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Causes Of Stiffness After Total Knee Arthroplasty: A Systematic Review

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Abstract

Background: Knee stiffness after Total Knee Arthroplasty (TKA) often leads to pain and discomfort, failing to meet patients' expectations on the surgical procedure. Despite the growing debate on the topic, a comprehensive literature analysis of stiffness causes has never been conducted. Thus, the purpose of the present study was to systematically review the literature regarding the main causes of stiffness after TKA.

Methods: Pubmed Central, Scopus, and EMBASE databases were systematically reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines for studies on stiffness and pain or discomfort after TKA through November 2020. Overall, 25 articles matched the selection criteria and were included in the study. Clinical relevance and strength of evidence of the included studies were graded using the risk of bias and the methodological index for non-randomized studies quality assessment tools.

Results: The main causes of pain and discomfort due to stiffness were surgery-related issues, i.e., component malpositioning and over-voluming, implant loosening, psychological distress, obesity, which could be considered "modifiable" factors, and expression of profibrotic markers, high material hypersensitivity-related cytokines level, male gender, previous contralateral TKA and high preoperative pain, which could be considered "non-modifiable" factors.

Conclusion: The use of alternative technologies such as surgical robots, anatomy-based devices, and more inert and less stiff component materials could help reducing stiffness caused by both modifiable and even some non-modifiable factors. Furthermore, early diagnostic detection of stiffness onset could consistently support surgeons in patient-specific decision making.

Keywords: Pain; Stiffness; Total Knee Arthroplasty

List of Abbreviations

Magnetic resonance images (MRI)

Knee Society Score (KSS)

Pain Catastrophizing Scale Score (PCS)

Oxford Knee Score (OKS)

Infrapatellar fat pad (FP)

Synovial membrane (SM)

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Quality of Well-Being scale (QWB-7)

Short Form (SF) 12 scores

The Knee injury and Osteoarthritis Outcome Score (KOOS)

External Rotation (ER)

Internal Rotation (IR)

Normal Rotation (NR)

Introduction

Total Knee Arthroplasty (TKA) is a well-established treatment for end-stage osteoarthritis (OA) that effectively reduces pain and improves knee functionality [10]. The primary patient's expectations are usually related to pain and joint mobility improvement [36].

However, about 20% of patients remain "unsatisfied" by the procedure [6]. The main complaints are discomfort or pain referred to the operated joint. A heterogeneous list of possible causes has been proposed. Excluding the most frequent and evident causes, i.e., aseptic or septic loosening and implant failure [16, 17], there are several other causes with less clear categorization and treatment path.

Knee stiffness consists of a decreased range of motion after TKA and has been investigated both as a cause of and as a complication due to pain and discomfort [4, 9, 33].

Although there is a growing interest in this topic, the literature is fragmented: it is not clear whether the reduced knee range of motion could be defined as a flexion contracture, a reduced flexion, or both, and no consensus about pathogenesis has been reached [31]. Moreover, no comprehensive analysis of stiffness causes after TKA has been conducted: previous literature reviews were mainly focused on the treatment of stiffness to increase the knee range of motion.

Hence, the purpose of this study was to systematically review the main causes of stiffness after TKA.

Material and method

A literature review was performed using a strategy search design to collect articles regarding stiffness and pain or discomfort after TKA. Inclusion criteria adopted were: (1) studies of patients who underwent primary TKA; (2) articles published in the last 10 years; (3) articles published in English; (4) involving human species. Review articles were excluded from the search.

Article Selection

The search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guidelines [24] by two independent reviewers on PubMed Central, Scopus and EMBASE, for studies available until November 2020. The keywords used for initial screening were ((TKA[Title/Abstract]) OR (TKR[Title/Abstract]) OR (Total Knee Replacement[Title/Abstract]) OR (Total Knee Arthroplasty[Title/Abstract])) AND (stiff*[Title/Abstract]) AND ((Pain[Title/Abstract]) OR (discomfort*[Title/Abstract])).

Two authors (A.M., N.P.) independently reviewed each article's title and abstract from the literature search. The assessors were not blinded to the authors of the publications. The full text was obtained and evaluated when eligibility could not be assessed from the first screening. Any disagreements were resolved via a consensus discussion between the reviewers, and a third reviewer (S.Z.) was consulted if the disagreement could not be resolved.

The Cochrane risk of bias (ROB) tool was used for the quality assessment of randomized controlled trials, while the methodological index for non-randomized studies (MINORS) was used for quality assessment of observational studies. Two authors (G.B., R.Z.) independently performed the quality assessment for each article. A third author (L.B.) was consulted in case of disagreement.

Results

After the exclusion process detailed above (Figure 1), the strategy search generated a systematic review of 25 articles. Among these articles, 7 were related to surgical issues. Six of them identified component malpositioning as a cause for stiffness [1, 2, 16, 28, 34, 37], reporting extension deficit, and poor subjective and objective clinical outcomes, such as the Knee Society Score (KSS). Component malpositioning was mainly identified as internal rotation of both the femoral and tibial components and sagittal plane malalignment. One article [23] detected component over-voluming in the 24% of retrospectively evaluated knees and identified it as a main cause of stiffness.

Three articles were related to stiffness due to TKA components loosening [13, 15, 32], identified as a major cause of pain and discomfort, and related to higher odds of revision rate.

One article [22] found that the genetic expression of profibrotic markers was a factor influencing the limited range of motion and subsequent patients' pain and discomfort, evaluated through the Oxford Knee Scores (OKS) and Pain Catastrophizing Scores (PCS).

Three articles were related to immunological and allergy [12, 26, 38] issues. The authors detected high levels of inflammatory cytokines in painful knees presenting stiffness [26, 38], as well as lower postoperative outcomes in poly-allergic patients [12].

Three articles were related to psychological issues [3, 19, 30]. Patients with anxiety, depressive symptoms, functional limitation, and severe preoperative pain were more likely to show stiffness and become more dissatisfied after TKA than other patients.

Eight studies focused on demographic and other factors [5, 7, 14, 18, 20, 21, 27, 29]. Young patients reported residual symptoms and limitations after modern TKAs, as well as male patients and patients with lung disease, diabetes, and preoperative stiffness. TKA performed after a knee injury (fracture or ligament injury) or a previous osteotomy and preoperative radiologic minimal joint space width were related to poorer outcomes after TKA.

The characteristics and the results of the included articles are reported in Table 1.

Methodological quality assessment

No randomized controlled trial study was retrieved. Therefore, the MINORS tool was used to perform the quality assessment of all the included articles. Of the 25 articles included in this analysis, 8 were comparative studies and 17 were non-comparative studies. The average score for the comparative studies was 18.4 (range 14 – 22), while the average score for the non-comparative studies was 11.0 (range 5 – 16) (Appendix A) [35].

Discussion

The purpose of the present study was to review the main causes of stiffness after TKA. Multiple causes with different incidence emerged from the literature review (Table 2). A distinction could be made between "modifiable" factors, i.e., surgical issues, loosening, psychological distress, obesity, and "non-modifiable" factors, i.e., male gender, young age, material hypersensitivity, high preoperative pain, and gene expression of profibrotic markers .

Among the modifiable factors, malposition and over-voluming were revealed to be critically leading to stiffness. Indeed, the prosthetic components' positioning is fundamental to allow correct kinematics and guarantee the long-term survival of modern TKAs. A mistake in component positioning can trigger chronic inflammation, leading to pain and functional limitation until implant failure [1, 2]. Thus, the prosthetic components' appropriate positioning is mandatory to avoid pain, discomfort, and, eventually, reduce the revision rate after TKA. To face this problem, in the last years, the use of computer-assisted surgery (CAS) and patient-specific instrumentation (PSI) has been developed to improving implant positioning. Both these technologies showed promising results concerning correct femoral positioning, perioperative blood loss, and operative time. However, the clinical relevance of such improvement remains uncertain [11].

The aseptic loosening was detected as a major cause for patients' dissatisfaction leading to implant revision. Several aspects can contribute to this fatal condition, e.g., cementation technique, bone quality, component design. In the last years, a significant effort has been put into improving bone-implant fixation, e.g., the tibial baseplate design and the cementation process. Moreover, the tribology of the material used in modern TKA has been questioned: pre-clinical studies have been conducted on alternative materials (ceramic and polymers) to demonstrate the influence of material stiffness on implant failure. In particular, a lower stress-shielding phenomenon was hypothesized using a less stiff material [25]. If confirmed in clinical studies, the use of less stiff materials could represent a promising alternative to standard TKA implant components.

The patient's psychological conditions have been detected as decisive factors influencing pain and discomfort after TKA. Since the rehabilitation phase needs active patient engagement to reach satisfying results, a positive attitude is highly required. During the patient's selection for this procedure, the surgeon should consider psychological aspects, and if any abnormalities are detected, the patient should be aware of the higher risk of poorer postoperative outcomes. Education programs have been introduced to prepare TKA patients from both physical and psychological sides. Recent studies [8] demonstrated the positive effects of these programs on postoperative patients' conditions during the rehabilitation phase.

Among the non-modifiable factors, the expression of profibrotic markers correlated with the onset of postsurgical stiffness, and high preoperative inflammatory cytokines level correlated with poorer postoperative outcomes. Even though these factors are a-specific, a substantial contribution to reducing the risk of inflammatory marker expression and the onset of stiffness in predisposed subjects could come from the biocompatibility of TKA components material. The use of more inert materials than classical cobalt-chrome alloy could indeed limit the alteration of intraarticular homeostasis and the inflammatory response.

Two main clinical implications could be deduced from the present review. First, the use of alternative technological solutions, e.g., surgical robots, PSI, and less stiff and more inert materials, could be crucial to act both on some modifiable (surgical issues and loosening) and non-modifiable factors (expression of pro-fibrotic markers or allergy). Such tools might induce a further reduction in the percentage of patients experiencing knee stiffness and subsequent pain and discomfort. However, clinical evidence is still missing and needs to be addressed.

Second, some of the factors leading to stiffness are difficult to be detected in routine clinical practice. Indeed, even this condition can be quite easily detected in the postoperative outpatient setting, a comprehensive and well-structured methodology to preventively identify the cohort of patients at risk to develop post-TKA stiffness is still lacking. Such clinical diagnosis could consistently support the surgeons in decision making on the type of implant and the surgical procedures to adopt per each patient.

The present review has some limitations. First, the heterogeneous approaches adopted in evaluating stiffness for the different factors did not allow a meta-analysis of the retrieved data. Second, the possibility of falling into article selection bias could have affected the validity and generalizability of this study. However, the authors rigorously followed the PRISMA guidelines [24] and decided to include both prospective and retrospective studies to provide the most comprehensive view on such a specific topic. Furthermore, the MINORS tool was used to assess the quality of the included articles. Although the literature is well-populated with studies regarding the postoperative treatment of stiffness after TKA, the present review confirmed a lack of consistent investigations on the causes of this clinical expression.

Conclusion

Stiffness after TKA might occur for different and, sometimes, multifactorial causes. Possible solutions should be looked for into alternative aspects, e.g., different component material properties and anatomy-based TKA designs. Moreover, further studies are needed to investigate the development of diagnostic strategies to detect stiffness onset as early as possible.

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Figure Legend

Fig.1: Flow diagram, describing the number of studies identified, included and excluded with relative reasons.

Appendix A: Methodological quality assessment. Individual MINORS criteria [35].

Study	A clear stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Abdelnasser et al. [1]	2	1	2	1	1	0	0	2	N/A	N/A	N/A	N/A	9
Bedard et al. [2]	2	2	2	1	1	1	0	2	N/A	N/A	N/A	N/A	11
Belford et al. [3]	2	2	2	1	1	2	1	2	N/A	N/A	N/A	N/A	13
Clement, Bardgett et al. [5]	2	2	2	1	1	2	1	2	2	1	2	2	20
Clement, Merrie et al. [7]	2	2	2	1	1	2	1	2	N/A	N/A	N/A	N/A	13
Graves et al. [12]	2	2	2	1	1	2	1	0	N/A	N/A	N/A	N/A	11
Gu et al. [13]	2	2	2	2	1	1	2	2	2	2	2	2	22
Gungor et al. [14]	2	2	2	2	2	2	2	2	N/A	N/A	N/A	N/A	16
Hagman et al. [15]	2	2	2	2	0	2	0	0	N/A	N/A	N/A	N/A	10
Hirschmann et al. [16]	1	1	2	1	0	0	0	0	N/A	N/A	N/A	N/A	5
Järvenpää et al. [18]	1	2	2	2	0	1	0	0	2	2	0	2	14
Lavernia et al. [19]	2	1	2	1	0	2	0	2	2	2	2	2	18
Liebensteiner et al. [20]	2	2	2	1	0	1	2	2	N/A	N/A	N/A	N/A	12
Liebs et al. [21]	2	2	2	2	0	2	1	2	N/A	N/A	N/A	N/A	13
Mann et al. [22]	1	2	2	1	2	1	0	2	N/A	N/A	N/A	N/A	11
Marmor et al. [23]	2	1	2	1	0	0	1	2	N/A	N/A	N/A	N/A	9
Paish et al. [26]	1	1	2	2	0	0	0	2	2	2	2	2	16
Parvazi et al. [27]	1	1	2	1	0	1	1	0	N/A	N/A	N/A	N/A	7
Planckaert et al. [28]	2	2	2	2	1	2	1	0	2	1	1	2	18
Putman et al. [29]	2	2	2	2	0	2	1	2	N/A	N/A	N/A	N/A	13
Razmjou et al. [30]	2	0	2	2	0	2	1	2	N/A	N/A	N/A	N/A	11
Sadoghi et al. [32]	2	2	2	2	2	2	2	0	2	2	2	2	22
Scott et al. [34]	2	1	2	2	0	2	1	0	2	2	1	2	17
White et al. [37]	2	2	2	2	0	2	2	0	N/A	N/A	N/A	N/A	12
Yang et al. [38]	2	1	2	2	0	2	2	0	N/A	N/A	N/A	N/A	11

Table

Click here to access/download;Table;Table 1.docx

Table 1: Characteristics and results of the included studies

Category	Authors	Year	Type of study	Level of evidence	Aim	Study subjects	Instruments	Results	Conclusions
Surgery-related issues	Abdelnasser et al.[10]	2020	Observational study	III	To investigate whether induced IR of the tibial component intraoperatively would change in vivo knee kinematics	31 TKA patients (14 M, 17 F) CR: 22; PS: 9	▪ Radiographs	▪ Tibial NR: CR -1.6 ± 3.4; PS 1.6 ± 3.9 ▪ Tibial IR: CR 3.7 ± 2.6; PS 8.8 ± 4.4	IR of the tibial component during TKA can lead to postoperative knee extension deficit, pain and limited motion.
	Bedard et al.[11]	2011	Observational study	IV	1. Incidence of IR of the femoral and tibial components in stiff TKAs; 2. If revision surgery that included correction of rotational positioning improved pain, ROM, and patellar tracking; 3. If revision altered nonrotational radiographic parameters	52 TKA patients 34 scanned Pre Revision; 18 scanned After Revision	▪ CT scans ▪ KSS	▪ Femoral IR: Pre 3.1 N24; Post 2.1 (n=15) ▪ Femoral ER: Pre 1.3 N10 ; Post 1.1 (n=3) ▪ Tibial IR: Pre 13.7 N33 ; Post 3.3 (n=3) ▪ Tibial ER: Pre 1.0 N1; Post 8.5 15 ▪ KSS - Pain: Pre10,3 ; Post 33,7 - Knee: Pre 41,6 ; Post 77,3 - Function: Pre 48 ; Post 65,7	The incidence of IR was 24 of 34 femoral and 33 of 34 tibial components; Revision arthroplasty improved Knee Society function, knee, and pain scores; Post-revision nonrotational parameters were unchanged.
	Hirschmann et al.[4]	2015	Observational study	IV	To evaluate the clinical value of SPECT/CT in patients with knee pain after primary TKA	23 TKA patients	▪ Hybrid SPECT/CT	▪ SPECT/CT imaging changed the suspected diagnosis and the proposed treatment in 19/23 (83%) knees ▪ Progression of patellofemoral OA (n = 11), loosening of the tibial (n = 3) and loosening of the femoral component (n = 2) were identified as the leading causes of pain after TKA	SPECT/CT was very helpful in establishing the diagnosis particularly in patients with patellofemoral problems and malpositioned or loose TKA.

	Planckeart et al.[12]	2018	Observational study	IV	To analyze knee 3D kinematics of TKA patients with unexplained anterior knee pain and compare them to those of an asymptomatic TKA group, and a healthy control group	62 knees: 24 asymptomatic, 21 painful, and 17 control	▪ CT scans ▪ Radiographs	▪ LEFS: 66.6 ± 8.2 Asympt; 43.6 ± 13.7 Pain; N/A Control ▪ KOOS - Pain 90.0 ± 11.2 Asympt; 59.5 ± 17.7 Pain; 93.1 ± 15.1 Control - Symptom 84.4 ± 16.0 Asympt; 62.1 ± 21.1 Pain; 91.7 ± 11.6 Control - AVQ 90.0 ± 10.3 Asympt; 60.9 ± 16.3 Pain; 94.0 ± 14.7 Control - Sport 55.0 ± 23.2 Asympt; 23.3 ± 19.1 Pain; 87.2 ± 22.3 Control - QoL 82.3 ± 21.1 Asympt; 43.5 ± 29.3 Pain; 86.7 ± 24.4 Control ▪ Component rotation - Tibial rotation: 7.8° ± 5.4°; 0.8° ± 6.8° Pain - Femoral rotation: − 0.5° ± 2.3° − 2.1° ± 2.6° Pain - Combined rotation:7.3° ± 6.1° − 1.4 °± 7.0° Pain	Painful TKA patients presented three well-known characteristics: a stiff knee gait, a valgus alignment when walking, and combined TKA components slightly internally rotated.

	Scott et al.[13]	2019	Case-Control Follow-up Study	IV	To investigate sagittal femoral component position as a predictor of anterior knee pain at long-term follow-up after cruciate-retaining single-radius TKA without routine patellofemoral resurfacing	162 TKA patients	▪ Radiographs ▪ SF-12 ▪ OKS ▪ PROMs ▪ HSS	▪ Femorotibial angle: 175.1° Pain; 177.9°No Pain ▪ Coronal plane - Medial proximal tibial angle: 89.7° Pain; 88.9° No Pain - Lateral distal femoral angle: 85.7° Pain; 85.7°No Pain ▪ Sagittal plane - Posterior tibial slope: 4.5° Pain; 5.3° No Pain - Femoral component flexion: 20.6 Pain; 1.4° No Pain - Posterior condylar offset ratio: 94.0% Pain; 97.3% No Pain - Anterior femoral offset ratio:17.2% Pain; 13.3% No Pain ▪ PCS 35.5 (11.6) Pain; 43.4 (10.6) No Pain ▪ MCS 48.5 (9.4) Pain; 51.5 (9.7) No Pain ▪ OKS 29.6 (10.9) Pain; 40.1 (7.1) No Pain ▪ Dissatisfied 14 (19) Pain; 4 (4) No Pain	Sagittal plane positioning and alignment of the femoral component were associated with long-term anterior knee pain, with femoral component extension being a major risk factor
	White et al.[14]	2016	Prospective study	IV	To restore a patient's anatomical geometry of the knee	74 TKA patients Patient-Specific TKA: 21 (7 M, 14 F) PFC PS: 42 (14 M, 28 F) PFC NC-	▪ WOMAC	Pre-op ▪ Patient-Specific TKA: 11.5 Pain; 4.6 Stiffness; 35.3 Function; 3.5 Satisfaction ▪ PFC PS: 11.1 Pain; 5.1 Stiffness; 36.2 Function; 2.1 Satisfaction ▪ PFC NC-CR: 7.8 Pain; 3.4 Stiffness; 30.1 Function; 0.8 Satisfaction 2 Years post-op ▪ Patient-Specific TKA: 4.8 Pain; 3.0 Stiffness; 15.2 Function; 7.0 Satisfaction	Patient-specific TKAs were associated with higher manipulation rate and lower satisfaction scores

						CR: 11 (10 M. 1 F)		▪ PFC PS: 2.8 Pain; 2.2 Stiffness; 10.4 Function; 8.3 Satisfaction ▪ PFC NC-CR: 1.2 Pain; 1.3 Stiffness 5.2 Function; 8.9 Satisfaction	
	Marmor et al.[15]	2019	Observational study	IV	1) To investigate differences in volumes of resected bone compared to implanted components in TKA 2) To determine the incidence and factors related to 'over-voluming'	100 TKA patients (45 M, 55 F)	▪ MRI	▪ HKA: 178.3° ± 4.1° ▪ Mechanical lateral femoral angle: 88.2° ± 2.9° ▪ Mechanical medial proximal tibial angle: 83.3° ± 3.5° ▪ Over-voluming: 24% of the TKA patients	Over-voluming could be associated with prosthetic overhang or excessive tensions within the joint capsule, and contribute to unexplained pain and stiffness following TKA
Loosening	Gu et al.[16]	2020	Observational study	III	To determine the relationship between prior Knee arthroscopy (KA) within 2 years of TKA on revision rates after TKA	138,019 TKA patients 3357 previous KA vs 134,662 No KA	▪ Current Procedural Terminology ▪ International Classification of Diseases	PREVIOUS KA ▪ Frequency of revision TKA: 2.77% ▪ Frequencies of aseptic loosening: 1.25% ▪ MUA: 4.28% ▪ PJI: 2.65% ▪ Periprosthetic fractures 0.15% ▪ Postoperative stiffness: 17.78% NO KA ▪ Frequency of revision TKA: 1.79% ▪ Frequencies of aseptic loosening: 0.75% ▪ MUA: 3.27% ▪ PJI: 1.83% ▪ Periprosthetic fractures: 0.34% ▪ Postoperative stiffness: 11.53%	Knee arthroscopy before TKA increases the rates of revision, PJI, aseptic loosening, and stiffness

	Hagman et al.[17]	2020	Retrospective study	IV	To establish long-term survival and complication rates in obese patients undergoing cemented, posterior-stabilized TKA with an average 10-year follow-up.	181 TKA patients (body mass index >35)	▪ Radiographs ▪ Blood analysis	▪ Aseptic loosening - Total: 25 (14%) - Tibial component only: 11 (6%) - Tibial and femoral components: 13 (7%) ▪ Aseptic patellar component loosening 1 (1%) ▪ Polyethylene wear 9 (5%) ▪ Prosthetic joint infection 2 (1%) ▪ Stiffness/immobilization syndrome 1 (1%) ▪ Instability 1 (1%) ▪ Patellofemoral pain 1 (1%) ▪ Total failures leading to revision total knee arthroplasty 39 (22%)	Aseptic loosening is the leading cause of failure following TKA in obese; Survivorship with aseptic loosening as the endpoint was 91.2% at 10 years and 86.7% at 15 years.
	Sadoghi et al.[18]	2011	Retrospective study	IV	To test for a correlation between knee pain and tibial radiolucent lines	56 TKA patients	▪ WOMAC ▪ KSS ▪ Radiographs	▪ Pain: 28 patients; 28 No pain: ▪ Radiolucent lines: 27 Pain patients; 6 No pain patients	Radiolucency should still be suspected as the possible cause of pain
Gene expression	Mann et al.[19]	2019	Observational study	III	To establish proof of principle of a link between phenotypic expression and stiffness after TKR	100 TKA patients	▪ Radiographs ▪ PCS ▪ OKS	Preoperative ▪ Extension: −6.47° ± 6.16° Stiff; −3.87° ± 4.98° No Stiff ▪ Flexion: 95.00° ± 9.78° Stiff; 95.53° ± 15.97° No Stiff ▪ OKS: 17.73 ± 5.48 Stiff; 15.80 ± 7.88 No Stiff Postoperative ▪ Extension: −10.07° ± 7.33° Stiff; −2.07° ± 2.37° No Stiff ▪ Flexion: 78.00° ± 13.34° Stiff; 105.67° ± 6.78° No Stiff ▪ OKS: 23.46 ± 8.62 Stiff;	Joint stiffness is a multifactorial problem after TKR but biological factors may play a significant role in stiffness after TKR

								21.47 ± 7.18 No Stiff ▪ PCS - Total Score: 18.60 ± 10.52 Stiff; 19.00 ± 16.60 No Stiff - Rumination): 6.73 ± 5.27 Stiff; 6.33 ± 6.00 No Stiff - Magnification: 2.87 ± 1.41 Stiff; 4.00 ± 3.68 No Stiff - Helplessness: 9.00 ± 5.32 Stiff; 8.73 ± 7.57 No Stiff	
Immunology & Allergy	Graves et al.[20]	2014	Observational study	III	To compare patient reported outcomes following total joint arthroplasty in patients with and without multiple reported allergies	459 THA or TKA patients	▪ WOMAC ▪ SF-36	Preoperative ▪ PCS:30.7 ± 0.4 (0-3 allergies); 29.3 ± 1.1 (4+ allergies) ▪ MCS: 49.4 ± 0.6 (0-3 allergies); 48.3 ± 1.5 (4+ allergies) ▪ WOMAC - Pain: 46.9 ± 1.1 (0-3 allergies); 43.4 ± 3.2 (4+ allergies) - Stiffness: 41.4 ± 1.1 (0-3 allergies); 35.8 ± 2.7 (4+ allergies) - Function: 45.5 ± 1.0 (0-3 allergies); 39.8 ± 2.4 (4+ allergies)	Patients with multiple reported allergies belong to a group with a statistically significant lower functional status after hip and knee arthroplasty per WOMAC and SF36
	Paish et al.[21]	2019	Retrospective cohort study	III	To investigate whether pro-inflammatory mediators are elevated in revision knee patients, indicating an active, ongoing inflammatory process that may contribute to pain	62 patients (29 Primary; 33 Revision) with TKA	▪ WOMAC ▪ SF ▪ FP ▪ SM	▪ WOMAC pain: 30 Primary TKA; 52 Revision TKA ▪ GM-CSF: 0.5 ± 0.2 Primary; 1.3 ± 0.3 Revision ▪ IL-5: 0.4 ± 0.1 Primary; 2.2 ± 0.8 Revision ▪ IL-8: 80 ± 31 Primary; 3,147 ± 1,552 Revision	A number of biologically active markers involved in inflammation and matrix deposition were significantly elevated many years

								▪ IL-10: 0.8 ± 0.5 Primary; 1.6 ± 0.4 Revision ▪ CCL2: 417 ± 38 Primary; 5,285 ± 1,004 Revision ▪ CCL3: 15.6 ± 3.3 Primary; 177 ± 51 Revision ▪ CCL4: 69.6 ± 8 Primary; 258 ± 54 Revision ▪ CCL13: 42.5 ± 20 Primary; 220 ± 76 Revision ▪ Flt--1: 97.6 ± 12 Primary; 1575 ± 612 Revision ▪ VEGF: 396.1 ± 46 Primary; 1724 ± 268 Revision ▪ VCAM--1: 105,613 ± 7,290 Primary; 134,770 ± 7,434 Revision ▪ ICAM--1: 862,890 ± 12,439 Primary; 150,915 ± 24118 Revision	following primary TKA
	Yang et al.[22]	2019	Retrospective cohort study	IV	To analyze the relationships between a positive LTT for metal, the histopathology from the revision surgery, and pre-revision and post-revision clinical and functional outcomes	27 TKA patients (6 M, 21 F)	▪ Radiograph ▪ KSS ▪ [3H]-thymidine	▪ LTT stimulation index: 9.4 ± 8.2 Pre-revision KSS ▪ Clinical: 49.8 ± 16.7 ▪ Functional: 44.8 ± 16.7 ▪ ROM: 93.2° ± 25.2° Post-revision KSS ▪ Clinical 75.6 ± 14.6 ▪ Functional 57.4 ± 15.5 ▪ ROM: 116.6° ± 19.9°	Positive LTT result may not indicate that an immune reaction is the cause of pain and stiffness post-TKA
Psychology	Belford et al.[23]	2020	Prospective study	IV	To examine the psychosocial factors that predicted pain, stiffness and physical	102 TKA patients	▪ OKS ▪ WOMAC	▪ WOMAC - Pain: Pre 12.04 (3.68); 1y after 5.68 (5.10)	The findings indicate that preoperative psychosocial factors

					functioning up to one year following TKA			- Function: Pre 41.62 (12.80); 1y after 21.83 (17.01) - Stiffness: Pre 5.19 (1.76); 1y after 3.15 (2.01) ▪ OKS: Pre 15.99 (7.95); 1y after 33.62 (10.40)	are important in understanding outcomes of TKA
	Lavernia et al.[24]	2015	Observational study	III	1. To assess patients outcomes, including Knee Society (KS) scores, of those patients who developed arthrofibrosis and underwent manipulation and compare them with a control group; 2. In patients with arthrofibrosis, to determine outcomes and KS scores of those with psychological distress and those without it	53 TKA patients (57 knees) with arthrofibrosis and underwent manipulation under anesthesia; 58 TKA patients (63 knees) without arthrofibrosis;	▪ QWB-7 ▪ SF-36 ▪ WOMAC ▪ KSS	Arthrofibrosis (group1) vs no Arthrofibrosis (group2): ▪ QWB-7 total Pre: Group1 0.522 (0.05); Group2 0.530 (0.06); Post: Group1 0.587 (0.10); Group2 0.609 (0.13) ▪ KSS knee score Pre: Group1 42.59 (22.9); Group2 43.27 (23.7) Post: Group1 81.18 (22.9); Group2 86.58 (22.7) ▪ KSS function score Pre: Group1 26.84 (20.5); Group2 37.06 (19.3) Post: Group1 51.30 (22.1); Group2 59.76 (21.4) ▪ KSS ROM: Pre: Group1 103.07 (18.7); Group2 104.92 (22.0) Post: Group1 101.63 (21.5); Group2 109.76 (17.0) ▪ WOMAC stiffness Pre: Group1 3.96 (2.3); Groups2 3.61 (2.2)	Patients who developed arthrofibrosis had worse preoperative KS function than patients without postoperative arthrofibrosis. Patients with arthrofibrosis and psychological distress perceived themselves as having worse quality of wellbeing and more stiffness before the surgical intervention and their worse quality of well-being perception was sustained after surgery

								Post: Groups1 1.23 (2.2); Group2 0.56 (1.2) ▪ WOMAC total Pre: Groups1 61.16 (18.2); Group2 57.06 (15.8) Post: Group1 17.00 (26.2); Group2 7.22 (13.6) ▪ Knee active flexion Pre: Group1 102.39 (19.1); Group2 102.44 (21.2) Post: Group1 96.71 (17.3); Group2 104.19 (16.1) Distressed (group1) vs nonDistressed (group2): ▪ QWB-7 total Pre: Group1 0.490 (0.04);Group20.547 (0.05) Post: Group1 0.537 (0.09); Group2 0.627 (0.10) ▪ KSS knee score: Pre: Group1 41.00 (22.7); Group2 43.78 (23.4) Post: Group1 80.32 (22.3); Group2 81.86 (23.8) ▪ KSS function score Pre: Group1 19.40 (18.5); Group2 32.66 (20.3) Post: Group1 50.00 (24.4); Group2 52.32 (20.6) ▪ KSS ROM:	

								Pre: Group1 105.40 (15.6); Group2 101.25 (21.0) Post: Group1 102.73 (21.0); Group2 100.83 (22.2) ▪ WOMAC stiffness Pre: Group1 4.92 (2.1); Groups2 3.22 (2.1) Post: Groups1 1.52 (2.2); Group2 1.0 (2.1) ▪ WOMAC total: Pre: Groups1 66.96 (17.0); Group2 56.81 (18.0) Post: Group1 20.64 (27.5); Group2 14.16 (25.2) ▪ Knee active flexion: Pre Group1 102.68 (16.4); Group2 102.16 (21.3) Post: Group1 96.23 (18.4); Group2 97.07 (16.8)	
	Razmjou et al.[25]	2015	Observational study	III	To determine whether reporting neuropathic pain (NP) at an average of 5 years after total knee arthroplasty (TKA) was related to patient age, sex, preoperative comorbidity, arthritis self-efficacy, or disability before surgery and at 1 year after surgery	63 TKA patients (16 M, 47 F)	▪ S-LANSS scores ▪ WOMAC ▪ PHQ-9	▪ NP: 9 patients ▪ No NP: 54 patients	Participants with NP reported higher levels of pain, stiffness, and physical dysfunction as early as 1 year after surgery that continued up to an average of 5 years after surgery
Demographics and others	Clement, Bardgett et al.[26]	2019	Retrospective study	III	1. To compare the WOMAC and SF12 outcome of patients with increased symptoms of stiffness 1 year after TKA with those who had no change or improvement in symptoms;	2589 TKA patients Increased Stiffness group (IS)	▪ WOMAC ▪ SF-12	Pre-Surgery ▪ WOMAC - Pain: IS 42.4 (15.9) ; NIS 35.1 (17.7) - Physical function: IS 45.3 (16.9); NIS 36.3 (16.9)	Patients with increased symptoms of stiffness after TKA have a worse functional outcome

					2. To identify independent predictors of increased symptoms of stiffness 1 year following TKA	vs Non Increased Stiffness group (NIS)		- Stiffness: IS 61.0 (22.4) ; NIS 36.0 (19.6) ▪ SF12 PCS: IS 28.4 (7.6); NIS 27.5 (7.4); ▪ SF12 MCS:IS 46.3 (13.3) ; NIS 47.1 (13.6) 1 year after ▪ WOMAC - Pain: IS 63.1 (24.0) ; NIS 81.0 (19.8) - Physical function: IS 55.4 (23.6); NIS 74.5 (20.7) - Stiffness: IS 41.0 (22.4) ; NIS 73.2 (21.3) ▪ SF12 PCS: IS 31.8 (8.8) ; NIS 37.9 (11.1) ▪ SF12 MCS:IS 44.0 (14.7) ; NIS 49.5 (12.7);	and a lower rate of patient satisfaction. Pain, function, and the total WOMAC scores were poor predictors of increasing stiffness after TKA
	Clemen, Merrie et al.[27]	2019	Retrospective study	II	1. To identify independent preoperative predictors of outcome and patient satisfaction for the second total knee arthroplasty 2. To compare the predictors of outcome and patient satisfaction of the first to the second TKA and whether dissatisfaction with the first TKA predicts satisfaction with the second TKA	454 asynchronous bilateral primary TKA patients First TKA vs Second TKA	▪ WOMAC	Pre Surgery ▪ WOMAC - Pain: FirstTKA 35.3 (17.4); SecondTKA 38.8 (16.8) - Physical function: First 36.0 (16.9); Second 40.4 (16.7) - Stiffness: First 36.7 (20.0); Second 41.2 (20.1) 1 year after ▪ WOMAC - Pain: First 83.7 (19.7) ; Second 80.2 (21.9) - Physical function: First 76.8 (19.9); Second 76.6 (19.5); - Stiffness: First 73.7 (22.1); Second 75.5 (20.8);	Improvement in pain and function is less with the second TKA, but the satisfaction rate remains similar. There are common independent predictors for change in the WOMAC score for the first and second TKA; however, the predictors of satisfaction were different with no common factors

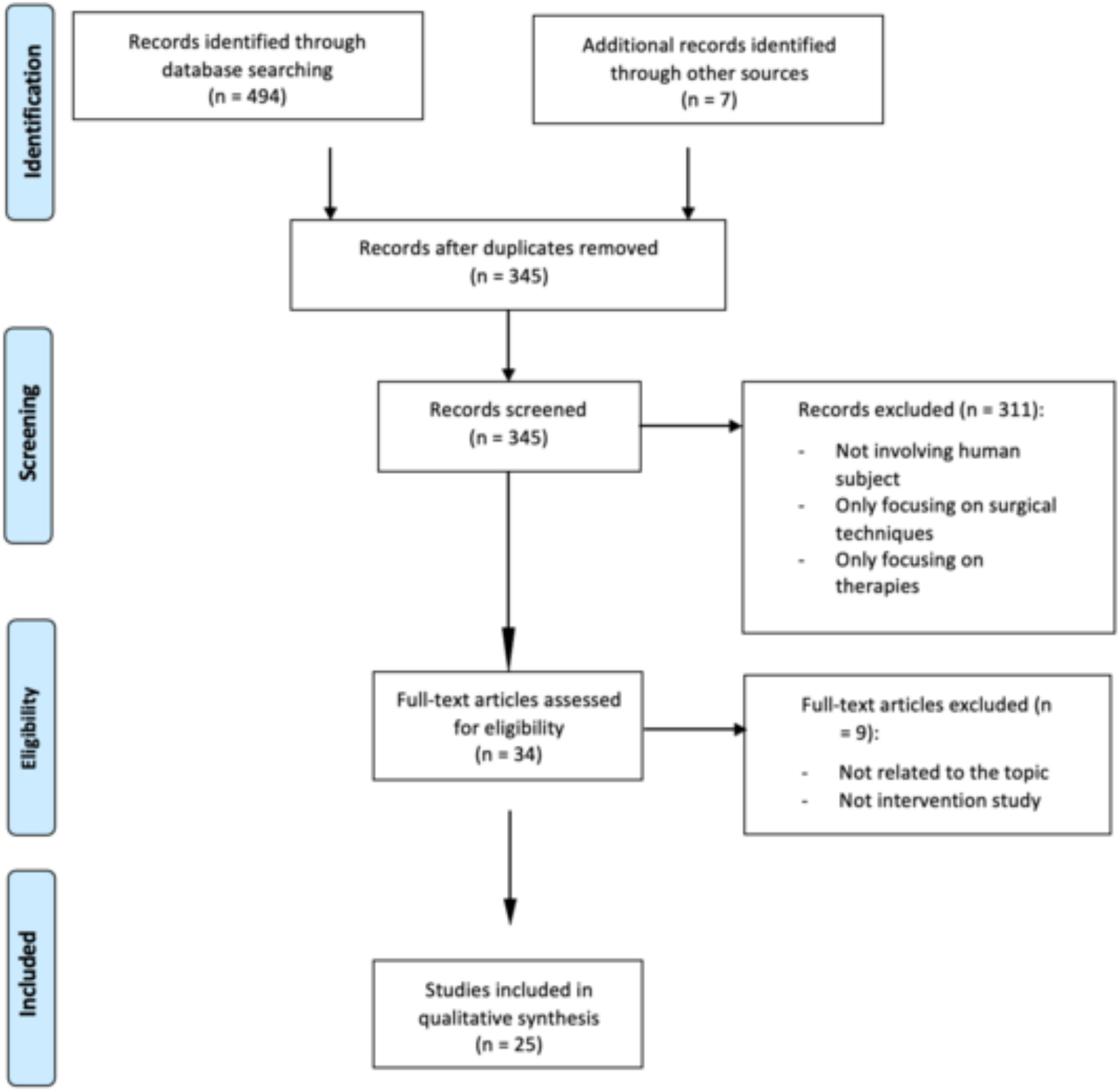
	Gungor et al.[28]	2019	Retrospective study	IV	1.To estimate the risk of developing moderate-to-severe Persistent Postsurgical Pain (PPP) after primary TKA; 2. To explore potential predictors of the development of PPP in this clinical setting	578 TKA patients	▪ Collaborative Orthopedic Replacement Registry	▪ The risk of PPP after TKA was 31.3%	This study estimated a high risk of moderate-to-severe PPP after primary TKA. Racial differences and types of peripheral nerve blocks might be associated with greater odds of developing moderate-to-severe PPP after TKA surgery
	Järvenpää et al.[29]	2012	Observational study	III	To analyze clinically and radiologically the results of total knee arthroplasty in obese patients	48 TKA patients (52 knees); 29 non-obese vs 23 obese	▪ KSS ▪ WOMAC ▪ TUG ▪ Radiographs	▪ KSS Knee score: 88.9 ± 16.3 Non-obese; 83.6 ± 13.0 Obese ▪ KSS Function score: 76.3 ± 31.5 Non-obese; 63.6 ± 30.1 Obese ▪ ROM: 109.6 ± 8.1 Non-obese; 104.6 ± 9.2 Obese ▪ WOMAC - Pain: 11.6 ± 17.9 Non-obese; 20.7 ± 24.7 Obese - Stiffness: 13.4 ± 21.2 Non-obese; 26.9 ± 24.3 Obese - Physical function: 14.4 ± 22.4 Non-obese; - 26.5 ± 10.7 Obese ▪ Walking distance: 2935 ± 2303 Non-obese; 1894 ± 1852 Obese ▪ TUG: 12.1 ± 6.3 Non-obese; 12.7 ± 4.9 Obese	Obese patients had poorer clinical success at final follow-up. WOMAC scores were significantly higher in obese patients.

								▪ Deviation from straight mech.axis: 3.3 ± 3.3 Non-obese;3.3 ± 2.4 Obese	
	Liebensteiner et al.[30]	2019	Retrospective comparative study	II	To determine if preoperative radiologic minimal joint space width (mJSW) is related to the outcome ofTKA	377 TKA patients (141 M, 236 F)	▪ Minimal Joint Space Width (mJSW) ▪ Radiograph ▪ WOMAC	Preoperative ▪ WOMAC - Pain: 50% (mJSW: 0–1 mm); 50% (mJSW: ≥2 mm) - Function: 49.5% (mJSW: 0–1 mm); 52% (mJSW: ≥2 mm) - Stiffness: 55% (mJSW: 0–1 mm); 55% (mJSW: ≥2 mm) - Total: 52% (mJSW: 0–1 mm); 53% (mJSW: ≥2 mm) Postoperative (1 year) ▪ WOMAC - Pain: 6% (mJSW: 0–1 mm); 14% (mJSW: ≥2 mm) - Stiffness: 15% (mJSW: 0–1 mm); 25% (mJSW: ≥2 mm) - Function: 9.5% (mJSW: 0–1 mm); 20% (mJSW: ≥2 mm) - Total: 10% (mJSW: 0–1 mm); 19% (mJSW: ≥2 mm)	Patients with preoperative complete joint space collapse (0 to 1 mm mJSW) achieve a significantly better WOMAC result from TKA than do those with a mJSW equal to or greater than 2 mm

	Liebs et al.[31]	2011	Retrospective cohort study	II	To estabilish whether (1) women had worse knee function and health-related quality of life after TKA compared with men, (2) lower improvements in scores, and (3) slower recovery after surgery	494 TKA patients (141 M, 353 F)	▪ WOMAC ▪ SF-36	After 2 years ▪ WOMAC - Pain: 11.9 ± 16.2 Male ; 13.6 ± 17.7 Female - Physical function: 15.9 ± 16.5 Male; 19.8 ±20.3 Female - Stiffness: 21.0 ± 23.3 Male; 22.1 ± 23.1 Female ▪ SF12 PCS: 43,0 ± 9.5 Male; 40.5 ± 10.0 Female ▪ SF12 MCS: 52.8 ± 9.6 Male; 50.2 ± 10.9 Female	Women had faster recovery at 3- and 6-month follow-ups than men. It could be attributable to the lower preoperative health-related quality of life in women
	Parvizi et al.[32]	2014	Multicenter study	III	To quantify the degree of residual symptoms and specific functional deficits in young patients who had undergone TKA	661 TKA patients	▪ Interview	▪ Patients satisfied of function: 90% ▪ Patients satisfied performing normal daily life activity: 89% ▪ Patients satisfied of pain relief: 91%	Many patients continue to experience knee symptoms after full recovery from TKA
	Putman et al.[33]	2018	Retrospective study	IV	To assess survival, functional outcomes, and the nature and frequency of complications	263 TKA patients (141 M, 122 F)	▪ KOOS ▪ Radiographs	▪ Survival rate: 89% ▪ KOOS: 159 little or no discomfort, 157 little or no pain, 41 extreme or severe distress ▪ HKA: 179°± 3.2°(range 171°-188°)	Although TKA improved knee range of motion, only 60% of patients were satisfied with the procedure

Table 2: Summary of incidence and causes of stiffness in TKA patients. The percentage of patients reporting stiffness was pooled from the different scores of each study.

Category	N° of studies	N° of TKA patients	% of patients with stiffness	Main Causes
Surgery-related issues	7	487	47%	• IR of tibial or femoral component (n=3) • Malalignment (n=3) • Over-voluming (n=1)
Loosening	3	138256	12%	• Cementation technique (n=1) • Bone quality (n=1) • Component design (n=1)
Gene expression	1	100	50%	• Expression of profibrotic markers (n=1)
Immunology & Allergy	3	332	25%	• High material hypersensitivity-related cytokines level (n=3)
Psychology	3	343	36%	• Anxiety (n=2) • Depressive symptoms (n=2) • Functional limitation (n=2) • Severe preoperative pain (n=1)
Demographics and others	8	5473	17%	• Young age (n=1) • Male gender (n=1) • Obesity (n=1) • Previous surgery (n=1) • Diabetes (n=1) • Preoperative stiffness (n=2)


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 494)
Additional records identified through other sources (n = 7)
Records after duplicates removed (n = 345)
Records screened (n = 345)
Records excluded (n = 311):
- Not involving human subject
- Only focusing on surgical techniques
- Only focusing on therapies
Full-text articles assessed for eligibility (n = 34)
Full-text articles excluded (n = 9):
- Not related to the topic
- Not intervention study
Studies included in qualitative synthesis (n = 25)