Observational Study

Predictive Factors of Chronic Post-Surgical Pain at 6 Months Following Knee Replacement: Influence of Postoperative Pain Trajectory and Genetics

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Background: The frequency of chronic postsurgical pain (CPSP) after knee replacement remains high, but might be decreased by improvements to prevention.

Objectives: To identify pre- and postsurgical factors predictive of CPSP 6 months after knee replacement.

Study Design: Single-center prospective observational study.

Setting: An orthopedic unit in a French hospital.

Methods: Consecutive patients referred for total or unicompartmental knee arthroplasty from March to July 2013 were prospectively invited to participate in this study. For each patient, we recorded preoperative pain intensity, anxiety and depression levels, and sensitivity and pain thresholds in response to an electrical stimulus. We analyzed OPRM1 and COMT single-nucleotide polymorphisms. Acute postoperative pain (APOP) in the first 5 days after surgery was modeled by a pain trajectory. Changes in the characteristics and consequences of the pain were monitored 3 and 6 months after surgery. Bivariate analysis and multivariate logistic regression were conducted to identify predictors of CPSP.

Results: We prospectively evaluated 104 patients in this study, 74 (28.8%) of whom reported CPSP at 6 months. Three preoperative factors were found to be associated with the presence of CPSP in multivariate logistic regression analysis: high school diploma level (OR = 3.83 [1.20 – 12.20]), consequences of pain in terms of walking ability, as assessed with the Brief Pain Inventory short form "walk" item (OR = 4.06 [1.18 – 13.94]), and a lack of physical activity in adulthood (OR = 4.01 [1.33 – 12.10]). One postoperative factor was associated with the presence of CPSP: a high-intensity APOP trajectory. An association of borderline statistical significance was found with the A allele of the COMT gene (OR = 3.4 [0.93 – 12.51]). Two groups of patients were identified on the basis of their APOP trajectory: high (n = 28, 26%) or low (n = 80, 74%) intensity. Patients with high-intensity APOP trajectory had higher anxiety levels and were less able to walk before surgery ($P < 0.05$).

Limitations: This was a single-center study and the sample may have been too small for the detection of some factors predictive of CPSP or to highlight the role of genetic factors.

Conclusion: Our findings suggest that several preoperative and postoperative characteristics could be used to facilitate the identification of patients at high risk of CPSP after knee surgery. All therapeutic strategies decreasing APOP, such as anxiety management or performing knee replacement before the pain has a serious effect on ability to walk, may help to decrease the risk of CPSP. Further prospective studies testing specific management practices, including a training program before surgery, are required.

Key words: Chronic postsurgical pain, opioids, arthroplasty, pain trajectory, genetics, COMT, predictive factors

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Osteoarthritis is a common disease that causes joint pain, stiffness, and loss of function. It affects 27 million people in the United States (1). With a prevalence of 16.7% for symptomatic knee osteoarthritis in patients over the age of 45 years, more than 500,000 knee replacements are performed annually in the United States (1,2). This number is projected to increase by 673% from 2005 to 2030 (2).

The International Association for the Study of Pain defines chronic postsurgical pain (CPSP) as a persistent pain, after healing, at least 2 months after the intervention (3). Our understanding of pain mechanisms and the management of pre- and postoperative pain has improved, but CPSP after knee replacement remains an important issue (4,5). CPSP has a prevalence of 10% to 34% in patients undergoing knee arthroplasty, and with the increasing number of knee replacements being performed, it is likely to generate large individual, social, and health care costs in the near future (5). The preoperative and acute postoperative periods are likely to be appropriate periods for identifying patients at risk of CPSP.

Several factors predictive of CPSP have already been described. Vulnerability to pain is present before surgery and is influenced by genetic background, pain history, and psychological factors (6). CPSP after knee replacement can also be predicted by a lower pain threshold measured by quantitative sensory testing after the delivery of a thermal, electrical, or pressure stimulus (7). Acute postoperative pain (APOP) after knee replacement is also associated with a higher risk of CPSP (8,9). The course of acute pain in the early postoperative period (APOP trajectory) has recently been identified as an indicator predictive of CPSP (10). Indeed, initial pain intensity and the slope of the pain resolution curve during the postoperative period have been shown to be 2 independent factors predictive of CPSP (11).

The catechol-O-methyltransferase (COMT) is a major degrading enzyme in the metabolic pathways of catecholaminergic neurotransmitters (12). The allelic variant Val 158 of the COMT gene affects COMT protein stability and is associated with individual differences in pain nociception, opioid requirement for acute pain, and the risk of chronic pain (13-15). Moreover, the allelic variant G of the OPRM1 gene, encoding for the mu opioid receptor, influences opioid requirement and may represent a predictive factor of chronic pain regarding the relationship between APOP and CPSP.

The aim of this prospective study was to identify pre- or postsurgical predictive factors of CPSP at 6 months following knee replacement, including acute postoperative pain trajectory and genetics. The identification of such factors would allow targeting additional postoperative pain management and pharmacological strategies for patients likely to benefit.

Methods

Patients

From March to July 2013, consecutive patients referred for total or unicompartmental knee arthroplasty were prospectively invited to participate in this study. Patients were included on the day before surgery, at the Orthopedics Unit of Lariboisière Hospital, France. Patients were not eligible for the study if revision surgery was planned or if they suffered from cognitive impairment, chronic alcohol consumption, drug addiction, uncontrolled psychiatric disease, or inflammatory rheumatic disease, or if they were treated with corticosteroids. The ethics committee approved the protocol (CPP Ile de France I, N° 2013-mars-13185) and all patients gave written informed consent.

At baseline, we collected demographic data for age, gender, education level (French high school diploma obtained or not), and patients were questioned about their history of regular physical activity in adulthood (during a pain-free period).

Postoperative analgesia was managed in accordance with the recommendations of the relevant scientific society. Patients received a local infiltration of ropivacaine and adrenaline in the perisurgical area. Ropivacaine was administered as a continuous peripheral femoral nerve block for 4 days. In the ward, the choice of opioid, and decisions concerning the possible coprescription of nefopam, acetaminophen, selective inhibitors of COX-2, and pregabalin, were left to the discretion of the anesthetist. Patients received opioids every 4 hours, according to their numerical rating scale (NRS) score for pain (opioids administered if NRS > 4). Physiotherapy was performed daily, one hour after an opioid administration.

Pain Intensity and Consequences

Pain and its consequences were assessed by trained personnel, in face-to-face interviews, before surgery (at baseline) and during the first 5 days after surgery, and then by phone at 3 and 6 months after surgery.

Pain Intensity

The time between the onset of knee pain and sur-

gery was recorded, together with the presence of pain elsewhere and presurgical analgesic consumption. Analgesics were classified as acetaminophen, non-steroidal anti-inflammatory drugs, or opioids (16). The use of co-analgesics (antidepressant or antiepileptic drugs) was also reported.

Pain intensity over the last 8 days, at rest and on movement, was assessed with a NRS extending from 0 (no pain) to 10 (worst possible pain).

APOP intensity at rest and on movement was assessed with a NRS, over a period of 5 days: from the day of surgery (Day 0) to the fourth day after surgery (Day 4). Pain at rest was assessed 3 times per day (8:00, 14:00, and 22:00) during hospitalization.

CPSP was defined as a NRS score ≥ 1/10 for the last 8 days, in an assessment 6 months after surgery.

Pain Consequences

The Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire evaluates 2 domains: the 6-item "intermittent" pain scale, for which scores range from 0 to 24, and the 5-item "constant" pain scale, for which scores range from 0 to 20. Higher scores indicate higher pain intensity, related distress, and impact of osteoarthritis pain on quality of life (17).

The Brief Pain Inventory-short form (BPIsf) assesses pain intensity and the extent to which it interferes with the patient's life (18). Consistency and validity have been reported for pain severity and the consequences of pain, but also for each separate item of the BPIsf (19). A NRS extending from 0 (no consequence) to 10 (major consequences) was used to assess 6 items measuring the consequences of pain for mood, walking ability, normal work, relations with others, sleep, and enjoyment of life.

The Hospital Anxiety and Depression (HAD) scale includes an anxiety subscale (HAD-A) and a depression subscale (HAD-D), each of which contains 7 intermingled items, providing a total score for each subscale ranging from zero to 21 (20).

Pain Matcher

Sensitivity and pain thresholds were determined with Pain Matcher (Cefar), an easy-to-use autoevaluation tool for pain, based on increasingly intense electrical stimulation of the territory of the median nerve (21). The threshold of sensitivity to an electrical signal was first determined. We then carried out 2 consecutive measurements of the pain threshold, with an interstimulus interval of 60 seconds; the mean value was retained. The sensitivity and pain threshold values are expressed as numerical values.

Genetic Analyses

DNA was extracted automatically from peripheral blood cells, with a Maxwell 16 instrument (Promega). Patients were genotyped for single-nucleotide polymorphisms of OPRM1 (c.118A>G; rs1799971) and COMT (c.675G>A -p.Val158Met-; rs4680), after bidirectional direct Sanger sequencing of the corresponding PCR products (ABI Prism 3700, Applied Biosystems). The oligonucleotides used for PCR and sequencing were OPRM1 forward 5'GCTTGGAACCCGAAAAGTCT3' / reverse 5'CCCTTAAGCCGCTGAAC3'; COMT forward 5' CCTGCTCTTTGGGAGAGGTG3' / reverse 5'TGGGTAAACTGCCAAGGTGG3'.

Statistical Analysis

The aim of this pilot study was to identify the main predictive factors for CPSP. It was not possible to determine the sample size required in advance without a hypothesis concerning the link between each of the main predictive factors and CPSP in this context. Quantitative data are expressed as the mean ± standard deviation and qualitative data are expressed as the number of patients and percentages. Chi-squared tests (or Fisher's exact tests if necessary) and Student's t tests (or Wilcoxon tests if necessary) were performed for bivariate analysis. All statistical tests were bilateral and a P value < 0.05 was considered significant. Analyses were performed only for patients with complete data, as less than 6% of the data were missing for each variable of interest.

Latent class growth analysis was used to investigate the possibility that there might be underlying groups of people displaying similar changes in APOP intensity over the 4 days following surgery (APOP trajectory) (22,23). In this technique, the number of groups is specified in advance and maximum likelihood estimation is used to model the probability of group membership for each individual and the shape (polynomial) of the mean trajectory in each group. We evaluated the fit of the models with one to 4 groups (number of groups specified in advance) to a curvilinear or quadratic trajectory shape. We used the recommended criteria to retain the best model: group size > 25 patients, smallest Akaike and Bayesian information criteria, highest entropy, and a significant bootstrap likelihood ratio test (24). Power analyses showed that, with a sample size of 109 patients, the power of Latent class growth

analysis was greater than 80% for pain trajectories constructed on the basis of pain intensity assessments at 4 time points (or 5, but no more) for each patient (25). We decided to use the daily mean APOP intensity calculated from the 3 assessments made at 8:00, 14:00, and 22:00 each day, from Day 1 to Day 4 after surgery.

Bivariate analyses were then performed to evaluate the crude association between CPSP and each candidate predictor recorded at baseline (patient characteristics, pain intensity and consequences, Pain Matcher, anesthetic procedure, genetics), and APOP trajectory group. Due to the limited sample size, a chronological approach was used for the multivariate analysis. The candidate predictors found to be significantly (*P* value < 0.05) associated with CPSP in bivariate analysis were classified into 3 groups of variables: patient characteristics, preoperative pain and pain consequences, postoperative acute pain. Three different multivariate logistic regression models were generated and we selected the model best fitting the variables of each of these 3 groups. An overall model was then fitted, including all the variables selected in the 3 initial models. The importance of each variable was checked by determining its Wald test statistic and estimated coefficient, and variables making no significant contribution to the model were eliminated one by one. The fit of the final model was evaluated with the Hosmer-Lemeshow test. The relationship between the continuous covariates and CPSP was assessed and, if necessary, continuous factors were categorized, before their entry into the multivariate models, on the basis of published percentiles or thresholds.

Table 1. *Population characteristics (mean ± standard deviation, unless otherwise stated).*

	Baseline n = 109
Male, n (%)	31 (28.4)
Age, years	69.2 ±9 .0
High school diploma, n (%)	31 (28.4)
Total knee arthroplasty, n (%)	90 (82.6)
General anesthesia, n (%)	66 (60.6)
BMI, kg/m²	30.8±5.4
Preoperative knee pain ≥ 3 years, n (%)	70 (64.2)
No regular physical activity, n (%)	45 (41.2)
History of previous hip or knee arthroplasty, n (%)	33 (30.3)
Pain elsewhere, n (%)	91 (87.5)
Sensitivity threshold (units)	6.4 ± 2.2
Pain threshold	13.7 ± 8.3
OPRM1 118G allele frequency	0.17
COMT 158Met allele frequency	0.67

BMI: body mass index; COMT: catechol-O-methyltransferase gene; OPRM1: μ opioid receptor gene

Results

Patients

In total, 109 of the 152 patients screened met the inclusion criteria; 39 patients met the exclusion criteria and 8 refused to participate. The characteristics of the 109 included patients are described in Table 1. We evaluated 103 of these 109 patients at 3 months, and 104 of these 109 patients at 6 months. Three of the 5 patients not evaluated at 6 months were lost to follow-up and the other 2 died during the study (one in the early postoperative period).

Pain Intensity and Consequences after Surgery

The changes in pain intensity, its consequences, and analgesic requirements from baseline to 6 months after surgery are shown in Table 2. An overall improvement was observed, with a decrease in each of the scores for pain intensity and consequences over this period, and a decrease in analgesic consumption.

For the 108 patients with an APOP intensity evaluation, mean daily APOP intensity decreased from the first day (Day 1) to the fourth day (Day 4) after surgery: 3.9 ± 2.1 on Day 1, 2.9 ± 2.1 on Day 2, 2.3 ± 1.8 on Day 3, and 2.5 ± 2.2 on Day 4 (Fig. 1).

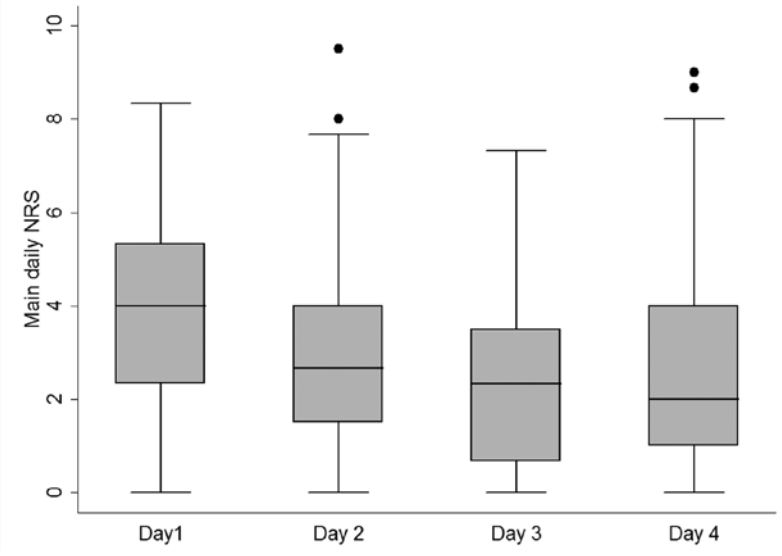
Latent class growth analysis showed that 2 APOP trajectory groups provided the best fit (Akaike information criteria = 1681.6; Bayesian information criteria = 1711.1; entropy = 0.92; bootstrap likelihood ratio test *P* value < 0.0001): a low-intensity (n = 80, 74.0%) and a high-intensity APOP trajectory group (Fig. 2). The mean predicted NRS score at D1 (mean predicted trajectory intercept) was 6.5 ± 0.3 for the high-intensity group and 3.1 ± 0.2 for the low-intensity group. A significant negative slope was observed for both groups (-1.6 ± 0.5 and -1.3 ± 0.2 points by day for the high- and low-intensity groups, respectively, *P* value < 0.001 for both), with a positive significant quadratic term (0.4 ± 0.2, *P* value = 0.013 for the high-intensity APOP trajectory group and 0.3 ± 0.1, *P* value < 0.001 for the low-intensity APOP trajectory group), so both the curves for both groups followed a declining quadratic trajectory over time. As shown on the Fig. 2, a feature of the individual APOP

Table 2. *Outcome of pain, functional impairment (walking) due to pain and analgesic use at baseline, and 3 and 6 months after surgery (mean ± standard deviation, unless otherwise stated).*

	Baseline	After surgery	
	n = 109	3 months n = 103	6 months n = 104
Pain at rest, NRS	4.1 ± 3.1	1.5 ± 2.4	1.2 ± 2.2
Pain on movement, NRS	7.5 ± 2.1	2.8 ± 2.5	2.2 ± 2.3
Pain at rest with NRS ≥1, n (%)	87 (80.6)	43 (41.7)	30 (28.8)
Hospital Anxiety and Depression Scale $			
Anxiety score	9 ± 5.0	4.1 ± 4.9	2.5 ± 3.8
Depression score	5.9 ± 4.0	2.7 ± 3.8	1.7 ± 3.1
Intermittent and Constant Osteoarthritis Pain Scale			
Constant *	9.7 ± 4.1	1.7 ± 3.4	1.7 ± 3.9
Intermittent **	12.2 ± 5.4	5 ± 4.8	4.2 ± 5.1
Brief Pain Inventory, short form $$			
Mood	4.1 ± 3.3	1.7 ± 2.7	1.2 ± 2.4
Walk	7.2 ± 2.1	2.2 ± 2.4	1.7 ± 2.4
Normal work	6.6 ± 2.8	2 ± 2.7	1.5 ± 2.3
Relations with others	2.7 ± 3.3	1.2 ± 2.4	0.6 ± 1.5
Sleep	4.5 ± 3.2	1.4 ± 2.6	0.9 ± 2.2
Enjoyment of life	3.7 ± 3.5	1.5 ± 2.6	0.8 ± 2.0
Total	28.8 ± 13.1	10 ± 13.0	6.8 ± 10.5
Analgesic use, n (%)	98 (89.9)	63 (60.6)	52 (50.0)
Acetaminophen, n (%)	**93 (85.3)**	**60 (58.3)**	**51 (49.0)**
Opioids, n (%)	44 (40.4)	28 (27.2)	40 (38.5)
NSAIDs, n (%)	20 (18.3)	2 (1.9)	1 (1.0)
Co-analgesics £, n (%)	5 (4.6)	7 (6.8)	10 (9.6)

NRS: Numerical rating scale; $ Scores range from 0 to 21, * scores range from 0 to 20, ** scores range from 0 to 24, $$ scores range from 0 (no interference) to 10 (complete interference) on a numerical rating scale; NSAIDs: non-steroidal anti-inflammatory drugs; opioids: tramadol, codeine, morphine, oxycodone or fentanyl; £ co-analgesics: antiepileptics, antidepressants

Fig. 1. *Box-plot of the mean daily numerical rating scale score (NRS) over time for the whole sample (n = 108).*



Footnotes: The central rectangle spans the first quartile to the third quartile, the segment inside the rectangle shows the median and the "whiskers" above and below the box show the locations of the minimum and maximum.

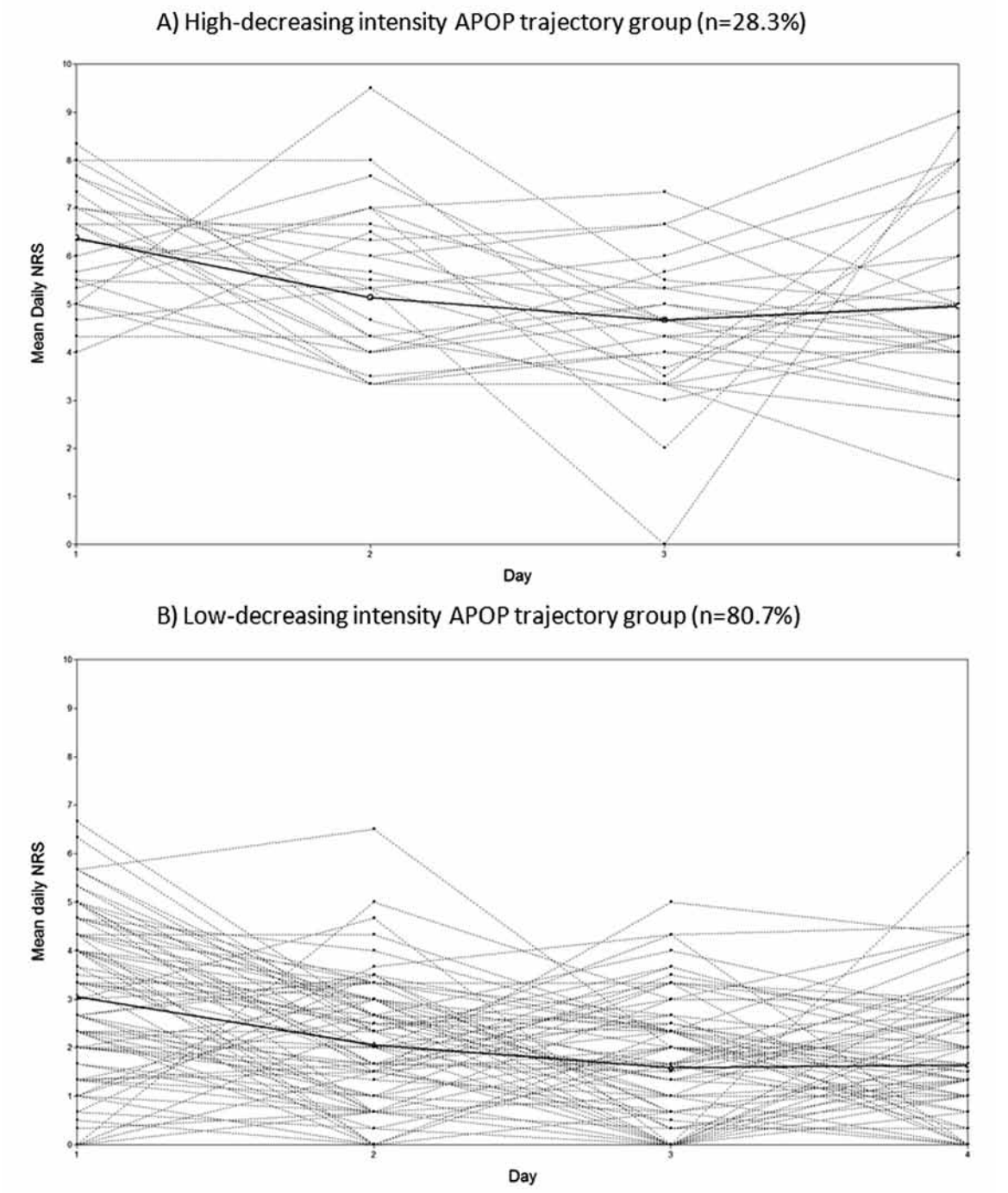


Fig. 2. *Observed individual trajectories of mean daily numerical rating scale score (NRS, dashed lines) and predicted mean trajectory (solid line) in the 2 groups retained after latent class growth analysis.*
High-intensity APOP trajectory group (n = 28, 26%)
Low-intensity APOP trajectory group (n = 80, 74%)
Footnotes: High-intensity APOP trajectory group: intensity mostly higher than 4 from day 1 to day 4.

trajectories in the high-intensity group is that APOP intensity was mostly higher than 4 from day 1 to day 4 for the patients in this group. The main characteristics of the 2 APOP trajectory groups are shown in Table 3.

Factors Predictive of Chronic Postoperative Pain

Thirty (28.8%) of the 104 patients reported CPSP at 6 months. Bivariate associations between each candidate predictor and CPSP are shown in Table 4. The "patient characteristics" group of candidate predictors included 4 predictors (gender, COMT-A carrier, high school diploma, and no regular physical activity in adulthood). Patients with CPSP were more likely to have obtained their high school diploma ($P = 0.007$), to not undertake regular physical activity in adulthood ($P = 0.02$), and to carry the A allele of COMT ($P = 0.047$). Although non-significant ($P = 0.104$), we retained gender as a candidate predictor in this group, as a trend towards a lower proportion of men in the group of patients with CPSP was observed. The "preoperative pain and pain consequences" group included 3 predictors (first analgesic use ≥ 3 years previously, HAD anxiety score ≥ 8, and BPIsf walk score at baseline ≥ 7), as patients with CPSP were found to be more likely to have been using analgesics for at least 3 years ($P = 0.039$), had higher levels of preoperative anxiety ($P = 0.006$), and higher BPIsf scores for walking ($P = 0.034$). Finally, the "postoperative pain" group included 2 factors (high-intensity APOP trajectory group and analgesic use in the acute postoperative period). Indeed, a larger proportion of patients with CPSP had a high-intensity

Table 3. *Main characteristics of the 2 acute postoperative pain trajectory groups (mean ± SD, unless otherwise stated).*

	Acute postoperative pain		*P* value
	Low intensity (n = 80, 74%)	High intensity (n = 28, 26%)	
Male, n (%)	25 (31.2)	5 (17.9)	0.173
Age	69.8 ± 8.9	67.1 ± 8.9	0.148
High school diploma, n (%)	22 (27.5)	9 (32.1)	0.640
No regular physical activity in adulthood, n (%)	31 (41.9)	14 (53.9)	0.292
BPI-sf walk score at baseline *	6.8 ± 2.0	8.3 ± 2.1	< 0.001
HAD anxiety score at baseline**	8 ± 4.5	11.6 ± 5.4	0.003

BPI-sf: Brief Pain Inventory-short form; * Score ranges from 0 (no interference) to 10 (complete interference) on a numerical rating scale; HAD: Hospital Anxiety and Depression Scale; ** score ranges from 0 to 21

Table 4. *Bivariate associations between patient characteristics, preoperative pain, pain consequences, and the presence or absence of chronic pain (NRS score ≥1) (mean ± SD, unless otherwise stated).*

	Chronic postsurgical pain		*P* value
	Absent n = 74	Present n = 30	
Main characteristics			
Male, n (%)	24 (32.4)	5 (16.7)	0.104
Mean age, years	69.8 ± 9.2	66.5 ± 8	0.089
High school diploma, n (%)	15 (20.3)	14 (46.7)	0.007
Mean BMI, kg/m²	30.3 ± 5.4	31.7 ± 5.5	0.266
No regular physical activity in adulthood, n (%)	26 (38.2)	18 (64.3)	0.020
Previous arthroplasty, n (%)	24 (32.4)	9 (30.0)	0.809
Pain elsewhere, n (%)	59 (85.5)	27 (90)	0.749
Surgery under general anesthesia, n (%)	29 (39.2)	13 (43.3)	0.696
Pain Matcher			
Sensitivity threshold, arbitrary units	6.4 ± 2.4	6.7 ± 1.8	0.507
Pain threshold, arbitrary units	13.9 ± 9.3	13.6 ± 5.6	0.664

Table 4 (cont). *Bivariate associations between patient characteristics, preoperative pain, pain consequences, and the presence or absence of chronic pain (NRS score ≥1) (mean ± SD, unless otherwise stated).*

		Chronic postsurgical pain		*P* value
		Absent n = 74	Present n = 30	
Preoperative pain				
Time since first knee pain ≥ 3 years, n (%)		44 (59.5)	22 (73.3)	0.183
First analgesic use ≥ 3 years previously, n (%)		28 (37.8)	18 (60.0)	0.039
Pain at rest, NRS		3.7 ± 2.8	4.8 ± 3.3	0.115
Pain at rest with NRS score ≥ 1, n (%)		59 (79.7)	25 (83.3)	0.673
Pain on movement, NRS score		7.2 ± 2.3	8 ± 1.8	0.084
Hospital Anxiety and Depression Scale				
Anxiety		8.1 ± 4.9	11.1 ± 4.9	0.006
Depression		5.9 ± 4.1	6.4 ± 3.9	0.514
Intermittent and Constant Osteoarthritis Pain				
Constant		9.1 ± 4.3	10.8 ± 3.5	0.075
Intermittent		12.1 ± 5.2	12.6 ± 6.2	0.681
Brief Pain Inventory-short form				
Mood		4.0 ± 3.3	4.5 ± 3.3	0.446
Walk		6.9 ± 2.2	7.9 ± 1.7	0.034
Normal work		6.3 ± 3	7.1 ± 2.4	0.172
Relations with others		2.7 ± 3.2	3 ± 3.7	0.638
Sleep		4.2 ± 3.3	5.2 ± 3.1	0.158
Enjoyment of life		3.4 ± 3.5	4.2 ± 3.6	0.353
Total		27.5 ± 12.9	31.9 ± 13.6	0.123
Genetic factors, n (%)				
COMT	AA	15 (20.3)	6 (20.0)	0.106
	AG	32 (43.2)	19 (63.3)	
	GG	27 (36.5)	5 (16.7)	
COMT_A carriers,		47 (63.5)	25 (83.3)	0.047
OPRM 1	AA	61 (82.4)	25 (83.3)	0.089
	AG	13 (17.6)	3 (10.0)	
	GG	0 (0.0)	2 (6.7)	
OPRM1_G carriers,		13 (17.6)	5 (16.7)	0.912
High-intensity APOP trajectory		14 (18.9)	14 (46.7)	0.004
Postoperative morphine consumption$, mg		56.1 ± 30.8	65.2 ± 25.7	0.084

BMI: body mass index; HTA: arterial hypertension; M0: baseline; NRS: numerical rating scale; COMT: catechol-O-methyltransferase; OPRM1: μ opioid receptor gene; APOP: acute postoperative pain; $: IV morphine equivalent

APOP trajectory (*P* = 0.004) and higher levels of analgesic use in the postoperative period (*P* = 0.084).

Following the construction of the 3 multivariate models with the variables of these 3 groups, 2 factors were found to be independent of the outcome once all the other factors were entered in the model: gender and first analgesic use ≥ 3 years previously. These 2 factors were therefore excluded from the list of candidate predictors to be introduced into the overall model. The final model, giving the best fit, is displayed in Table 5. HAD anxiety score was independent of outcome in the overall model. Four factors were found to be independently and significantly associated with the presence of CPSP: having obtained a high school diploma (OR = 3.8,

Table 5. *Factors predictive of chronic pain in multivariate logistic regression analysis (n = 95).*

	OR	95% CI (OR)	*P* value
COMT_A			
Non-carriers	Reference		
Carriers	3.42	0.93 – 12.51	0.063
Educational level			
Below high school diploma	Reference		
High school diploma	3.83	1.20 – 12.20	0.023
Physical activity in adulthood			
Regular	Reference		
Not regular	4.01	1.33 – 12.10	0.014
BPI-sf walk at baseline			
Score < 7	Reference		
Score ≥ 7	4.06	1.18 – 13.94	0.026
APOP trajectory			
Low-intensity	Reference		
High-intensity	4.23	1.39 – 12.88	0.011

OR: odds ratio, COMT: catechol-O-methyltransferase, COMT_A: carriers of allele A; BPI-sf: Brief Pain Inventory-short form; APOP: acute post-operative pain

95% CI = [1.2 – 12.2], *P* = 0.02), a BPIsf walk score ≥ 7 at baseline (OR = 4.1, 95% CI = [1.2 – 13.9], *P* = 0.03), no regular physical activity in adulthood (OR = 4.01, 95% CI = [1.22 – 12.10], *P* = 0.02), and a high-intensity APOP trajectory (OR = 4.2, 95% CI = [1.4 – 12.9], *P* = 0.01). The genetic COMT_A carrier factor was of borderline significance as a predictive factor (OR = 3.4, 95% CI = [0.9 – 12.5], *P* = 0.06). The Hosmer-Lemeshow test gave a non-significant result (*P* value = 0.710), indicating an absence of fit issues for this final model.

Discussion

In this prospective study, 4 factors were found to be associated with the presence of CPSP in patients 6 months after knee replacement: 3 preoperative factors (high school diploma, consequences of the pain for walking ability, as assessed with BPIsf walk, and an absence of regular physical activity in adulthood) and one postoperative factor (APOP trajectory). An association with a *P* value only slightly greater than the significance threshold was found for a genetic factor, the A allele of the COMT gene.

Knee replacement improved pain and function at 3 and 6 months after surgery, as previously reported (26). The prevalence of CPSP at 6 months of 28.8% reported here is consistent with previous findings (5).

A high-intensity APOP trajectory over the first 4 days after surgery was significantly and strongly associated with the presence of CPSP 6 months after surgery. In this group, the mean daily NRS score for the predicted mean trajectory was always greater than 5 points, whereas, in the low-intensity APOP trajectory group, the mean predicted daily NRS score was 3.1 ± 0.2 points at D1 and never greater than 3 points over the following days. Patients with a mean daily NRS score of more than 5 points over the first 5 days following knee replacement were at high risk of CPSP. Better APOP management might decrease the prevalence of CPSP 6 months after surgery. Our results are consistent with those of Puolakka et al (9), who showed that patients with severe acute pain after knee replacement had a 10 times higher risk of CPSP. Our results are also consistent with those of Fletcher et al (27), who showed that orthopedic surgery and percentage of time in severe pain on the first day are risk factors of CPSP. Althaus et al (11), who also used latent growth curve modeling, showed that a high initial post-operative pain intensity and a lower rate of pain resolution were associated with higher pain intensity during follow-up. Rather than using the slope and intercept of the APOP trajectory of each patient as predictors of CPSP, like Althaus et al (11), we decided to investigate the possibility that there might be underlying groups of people with similar APOP trajectories. Chapman et al (10) used a similar approach, but their model was very different from the model generated by the Latent class growth

analysis method used here. They showed that APOP was higher in patients using opioids before orthopedic surgery than in patients not using these drugs, suggesting possible opioid-induced hyperalgesia (28). We chose to use the Latent class growth analysis method, as this approach requires fewer prior hypotheses concerning APOP trajectory shape than Chapman's method, in which 3 trajectory shapes are constrained: stable, increasing, and decreasing (10).

In bivariate analyses, preoperative anxiety level was associated with a strongly decreasing APOP trajectory and with CPSP. However, once entered into the multivariate model with the APOP trajectory group for CPSP prediction, no significant association was found between anxiety level and CPSP. This suggests that APOP trajectory group is an intermediate factor between preoperative anxiety level and CPSP 6 months after surgery. Reducing anxiety levels before surgery might therefore affect APOP trajectory, in turn decreasing the risk of CPSP. Consistent with this hypothesis, anxiety and pain catastrophizing are well known predictors of APOP and CPSP (29-31).

Education to at least high school diploma level is a patient characteristic that could be used to identify patients at high risk of CPSP. Several studies have shown that high levels of education are associated with positive expectations and lower levels of satisfaction after functional surgery, both for APOP and in the longer term (32,33).

An impact of pain on walking ability, defined as a BPIsf walk score ≥ 7, was found to be predictive of CPSP, whereas preoperative pain intensity was not. Althaus et al (34), who developed a risk index for CPSP, reported that capacity overload increased the risk of CPSP, supporting the hypothesis that difficulty coping with pain increases the risk of CPSP. Consistently, the Osteoarthritis Research Society International and Outcome Measures in Rheumatology Arthritis Clinical Trials (OARSI/OMERACT) proposed a discriminatory cutoff point to define an indication for joint replacement that included both the level of pain and function: pain (0 – 100) + physical function (0 – 100) > 80 (35). A worse functional status at baseline has been shown to be associated with poor outcomes 6 months after total joint replacement (36,37), whereas preoperative walking training programs have been shown to have a positive effect on postoperative rehabilitation (38,39). The benefits of specific preoperative management in patients with a high impact of pain on walking ability, in terms of the reduction of chronic pain, should be investigated.

An absence of regular physical activity in adulthood was found to increase the risk of CPSP. Patients with regular physical activity in adulthood would be expected to have greater muscular strength and bone density, and this might contribute to this finding (40). It remains unclear whether regular physical activity during pain-free periods is associated with lower baseline levels of nociception (41). But physical activity has been found to be associated with a modulation of nociception (42,43). However, physical activity may decrease the chronic low-grade inflammation involved in osteoarthritis and reduce the risk of disability onset and progression in adults with osteoarthritis (44,45). Overall, physical activity seems to have several positive effects on function and pain at different stages of osteoarthritis. This should encourage the prescription of specific preoperative programs including physical activity, even in patients with poor function and high levels of pain. Further studies evaluating the type, intensity, and frequency of physical activity may improve our understanding of the relationship between physical activity and CPSP prevention.

In bivariate analyses, the proportion of patients carrying the A allele of the COMT gene was higher in patients with CPSP than in patients without CPSP, but this association was not quite significant following adjustment for the other factors entered into the multivariate model. This may be due to a lack of power, as suggested by the width of the OR confidence interval. The Val158Met polymorphism decreases COMT activity by a factor of 3 to 15 and is associated with higher catecholamine levels. It is associated with experimental pain sensitivity (12,14) and morphine requirement in patients with cancer pain (46). The contribution of the A allele to the occurrence of CPSP after knee replacement has never been studied before, but this allele is recognized as a risk factor for APOP, opioid requirement, and chronic pain following other types of surgery (13,47,48).

Some clinical factors, such as pain sensitivity and pain threshold measured with Pain Matcher, were not associated with the risk of CPSP. Pain threshold, measured by Pain Matcher, can predict APOP in other surgical contexts, but it did not seem to be suitable for the prediction of APOP and CPSP in our study, unlike QST (49-51). Despite several reports of a higher risk of APOP in carriers of the G allele of OPRM1, these patients were not found to have a higher risk of CPSP. Finally, the proportion of patients with pain elsewhere in the body was not found to be higher in the group of pa-

tients with CPSP, by contrast to other studies on larger samples of patients, which have suggested that pain at several sites reflects a higher pain sensitivity (34,52).

This study had several limitations. The sample size may have been too small for the detection of some of the factors predictive of CPSP. In addition, haplotype analysis based on polymorphisms at several gene loci would have been more appropriate, making it possible to draw conclusions about the contribution of genetic factors to CPSP. Moreover, although the patients were recruited over a period of 9 months and had general characteristics similar to those of patients included in other studies, the single-center nature of this study may limit its generalizability.

The results of this study provide a basis for the identification of patients at high risk of chronic pain following knee replacement and raise several possibilities for preventive therapeutic strategies, by highlighting several modifiable factors. All therapeutic strategies decreasing APOP, such as the management of anxiety including hypnosis, relaxation therapy or treatment of sleep disorder, and individualization of pain management in the postoperative period, appear to be of potential utility for reducing the risk of APOP and CPSP. The patients might be informed of these modifying factors, as they are directly involved in their management. Performing knee replacement before a critical state of pain with a major impact on walking ability is reached may help to decrease the risk of CPSP. However, if this critical level of pain is reached, specific preoperative management, including a physical training program, may be relevant. Further prospective studies are required to assess the utility of these strategies.

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