in Perthes patients.
Liu *et al*[50] (2015)	Age- and sex-matched serum samples from 10 control subjects and 10 patients with LCPD were compared using the isobaric tags for relative and absolute quantification (iTRAQ) technique.	Serum proteomes in LCPD	The complement and coagulation cascades, and abnormal lipid metabolism may be involved in the pathogenesis of LCPD.
Srzentić *et al*[51] (2014)	37 patients with Perthes disease and 50 healthy controls	LCPD and IL-6	Our study revealed that heterozygote subjects for the IL-6 G-174C/G-597A polymorphisms were significantly overrepresented in the control group than in the Perthes patient group.
Kamiya *et al*[52] (2015)	28 patients with matched controls	LCPD and IL-6	In the synovial fluid of the affected hips, IL-6 protein levels were significantly increased (LCPD: 509 pg/mL±519pg/mL, non-LCPD: 19 pg/mL±22pg/mL; P=0.0005) on the multi-cytokine assay.
Su *et al*[55] (2010)	a five-generation family with 42 members with a new type II collagenopathy	LCPD and *COL2A1*	Our study demonstrated that the p.Gly1170Ser mutation of *COL2A1* caused significant structural alterations in articular cartilage, which are responsible for the new type II collagenopathy.

Matsumoto *et al*[84] (1998)	27 children with Perthes' disease and 10 age-matched control subjects	IGF binding protein-3 and LCPD	The bone age was delayed, 2 years or more compared with the chronological age in 7 of 18 patients, and all of them, except 1, showed decreased levels of IGFBP-3 on WLB.
Graseman *et al*[85] (1996)	23 children with unilateral LCPD and in 23 sex and age matched controls	IGF binding protein-3 and LCPD	Our data confirm that most children with LCPD are skeletally immature. However, IGF-I measured with IGF-II-blocked IGFBP binding sites, and IGFBP-3 serum concentrations analysed with respect to bone age show no evidence for a disturbance of the hypothalamo-pituitary-somatomedin axis in these children.
Neidel *et al*[86] (1993)	55 children with Perthes' disease and 55 age- and sex-matched controls	IGF and LCPD	Our findings indicate that low levels of circulating IGF I in Perthes' disease, as we have reported previously, are caused neither by altered concentrations of the principal IGF-binding protein, IGFBP-3, nor by an underlying growth hormone deficiency.

LCPD: Legg-Calvé-Perthes disease; COL2A1: Collagen type II gene; IGF: Insulin-like growth factor.

distribution in a population of 135 adult hips of patients who had been treated for LCPD. Contra-lateral hips with no record of disease were taken as control. The contact hip stress gradient index was 148% higher ($P < 0.001$); expressing an unfavourable, steep decrease of contact stress at the lateral acetabular rim. On the contrary, Pinheiro *et al*[80] reported how the anatomical variations appear to have only a limited effect on the stress distribution in the femoral epiphysis, even during high impact activities and in the presence of a skeletally immature epiphysis. However, the same group recently published a study[65] on a new biomechanical model and reported a possible involvement of vascular obstruction to the epiphysis that may arise when there is delayed ossification and when articular cartilage has reduced stiffness under compression.

Vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF-1): In 2004, an animal study[49] involving piglets with avascular necrosis reported increased VEGF protein and mRNA expression in the epiphyseal cartilage of the infarcted heads compared with the contralateral normal heads. Therefore, VEGF upregulation in the proliferative zone after ischemic damage was proposed as a possible stimulator of vascular invasion and granulation tissue formation. Zhang *et al*[81] reported also a higher expression of VEGF and HIF-1 in rat model chondrocytes.

VEGF was found to be low in LCPD patients in an Indian population-based study[49]. In 2014, 28 LCPD cases (mean age: 8 ± 3.8) and 25 healthy age-matched control subjects were investigated, and VEGF, endothelial progenitor cell and immunoglobulins were not significantly different between the groups ($P = 0.354$). The endothelial progenitor cell count was inversely correlated with serum immunoglobulin G levels in the LCPD group ($r = 0.403$, $P = 0.03$). The absolute endothelial progenitor cell count was also significantly higher in the fragmentation stage than in the healing stage, and they were greater in bilaterally affected cases than in unilaterally affected patients. Similar results were found in a pig model[82] and Sprague-Dawley rats[81]. In the rat model, however, the interruption of vascularization in the proximal femoral growth plate was not followed by diffuse damage.

Insulin growth factor 1 (IGF-1): The role of IGF-1 role in LCPD aetiology was investigated. In particular, a study in spontaneously hypertensive rat (SHR) demonstrated altered IGF-I expression during early postnatal life and suggested that the altered IGF-I expression may cause the mechanical vulnerability of the femoral epiphysis. Low levels of serum IGF-1 and IGF-1 binding protein 3 have been reported in patients with LCPD[83,84]. However, these results conflict with another two studies that reported normal IGF-1 binding protein levels[85,86].

DISCUSSION

The aetiology of LCPD is still mainly unknown. The heterogeneous prevalence reported opens the discussion for the examination of possible environmental and

social factors involved in the aetiology of the disease[1-3,29]. In support of this, three studies[21,26,87] reported a possible association between the decrease in the incidence and lifestyle changes over recent years, exposure to environmental risk factors like smoking, delayed epiphyseal ossification, low birthweight, child deprivation and obesity. However, the results are not definitive.

Several studies reported strong evidence supporting the role of social and economic deprivation in the incidence of LCPD in children[14,17,28,18-22,24-26]. This was proposed as a possible consequence of two factors: low birth weight and smoking habits. In addition, maternal smoking is associated with a low birthweight[88,89]. Thus, low birthweight could be often falsely associated with LCPD because of the smoking habit typically present in these families, which is the more probable cause of the higher incidence of LCPD. For these reasons, the role of low birth weight lacks strong evidence[12-17,29], and the smoking habit, being more common in social-economical deprived families, may play a more important role in the etiopathogenesis of LCPD. This was further confirmed by studies investigating the association between smoking and LCPD, which reported a significant augmentation of the risk in smokers and smoke-exposed family. The mechanism proposed is the smoke-dependent damage of vessel endothelium, which could ultimately lead to epiphyseal infarction[17].

In addition, recent evidence supports obesity as a major risk factor[38]. Leptin is a hormone that is expressed in adipose tissue and, at lower levels, in gastric epithelium and placenta associated with both obesity and bone metabolism[90,91]. It has been reported that both leptin and obesity are positively associated with the severity of LCPD[38,39]. Most obese humans have very high plasma leptin concentrations, suggesting they are resistant to its anorectic and metabolic effects[92]. Based on these findings, Bartell *et al*[93] conducted a study involving intracerebroventricular and subcutaneous administration of leptin in leptin-deficient ob/ob mice, investigating its effect on bone and muscular tissues. In both experiments, leptin had a key role in the decrease of body weight, food intake and body fat and in the increase of muscle mass, bone mineral density, bone mineral content, bone area, marrow adipocyte number and mineral apposition rate. Thus, leptin administration seemed to be really effective in obese patient bone metabolism. Following this rationale, Zhou *et al*[94] in 2015 tested these effects in a LCPD obese rat model. Six weeks after surgery induced avascular necrosis of the femoral head, radiologic and histomorphometric assessments were performed. Radiographs showed better preservation of the femoral head architecture in the leptin-treated group. Histology and immunohistochemistry revealed that the leptin group had significantly increased osteoblastic proliferation and vascularity in infarcted femoral heads compared with control groups. The mechanism proposed is linked to both a direct action of leptin on bone metabolism and an indirect action through the upregulation of VEGF[95]. In particular, leptin acts physiologically through MAPK/ERK 1/2 and PI-3K/AKT1 pathways and a series of transcription factors such as HIF-1α[92,96]. Emerging evidence supports how leptin and obesity may play a role in LCPD etiopathogenesis. We strongly encourage further studies on leptin and obesity, associated with their effects of bone metabolism, in LCPD patients. These studies should be conducted both as a therapeutic option and as a possible actor in the aetiology of the disease.

The dissimilarity in incidence between male and female subjects was initially thought to rely on the different etiopathogenesis of the disease. In particular, pioneer studies on these differences reported a more severe presentation and prognosis in female patients than in male subjects[97]. However, recent high profile epidemiological studies reported no significant differences in clinical presentation, outcome and prognosis between boys and girls[98,99]. Thus, the LCPD male/female ratio appears not to be associated with different clinical presentation and should not be part of the clinical treatment algorithm.

While the reviewed literature provided evidence of cases of LCPD running in families[41-46], and epidemiological studies suggested a genetic role[29], twin studies[27,28] reported no significant concordance. This was further investigated by another recent study[48] involving 37 patients and 100 controls that reported no difference in genotype variants and expression of coagulation and inflammatory factors. However, Zheng *et al*[100] investigated the relationship between global DNA methylation involving 82 children with LCPD and 120 matched controls. They reported significant differences in the global methylation of peripheral blood DNA between patients with LCPD and matched controls. Further high-profile epigenetic studies in key tissues should be conducted providing new protagonists of the LCPD aetiology. *COL2A1* alterations were also investigated. Several case reports and studies were reported in our review[42-46]. Their association with the disease was found to be weak in a case study published by Kenet *et al*[101] involving 119 LCPD affected children and 276 controls, further supported by a review of the literature. In the same study, the absence of significant association with Gaucher's disease and Factor V Leiden alterations was

also reported. On the contrary, further histological and ultrastructural studies found how p.Gly1170Ser mutation of *COL2A1* is involved in the pathogenesis of a type II collagenopathy[55]. This alteration leads to an amino acid change that perturbs a Gly-X-Y triple-helix repeat, which is a fundamental structure in type II collagen function[102]. Thus, *COL2A1* alterations should be further studied to clarify their role in the pathogenesis and aetiology of the LCPD.

Besides factor V Leiden and Prothrombin II polymorphisms being associated with a three times higher likelihood of disease and a 1.5-fold increase of risk, the results were not statistically significant[47]. Thus, even though the topic was extensively studied, recent evidence of hypercoagulability is inconclusive. Baltzer *et al*[103] reported a case of a child affected by Kienbock's disease and factor V thrombophilia who developed LCPD. The patient's hypercoagulability state may link with the bilateral manifestation of Perthes disease. After a further review of the literature, the authors also found two other cases of multifocal osteonecrosis and hypercoagulable disorder in adult patients. We encourage additional molecular and clinical studies on hypercoagulative states and LCPD.

Among the studied molecules, inflammatory cytokines involved in immune responses provide a crucial prospective of research. In particular, a study[51] found how a polymorphism of IL-6, a proinflammatory cytokine involved in chronic inflammation and immune response[104], was found to be associated with LCPD. In addition, another study[52] reported a high synovial level of IL-6 in LCPD patients. This suggests that IL-6 is a possible future protagonist of new therapeutic approaches and translational research. We strongly encourage further studies on the IL-6 pathway. Another molecule studied is SIRT1, the mammalian ortholog of the yeast SIR2 (Silencing Information Regulator) and a member of the Sirtuin family. It was reported that it can inhibit nuclear factor kappa B (NF-kB) transactivational activity by deacetylating Lys310 of the RelA/p65 subunits. Thus, SIRT1 inhibits both its transcriptional activity and the release of inflammatory cytokines mediated by NF-kB[105]. What emerged in a recent research project held in 2017 is that treatment with interferon-β increased SIRT1 expression and inhibited secretion of IL-6 in avascular femoral head necrosis mouse model. Interferon-β activated SIRT1 in the RAW 264.7 cell and bone marrow-derived osteoclasts and decreased IL-6 secretion. What we can assume from these papers is that IL-6, NF-kB, SIRT1 and other molecules involved in the autoimmune response could be linked with LCPD aetiology and should be further investigated both as a possible cause of the disease and as a new potential therapeutic target.

A study of 2003[78] found how retarded epiphyseal ossification could be linked to LCPD. However, there is lack of consensus on the role of these anatomical alterations[65,79,80]. During development, the epiphyseal blood supply is almost exclusively provided by the deep branch of the medial femoral circumflex artery[75]. Both imaging and histological studies have shown a partial or complete loss of blood flow[61,77] and the development of ischemic necrosis[54] of the femoral head in LCPD. Mechanical-induced ischemia is one of the most supported hypotheses for the aetiology of LCPD[54,61,75-77]. Emerging evidence is supporting a role of repetitive mechanical stress to the epiphysis and de subsequent ischemia, as stated in different experimental models[65-69,73,74]. In addition, the association with ADHD[30-34,36] and hyperactive modification of behaviour could be easily explained with repetitive activity-induced mechanical stress. This was further explained with an higher risk of injury[35] in LCPD patients. The recent evidence strongly supports the role of mechanical stress in the aetiology of LCPD. We encourage high profile clinical studies to investigate more this etiopathogenesis.

Our study has some strengths. We extensively searched and identified all relevant genetic association studies, the most common comorbid and the possible etiologic hypothesis. Therefore, risk of bias assessment showed moderate overall risk that could influence our analysis.

The literature available on the aetiology of LCPD presents major limitations in terms of great heterogeneity and lack of high-profile studies. Although a lot of studies focused on the genetic, biomechanical and radiological background of the disease, there is lack of consensus on one or multiple major actors of the etiopathogenesis. While obesity, smoking exposure and child deprivation seems to be associated with LCPD aetiology, more studies are needed to understand the complex and multifactorial genesis of the avascular necrosis characterizing the disease.

ARTICLE HIGHLIGHTS

Research background

Legg-Calvé-Perthes disease (LCPD) is a complex disease with a multifactorial aetiology. The

etiopathogenesis of the disease was widely investigated in the last 20 years, but it is still unknown.

Research motivation
Numerous studies tried to explain the major actors in LCPD aetiology, but there is a lack of synthesis of the evidence.

Research objectives
The purpose of the study was to summarize the current evidence on the aetiology of LCPD.

Research methods
Two databases (PubMed and Science Direct) were systematically searched for relevant articles by two independent reviewers from their date of inception to the 20th of May 2018. Every step of the review was done according to PRISMA guidelines. Due to article heterogeneity and the topic after data analysis, a descriptive (synthesis) analysis was performed.

Research results
Sixty-four articles were included in this systematic review after applying our inclusion and exclusion criteria. Available evidence on LCPD aetiology is still inconclusive. Several hypotheses have been researched but none of them was found decisive.

Research conclusions
After our systematic review of the available evidence we conclude that LCPD aetiology relies on a multifactorial basis where environment in genetically predisposed patients participates in the pathogenesis of the disease.

Research perspectives
Further clinical and preclinical studies are strongly encouraged to understand better the mechanical and vascular basis of the etiopathogenesis of the disease. Interesting perspectives from studies on Leptin, obesity, and mechanical trauma were found and should be further investigated.

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SYSTEMATIC REVIEW

Changing trends in the mortality rate at 1-year post hip fracture - a systematic review

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Abstract

BACKGROUND

Traditionally, the mortality rate at 1-year post hip fracture was quoted as approximately 30% of all hip fractures. There have been recent improvements in hip fracture care in the main driven by national hip fracture registries with reductions in 30-d mortality rates reported.

AIM

To address recent 1-year post hip fracture mortality rates in the literature.

METHODS

Systematic literature review, national hip fracture registries/databases, local studies on hip fracture mortality, 5 years limitation (2013-2017), cohorts > 100, studies in English. Outcome measure: Mortality rate at 1-year post hip fracture.

RESULTS

Recent 1-year mortality rates were reviewed using the literature from 8 National Registries and 36 different countries. Recently published 1-year mortality rates appear lower than traditional figures and may represent a downward trend.

CONCLUSION

There appears to be a consistent worldwide reduction in mortality at 1-year post hip fracture compared to previously published research. Globally, those which suffer hip fractures may currently be benefiting from the results of approximately 30 years of national registries, rigorous audit processes and international collaboration. The previously quoted mortality rates of 10% at 1-mo and 30% at 1-year may be outdated.

Key words: Hip fracture; Mortality; Registries; Databases

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Core tip: This review reports a global downward trend in 1-year mortality rate post hip fracture. The results of this study suggest that the previously reported 1-year mortality rate of 30% is out-dated and a figure of 22% is a more accurate, up-to-date estimation of 1-year mortality rate post hip fracture.

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INTRODUCTION

Hip fracture care continues to improve secondary to international audit and optimization of hip fracture management. Hip fractures are exceedingly common presentations to global emergency departments with approximately 3600 in Ireland per year[1], approximately 65000 in the United Kingdom[2], approximately 620000 in the European Union[3], approximately 300000 in the United States[4] and roughly 2 million worldwide[5]. This global figure is modest projected to increase threefold by 2050[6].

There is significant cost associated with hip fractures regarding: (A) financial cost to the health service providing care; and (B) morbidity and mortality cost to the patient. Recent research estimates the year 1 hospital cost secondary to an index hip fracture to be £14000 (€15900/$18750) per patient[7]. The annual cost of treatment in the European Union and the United States has been recently reported as €32 billion and $20 billion respectively[8].

The literature describes that after suffering a hip fracture, the patient will experience a reduction in overall functional status, social independence, mobility and increasing scores in depressive symptoms[9-10]. Due to the high prevalence of hip fractures and the disadvantage to both the patient and the local health service responsible for care, optimisation and the standardisation of hip fracture management has been targeted to reduce morbidity, mortality and financial expense. This optimisation and standardization, in the form of a national registry, has been shown previously to improve the quality of care and outcomes of hip fracture patients[11].

The earliest hip fracture registry established is "RIKSHÖFT", the Swedish national hip fracture registry, set up in 1988, following on from the successful local implementation of national knee and hip arthroplasty registers in the 1970s[12]. In 1993, the Scottish Hip Fracture Audit (SHFA) implemented a registry that reported annually until 2008, after which, the audit was stepped down to capture "snapshot" data only. Following audit and the recognition of deterioration in outcomes post step down[13], the SHFA was re-implemented in May 2016 and year round data collection was re-instituted[14]. In 1995, the European Commission funded the initiation of the Standardised Audit of Hip Fracture in Europe due to the triumphs in outcomes secondary to the "RIKSHÖFT" audit in Sweden[15]. The Danish orthopaedic community established the Danish Hip Fracture Database in 2003[5] whilst the Norwegian community set up their database, the "NOREPOS", in 2005[16].

In 2007, an important milestone was reached regarding the initiation of the largest and fastest growing national hip fracture registry by the United Kingdom. After publishing the "Blue Book", which set quality standards established by the British Orthopaedic Association and the British Geriatrics Society, the National Hip Fracture Database (NFHD) began to collect and publish data annually regarding hip fractures[3]. In 2010, a European Union program, named euroHOPE (Healthcare Outcomes, Performance, Efficiency), was created to compare healthcare performance regarding hip fracture treatment across 7 European countries[17]. The fragility fracture network was then established in 2011, a global network, with a mission to optimize the multidisciplinary management of patients with fragility fracture globally and prevent secondary fracture[18]. This was followed by the foundation of the Irish Hip Fracture Database in 2012[1] and more recently the Australian and New Zealand Hip Fracture Registries in 2016[19]. Several countries are currently piloting their own national hip registries following the achievements published by the registries described above including Greece, Malta, Nederlands, Slovenia, Spain, Lebanon and Argentina.

Traditionally, orthopaedic trainees are taught that the mortality rates in this fragile

population were approximately 10% at 30 d and approximately 30% at 1 year[20]. These figures are important at: (A) a patient level with regards to family discussions surrounding realistic expectations and prognosis following hip fracture; and (B) at a hospital and national level with regards to the optimisation of care and distribution of finite resources.

In 2015, following a review of 471590 patients which suffered a hip fracture in the United Kingdom between 2003-2011, it was concluded that "the launch of a national clinician-led audit initiative was associated with substantial improvements in care and survival of older people"[21]. This group reported significant reductions in 30-d mortality.

Following review of the recent literature emanating from the national registries, it was noted that whilst 87.5% of the national registries publish annual data on in-patient mortality and 62.5% publish annually on 30-d mortality, only 12.5% (1 registry) published mortality rate at 1-year post hip fracture. In order to explore whether there have been any recent global reductions in 1-year mortality post fracture, a systematic literature review was undertaken.

MATERIALS AND METHODS

A review of the available literature on (A) national hip fracture registries/databases and (B) local hip fracture studies which included 1-year mortality data was conducted using Pubmed and Google Scholar. The following keywords were used: "hip fracture", "mortality", "year", "death", "outcomes", "registry", "registries", "database" and "databases". The inclusion criteria were those studies published within the last 5 years (2013-2017), studies including a cohort > 100 and those in the English language. The most recent national registry reports were obtained and personal contact to authors of the Swedish and Danish reports *via* e-mail was required as these are reported in local language only.

RESULTS

National Registries

Table 1 lists the countries, registry names, foundation year, age inclusion criteria, recent annual reports with reference and the mortality data published by each of the 8 national databases. 87.5% of the registries have an age inclusion criteria of 50 years or more. The table shows a dearth in published data for 1-year mortality rates post hip fracture.

Europe

Recent (previous 5 years) 1-year mortality research data from the European continent was extracted from the literature and is summarised in Table 2. There were 22 articles reviewed with a mean 1-year mortality of 23.3% [standard deviation (SD) 6.3%, median 23.4%] reported. The lowest figure was 9.7% with the highest 34.8%. 19 of the 22 articles (86%) reported data regarding cohort numbers ranging from 124 to 31668 patients included (median 444, mean 6902, SD 11804). 91% reported age related inclusion criteria, with 55% including > 60 years only and the remaining 45% including patients < 60 years old. 82% of the articles were published within the period 2015-2017.

Asia

One year mortality data (2013-2017) from the Asian continent was extracted from the literature and is summarised in Table 3. There were 10 articles reviewed with a mean 1-year mortality of 17.89% (SD 8.7%, median 18.9%) reported in studies selected. The lowest figure was 2.4% with the highest 30.4%. All of the articles reported data regarding cohort numbers, which ranged from 110 to 43830 patients included (median 400, mean 5621, SD 13566). 90% reported age related inclusion criteria, with 67% including > 60 years only and the remaining 33% including patients < 60 years old. 70% of the articles were published in the year 2017 with 90% published within 2015-2017.

Oceania

Table 4 lists the results from a large study undertaken in New South Wales, Australia which published a 1-year mortality rate post hip fracture of 24.9%. This study included 27888 patients which were aged > 60 years. To the best of the author's knowledge, there were no recent local studies emanating from New Zealand

Table 1 Data from the National Registries

Country	Registry	Setup	Age	Report	Inpatient (%)	30-d (%)	1-Yr (%)
Sweden	RIKSHÖFT	1988	> 50	2016[22]	3.39	-	-
Scotland	SHFA	1993	> 50	201 [23]	5	-	-
Denmark	DHFD	2003	> 65	2016[24]	3	10	-
Norway	NHFR	2005	> 18	2016[25]	-	7.7	24
UK*	NHFD	2007	> 60	2016[2]	7	6.7	-
Ireland	IHFD	2012	> 60	2016[1]	5	-	-
Australia	ANZHFR	2016	> 50	2016[19]	5	5	-
New Zealand	ANZHFR	2016	> 50	2016[19]	4	3	-

*England, Wales & Northern Ireland. SHFA: Scottish Hip Fracture Audit; DHFD: Danish Hip Fracture Database; NHFD: National Hip Fracture Database; ANZHFR: Australian and New Zealand Guideline for Hip Fracture Care.

regarding mortality post hip fracture.

North America

Table 5 lists the results from a large study undertaken in the United States using the Kaiser Permanente database. This recent publication describes a 1-year mortality rate post hip fracture of 21%. This study included 14294 patients which were aged > 60 years. To the best of the author's knowledge, there were no recent local studies published from Canada regarding 1-year mortality post hip fracture.

South America

One year mortality data from the South American continent was extracted from the literature and is summarised in Table 6. There were 2 articles reviewed with a mean 1-year mortality of 26.8% (SD 4.5%). The articles included small cohorts with 100 and 213 patients respectively. Both of the studies included patients > 65 only.

Africa

There has been no research regarding hip fracture mortality published throughout the African continent during the past 5 years to the best of the authors' knowledge.

Global overview

Overall, local hip fracture related studies from 36 different countries were reviewed with regards to 1-year mortality rates post hip fracture. The mean overall 1-year mortality rate was 22.0% (SD 7.2%, median 22.8%) with a range from 2.4%-34.8%. A combined total of 229851 patients were included, with a range of 100-43830 patients from the smallest and largest cohort respectively. The median cohort was 402 patients. 61% of the studies involved a cohort between 100-1000 patients, with 18% between 1001-10000 and the remaining 21% including more than 10001 patients. 58.3% of the studies included patients > 60 years only, with 33.3% including patients < 60 also with a small proportion not declaring age inclusion/exclusion criteria. Using studies which included patients > 60 years only (n = 21/36) may result in a more accurate representation of fragility hip fracture cohorts, however the results were quite similar with a mean rate of 21.8% (SD 7.6%, median 23.6%) mortality 1-year post hip fracture. 83.3% of the local studies research included in this study was published in the years 2015-2017.

DISCUSSION

The mortality at 1 year post hip fracture has traditionally been reported as 30%[20] and more recently described as "around a third within a year"[60], whilst the 2017 NFHD annual report suggests "up to a third die within a year following a hip fracture"[2]. There have been significant developments with regards to data collection in the areas of casemix, surgical/anaesthetic practice, process and outcomes of hip fracture care by the national registries. However, only 1 of the 8 national registries is publishing data regarding mortality at 1-year post hip fracture. There is therefore a void in the published literature on this topic.

After reviewing the recent hip fracture related mortality literature, it was found that the mean 1-year mortality rate in Europe was 23.3% (22 studies), whilst in Asia

Table 2 Data from local hip fracture studies in Europe

Country	Origin	Published	*n*	Age	1-Yr (%)
Ireland	Limerick[26]	2017	206	> 60	9.7
Sweden	Lund[27]	2016	373	> 50	9.91
Denmark	Copenhagen[28]	2017	444	> 60	16
Italy	euroHOPE Registry[17]	2015	-	-	19.1
Switzerland	National Medical Statistic[29]	2014	24,678	> 18	20
Austria	Austrian Social Insur. Data[30]	2014	31,668	> 50	20.2
Portugal	Nat. Hosp. Discharge Reg[31]	2015	186	> 60	20.4
UK	Clin. Practice Res. Datalink[32]	2014	31,495	> 18	20.5
Romania	Timisoara[33]	2014	1,866	> 55	21.1
Nor. Ireland	FORD Database[34]	2017	27,055	> 18	21.7
Netherlands	National Discharge Register[35]	2017	850	> 70	23.2
Finland	National Discharge Register[17]	2015	-	> 60	23.6
Malta	National Mortality Register[36]	2016	281	> 60	25.6
Norway	Trondheim[37]	2017	1,820	> 65	25.9
Iceland	Reykjavik [38]	2016	255	> 60	27
Spain	Igualada[39]	2017	792	> 69	27.3
Estonia	Health Insurance Fund[40]	2017	8,298	>50	28.3
Croatia	Zagreb[41]	2017	236	> 18	28.4
Belgium	Brussels[42]	2016	286	> 64	28.7
Turkey	Ankara[43]	2016	124	> 23	29.2
Germany	Trauma Registries[44]	2017	231	> 70	31.4
Hungary	euroHOPE Registry[17]	2015	-	-	34.8
Greece	Pilot Program	-	-	-	-
Slovenia	Pilot Program	-	-	-	-

was 17.9% (10 studies). The figures for the United States and Australia were 21% and 24.9% respectively. The figure in South America was 26.8%, however, this originated from small studies. On analysis of data from all 36 studies (n = 229851 patients), the mean 1-year global mortality rate was 22% (SD 7.2%, median 22.8%).

These results are at odds with those reported previously and may suggest a consistent global improvement in longer-term survival following hip fracture. Best practice guidelines have been developed by way of continuous optimization through the auditing process of the national registries and continue to be developed, refined or discarded based on continuous audit cycle. The improvement in longer term survival post hip fracture may be secondary to worldwide adoption of current best practice in the care and secondary prevention of hip fracture.

This is the first study that has reviewed recent worldwide-published data on 1-year mortality rates including data collected from 229851 patients. Although the literature review included studies within the last 5 years, it is worth noting that the vast majority (83%) of the local studies (30/36) were published within the last 3 years (2015-2017). It is also worth noting that the most recent papers on this topic (published in 2018) confirm that the changing trend in 1-year mortality continues to be observed[61-63]. Cancio *et al*[64] this year published a 1-year mortality rate of 22% for a large hip fracture cohort (n = 30552), which is similar to our findings described above.

Whilst this article reports a decreasing trend in mortality at 1-year post hip fracture, it is important to recognize limitations of this study. A potential source of error is the use of data from all 36 studies to ascertain a mean mortality rate as some of the studies included patients < 60 years of age. However, limiting the inclusion criteria to those studies that include patients > 60 years only, the mortality rate is 21.8% (SD 7.6%, median 23.6%) which is a similar finding. Another limitation is equal weighting to mortality rates despite wide variation in cohort numbers. Limiting the inclusion criteria to those studies which include > 10001 patients only (n = 7), the mean mortality rate is 20.7% (SD 2.4%, median 20.5%) which also is a similar finding.

It is also worth noting that as an index hip fracture outcome measure, mortality is an imperfect quality indicator and is affected by both patient age and casemix (multiple comorbidities typically). Therefore, it is the trend in mortality rate data over time that is more useful as a quality indicator.

Table 3 Data from local hip fracture studies in Asia

Country	Origin	Published	*n*	Age	1-Yr (%)
Japan	Tsukuba[45]	2017	110	> 60	2.4
Thailand	Bangkok[46]	2015	120	> 50	9.2
South Korea	Daejeom[47]	2017	402	> 60	9.5
Hong Kong	Laichikok/Shamshuipo[48]	2017	43830	> 65	16.8
Taiwan	Kaohsiun[49]	2017	5442	> 60	16.8
Kazachstan	Almaty[50]	2017	398	> 50	21
Iran	Tehran[51]	2017	1015	> 50	22.4
China	Beijing[52]	2016	4504	> 60	23.4
Saudi Arabia	Al Khobar/Dammam[53]	2017	203	-	27
India	New Delhi[54]	2013	188	> 60	30.4
Lebanon	Pilot Program	-	-	-	-

Osteoporosis currently causes approximately 9 million fractures annually around the world[65]. As alluded to in the introduction, hip fractures are increasing with excess of 6 million per year predicted in 2050. The greatest increases are expected in Asia[66]. The World Health Organisation predicts that between 2000 and 2050, the proportion of those aged > 60 will double in numbers from 11 to 22% or 605 million to 2 billion people[67]. It is important that this expected rise is planned for and this literature review suggests that as a global orthopaedic and orthogeriatric community, vast strides are being made in the optimisation of care with hip fracture patients to mitigate for the impending surge in hip fracture incidence. The reduction in 1-year mortality provides feedback that following adoption of hip fracture management standards of care, it is not simply improvements in early mortality with deferral of mortality outside of the acute window (30 d) but longer-term survival at 1-year post hip fracture. The United Kingdom National Hip Fracture Database website publishes monthly on overall performance measures including national average 30-d mortality. The most recent figure was 5.7% (July, 2018)[68] with almost month-to-month reductions since initially published in April 2012. These findings are very positive. Another recent positive development in hip fracture care is the increasing involvement of orthogeriatricians in the care of these fragile patients and their corresponding impact on mortality reduction[60].

The data collected by the national registries allow us as a community to tackle a complex international problem to minimise morbidity, mortality and costs associated with hip fractures. These registries continue to be optimised and it has been recently suggested that (1) simplicity; (2) continuous collection of all cases as routine practice; (3) definition of variables collected; and (4) a common set of variables collected will fulfil the criteria of a model registry which should allow direct national and international comparison and further improvements in care delivered[3].

In conclusion, globally, those which suffer hip fractures may currently be benefiting from 30 years of national registries, rigorous audit processes and international collaboration. This literature review suggests a decrease in trends in mortality at 1-year post hip fracture compared to previous research on this topic. Further improvements in hip fracture care quality indicators are expected by the authors in light of increased involvement of the orthogeriatric subspeciality and the continuous refinement process of the national registries. The results of 7 novel national pilot registries are anticipated.

Table 4 Data from local hip fracture studies in Oceania

Country	Origin	Published	*n*	Age	1-Yr (%)
Australia	New South Wales[55]	2017	27888	> 65	24.9
New Zealand	-	-	-	-	-

Table 5 Data from local hip fracture studies in North America

Country	Origin	Published	*n*	Age	1-Yr (%)
United States	Kaiser Permanente[56]	2017	14294	> 60	21
Canada	-	-	-	-	-

Table 6 Data from local hip fracture studies in South America

Country	Origin	Published	*n*	Age	1-Yr (%)
Brazil	Canoas[57]	2017	213	> 65	23.6
Mexico	Toluca[58]	2014	100	> 65	30
Argentina	Pilot Program[59]	-	-	-	-

ARTICLE HIGHLIGHTS

Research background

Hip fracture audit is increasing globally with 8 countries producing national reports annually and several countries currently piloting hip fracture audit schemes. Hip fracture audit has been shown to result in improvements in care and survival of older people. Short-term mortality rates (in-patient and 30-d) are published by the majority of national registries and there is evidence that short term mortality rates are decreasing. The 1-year mortality rate post hip fracture is currently recognized as approximately 30%. Recent longer-term (1-year) mortality information is lacking in the literature.

Research motivation

Our research group believes there may also be a changing trend (decreasing) in 1-year mortality post hip fracture. Knowledge of a more current, up-to-date figure will lead to a more informed discussion with family of those affected and optimization of care of this fragile cohort at hospital and national levels.

Research objectives

To determine the current 1-year mortality rate post hip fracture.

Research methods

Systematic literature review. The following keywords were used: "hip fracture", "mortality", "year", "death", "outcomes", "registry", "registries", "database" and "databases" (PubMed and Google Scholar). The inclusion criteria were those studies published within the last 5 years (2013-2017), studies including a cohort >100 and those in the English language.

Research results

Data from 8 national registries and 36 countries (6 continents) were reviewed. Recently published 1-year mortality rates appear lower than traditional figures and suggest a downward trend.

Research conclusions

The previously quoted 1-year mortality rate of approximately 30% appears to be outdated. A figure of 22% is a more accurate, up-to-date figure for 1-year mortality rate post hip fracture.

Research perspectives

This research provides a more current, up-to-date figure for 1-year mortality rate post hip fracture.

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