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Multidimensional evaluation of the pain profile as prognostic factor in individuals with hip or knee osteoarthritis receiving total joint replacement: protocol of a 2-year longitudinal prognostic cohort study

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ABSTRACT

Introduction Knee and hip osteoarthritis are two highly prevalent musculoskeletal pain conditions. Unsuccessful rates after hip/knee replacement range from 10% to 20%. Subjects with sensitisation manifestations are vulnerable to worse clinical outcomes. Most studies have analysed outcomes up to 1 year after surgery. The aim of this 2-year longitudinal study will be to evaluate sensory-related, psychological and psychophysical pain sensitisation manifestations and a potential epigenetic biomarker as prognostic clinical outcomes for the development of chronic postoperative pain after knee or hip replacement.

Methods and analysis A prospective longitudinal study with a 2-year follow-up period will be conducted. The prognostic variables will include pain, function, related-disability, anxiety, depression, quality of life, sensitisation-associated symptoms, kinesiophobia, neuropathic pain and catastrophising, and expectative of the intervention will be assessed before surgery. We will also evaluate the presence of the Val158Met polymorphism as a possible epigenetic marker. Clinical outcomes including pain, related-disability and self-perceived satisfaction, sensitisation-associated symptoms and neuropathic pain will be assessed 3, 6, 12, 18 and 24 months after surgery. These variables will be used to construct three prediction models: (1) pain and function, (2) sensitisation-associated symptomatology and (3) neuropathic pain features classifying those patients in responders and non-responders. Data from knee or hip osteoarthritis will be analysed separately. Statistical analyses will be conducted with logistic regressions.

Ethics and dissemination The study has been approved by the Ethics Committee of both institutions involved (Hospital Universitario Fundación Alcorcón (HUFA) 19–141 and Universidad Rey Juan Carlos (URJC) 0312201917319). Participants will sign the written informed consent before their inclusion. Study results will be disseminated through peer-reviewed publications and presentations at scientific meetings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The first study including multidimensional evaluation for predicting variables associated with postoperative knee or hip pain.
⇒ The first prospective longitudinal study with a 2-year follow-up period.
⇒ The main limitation will be a potential dropout rate during the 2-year follow-up.

INTRODUCTION

Osteoarthritis (OA) is a chronic musculoskeletal disease that causes pain and disability. According to the Global Burden Disease 2019, the knee and hip are the most prevalent affected joints.[1] In fact, knee and hip OA had increased their prevalence worldwide between 1990 and 2019.[1] With the expected global growth in the elderly population and concomitant rise in stationary lifestyle choices, the incidence of OA is predicted to increase in the coming years.

Treatment of OA-related pain can be conservative or surgical. Total replacement surgery probably represents the standard surgical treatment. Although surgery generates good results both in subjects with knee or hip OA, approximately 13% of individuals who receive knee replacement and 30% of subjects receiving hip replacement report postoperative pain in the first 2 years, which can become disabling.[2–4] Moreover, about 10%–20% of patients who underwent to total knee replacement (TKR) or total hip replacement (THR) were not satisfied with their surgery.[5 6]

Several factors could contribute to patient's dissatisfaction, such as residual pain, remaining disability and expectations.[7–11] There has been a wide effort in the literature to identify which preoperative characteristics could predict postsurgery pain or residual related-disability in patients after THR or TKR. Some studies have observed that the presence of sensitisation-associated symptomatology prior to surgery or neuropathic pain symptoms is associated with persistent postoperative pain and worse clinical outcome in individuals receiving TKR or THR,[12–15] although this association seems to depend on the degree of joint injury prior to surgery.[16 17] Overall, these studies observed that the presence of higher generalised mechanical pain hyperalgesia prior to surgery was associated with worse clinical outcomes after surgery, resulting in greater postoperative pain or related-disability. However, other studies have found no association between mechanical hyperalgesia and clinical outcomes after TKR.[16 18] Cognitive factors, such as pain catastrophising, kinesiophobia, and anxiety or depression, have also been identified as predictive factor to worse prognosis after TKR.[19–23] However, this association between psychological variables before surgery and patient outcomes is controversial.[24] Most of previous published prospective studies addressing potential predictive factors of worse prognosis in patients with TKR or THR included 12-month follow-up periods since those studies including data from 24 months are more often retrospective studies.[14]

Another important factor associated to postsurgical pain is genetic predisposition. Genetic profile related to the catechol-O-methyltransferase (COMT) gene has also been considered among the determinant factors related to nociceptive.[25] The Val158Met polymorphism of the COMT gene is a predisposing factor associated to worse clinical presentations in patients with different chronic pain conditions.[26–29] In fact, in individuals with OA, the Met allele has been associated with increased pain levels in those patients with hip OA[30] but not in those with knee OA.[31] However, study probing the association of the Val158Met polymorphism with the presence of pain after THR has showed inconclusive data.[32 33]

There is a lack of studies investigating the combination of different types of predictive factors of worse clinical prognosis after TKR in the same sample, a lack of data about individuals receiving THR and few prospective studies including longer follow-ups in both TKR and THR. It should be noted that most studies have investigated proxied for sensitisation by analysing quantitative sensory tests (mainly pressure algometry, temporal summation of pain or descending pain modulation) or using single questionnaires, which may represent a limited view of manifestations of pain sensitisation. In fact, there are several clinical manifestations of sensitisation, such as spreading pain symptoms, sleep disturbances, pain hypervigilance, fear of movement (kinesiophobia) or pain catastrophic thoughts, which have not been consistently included as predictive factors in several studies. All these features present in individuals with knee or hip OA are central nervous system-derived symptoms associated with nociplastic pain conditions.[34] While patients with nociplastic pain and hip OA may benefit from THR, many patients with nociplasticity do not improve or worsen after THR.[35] It has been observed that the presence of nociplasticity, that is, central nervous system hyperexcitability, predicts poorer outcomes after surgery.[36] Furthermore, patients presenting with nociplastic pain also exhibit worse outcomes in general after TKR.[37 38]

Identifying preoperative predictors of poor outcomes after TKR or THR associated with the presence of nociplastic pain could alter preoperative procedures (including counselling of the patients) and rehabilitation methods. Current randomised controlled trials using exercise programmes postoperatively in individuals after TKR or THR have not accounted for the presence of pain mechanisms and psychosocial variables at the same time. Therefore, tailoring pain management strategies to include pain mechanisms and psychosocial variables has shown to enhance patient outcomes in patients with nociplastic pain.[39] In fact, rehabilitation strategies aimed at improving nociplasticity, such as pain education, manual therapy and exercise programmes, could be multimodally used to further enhance outcomes, particularly in those at risk for poorer outcomes.[40–42]

Accordingly, we plan to conduct a longitudinal cohort study including variables of pain sensitisation, psychological/emotional and cognitive variables, as well as genetic predisposition, all manifestations of a nociplastic pain condition, as prognosis variables of clinical outcomes after TKR or THR with a follow-up period of 2 years after surgery. The primary aim of this 2-year longitudinal prognostic cohort study is to determine which clinical, psychological and psychophysical proxies for sensitisation are associated to worse short-term, mid-term and long-term responses after a TKR or THR in people with knee or hip OA, considering function and pain dimensions as main outcomes. The secondary aim of the study will be to identify if the Val158Met polymorphism of the COMT gene has also an influence on the clinical response/progression and on the pain sensitisation after TKR or THR.

METHODS AND ANALYSIS

Study design

A longitudinal prognostic cohort study will be conducted. The participants will be evaluated before receiving TKR or THR and during the following follow-up periods: 3, 6, 12, 18 and 24 months (figure 1). The study recruitment is planned to begin in September 2022 and to finish the follow-up in 2025.

Participants will be recruited from the Orthopaedic and Traumatological Surgery Department of the Hospital Universitario Fundación Alcorcón (HUFA), an urban hospital in Madrid (Spain). They will be assessed throughout the study at Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine of Universidad Rey Juan Carlos (URJC). As

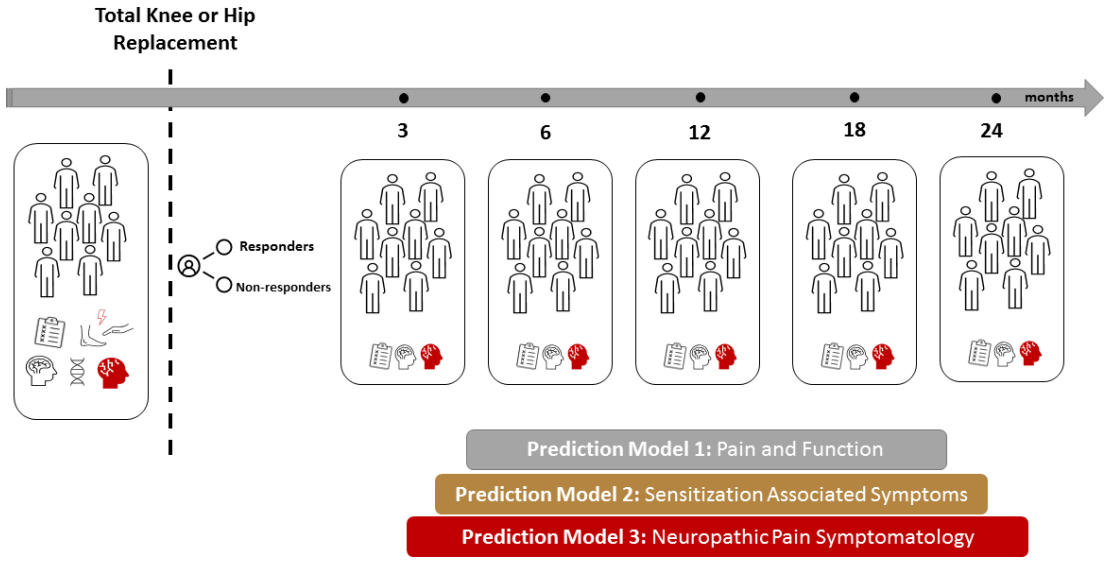

Figure 1 Study design: longitudinal prognostic cohort study. Patients will be assessed at baseline for all the predictor variables (see text) and at 3, 6, 12, 18 and 24 months after surgery for clinical (prediction model one), sensitisation-associated symptomatology (prediction model two) and neuropathic pain features (prediction model three).

an attempt to reduce the drop-out considering the long follow-up period, phone calls will be performed every 3 months.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Participants

A non-probabilistic sampling of consecutive cases will be adopted. Inclusion criteria will be patients with knee or hip OA recruited from the Orthopaedic and Traumatological Surgery Department of the HUFA who are currently in the hospital waiting list for knee or hip arthroplasty. The clinical criteria for TKR or THR will be determined by experts in joint replacement with 20 years of experience from the orthopaedic and trauma service of this hospital independently of the study protocol. The OA stage is classified according to the Kellgren and Lawrence radiological levels,[43] and the proposal of surgery is based on the clinical situation of the patient.

Exclusion criteria will be: (1) older than 75 years; (2) previous surgical intervention; (3) previous lower extremity trauma; (4) medical diagnosis of fibromyalgia; (5) regular consumption of opioids as painkiller or (6) refuse to participate in the study.

In case of revision surgery, the patients will be excluded from the cohort study but will be analysed separately for any preoperative predictors.

Postsurgical outcomes

The clinical outcomes of interest after surgery will be: (1) self-reported perception of change; (2) function or related-disability; (3) sensitisation-associated symptomatology and (4) presence of neuropathic pain symptoms. These clinical outcomes will create three different prediction models as depicted in figure 1.

Prediction model 1: pain and function

This model will consider the following clinical outcomes: pain, function and self-perception of change. Pain intensity will be assessed with an 11-point Numeric Pain Rating Scale (NPRS, 0–10). Participants will rate their mean pain intensity at rest, the most intense pain at rest and their pain during daily activities in the last week, and the mean will be used in the main analysis. The minimum clinically important difference (MCID) for the NPRS has been shown to be 1.74 in patients with chronic pain conditions;[44] however, the MCID for knee or hip OA has not yet been established. In the current study, we considered a change of 2 points or a 30% decrease in pain from baseline as our MCID.[45]

Function will be assessed by the Spanish version of the Western Ontario and McMaster Universities OA Index (WOMAC) which assess three dimensions: pain (5 items), stiffness (5 items) and function (17 items).[46] All items are scored on a scale of 0–4 (lower scores indicate lower levels of symptoms or physical disability). Dimensions can be scored separately or in a total score.[47] In patients with OA of the lower extremities, changes from 9% to 12% of the baseline score can be considered as the MCID for the WOMAC.[48 49]

Self-perception of patient change will be assessed with a 15-point Global Rating of Change (GROC) Scale, ranging from −7 (a very great deal worse) to 0 (no change) to 7 (a very great deal better).[50] Scores of +4 and +5 have typically been indicative of moderate changes in patient status.[50]

Patients will be classified as responders to the surgery to this first prediction model when changes in the NPRS or

WOMAC surpassed the MCID and the GROC has a score over +4 points.

Prediction model 2: sensitisation-associated symptoms

The presence of sensitisation-associated symptoms will be assessed by the Spanish version of the Central Sensitisation Inventory (CSI).[51] The CSI evaluates 25 items related to symptoms associated with sensitisation, providing a score ranging from 0 to 100 points.[52] Values above 40 points represent the presence of sensitisation-associated symptoms.[52] Patients will be classified as responders to the surgery to this second prediction model when the CSI score after surgery is lower than 40 points.

Prediction model 3: neuropathic pain symptomatology

Neuropathic pain-like symptoms will be assessed by the Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and by the PainDETECT.[53 54] The S-LANSS assesses seven questions to determine the presence of neuropathic symptoms, on a score of 0–24 points.[55] A score of ≥12 points suggests the presence of potential neuropathic pain features.

The PainDETECT assesses different responses to pain-related questions during the previous 4 weeks. The PainDETECT questionnaire has a score between 0 and 38 points, where >18 points suggest features of likely neuropathic origin, and scores ranging between 12 and 18 points suggest ambiguous neuropathic pain origin.[54]

Patients will be classified as responders to the surgery to this third prediction model when the S-LANSS score is <12 points, and the PainDETECT score is also <18 points after surgery at each follow-up.

Predictor variables

Clinical variables

Individual and clinical data collection will include age, sex, height, weight, years with symptoms, affected side and Kellgren and Lawrence radiological level (collected from medical records). Pain localisation and extent will be registered by body maps using the software Inkscape (V.0.91). Four digital body charts (ventral and dorsal lower quadrant as well as both sides views) representing the female/male human body will be provided to all participants. Patients will be instructed to complete a pain drawing by shading, with a red pencil, their pain symptoms (figure 2). We asked for shading the distribution of their pain symptoms as accurately as possible regardless of their intensity and their type avoiding the use of circle outlines or cross-marks. The reliability of this procedure has been previously confirmed.[56]

For pain intensity, the participants will rate their mean pain intensity at rest, the most intense pain at rest and their pain during daily activities in the last week using the 11-point NPRS, and a mean score will be calculated. Function will be assessed by the WOMAC questionnaire as previously described in the first model.[46]

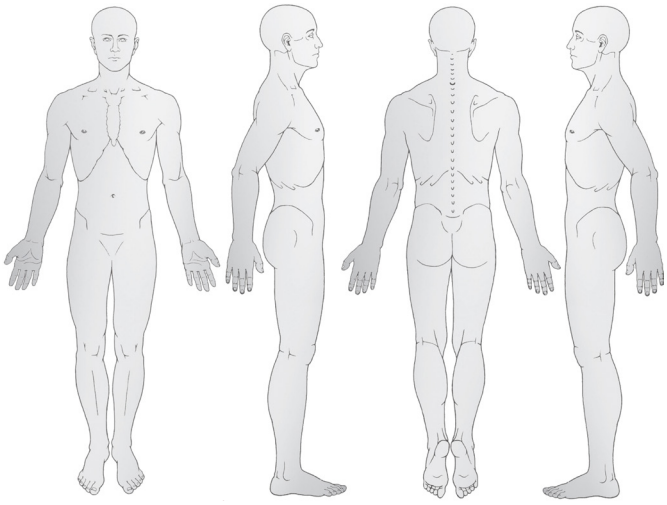

Figure 2 Digital body charts used for evaluating pain extent.

Health-related quality of life

To assess general health status, the SF-12 questionnaire, a reduced version of the SF-36, will be used.[57] The SF-12 total score ranges from 0 to 100, higher values corresponding to higher perceived quality of life. The questionnaire contemplates the same eight domains as the SF-36 but is grouped into physical and mental components and has shown good psychometric properties.[58 59]

The EuroQol-5D questionnaire will be also used to measure health-related quality of life, being expressed in terms of utility.[60 61] EuroQol-5D scores from 0 to 100, 0 point represents the worst possible health status, while 100 points represent the best possible health status. Responses will be converted into a single index number between 0 (death) and 1 (optimal health), by applying crosswalk index values for Spain life.[62] The EuroQol-5D has been found to be equally valid and reliable as the WOMAC in knee OA.[63]

Psychological and cognitive variables

The variables within the psychological/cognitive domain that will be assessed are symptoms of anxiety and depression, hypervigilance, pain catastrophising and kinesiophobia.

Anxiety and depressive symptoms will be assessed with the Hospital Anxiety and Depression Scale. It is a 14-item self-reported questionnaire, composed of 7 items related to anxiety and 7 items related to depression symptoms.[64 65] The total score of each scale ranges from 0 to 21 points where higher values represent more anxiety or depressive levels.

Pain hypervigilance will be assessed by the Pain Vigilance and Awareness Questionnaire.[66] The Spanish version is composed of nine items, with responses ranging from 0 (never) to 5 points (always). This version presented appropriate validity.[67]

Pain catastrophising will be assessed by the Pain Catastrophisation Scale, which is a 13-item self-reported scale with three dimensions (rumination, magnification and helplessness).[68 69] The items describe different thoughts

and feelings that individuals may experience when they are in pain. The total score ranges from 0 to 52 points.[69]

Kinesiophobia levels, that is, fear to motion, will be assessed by the shortened version of the Tampa Kinesiophobia Scale (TKS-11) that is composed of 11 items to be answered on a scale from 1 (totally disagree) to 4 (totally agree), with scores ranging from 11 to 44 points. Items are related to the fear of movement or fear of (re)injury during movement. The TKS-11 have shown appropriated structure for assessing fear to motion in both acute and chronic pain conditions in Spanish population.[70]

Self-reported variables related to sensitisation

The following self-reported questionnaires assessing symptoms associated with sensitisation will be assessed: S-LANSS, PainDETECT, CSI and Pittsburgh Sleep Quality Index. The S-LANSS and PainDETECT will be used to assess symptoms of neuropathic pain as previously explained in the first model section.

The CSI assesses the presence of 25 associated symptoms of central sensitisation with scores ranging from 0 to 100 point.[51 52] A score >40 points suggests the presence of sensitisation-associated symptoms.[52]

The Pittsburgh Sleep Quality Index will assess the sleep quality in the previous month.[71] It is composed of 19 self-reported items that generate 7 components. The global score ranges from 0 to 21 points; the higher score indicates worse sleep quality.[71]

Psychophysical outcomes: pressure pain thresholds

Pressure pain thresholds (PPT) will be assessed bilaterally nearby the affected joint and also remote areas with an electronic algometer (Somedic AB, Farsta, Sweden). The pressure will be applied perpendicularly to the point at a rate of approximately 30 kPa/s. Three repetitions of each point assessment will be registered with 30 s interval between them to avoid temporal summation.

For patients with knee OA, PPT will be calculated over eight test points around the peripatellar region: point 1: 2 cm distal to the inferior medial edge of patella; point 2: 2 cm distal to the inferior lateral edge of patella; point 3: 3 cm lateral to the midpoint on the lateral edge of patella; point 4: 2 cm proximal to the superior lateral edge of patella; point 5: 2 cm proximal to the superior edge of patella; point 6: 2 cm proximal to the superior medial edge of patella; point 7: 3 cm medial to the midpoint on the medial edge of patella; point 8: at centre of patella (figure 3).[72] Furthermore, PPTs over the tibialis anterior (5 cm distal to the tibial tuberosity) and the dorsal forearm (5 cm distal to lateral epicondyle of humerus) will be used as remote areas.

For patients with hip OA, the pressure will be applied on the following three point around the joint: point 1: anterior to the joint, at the tensor fasciae latae muscle; point 2: lateral to the joint, at the gluteus medius muscle; point 3: posterior to the joint, at the gluteus maximus muscle (figure 4). The same points at the tibialis anterior (5 cm distal to the tibial tuberosity) and at the dorsal forearm (5 cm distal to lateral epicondyle of humerus) will be used as remote areas.[73]

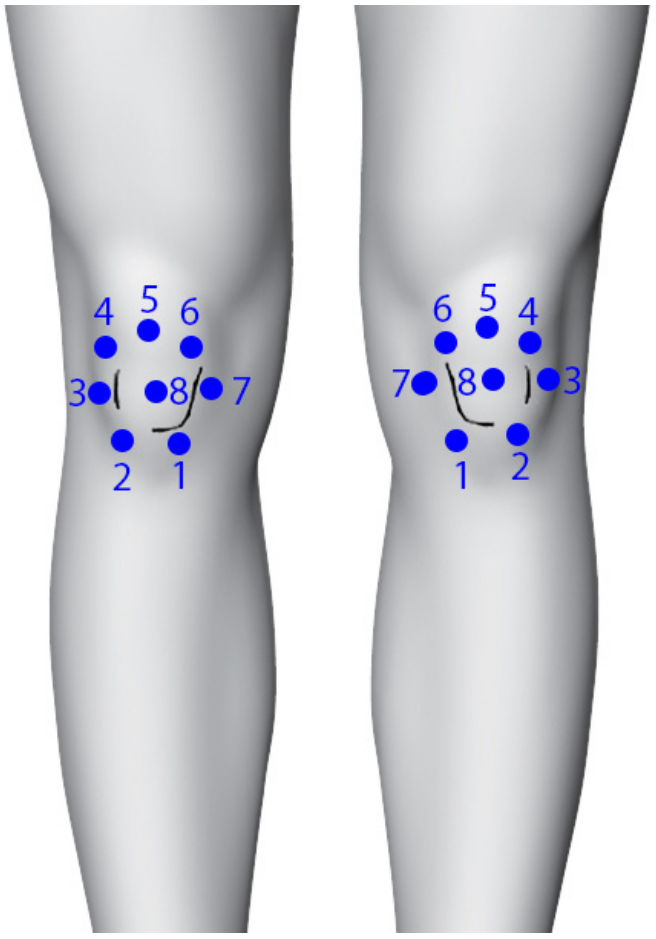

Figure 3 Pressure pain sensitivity map over around the peripatellar region (based on Arendt-Nielsen *et al*[72]).

Epigenetics: Val158Met polymorphism of the COMT gene

Non-stimulated whole-saliva samples will be collected during 5 min into collection tubes (passive drooling technique) according to standardised procedures. We decided to collect saliva instead of blood since the salivary collection is a non-invasive, stress-free assessment to collect the data of interest. The volume of saliva secreted will be measured using a 200–1000 µL micropipette. The samples will be centrifuged at 3000 revolutions per

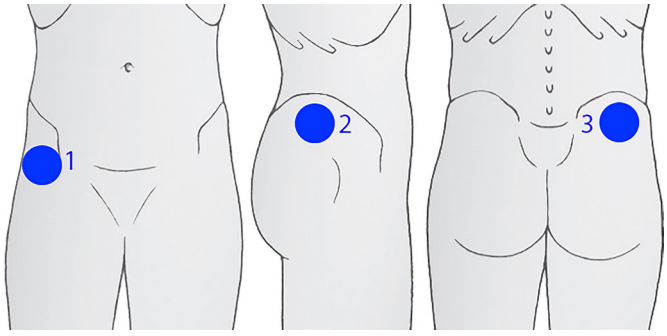

Figure 4 Points of assessment of pressure pain sensitivity around the hip region.

minute for 15 min and then the supernatant and the precipitate (cells for DNA extraction) will be aliquoted into Eppendorf tubes. The supernatant will be stored at −80°C and the pellet at −20°C. From the precipitate samples, genomic DNA extraction and purification will be performed using the REALPURE 'SSS' kit (Genomic DNA Extraction-Purification Kit), from which the Val158Met polymorphisms will be determined by means of TaqMan probes in a Real-Time PCR system (TaqMan Drug Metabolism Genotyping Assays on a Real-Time PCR ABI Prism 7000 Sequence Detection System), carried out by the Technological Support Centre of the URJC. The Val158Met polymorphism will be determined by the analysis of an adenine to guanine change in the sequence: CCAGCGGATGGTGGATTTCGCTGGC **[A/G]** TGAA GGACAAGGTGTGCATGCCTGA.

Surgical procedure

Total knee or hip replacement will be performed by expert orthopaedic surgeons according to protocols used in the Orthopaedic and Traumatological Surgery Department of the HUFA, Spain. Surgeries will be performed under spinal (epidural)/general anaesthesia depending on the patient's features according to standardised protocols. All patients will receive 3 weeks of face-to-face rehabilitation, mainly consisting of motion of the knee; manual movement of the knee by the therapist; isometric quadriceps exercises and assisted exercises (active knee flexion and extension and progressive muscle strengthening ceremonies); gait training and transfer; and training on stairs, ramps and obstacles.

Sample size calculation

Two different sample size calculations were conducted; the first one focused on differences in pain/function between responders and non-responders (prediction model one) and the second one based on the multivariate analysis for identifying risk factors. The first power analysis revealed that to detect a 2-point NPRS difference in pain level, to detect a 10% difference from the baseline score for the WOMAC score and to detect a 2-point difference in satisfaction with an 80% power, using a two-sided hypothesis test at an alpha level of 0.05, the total sample size needed would be 205 subjects.

An alternative sample size calculation according to the multiple linear regression model (GPower 3.1 software), estimating a mean effect size of 0.15, an alpha level 0.05, a power of 0.9 and the presence of four predictors, the sample size required would be 108 subjects. To increase the power of the study, we will include the highest sample estimated (n=205 patients on each group). In addition, considering a potential lost to follow-up of 20% due to the 2-year follow-up period, we will finally include 250 patients with knee OA and 250 patients with hip OA.

Statistical analysis proposal

Descriptive analyses will be based on the frequencies and percentages for categorical variables and the mean and SD for continuous variables. Participants will be stratified as responder and non-responders according to each cut-off determined on each model at each follow-up: 3, 6, 12, 18 and 24 months after surgery. Differences in all the postsurgical outcomes between responders and non-responders at each follow-up period (3, 6, 12, 18 and 24 months after surgery) will be assessed with Student's t-test for continuous variables and χ^2/Fisher's exact tests for categorical variables.

Correlation analyses will be conducted used to evaluate the association between baseline predictor variables and change scores in all postsurgical variables. Finally, to identify independent predictors among the variables assessed before surgery for being responder or non-responder at each follow-up period after surgery, multivariate logistic regression analyses will be used independently for each model, and their adjusted OR with 95% CI will be calculated. Therefore, distinct linear regression models will be performed to verify which clinical, psychological and/or psychophysical variable, as well as epigenetic contribution, collected before the surgery, could predict: (1) pain and function; (2) sensitisation associated symptoms, according to CSI scores and (3) neuropathic pain symptomatology, according to S-LANSS and PainDETECT scores (as described previously).

Ethics and dissemination

This project was approved by the local Ethics Committee of both institutions involved (HUFA 19–141 and URJC 0312201917319). All participants will receive informed consent in accordance with current legislation and should sign before their enrolment in the study. All procedures in this study will follow the ethical standards of the Declaration of Helsinki. The confidentiality of the data of all the participants will be guaranteed in accordance with the local legislation. Study findings will be submitted to be published in peer-reviewed scientific journals and will be presented at international meetings.

Limitations of the study

The main limitation of the current protocol is the potential loss due to the large follow-up. To avoid this loss to follow-up period, phone calls every 3 months to maintain the contact and to remember their participation are planned to attenuate the dropout rate. Nevertheless, we expected a potential loss of 20% during the follow-up period. As the cohort consists of elderly people, other comorbid conditions may develop during the 2-year period and act as a confounding factor. The use of analgesics is a factor which cannot be controlled for and may introduce some bias in the outcomes.

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Contributors LLF, LAN and CFdlP constructed the protocol and study design. LLF, MPC and SFN made the first draft of this manuscript. ROS and JLAB contributed with statistical advice and study design. AldlLR, SAQ and MCM contributed with a thorough evaluation of the design, method and manuscript. All authors accepted the final manuscript version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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