Low-grade systemic inflammation, but not neuroinflammation, is associated with 12-month postoperative outcome after total hip arthroplasty in patients with painful osteoarthritis

an explorative study

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Aims

Better prediction of outcome after total hip arthroplasty (THA) is warranted. Systemic inflammation and central neuroinflammation are possibly involved in progression of osteoarthritis and pain. We explored whether inflammatory biomarkers in blood and cerebrospinal fluid (CSF) were associated with clinical outcome, and baseline pain or disability, 12 months after THA.

Methods

A total of 50 patients from the Danish Pain Research Biobank (DANPAIN-Biobank) between January and June 2018 were included. Postoperative outcome was assessed as change in Oxford Hip Score (OHS) from baseline to 12 months after THA, pain was assessed on a numerical rating scale, and disability using the Pain Disability Index. Multiple regression models for each clinical outcome were included for biomarkers in blood and CSF, respectively, including age, sex, BMI, and Kellgren-Lawrence score.

Results

Change in OHS was associated with blood concentrations of tumour necrosis factor (TNF), interleukin-8 (IL-8), interleukin-6 receptor (IL-6R), glycoprotein 130 (gp130), and IL-1β (R^2 = 0.28, p = 0.006), but not with CSF biomarkers. Baseline pain was associated with blood concentrations of lymphotoxin alpha (LTα), TNFR1, TNFR2, and IL-6R (R^2 = 0.37, p < 0.001) and CSF

concentrations of TNFR1, TNFR2, IL-6, IL-6R, and IL-1Ra (R^2 = 0.40, p = 0.001). Baseline disability was associated with blood concentrations of TNF, LTα, IL-8, IL-6, and IL-1α (R^2 = 0.53, p < 0.001) and CSF concentrations of gp130, TNF, and IL-1β (R^2 = 0.26, p = 0.002). Thus, preoperative systemic low-grade inflammation predicted 12-month postoperative outcome after THA, and was associated with preoperative pain and disability.

Conclusion

This study highlights the importance of systemic inflammation in osteoarthritis, and presents a possible path for better patient selection for THA in the future. Preoperative central neuroinflammation was associated with preoperative pain and disability, but not change in OHS after THA.

Article focus

- This study explored whether preoperative inflammatory biomarkers in blood and cerebrospinal fluid (CSF) were associated with postoperative outcome 12 months after total hip arthroplasty (THA).
- We also explored the association between the same biomarkers and preoperative pain and disability in patients with hip osteoarthritis (OA).

Key messages

- Preoperative blood biomarkers from the tumour necrosis factor (TNF), interleukin-1 (IL-1), and IL-6 superfamilies, and IL-8 in blood (but not CSF), was associated with postoperative outcome 12 months after THA.
- Inflammatory biomarkers from both blood and CSF predicted both pain and disability at baseline in patients with hip OA.

Strengths and limitations

- We studied a comprehensive panel of biomarkers from the most important cytokine superfamilies which have been associated with OA and inflammation.
- The study is exploratory and larger studies are needed to confirm the results.

Introduction

Osteoarthritis (OA) is a prevalent cause of chronic pain and disability worldwide, estimated to affect approximately 300 million people.[1] While there is no effective cure for hip OA, total hip arthroplasty (THA) is effective in relieving pain and functional limitations in the majority of patients. However, 9% to 20% report persisting pain after THA.[2] In the light of an obesity epidemic and an ageing population, both of which increase the risk of OA, the demand for THA is estimated to increase by 200% to 400% during the next two decades.[3] Hence, there is a need for precise patient selection for THA and better predictors of the postoperative outcome.

Pain in OA is considered a complex and multifactorial disorder in which inflammatory mediators play a key role.[4-7] While the importance of local inflammation in the joint and synovial tissue in disease progression and pain due to OA is well established,[4,8] the importance of systemic inflammation and central neuroinflammation is unclarified. A few studies, however, have associated proinflammatory cytokines in the blood, especially tumour necrosis factor (TNF), interleukin (IL)-1β, and IL-6, with disease progression,[9-11] pain, and functional impairments in OA.[12-15] It has therefore been proposed that OA is partly driven by inflammaging, which describes a state of chronic, sterile, low-grade inflammation involved in several age-related diseases.[4,5,8,16] Additionally, inflammatory activity in the central nervous system – neuroinflammation – has been proposed to play a role in OA pain processing, as proinflammatory cytokines, including IL-8, in the cerebrospinal fluid (CSF) have been associated with sensory indicators of central hypersensitivity.[17] Another hypothesis is that different subtypes of OA exist which could be driven by bone, cartilage, inflammation, or idiopathic, and that patients with the inflammation-driven subtype might benefit less from traditional treatment of OA.[18]

The primary aim of this study was to explore if preoperative levels of inflammatory biomarkers in blood and CSF of patients with painful hip OA was associated with postoperative outcome 12 months after THA, and secondarily whether they were associated with preoperative pain and disability. We hypothesized that low-grade systemic inflammation and neuroinflammation are important factors for OA pain in some patients and that these patients would benefit less from THA because the pathology in these patients goes beyond the local joint treated.

Methods

Study design and patients

This is an exploratory, longitudinal, observational study using data from the DANPAIN-Biobank.[19] Patients with end-stage hip OA scheduled for THA and 12 months' follow-up data after surgery were included in the analyses. Assessment of end-stage OA was based on the surgeon's assessment of the patient history, objective examination, and radiological examinations, and the decision for surgery was made in collaboration between the surgeon and the patient based on this assessment. Patients were included between January and June 2018 if they were aged between 18 and 80 years, scheduled for THA on the indication of painful OA in spinal anaesthesia at the Department of Orthopaedic Surgery, and presented sufficient skills in speaking, reading, and writing the local language to fill in questionnaires. Exclusion criteria were immunological, inflammatory, infectious, or malignant disease; pregnancy; ongoing immunotherapy or chemotherapy; steroid treatment; non-steroid anti-inflammatory drug (NSAID) treatment within three days before sample collection; dementia or a similar condition; abuse of alcohol or psychedelic drugs; arthroplasty surgery or any other operation of a similar size within three months; dysfunction of or complications to existing arthroplasty in the hip or knee; or any chronic pain other than the hip pain.

The study was approved by the Regional Ethics Committee and was reported to the Danish Data Protection

Agency and adhered to the Declaration of Helsinki.[20] Written informed consent was obtained from all participants.

Sample collection and study flow

Blood and CSF samples were collected between 7.30am and 2.30pm. Blood samples were collected from participants upon arrival to the ward. CSF samples were collected before injection of the spinal analgesic, which was usually within two hours after patient arrival. Patients received Celecoxib one to two hours prior to surgery, after blood sampling but prior to CSF sampling.

Blood samples for plasma analysis were collected in two 4 ml ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged immediately, while blood for serum analysis was collected in plain tubes and left untouched for 30 minutes before centrifugation. All blood samples were centrifuged at 2,000 ×g for ten minutes at 4°C, aliquoted on ice blocks, and immediately stored in a -80°C freezer. CSF samples were collected in plain tubes, stored in iced water, transferred immediately to the laboratory where they were centrifuged at 2,000 ×g for ten minutes at 4°C, aliquoted on ice blocks into polypropylene Sarstedt tubes, and stored directly in a freezer at -80°C.[19]

A total of 50 patients were available for blood analysis, but only 44 of these patients were available for CSF analysis due to blood contamination in six samples.[19] The median age was 69 years (IQR 62 to 75), there was an equal distribution of males and females, and patients were generally overweight but not obese. Demographic and clinical data are presented in Table I.

Clinical data and pain outcomes

Longitudinal data included the validated Oxford Hip Score (OHS)[21,22] at baseline and 12 months post-surgery. The OHS assesses pain and hip function whereby 12 items are scored on a 0 to 4 Likert scale (0 = worst, 4 = best). The item scores are summed to a composite score of 0 to 48, with a higher score representing better hip function. The 12-month postoperative outcome was defined as the change in OHS between 12 months post-surgery and baseline (ΔOHS).

Baseline data were collected via an online questionnaire within 24 hours before the operation and included biological sex, age, height, weight, and work situation. Furthermore, participants were asked to estimate their general physical activity into either primarily sedentary purposes, physical activity for at least four hours per week, active sports/heavy work, or competitive sports. Pain intensity was assessed using a numerical rating scale (NRS) ranging from 0 to 10, with 0 indicating "no pain" and 10 "worst pain imaginable".[23] A total pain score was calculated as the sum score of the worst pain, average pain, and pain at rest during the last week. The pain sum score was used in the analysis. Pain-related interference on daily life at baseline was assessed using the Pain Disability Index (PDI),[24] in which interference with different daily activities is scored on a zero- to ten-point Likert scale, with 0 indicating "no disability" and 10 "worst disability". Only the five voluntary activity items from the PDI were collected, as previous psychometric analyses indicated that the obligatory activation subscale (self-care activities and life-support activities) has low internal reliability in this population.[25] This created a total score of 0 to 50, with higher scores expressing higher levels of pain interference. Additionally, at baseline, OA severity was assessed visually by a consultant orthopaedic surgeon (CV) based on radiographs of the affected hip, using the Kellgren-Lawrence (KG) classification grading OA from 0 "no signs of OA" to 4 "severe OA".[26]

Laboratory analysis

From the TNF superfamily, we quantified TNF and lymphotoxin α (LTα) levels, as well as the levels of the cognate receptors TNF Receptor 1 (TNFR1) and TNF Receptor 2 (TNFR2). From the interleukin (IL)-1 family, we quantified levels of IL-1α, IL-1β, and IL-1 receptor-antagonist (IL-1Ra), where the latter competes the two first for binding to the IL-1 receptor. We also quantified IL-6 levels, as well as levels of its signalling transducing receptor glycoprotein 130 (gp130) and the IL-6 receptor (IL-6R). Finally, we quantified IL-8 levels.

CSF and plasma concentrations of TNF, LTα, IL-8, IL-6, IL-1α, IL-1β, and IL-1Ra were measured using V-PLEX Custom Human Proinflammatory Panel1 Biomarker assay (K151A9H-2), while CSF and serum concentrations of IL-6R were measured using a R-PLEX Human IL-6R assay (K1510GR-22), gp130 using a R-PLEX Human gp130 (soluble) assay (K1511BR-22), TNFR1 using a R-PLEX Human TNF-RI assay (K1510VR-22), and TNFR2 using R-PLEX Human TNF-RII assay (K151ZSR-22) (all from Mesoscale Discovery). Samples were diluted in Diluent-41 and analyzed in duplicates according to the manufacturer's instructions. Analysis was performed on a SECTOR Imager 6000 plate reader, and MSD Discovery Workbench software was used for analysis (Meso Scale Discovery, USA).[27,28]

Sample replicates with coefficient of variation values > 25% in individual analyses were excluded and counted as missing data. In cases of measurements below detection level, a value was calculated as 50% of lower levels of detection (LLOD) limit. LLODs are presented in the Supplementary Material.

Statistical analysis

Parametric statistics are presented as means (SDs), while non-parametric statistics are presented as medians (IQRs). The association between the individual NRS scores and the NRS sumscore was calculated using Spearman's correlation, and the association between concentrations of the individual biomarkers in blood and CSF was tested using pairwise correlation. To explore whether baseline biomarkers predicted ΔOHS, we used multiple regression. We also used multiple regression to explore the association between baseline biomarkers and baseline symptoms (pain and disability), to examine whether one or more biomarkers predicted the clinical outcome. Thus, we made three models for blood biomarkers with ΔOHS, baseline pain, and baseline PDI, respectively, as outcome variables. We used two-step multiple regression models with robust standard errors. In step one, we used all measured blood biomarkers as candidate variables. Stepwise backward selection of independent variables, including predictors with $p < 0.1$, was used to achieve the best predictive model. In step two, forward selection was used on the biomarkers that were excluded from the model in step one as well as age, sex, BMI, and KG grade, which are possible confounders.[29–31] In step two, variables were selected using the lowest possible mean squared error (MSE) value, and the best predictive model was defined as the one with the lowest

Table I. Patient characteristics (n = 50).

Characteristic	Value	Missing data, n (%)
Median age, yrs (IQR)	69 (62 to 75)	0
Female, n (%)	23 (46)	0
Mean BMI, kg/m² (SD)	26.5 (4.1)	0
Work situation, n (%)		2 (4)
Normal working hours	12 (24)	
Sick leave (part-time or full-time)	2 (4)	
Pension	30 (60)	
Other	4 (8)	
Physical activity, n (%)		2 (4)
Primarily sedentary pursuits	7 (14)	
Physical activity at least 4 hours per week	33 (66)	
Active sports activities/heavy work	8 (16)	
Median pain at rest, NRS 0 to 10* (IQR)	2 (1 to 4)	8 (16)
Mean average pain, NRS 0 to 10* (SD)	5 (4 to 6)	8 (16)
Mean worst pain, NRS 0 to 10* (SD)	6 (5 to 8)	8 (16)
Mean total pain,† 0 to 30* (SD)	14.6 (5.3)	8 (16)
Mean Pain Disability Index (5 items: 0 to 50*) (SD)	24.9 (13.6)	8 (16)
Median KG grade, 0 to 4* (IQR)	3 (2 to 3)	0
Mean OHS baseline (SD)	23.2 (6.9)	0
Median OHS 12 mths postoperatively (IQR)	46 (43 to 48)	0
Mean ΔOHS,‡ (SD)	20.9 (9)	0
Biomarker concentration blood (n = 50)		
Mean TNF, pg/ml (SD)	1.08 (0.32)	3 (6)
Mean LTα, pg/ml (SD)	0.20 (0.06)	0
Mean TNFR1, pg/ml (SD)	2,263 (591)	0
Mean TNFR2, pg/ml (SD)	7,920 (1,991)	0
Mean IL-8, pg/ml (SD)	3.64 (1.3)	3 (6)
Mean IL-6, pg/ml (SD)	1.19 (0.90)	1 (2)
Mean IL-6R, pg/ml (SD)	42,182 (13,422)	0
Mean gp130, pg/ml (SD)	421,573 (106,333)	1
Mean IL-1α, pg/ml (SD)	0.38 (0.35)	8 (16)
Mean IL-1β, pg/ml (SD)	0.045 (0.057)	1 (2)
Mean IL-1Ra, pg/ml (SD)	154 (75.5)	0
Biomarker concentration in CSF (n = 44)		
Mean TNF, pg/ml (SD)	0.13 (0.06)	0
Mean LTα, pg/ml (SD)	0.043 (0.03)	1 (2)
Mean TNFR1, pg/ml (SD)	1,041 (292)	1 (2)
Mean TNFR2, pg/ml (SD)	1,037 (331)	1 (2)
Mean IL-8, pg/ml (SD)	40.44 (9.98)	0
Mean IL-6, pg/ml (SD)	1.05 (0.41)	0
Mean IL-6R, pg/ml (SD)	1,371 (484)	0
Mean Gp130, pg/ml (SD)	76,456 (25,773)	0
Mean IL-1α, pg/ml (SD)	0.23 (0.28)	10 (23)
Mean IL-1β, pg/ml (SD)	0.039 (0.021)	0
Mean IL-1Ra, pg/ml (SD)	23.12 (9.34)	0

*Higher is worse.
†Total pain = NRS max + NRS average + NRS rest.
‡ΔOHS = OHS 12 months – OHS baseline, lower is worse.
gp130, glycoprotein 130; IL-6, interleukin 6; IL-8, interleukin-8; IL-6R, interleukin 6 receptor; IL-1Ra, interleukin 1 receptor antagonist; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; KG, Kellgren-Lawrence ; LTα, lymphotoxin-alpha; NRS, numerical rating scale; OHS, Oxford Hip Score; TNF, tumour necrosis factor; TNFR1, tumour necrosis factor receptor 1; TNFR2, tumour necrosis factor receptor 2.

possible MSE value.[32,33] The same procedure was used for CSF biomarkers producing three models with the same three outcome biomarkers. The present study aimed at within-sample prediction and not beyond-sample prediction. Therefore, we applied a manual forward/backward selection and not a mechanistic one. This also implies that more sophisticated but still mechanistic approaches like LASSO[34] and elastic net[35] were not considered. For the same reason, we did not consider beyond-sample forecast properties. Outliers were defined as observations with biomarker concentrations outside the band of mean ± three SDs, and were removed if they affected the model.[36] A two-sided p-value < 0.05 was considered statistically significant.

Results

Each of the individual NRS scores was significantly associated with the total sum score (NRS rest: Spearman's rho 0.87, p < 0.001; NRS average: Spearman's rho 0.94, p < 0.001; NRS worst: Spearman's rho 0.84, p < 0.001).

Association with postoperative outcome

In blood, the change in the OHS was associated with the combination of elevated concentrations of TNF and IL-6R, and reduced concentrations of IL-8, gp130, and IL-1β (R^2 = 0.28, p = 0.006, multiple regression) in the best fitted model, which explained 28% of the variation (Table II). Thus, none of the biomarkers alone were associated with change in OHS, but the combination of biomarkers from all three of the included cytokine families was associated with postoperative outcome. Adding age, sex, BMI, or KG grade did not improve the model and were thus not included. There was no association between biomarkers in CSF and change in OHS.

Table II. Best predictive models in blood.

Variable	Coefficient	SE	p-value	R-squared	95% CI
Preoperative OA pain (n = 39)					
(higher is worse)			< 0.001	0.37	
LTα	34.24	12.27	0.009		9.31 to 59.18
TNFR1	0.006	0.002	0.011		0.001 to 0.01
TNFR2	-0.001	0.0006	0.059		-0.002 to 0.00004
IL-6R	0.0001	0.00005	0.006		0.00004 to 0.0002
Preoperative pain disability (n = 31)					
(higher is worse)			< 0.001	0.53	
TNF	13.66	7.93	0.098		-2.69 to 30
LTα	71.62	40.86	0.092		-12.53 to 155.76
IL-8	-5.55	1.43	0.001		-8.5 to -2.6
IL-6	5.57	1.25	< 0.001		3 to 8.14
IL-1α	-18.6	5.65	0.003		-30.24 to -6.96
ΔOHS (n = 39)					
(higher is better)			0.006	0.28	
TNF	21.97	5.96	0.001		9.85 to 34.09
IL-8	-4.15	1.33	0.004		-6.86 to -1.45
IL-6R	0.0004	0.0002	0.030		0.00004 to 0.0007
gp130	-0.00005	0.00002	0.024		-0.0001 to -7.52e-06
IL-1β	-50.68	27.81	0.078		-107.27 to 5.91

gp130, glycoprotein 130; IL-6, interleukin 6; IL-8, interleukin 8; IL-6R, interleuken 6 receptor; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; LTα, lymphotoxin-alpha; OA, osteoarthritis; SE, standard error; TNF, tumour necrosis factor; TNFR1, tumour necrosis factor receptor 1; TNFR2, tumour necrosis factor receptor 2; ΔOHS, OHS 12 months – OHS baseline.

Association with baseline pain and pain disability

In blood, both pain and PDI were associated with biomarker activity. The best fitted model for total OA pain included elevated concentrations of LTα, TNFR1, and IL-6R and reduced concentrations of TNFR2 (R^2 = 0.37, p < 0.001, multiple regression), while the best predictive model for PDI included elevated concentrations of TNF, LTα, and IL-6, and reduced concentrations of IL-8 and IL-1α (R^2 = 0.53, p < 0.001) (Table II).

Also in CSF, the activity of inflammatory biomarkers was associated with pain and PDI. The best predictive model for OA pain included reduced CSF levels of TNFR1 and IL-1Ra and elevated concentrations of TNFR2, IL-6, and IL-6R (R^2 = 0.40, p = 0.001). The best predictive model for PDI included reduced levels of gp130 and TNF, and elevated IL-1β levels (R^2 = 0.26, p = 0.002) (Table III). Adding age, sex, BMI, or KG grade did not improve the models.

Discussion

This exploratory study shows that postoperative outcome after THA, assessed as the change in OHS from baseline to 12 months post-surgery, was associated with preoperative activity of several inflammatory mediators in the blood but not in the CSF. Furthermore, baseline pain and PDI were associated with the preoperative activity of inflammatory biomarkers in both blood and CSF. This highlights the importance of systemic low-grade inflammation or inflammaging in hip OA. It also supports the hypothesis that central sensitization plays a role in OA pain.

Several studies have demonstrated that systemic low-grade inflammation plays a role in OA, and IL-6,[12,13] IL-8,[37] TNFR1, and TNFR2[14] have been associated with OA pain and functional impairment. This is supported by our findings wherein biomarkers of both the IL-6 and TNF family were associated with pain and PDI together with IL-8 and IL-1α. Thus, the models included several biomarkers from several different cytokine families. This is also in accordance with previous studies of low-grade systemic inflammation, where outcomes were better predicted by a combination of biomarkers from several levels of the inflammatory system than from one biomarker alone.[12,38]

We are not aware of any previous studies exploring the association between low-grade systemic inflammation and outcome after THA. However, in patients with knee OA, Giordano et al[39] found one subgroup of patients in whom altered preoperative levels of inflammatory biomarkers were associated with worse pain intensity and function score 12 months after total knee arthroplasty. In another study of knee OA, the effect of a diet and exercise programme was evaluated.[12] Improvements of pain and function were predicted by the combined change in TNF, IL-6, soluble IL-1

Table III. Best predictive models in cerebrospinal fluid.

Variable	Coefficient	SE	p-value	R-squared	95% CI
Preoperative OA pain (n = 36) (higher is worse)			0.001	0.40	
TNFR1	-0.0076	0.0042	0.077		-0.016 to 0.0009
TNFR2	0.0075	0.0036	0.046		0.0002 to 0.015
IL-6	5.15	1.91	0.012		1.24 to 9.06
IL-6R	0.0045	0.002	0.034		0.004 to 0.009
IL-1Ra	-0.29	0.079	0.001		-0.45 to -0.13
Preoperative pain disability (n = 33) (higher is worse)			0.002	0.26	
gp130	-0.0002	0.000061	0.003		-0.0003 to -0.00008
TNF	-71.95	42.23	0.099		-158.32 to 14.43
IL-1β	213.13	122.5	0.092		-37.4 to 463.67

gp130, glycoprotein 130; IL-6, interleukin 6; IL-6R, interleukin 6 receptor; IL-1Ra, interleukin 1 receptor antagonist; IL-1β, interleukin-1 beta; OA, osteoarthritis; TNF, tumour necrosis factor; TNFR1, tumour necrosis factor receptor 1; TNFR2, tumour necrosis factor receptor 2.

receptor, and CRP, independent of weight loss. This supports our findings that low-grade systemic inflammation not only plays a role in symptom presentation of OA, but could also be a predictor of the response to treatment of OA. The mechanism behind this association remains to be elucidated, but OA pain and persisting pain after THA are multifactorial,[8] and the association with structural pathology is relatively weak.[4,40–42] It has been hypothesized that several subtypes of OA exist, where inflammation plays a more important role in some subtypes.[18] Our results support the hypothesis that in cases where systemic inflammation is an important driver of pain and functional impairment, surgical treatment may be less effective. The potential for using preoperative profiles of inflammatory blood biomarkers, possibly together with existing pretreatment predictors, for a more stratified patient selection for THA, should be explored in larger studies.

The exact role of neuroinflammation in OA pain in humans is not fully clear. Elevated levels of pro-inflammatory biomarkers, including IL-1β and IL-8, have been inconsistently demonstrated in patients with OA and interpreted as a sign of central neuroinflammation.[17,43–45] While some studies have reported an association between elevated pro-inflammatory biomarkers in CSF, central sensitization, and pain,[45] other studies have conversely reported a negative correlation between pro-inflammatory CSF biomarkers, pain, and disability.[43,44] In our study, we did not find a simple picture of elevated pro-inflammatory and reduced anti-inflammatory biomarkers to be associated with pain and PDI. Rather, we found pain to be associated with higher levels of IL-6, IL-6R, and TNFR2 and reduced levels of IL-1Ra and TNFR1. TNFR2 and IL-1Ra are predominantly considered anti-inflammatory, while the rest are considered pro-inflammatory. Worse PDI was associated with lower levels of gp130 and TNF, and higher levels of IL-1β, which are all considered predominantly pro-inflammatory. However, this complexity is well documented in studies of chronic inflammation and inflammaging,[38,46] where activation of the immune system was associated with a variation of simultaneous changes in both pro- and anti-inflammatory markers, illustrating the complex and sometimes subtle feedback mechanisms in the inflammatory response.

Our study has several limitations. The relatively limited number of participants entails that the multiple regression analyses should be interpreted with caution. As mentioned previously, the study aims at within-sample prediction and is thus hypothesis-generating by nature. Confirmation of the results in a larger cohort is mandatory. Secondly, the relative interdependence of some of the biomarkers may introduce some degree of collinearity into the model. While collinearity does not affect the overall predictive power of the model, it introduces increased variance to the individual biomarker in the model, which possibly affects the sign and size of the regression coefficients, their standard error, or the associated *t*-tests, which therefore should be interpreted with caution.[47,48] Finally, all patients received Celecoxib preoperatively as pre-anaesthetic drugs. We do not, however, consider this a serious source of bias, since it was administered at the same time that the blood samples were collected, thereby not affecting blood values. The CSF samples were collected one to two hours after administration. Maximum plasma concentration is achieved after two to four hours,[49] and crossing the blood-brain barrier induces a further delay of 1.1 hours before maximum CSF concentration is reached (which equals a maximum CSF concentration after 3 to 5 hours).[50] Since the mechanism of action is on blocking the synthesis of prostanoids via inhibition of the cyclooxygenase 2 enzyme, thereby possibly inhibiting cytokine levels,[51] we estimate that an effect on CSF concentrations of cytokines and associated receptors one to two hours after oral administration would be minimal.

In conclusion, we demonstrated that preoperative low-grade systemic inflammation in the blood was associated with changes in OHS 12 months after THA and were associated with baseline pain and disability. We also demonstrated that

biomarkers of neuroinflammation in the CSF were associated with baseline pain and disability in hip OA patients, but did not predict change in OHS 12 months after THA.

While the results should be confirmed in a larger study, we hypothesize that low-grade systemic inflammation is an important factor in OA pain in some patients, and that these patients would benefit less from THA because the problem goes beyond the local joint treated.

Supplementary material

Lower levels of detection (LLOD) for the examined biomarkers.

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The study was approved by the Regional Ethics Committee and was reported to the Data Protection Agency and adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants.

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