#### **KNEE**



# Anxiety is the cause of the worse outcomes of allergic patients after total knee arthroplasty

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#### **Abstract**

**Purpose** The presence of allergies has been proposed as a risk factor for worse outcomes in total knee arthroplasty surgery. The aim of this study is to evaluate if the presence of some psychiatric disorders is more frequent in patients who report allergies and if they could be the main cause for the worse outcomes.

**Methods** A prospective study, including patients undergoing a primary total knee arthroplasty, was designed. In the preoperative visit, all the patients completed a questionnaire about the presence of allergies and also psychiatric tests for anxiety (State-Trait Anxiety Inventory–STAI-), depression (Remission from Depression Questionnaire–RDQ-), somatization disorder (Patient Health Questionnaire–15–PHQ-15-), pain catastrophizing syndrome (Pain Catastrophizing Scale–PCS), and personality disorder (Reduced NEO-Inventory of Five Factors–NEO-FFI-). In the preoperative and at 6 months of follow up, the functional results of the surgery were assessed by the WOMAC, the SF-12, and the KSS scores.

**Results** A total of 209 patients was included: 136 (65%) did not have reported allergies and 73 (35%) did report some allergies. The psychiatric questionnaires showed that the presence of anxiety was more prevalent in the group of patients with reported allergies (STAI-T: no allergies 24.08 points vs. allergies 19.18 points, p = 0.039). When comparing the functional outcomes at 6 months of follow up, most of the analyzed scores improved less in the group of patients with reported allergies than in the no allergy-referred group: WOMAC-total score (34.37 vs. 40.10 points, p = 0.023), WOMAC-pain score (6.03 vs. 7.50 points, p = 0.018), WOMAC-function score (22.97 vs. 27.24 points, p = 0.023), KSS-knee score (25.37 vs. 33.79 points, p = 0.002), and SF-12 physical score (7.89 vs. 11.15 points, p = 0.046). The significance of the difference in the outcomes scores in this group was lost after adjusting for anxiety (p > 0.05).

**Conclusion** Allergies reported by patients are confirmed as a risk factor for worse results after TKA surgery. The relationship with anxiety disorder seems to explain the association between self-reported allergies and sub-optimal outcomes. **Level of evidence** II.

**Keywords** Total knee arthroplasty · Outcomes · Allergies · Anxiety · Psychological disorders

# Introduction

Different surgical, clinical, and personal risk factors for sub-optimal results after TKA have been described in the literature. They include elder patients, female gender, obesity, some co-morbidities, and severe preoperative pain [9,

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29]. It has also been stated that some psychological factors could affect the outcomes after TKA: depression, anxiety, pain catastrophizing syndrome, and some others [30, 32]. Recently, the presence of self-reported allergies has also been proposed as a risk factor for worse outcomes in this type of surgery [13, 16, 21, 36].

The relationship between reported allergies and psychiatric disorders has been suspected for many years, but has been poorly studied so far. Patten et al. reported a higher prevalence of both anxiety disorders and mood disorders (including both major depressive disorder and bipolar disorder) in subjects reporting allergies [26]. Another study focused on the relationship of some allergic symptoms and



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psychiatric disorders and an association between anxiety and allergic rhinitis was reported [33]. Also physician-diagnosed asthma and DSM-IV mental disorders such as anxiety, panic, or bipolar disorders have been correlated [14].

Patient-reported allergies may be a true allergy, a side effect or potentially a misperception. Anyway, self-reported allergies are a clinically detectable characteristic that may be easily identified in the anamnesis as potential risk factors for surgery.

The aim of this study was to evaluate if the presence of some psychiatric disorders (anxiety, depression, somatization disorder, pain catastrophizing syndrome, or personality disorder) is more frequent in patients who report allergies and if they could be the main cause for the worse outcomes of patients with reported allergies after TKA surgery. The relationship between self-reported allergies and the main psychiatric disorders considered risk factors in TKA surgery has never been studied before. The hypothesis of the study was that there is some psychiatric disorder or personality trait linked to patients who refer allergies that is conditioning the poorer outcomes after TKA.

## Materials and methods

#### Patients and data collection

A prospective study was designed. After it had previously approved by the ethical committee of the hospital (2016/7013/I), we included all the patients undergoing a primary TKA, because of knee osteoarthritis from November 2016 until June 2017 at the same hospital. An informed consent was signed by all the patients who willed to participate in the study. Exclusion criteria were revision or unicompartmental knee arthroplasties, diagnosis different from primary knee osteoarthritis, the inability to understand or answer psychological tests and outcomes scores and patients unwilling to participate in the study.

The following demographic and medical data of the patients have been collected: age, gender, body mass index (BMI), laterality, anesthetic risk according to the American Society of Anesthesiologists (ASA) classification and the presence of a diagnosed depression in the medical history.

During the preoperative visit, all the patients completed a questionnaire about the presence of allergies to medications and environmental agents. Any allergy invasive test was done to confirm them. The criteria to classify the patients into the allergic or no allergic group were the presence of self-reported allergies by a specific questionnaire.

In the preoperative visit, they also completed five psychiatric tests. For anxiety, the State-Trait Anxiety Inventory (STAI), validated in Spanish language [8], was performed. It consists in two subscales Anxiety-State and Anxiety-Trait

(STAI-T). STAI-T is the most stable in time, and therefore the one used in surgical context [3]. Patient Health Questionnaire-15 (PHQ-15), in its translated and validated version in Spanish, was used to assess the somatization disorders [18, 27]. It describes the fifteen more prevalent somatic symptoms of the somatization disorder described in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Also validated in Spanish, the Pain Catastrophizing Scale (PCS) was performed to assess the catastrophization of pain in its three dimensions: rumination, magnification, and helplessness [12, 31]. The reduced NEO-Inventory of Five Factors (NEO-FFI) was used to evaluate the five traits of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness (NEO-FFI). It is also translated and validated in Spanish [23]. The Remission from Depression Questionnaire (RDQ) is not validated in the Spanish version, but it is suitable for the purpose of the study, because it evaluates not only the depressive symptomatology, but also its repercussion to functioning and psychosocial well-being [37].

The assessment of the functional results after the TKA surgery was done both in the preoperative and at 6 months of follow up. The patients were asked to fulfill the Spanish versions of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [11], the 12-item Short Form Health Survey (SF-12) [28], and the Knee Society Score (KSS) [2].

#### Operative technique and rehabilitation protocol

In all cases, a standard anterior incision and a medial parapatellar approach were used. The prosthetic components were implanted with cement after standard bone cuts and, when necessary, soft tissue release. The patella was always replaced. Prophylactic antibiotics and compression stockinet were used. Seven different surgeons were involved in the procedures.

All the patients followed the same postoperative rehabilitation protocol, beginning with continuous passive motion (CPM) of the knee 24 h after surgery. It was carried out with two CPM sessions per day for 4 days until hospital discharge, following the hospital's clinical pathway. Patients began full weight-bearing walking with crutches at 48 h after surgery. After discharge, the patients came to the hospital for ten additional physiotherapy sessions for 2 weeks.

#### Statistical analysis

For descriptive statistics, quantitative variables were described through mean and standard deviation. Qualitative variables were described through frequencies table (number and percentage). For each outcome, score parameter differences postoperative minus preoperative were calculated.



Differences between groups (reported allergies or not) were tested through *t* test.

Evolution for each dependent variable (KSS, SF-12, WOMAC and their sub-scores) was analyzed using linear-mixed models for repeated measures. An interaction term (time by reported allergies or not) was added to check differences between groups in the evolution of dependent variables. Moreover, all models were adjusted by psychological tests variables to check possible confounding effects.

STATA version 15.1 (StataCorp, College Station, TX, USA) was used for statistical analysis. p values < 0.05 were considered statistically significant.

# Table 1 Biometric data in the groups of patients with and

without self-reported allergies in their medical record

	No allergies $(n=136)$	Allergies $(n=73)$	Total (n = 209)	p value
Age	72.76 (SD 8.21)	72.99 (SD 8.57)	72.84 (SD 8.32)	0.932
BMI	31.35 (SD 4.66)	31.40 (SD 4.72)	31.37 (SD 4.67)	0.803
ASA class	I: 7 (87.5%)	I: 1 (12.5%)	I: 8	0.481
	II: 91 (62.8%)	II: 54 (37.2%)	II: 145	
	III: 37 (67.3%)	III: 18 (32.7%)	III: 55	
	IV: 1 (100%)	IV: 0 (0%)	IV: 1	
Gender	48 M (35%)	20 M (27%)	68 M (33%)	0.245
	88 F (65%)	53 F (73%)	141 F (67%)	
Diagnosis of	110 N (81%)	54 N (74%)	164 N (79%)	0.247
depression	26 Y (19%)	19 Y (26%)	45 Y (21%)	
Laterality	67 R (49%)	39 R (53%)	106 R (51%)	0.566
	69 L (51%)	34 L (47%)	103 L (49%)	

BMI body mass index (kg/m<sup>2</sup>), ASA class American Society of Anesthesiologists Classification, SD standard deviation, M male; F female, N no, Y yes, R right knee, L left knee

Table 2 Preoperative psychiatric tests scores in the groups of patients with and without self-reported allergies in their medical record

	No allergies $(n=136)$	Allergies $(n=73)$	p value
STAI-T	24.08 (SD 13.25)	19.18 (SD 10.09)	0.039
NEO-FFI neuroticism	56.14 (SD 9.50)	54.15 (SD 11.36)	0.374
NEO-FFI extraversion	45.50 (SD 10.72)	45.96 (SD 11.15)	0.859
NEO-FFI agreeableness	49.39 (SD 9.23)	52.25 (SD 9.47)	0.074
NEO-FFI openness to experience	41.88 (SD 9.12)	42.94 (SD 11.04)	0.846
NEO-FFI conscientiousness	46.58 (SD 10.53)	48.81 (SD 12.29)	0.475
PHQ-15	7.27 (SD 4.47)	7.66 (SD 3.71)	0.332
PCS total	13.77 (SD 14.60)	11.04 (SD 13.52)	0.285
PCS rumination	5.13 (SD 5.36)	4.01 (SD 4.87)	0.187
PCS magnification	2.81 (SD 3.33)	2.21 (SD 3.08)	0.160
PCS helplessness	5.51 (SD 6.45)	4.81 (SD 6.32)	0.554
RDQ	17.32 (SD 18.06)	15.21 (SD 15.66)	0.557

STAI-T Stait Trait Anxiety Inventory-Trait anxiety, NEO-FFI NEO Five-Factor Inventory, PHQ-15 Patient Health Questionnaire 15-Item Somatic Symptom Severity Scale, PCS Pain Catastrophizing Scale, RDQ Remission from Depression Questionnaire

p values in bold when < 0.05

#### Results

A total of 209 patients undergoing a primary TKA was included in this study: 136 (65%) did not have reported allergies and 73 (35%) did report some allergies (15% to one substance, 8% to two, 5% to three, 4% to four, and 3% to five or more substances). The groups of patients with and without reported allergies were similar in terms of age, BMI, ASA class, gender, depression, and laterality (p > 0.05) (Table 1).

The psychiatric questionnaires showed differences between the two groups regarding the presence of anxiety (STAI-T p = 0.039), being more prevalent in the group of patients with reported allergies. No differences were

observed between the two groups for all the other analyzed psychiatric disorders (Table 2).

When comparing the functional outcomes in the groups of patients with and without self-reported allergies, no preoperative differences were found between the two groups. At 6 months of follow up, patients with referred allergies presented worse outcomes for most of the scores (SF-12 physical, WOMAC-score and WOMAC-pain, and function sub-scores (Table 3).

Both groups (with or without reported allergies) significantly improved in the postoperative respect to the preoperative evaluation in all the analyzed scores except the SF-12 mental condition. Most of the analyzed scores (WOMAC score and WOMAC pain and function sub-scores, KSS-knee score, and SF-12 physical score) improved less (postoperative minus preoperative scores) in the group of patients with reported allergies (Table 4).

As anxiety had been detected to be more frequent in patients reporting allergies, we adjusted the results for anxiety. The significance of the difference in the outcomes scores in the group of allergic patients was lost after adjusting for anxiety, as it can be seen in the Table 4. Therefore, we can consider that anxiety is a confounding factor of the worse outcomes scores in the group of patients reporting allergies.

#### Discussion

The most important finding of this study is that anxiety trait seems to be a risk factor associated with allergy that could explain the worse results after TKA surgery in patients reporting allergies.

The results of previous studies referring the presence of allergies reported by the patient as a risk factor for worse outcomes after TKA surgery are also confirmed by our findings. Graves et al. [13] exposed in a first study that patients with four or more allergies had worse results after knee or

Table 3 Preoperative and postoperative scores in the groups of patients with and without self-reported allergies in their medical record

	Preoperative		Post-operative			
	No allergies $(n=136)$	Allergies $(n=73)$	p value	No allergies $(n=136)$	Allergies $(n=73)$	p value
WOMAC (total)	65.83 (SD 9.49)	66.12 (SD 11.78)	0.657	25.57 (SD 16.00)	30.89 (SD 19.33)	0.046
WOMAC-pain	13.07 (SD 2.44)	13.18 (SD 2.53)	0.825	5.56 (SD 3.61)	7.12 (SD 4.19)	0.013
WOMAC-stiffness	6.57 (SD 1.19)	6.48 (SD 1.54)	0.672	2.38 (SD 1.85)	2.72 (SD 1.57)	0.109
WOMAC-function	46.19 (SD 6.67)	46.46 (SD 8.48)	0.666	18.95 (SD 11.22)	23.82 (SD 13.37)	0.012
KSS-knee	54.69 (SD 14.26)	58.74 (SD 12.46)	0.106	88.13 (SD 12.15)	85.19 (SD 14.81)	0.109
KSS-function	47.52 (SD 18.24)	49.09 (SD 15.83)	0.349	75.96 (SD 19.28)	72.91 (SD 22.78)	0.420
SF-12 physical	30.52 (SD 5.38)	29.63 (SD 5.15)	0.390	41.68 (SD 9.38)	37.52 (SD 7.74)	0.004
SF-12 mental	49.72 (SD 10.19)	47.46 (SD 11.95)	0.246	49.65 (SD 10.29)	48.22 (SD 9.88)	0.338

WOMAC Western Ontario and McMaster Universities Arthritis Index, KSS Knee Society Score, SF-12 12-item Short Form Health Survey, SD standard deviation

p values in bold when < 0.05

Table 4 Improvement scores (postoperative minus preoperative differences) in the groups of patients with and without self-reported allergies and after adjustment for Trait Anxiety in the Mixed-Model

	Improvement			Mixed-model	
	No allergies $(n=136)$	Allergies $(n=73)$	p value	p value	
WOMAC (total)	40.10 (SD 17.45)	34.37 (SD 17.90)	0.023	0.087	
WOMAC-pain	7.50 (SD 4.06)	6.03 (SD 4.13)	0.018	0.709	
WOMAC-stiffness	4.20 (SD 2.17)	3.86 (SD 1.93)	0.191	0.246	
WOMAC-function	27.24 (SD 12.36)	22.97 (SD 12.70)	0.023	0.565	
KSS-knee	33.79 (SD 18.59)	25.37 (SD 18.08)	0.002	0.267	
KSS-function	28.05 (SD 25.22)	23.06 (SD 27.41)	0.306	0.423	
SF-12 physical	11.15 (SD 10.22)	7.89 (SD 8.96)	0.046	0.310	
SF-12 mental	-0.07 (SD 13.06)	0.76 (SD 10.37)	0.794	0.241	

WOMAC Western Ontario and McMaster Universities Arthritis Index, KSS Knee Society Score, SF-12 12-item Short Form Health Survey, SD standard deviation

p values in bold when < 0.05



hip arthroplasties, independently of co-morbidities, with smaller increase in the physical SF-36 and WOMAC-function. In a subsequent prospective work, they confirmed these results [25]. Mc Lawhorn et al. [21] found that there was an inverse relationship between number of reported allergies and results after hip and knee arthroplasties in terms of satisfaction, pre and postoperative WOMAC scores, and WOMAC improvement and they also had a longer hospital stay. Recent studies have shown reported allergies as a risk factor for worth outcomes in other types of orthopedic surgeries such as spine or foot and ankle, but are critics with some aspects like the clinical relevance of the differences found [24] or that they would be minimized with a longer term follow up [36].

In a previous study [16], we already observed postoperative differences in total WOMAC, function, and knee KSS in patients with self-reported allergies and we ruled out the presence of depression as a possible confounding factor to explain these results. However, we suspected that the explanation of the worse outcomes in these patients would probably be found in some factors of the psychological sphere. The possible relationship between some psychiatric disorders and the presence of allergy has been little studied so far [14, 26, 33]. Therefore, the main objective of this work was to study the presence of certain disorders (somatization disorder, pain catastrophizing syndrome, personality disorder, anxiety, and depression) in patients with reported allergies, as a possible explanation of these worse results.

Somatization disorders or "symptoms that cannot be explained medically" have been described in patients who report allergies [15]. However, according to our results, somatization disorders are not more prevalent in allergic patients. Pain catastrophizing, understood as an exaggeratedly negative mentality toward painful experience, has been related to worse results after TKA [5, 32], but its relationship with the presence of allergies has not been previously studied. The findings in the present work seem to rule out such an association. Some "personality disorders" such as neuroticism or cluster type C [20, 33] have been associated with the presence of allergies. In the present work, there does not seem to be any association between these variables either. Anxiety and depression have been described as prevalent co-morbidities in patients with allergy symptoms [14, 26]. As it was described in a previous study [16], we can confirm that when we assessed with the RDQ questionnaire, there is no clear relationship between the presence of allergy and depression. On the other hand, we have found a higher prevalence of anxiety in patients with reported allergies. This disorder has previously been proposed as a risk factor for worse outcomes after TKA [32]. When comparing the functional results of allergic patients with respect to non-allergic patients, we see that they no longer present significant differences in the functional results after TKA, when the variable anxiety is taken into account as a confounder. It seems that it would be an association between allergy and anxiety that would enhance them as risk factors beyond their role as isolated factors. In this sense, the relationship between allergy and anxiety could explain the worse functional results of allergic patients in prosthetic knee surgery. Therefore, the presence of self-reported allergies could constitute an easily detectable antecedent in the anamnesis of patients, which is associated with more anxiety and worse results after TKA surgery in this study.

Some theories have been proposed for the relationship between psychiatric disorders and self-reported allergies; it suggested a common pro-inflammatory pathway based on the higher levels of pro-inflammatory cytokines present in patients with psychiatric disease [1]. Psychological stress perception has the ability to dysregulate neuroendocrine and immunological processes relevant to inflammatory responses [22], but it has not been possible to evaluate the potential role of immunologic changes, which could be affected in them. Alternatively, the presence of psychiatric disease would influence patients' identification and characterization of their allergies, as patient-reported allergies not always correspond to true allergies. It has also been proposed that there could be a causal relationship between them or their co-occurrence could be driven by exposure to common social, genetic, or environmental risk factors for both allergy and mental health problems.

One of the possible explanations of the relationship between anxiety and worse results in TKA could be within the "fear-avoidance model", in which other disorders of the same sphere, such as kinesophobia, would also be included. The amplification of these cognitive and behavioral disorders may interfere with patients' recovery [10]. Also, there are the studies by Bulbena et al. [4] about "joint laxity (hypermobility) syndrome" that propose a relationship between hyperlaxity and anxiety. They would be included in a "New Psychosomatic Phenotype: The Neuroconnective Phenotype" with other joint or extra-articular clinical characteristics related to the connective tissue: arthralgia, lumbalgia, epicondylitis, tenosynovitis, bursitis, recurrent dislocations, hypertrophic scars and keloids, fibromyalgia, and other conditions. The presence of higher anxiety, depression, and interpersonal sensitivity scores, as well as higher scores for the symptomatology checklist and pain scales in these patients would make the study of this syndrome very interesting in a sample of patients like ours to assess their possible involvement.

The clinical relevance of the statistically significant differences we have found could be discussed. Previous studies have proposed minimum clinically important difference (MCID) values for some of the used questionnaires (11, 9, and 8 points for WOMAC subscales and 10 points for WOMAC-total score [6]; 5.3–5.9 points for KSS-knee and

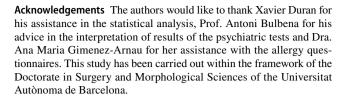


6.1-6.4 for KSS-function scores [19]; and 4-5 points for the SF-12 physical score [7]. The differences found in our results are close to MCID for WOMAC-total (6 points) and SF-12 physical (3 points) and even achieve it for KSS-knee (8 points). In any case, the clinical applicability of this study is to recognize the worse outcomes in this group of patients, so that both the surgeon and the patient have the maximum information and can adjust the expectations of the surgery. In the self-reported allergies, patients' very significant improvements in the outcomes scores can also be expected, so based on the findings of the work, we should not advise against TKA surgery in allergic patients. The finding that allergy is associated with psychiatric disorders can alert the physician that increased efforts at communication and more time discussing psychosocial issues may be needed to assure patient satisfaction.

The main limitation in this study is that allergies reported by the patient have been registered from a special questionnaire and specific allergy tests have not been performed to confirm them. In fact, it has not been demonstrated that the allergies reported by the patient correspond with hypersensitivity reactions mediated by immunological mechanisms [34]. Some studies talk about a very low percentage of real allergic reactions in patients who refer them so they may be a true allergy, a side effect, or potentially a misperception. For example, more than 80% of patients with a self-reported allergy to penicillin will have a negative skin allergen test [17, 35]. In any case, the objective of the study was not to clarify if the patients were really allergic or not by any invasive test. Undertaking preoperative validated screening tools, including complex psychological questionnaires, to identify psychological distress when advising patients about the suitability of TKA, as proposed by some studies [30] would be more difficult in the daily practice. In this way, allergies reported by patients are easily detectable by the doctor during the anamnesis and, as they are associated with anxiety, they may be considered a risk factor for poorer outcomes in this surgery.

#### Conclusion

Allergies reported by patients are confirmed as a risk factor for worse results after TKA surgery. The relationship with anxiety disorder seems to explain the association between self-reported allergies and sub-optimal outcomes. The presence of self-reported allergies is an easily detectable antecedent in the anamnesis of the patients who are candidates for TKA, which should make us suspect that they are more anxious and the expected outcome scores after TKA surgery can be lower.



### Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

**Ethical approval** The present study received IRB approval by the Parc de Salut Mar Ethical Committee (2016/7013/I).

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