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High rate of radiolucent lines following the cemented original design of the ATTUNE® total knee arthroplasty. A systematic review and meta-analysis

Aims: Component loosening can be associated with the development of radiolucent lines (RLLs). Our study aimed to assess the RLL rate in the cemented original version of the ATTUNE® TKA and their relationship to loosening.

Materials and Methods: A systematic search was undertaken using the Cochrane methodology in four online databases. Studies were screened against predetermined criteria, and data were extracted. Available National Joint Registries in the Network of Orthopaedic Registries of Europe were also screened. Random effects model meta-analysis was conducted.

Results: Twelve of 263 studies (n=3,869) were included. Meta-analysis of 10 studies showed high rates of overall tibial or femoral RLLs for the cemented original version of the ATTUNE® TKA. The rate of any RLL was estimated at 21.4% (95%CI: 12.7-33.7%) for all implant types but was higher for certain subgroups: 27.4% (95%CI: 13.4-47.9%) for the CR type, and 29.9% (95%CI: 15.6-49.6%) for the fixed-bearing type. Meta-analysis of 5 studies comparing the ATTUNE with other implants showed a higher risk of overall tibial or femoral RLLs (OR: 2.841; 95%CI: 1.219-6.623, P=0.016) in the ATTUNE. Component loosening or revision for loosening as reported by research studies were lower, estimated at 1.2% and 0.9% respectively, but reported rates varied from 0 to 16.3%. The registry data examined did not report specifically on the original ATTUNE® TKA or on revision due to loosening, but "all-cause" 5-year revision rates varied from 2.6 to 5.9% at 5 years between registries.

Conclusion: The original cemented ATTUNE® TKA system is associated with high rates of RLLs, but their clinical significance is uncertain given the overall low reported rates of component loosening and revision. However, in view of the observed high RLL rates and the observed variation in the rates of component loosening and revision between studies and registries, close surveillance of the original ATTUNE® system is recommended.

TAKE HOME MESSAGE

- The original ATTUNE® TKA system is associated with a high rate of radiolucencies.
- The mechanism accounting for these radiolucencies is uncertain, hence it cannot be concluded if modifications of the tibial tray under surface will address these issues.
- Close surveillance of the original design of the ATTUNE TKAs is recommended.

INTRODUCTION

The ATTUNE® (DePuy Synthes, Warsaw, IN, USA) was the successor to the PFC Sigma, (DePuy Orthopaedics Inc., Warsaw, IN, USA) in part due to reported anterior knee problems and dissatisfaction rates up to 21% [43, 50]. The ATTUNE® knee prosthesis was introduced in a limited launch in 2011 and in general sale in 2013 [21]. In 2014 a rotating platform type implant was added [52]. The ATTUNE® was marketed as having a novel patella tracking system designed to optimize patella tracking while maintaining bone coverage. This new design had a gradually reduced femoral radius, enhancing the conformity between the femoral component and the polyethylene (PE) insert to allow gradual femoral rollback and greater mid-flexion stability [20, 33]. There was also a change from a tibial base peripheral locking design to a patented central locking system aiming to provide a more constraint fixation and reduce backside micromotion [16]. The original ATTUNE tibial tray had less extensive grooves (cement pockets) in its under surface [38].

Since its release, there have been reports of higher-than-expected rates of tibial loosening with the ATTUNE® system. The first of these reporting early tibial loosening at the implant-cement interface for the ATTUNE® TKA was in 2017 with 15 cases requiring revision within 2 years from surgery [12]. As this study did not define the population from which those revisions arose, the revision rate for loosening could not be determined.

Progressive radiolucency at the implant-cement interface may be an early indicator for loosening [63]. The primary aim of this study was to assess the reported rates of radiolucent lines (RLLs) following the cemented original version of the ATTUNE® TKA and compare these to those of other established systems. Secondary aims were to determine if these RLLs are progressive and examine the relationship between RLL rates and loosening as reported by research studies and national joint registries.

MATERIALS AND METHODS

The Cochrane methodology for systematic reviews was followed [31]. The predefined protocol was published in PROSPERO (CRD42021277816). The systematic literature search strategy included searching of electronic databases and scrutinizing the references of included studies. The following databases were searched in November 2022 for any studies published since

2012: MEDLINE (Interface: EBSCOhost); Embase (Interface: OvidSP); and CINAHL (Interface: EBSCOhost). Only studies available in English were included. The search algorithm comprised of 2 searches: (i) "(ATTUNE OR total knee OR TKA OR TKR") AND ("radiolucen* OR loosen*) (ii) ATTUNE AND knee. Results from both searches were combined and screened for studies eligible for inclusion. All available national and regional joint registries in and outside Europe were identified through the Network of Orthopaedic Registries of Europe [4], and were screened for reported loosening and revision rates for the cemented ATTUNE® TKA.

Inclusion/Exclusion criteria

Population/Intervention/comparators: The intervention was primary cemented ATTUNE® TKA.

Outcomes: Primary outcomes were the reported presence of RLLs at the implant-cement interface on AP and/or lateral follow-up postoperative radiographs. Radiolucency was defined as any RLL at the implant-cement interface on AP and/or lateral standing radiographs [23]. Secondary outcomes were: (i) whether RLLs were progressive and (ii) loosening rates and revision rates due to loosening assessed from research clinical studies and national joint registries.

Study designs: Randomized controlled studies, prospective and retrospective cohort studies, case-control studies, and case series with at least 20 patients were included. The study methodology was classified according to Mathes and Pieper (2017) [42].

Two reviewers (ADP, GDC) screened independently titles and abstracts. Duplicates were removed and full texts of studies considered eligible were reviewed independently. Any disagreements for inclusion were discussed between reviewers and, if unresolved, with the senior experienced author.

Data extraction

Two reviewers extracted relevant data about demographics, type of implants used, cement type, definition of RLLs and radiographic evaluation system. Data about loosening and revision due to loosening were also extracted as reported from included studies and from National Joint Registries. Numbers reported for each group (n) in the analysis refer to numbers of TKAs rather than number of patients.

Data analysis – Statistical analysis

The rate of RLLs reported post-operatively was the primary outcome. The rates of aseptic loosening and rates of revision due to loosening (as reported by research studies and national joint registries) were the secondary outcomes. For each study, post-operative RLLs, loosening rates and revision rates were reported as absolute numbers and rates. Any statistically significant difference between groups of comparison was calculated and reported ($p < 0.05$). Risk ratios and 95% confidence intervals (CIs) were calculated for both primary and secondary outcomes and combined in a random-effects model meta-analysis [22]. Heterogeneity was assessed using tau^2, I^2, Q and P values. Data were analysed with Comprehensive Meta-analysis version 2 (Biostat).

Assessment of methodological quality of studies and quality of evidence

The Cochrane Risk of Bias Tool for randomised controlled trials (RCTs) [30], Newcastle-Ottawa scale (NOS) for prospective cohort studies [64], and the revised and validated version of Methodological Index for Non-Randomised Studies (MINORS) for the retrospective comparative studies [58] were used. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence of the review [27].

RESULTS

Findings of the database searches

4,910 records were identified by title, 12 of which met the inclusion criteria [8, 26, 32, 36, 37, 40, 51, 57, 59-62]. **Figure 1** shows the Preferred Reporting Items for Systematic reviews and meta-analyses (PRISMA) flow diagram [46].

Characteristics of included studies

Table 1 summarises the characteristics of included studies [8, 26, 32, 36, 37, 40, 51, 57, 59-62]. The total number of TKAs included was 3,869 (2,600 ATTUNE TKAs, 1,269 other systems). Five studies that had a control group for comparison had no significant difference of age, gender, and BMI between groups [8, 36, 37, 51, 60]. The mean age of patients having an ATTUNE TKA was 69.6 years with 894 males and 1,636 females. All studies used the original design of the cemented ATTUNE TKA system. One study did not specify the use of only the ATTUNE's original version but as it was used in their institution past their patient inclusion period, that series was considered to be of the original version [59]. All studies reported on post-operative RLLs either on tibia and/or femur. Most studies reported a mean follow-up of about 2 years, but with variation in their range of follow-up from 3 months to 5.4 years; this didn't allow subgroup analysis according to length of follow-up (**Table 1**).

Radiographic outcomes: Radiolucent lines

The definition of RLLs and the radiographic evaluation system utilised are shown in **Table 2**. The systems used were the Knee Society Radiographic Evaluation System and Methodology (KSRESM) (**Figure 2a**) [23], and the Modern Knee Society Radiographic Evaluation System and Methodology (MKSRESM) (**Figure 2b**) [44]. One study defined as radiolucency any medial tibial bone resorption on AP and lateral radiographs and classified it using a novel classification system. Data from this referring to RLLs at the implant cement interface were extracted [59].

Results are summarised in **Table 3**. Four studies with a control group showed higher rates of RLLs, predominantly tibial or overall, for the ATTUNE groups [8, 36, 37, 60]; with two demonstrating a significant difference [37, 60]. Two studies reported no RLL for the ATTUNE group in either the tibia or femur (mean follow-up 2 years) [51, 62]. Three studies reported on progression of RLLs [36, 37, 57], with two studies showing no progression of the reported RLLs [36, 57]. One reported that medial tibia RLLs were progressive: increasing from 17% for the ATTUNE group at 2 weeks follow-up to 42% at 2 years follow-up [37]. One study compared patients in the ATTUNE group that had RLLs with those without RLLs [32]. BMI was associated with increased rates of RLLs (p=0.003), with an increase of one unit of BMI increasing the odds of RLL by 8%. There was no difference in implant constraint (p=0.818), cement type (p=0.340), patella resurfacing (p=0.286), age (p=0.984), and sex (p=0.376) between those with and without RLLs.

Meta-analysis

Prevalence of RLL in the ATTUNE® groups (**Table 4**)

All studies, (1,858 ATTUNE® TKAs), examined the prevalence of RLLs either tibial, femoral or overall (any tibial or femoral), with 3 studies reporting on RLL if ≥ 2mm or progressive [8, 36, 62]. Meta-analysis of 10 studies (n=1,558) showed a prevalence of 21.4%% (95%CI: 12.7-33.7%) for any RLL (tibial or femoral) overall [8, 26, 32, 36, 37, 40, 51, 57, 60, 62].

RLLs - Sub-group analysis (CR, PS, Fixed-bearing implants) (**Table 4**)

There was heterogeneity in the characteristics of the ATTUNE TKA implant types, such as CR/PS, fixed/mobile bearing, patella resurfaced/not and type of cement used. Meta-analysis showed a prevalence of 27.4% (95%CI: 13.4-47.9%) for any RLL (tibial or femoral) overall

for the CR type (either fixed or mobile-bearing) [8, 37, 57], and 29.9% (95%CI: 15.6-49.6%) for the fixed-bearing type (either CR or PS) [26, 32, 36, 37, 40, 57]. The rest of the meta-analysis results are summarised in **Table 4**.

Meta-analysis was also performed to compare the reported tibial versus femoral RLLs. Meta-analysis of 4 studies (n=636) reporting on both tibial and femoral RLLs showed no significant difference between rates of tibial and femoral RLLs in the ATTUNE group (estimated OR: 0.845; 95%CI: 0.461-1.548, P=0.586; heterogeneity: tau^2=0.183, I^2=56.084, Q=6.831, P=0.077) [8, 26, 36, 60].

RLLs - Comparison with control group

Meta-analysis (6 studies) compared RLLs of the ATTUNE® TKA with a variety of other systems (PFC Sigma®, Vanguard®, PERSONA®, LCS®) [8, 36, 37, 57, 60]. One study (n=200) reported no RLL in either group [51]. In meta-analysis methodology, studies with zero events are discarded, hence this study was excluded. Meta-analysis of the remaining 5 studies (1,228 TKAs) showed a significantly higher rate of any RLL (tibial or femoral) overall (estimated OR: 2.841; 95%CI: 1.219-6.623, P=0.016; heterogeneity: tau^2=0.705, I^2=80.805, Q=20.838, P<0.001, **Figure 3**) in the ATTUNE group as compared to the control. When excluding two studies reporting only on RLLs ≥ 2mm [8, 36], the odds ratio was even higher (estimated OR: 4.258; 95%CI: 1.271-14.261, P=0.019). Meta-analysis of 2 studies (n= 603 TKAs) comparing the ATTUNE® with the PFC Sigma® showed a significantly higher rate of any RLL (tibial or femoral) overall in the ATTUNE group as compared to the PFC group (estimated OR: 7.039; 95%CI: 4.298-11.526, P<0.001; heterogeneity: tau^2=0.001, I^2=0.001, Q=0.298, P=0.585) [37, 60].

Loosening rates (**Table 5**)

Studies reporting on loosening rates of the ATTUNE TKA and their demographics are shown in **Table 5**. It is of note that there was substantial variation in the loosening rates reported between studies, varying from 0-16.3%. Meta-analysis of 6 studies showed an overall reported loosening rate of 1.2% (95%CI: 0.2-6.3%) (heterogeneity: tau^2=6.092, I^2=93.273, Q=29.731, P<0.001) [26, 36, 40, 57, 60, 61]. Meta-analysis of 3 studies reporting on loosening rates with fixed-bearing components showed an overall reported loosening rate of 2.4% (95%CI: 0.2-25.5%) (heterogeneity: tau^2=4.605, I^2=91.283, Q=22.942, P<0.001) [26, 40, 57]. Meta-analysis of 3 studies reporting on loosening rates with PS components showed a rate of 1.5% (95%CI: 0.1-22.6%) (heterogeneity: tau^2=3.936, I^2=93.702, Q=79.394, P<0.001) [26, 40, 59].

Revision due to loosening (**Table 5**)

There was substantial variation between studies in the reported revision due to loosening rates, from 0-16.3% (**Table 5**). Meta-analysis of 6 studies reporting on revision due to loosening showed an overall rate of 0.9% (95%CI: 0.2-5.1%) (heterogeneity: tau^2=3.587, I^2=93.131, Q=72.789, P<0.001) [26, 40, 59-62].

Seven national joint registries reporting on the ATTUNE® knee were identified and their recent reports were assessed for revision rates due to loosening (UK, Australia, New Zealand, Swedish, German, Dutch, Swiss) [1-3, 5, 48, 53, 54]. The reported revision rates are shown in **Table 6**. The registry data examined do not report specifically on the original version of the ATTUNE or on revision due to loosening, but "all-cause" 5-year revision rates for the cemented ATTUNE varied from 2.6 to 5.9% between registries [2, 6, 48], whilst for all fixation types reported rates varied from 1.37 to 6.3% [6, 48].

Assessment of methodological quality of the studies and quality of evidence

The RCT had "low risk of bias" [30], having adequate sequence generated, concealed allocation and blinding of participants without any other source of bias [37]. Both prospective studies scored the highest score of 9 stars in the assessment (**Table 7**). The average MINORS score of the 9 retrospective studies was 17 (**Table 8**). The quality of evidence (GRADE approach) was "low" [27].

DISCUSSION

Our meta-analysis showed high rates of overall tibial or femoral RLLs for the cemented original version of the ATTUNE TKA. The rate of RLLs was estimated at 21.4% for all implant types but was even higher for certain subgroups (27.4% for the CR type, and 29.9% for the fixed-bearing type). Analysis of studies comparing RLLs of the ATTUNE versus other knee systems showed that the odds of having RLL was 2.8-fold higher with the ATTUNE when any RLL was considered or 4.3-fold higher when RLLs ≥ 2mm were considered. Comparison of the ATTUNE® with the PFC Sigma® showed that the odds of having RLL was 7-fold higher with the ATTUNE. Rates of component loosening or revision for loosening reported within published studies were much lower. Overall, these rates are estimated at 1.2% and 0.9%

respectively, however, reported rates varied significantly (0 to 16.3%) between studies. Although, the registry data examined did not report specifically on revision of the original version of the ATTUNE or on revision due to loosening, in most registries overall revision rates are also low.

RLLs in TKA may be related to multiple mechanisms [7]. Early radiolucency has been attributed to component design and constraint, malalignment, surface roughness of the tibial component, cement type, and cementation techniques [39, 56]. Late radiolucency around a cemented tibial component has been associated with PE wear and osteolysis or stress shielding related to the component material and design[24, 25, 41]. Stress shielding is influenced by the tibial tray material and thickness as well as stem length and geometry [24, 41, 55]. Patient factors, such as age, BMI or activity level, have also been linked to tibial component radiolucency [9, 56].

Several mechanisms have been postulated to explain the high rate of RLLs noted in the ATTUNE®. A retrieval analysis examining ATTUNE implants compared with titanium PFC Sigma and CoCr PFC Sigma showed no evidence of cement remain on any of the ATTUNE trays [17]. This was felt possibly related to tibial tray design, in particular the absence of separate cement pockets/grooves in the backside surface as well as the higher stem surface roughness in the ATTUNE. The ATTUNE® tibial tray also has a patented central locking mechanism claiming to provide more secure fixation with less backside micromotion [16]. However, a comparative retrieval analysis showed that TKA designs with central locking trays had significant less cement cover compared with peripheral locking trays; the PE inserts in the central locking systems had a characteristic pattern of deformation of their outer edges, which could increase the localized frictional torque and lead to debonding of the tray from the cement mantle [11]. A further possibility is that the different design and instrumentation of the ATTUNE system leads to inadequate cement mantle in comparison with its predecessors, with recent reports showing that excessive press fit may lead to incomplete seating or tilting of the tibial component especially in hard and uneven sclerotic bone [35]. Another factor attributed to tibial loosening is stress shielding. The ATTUNE system uses a thick CoCr tibial baseplate and there are reported series suggesting that medial tibial bone resorption is common with the ATTUNE, presenting in various locations and severities around the baseplate [59].

Cement debonding at the tibial cement-implant interface has been related to cement type and cementation technique in modern TKA[7, 19, 45, 39]. High-viscosity (H-V) cement reaches the

dough phase more quickly and it is popular in TKA, however, there are reports linking H-V cement with possible debonding at the implant-cement interface [7, 14, 39]. In our review, a standard H-V cement (Palacos R+G, Heraus Medical, Germany) was used in six of the studies [8, 26, 32, 37, 57, 60]; with one study using a fast-setting H-V cement in some TKAs (CMW-1, DePuy, CMW, UK) [32].

In 2017 DePuy launched a modification of the tibial component (Attune S+) incorporating backside grooves which may facilitate cement interdigitation and improve fixation performance [34], but an estimated 600,000 TKAs were implanted before this design change [16]. Furthermore, the rest of the design features remained the same and there is, yet, little clinical evidence that these changes have influenced the rates of RLL.

Radiolucencies are recognised following most cemented TKA designs and 3 studies in our analysis have compared the ATTUNE® and PFC Sigma® systems with regards to RLLs [37, 51, 60]. Two of them showed a significantly higher rate of RLLs (both overall and especially at the medial tibia implant-cement interface) in the ATTUNE as compared to the PFC ($p<0.001$) [37, 60], and with RLLs being progressive up to the 2 year follow-up in one of these studies [37].

Radiolucencies in TKA may be a surrogate marker of aseptic loosening. Loosening is likely to be a progressive process and early RLLs may be a herald of failure at a later stage. Aseptic loosening is the principal cause for early and late revisions, so understanding the rates of RLLs in the ATTUNE TKA and their clinical significance may help guide surgical practice.

Our results show that despite the high rate of RLLs observed with the original ATTUNE system, the reported rates of loosening within published studies are low. Although, no registry data are available that report specifically on revision due to loosening, in most registries overall revision rates are also low. Overall revision rates of the ATTUNE knee as reported by registries may reasonably be used as an indicator of revision rates for aseptic loosening, unless there were other causes of revision which have lower rates with the ATTUNE. Thus, the clinical significance of high rates of postoperative RLLs in the ATTUNE remains unclear. The observed discrepancy with high rates of RLLs but low reported rates of component loosening or revision may signify that RLLs are not clinically important in the ATTUNE® system. Alternatively, it is possible that RLLs are clinically important but for other reasons their rate of occurrence is not mirrored by loosening and revision rates.

It is reasonable to expect that rates of RLLs are higher than those of aseptic component loosening which in turn are expected to be higher than revision rates. RLLs do not necessarily equate to loosening and component loosening may not lead to revision surgery. Furthermore, diagnosis of early component loosening in the absence of overt clinical features or significant radiological features such as implant migration or substantial bone loss can be difficult. This diagnosis may be made intra-operatively at the time of revision, but may also be relevant to the substantial proportion of patients who continue with unexplained pain following TKA [10]. In line with such diagnostic challenges, Bonutti et al. reported that 15 patients revised for ATTUNE tibial loosening had developed increasing pain with initiation of weight bearing and loss of active ROM following an initial symptom-free period [13]. They also reported that all these patients had tenderness on palpation of the medial and lateral part of the tibial plateau and their plain radiographs showed radiolucencies, but they didn't report the presence of overt radiographic evidence of loosening or bone loss. Similar clinical findings of pain and localised tenderness at or just below the joint line were also reported more recently by Murphy et al [47] in 3 cases of early aseptic failure of the tibial component-cement interface in the ATTUNE prosthesis.

Even if component aseptic loosening is clear, it is likely that some if not most revisions for this are only carried out when the patient becomes significantly symptomatic. Patients with minor symptoms and no significant bone loss may be monitored rather than proceeding with revision. Assuming this is correct, there will always be a lag between the early stages of a loose component and the reported rates of revision surgery. Moreover, in many healthcare settings such as the UK's National Health System (NHS), there is a further lag between making a decision to carry out revision surgery and actually performing the procedure, with evidence this effect is exacerbated by the backlog due to the COVID-19 pandemic [15, 28].

Although the overall reported loosening and revision rates for the original ATTUNE knee are low, it is notable that there is substantial variation in reported loosening rates between research studies (0 to 16.3%), as well as in overall revision rates reported by registries (2.6% at 5 years in the Australian registry to 5.9% at 5 years in the German registry) [48, 53]. This variation allied to high rates of RLLs warrants further investigation to fully determine if there is more concern with specific component/design, surgical or cementation technique or patient characteristics. This is also important as registries do not allow clarification of the multiple versions or

combinations of an implant and the revision rates for such versions or combinations cannot be easily reviewed [49].

Our study has several limitations. Firstly, the quality of evidence was limited with only one RCT and two prospective cohort studies available [37, 51, 57], the rest being retrospective, and some with no control group. Another limitation was the heterogeneity in the specifics of the ATTUNE® TKA implant with differences in the type of components or cement used. In 4 studies that had a control group, the TKA system used as control varied between studies, but, despite this, there was a relative consistency in the findings. We feel this is a valid comparison as it helps demonstrates how the ATTUNE TKA system is performing against a general population of other TKAs performed by the same surgeons, using similar techniques, in similar patient populations. Radiographs can assess RLLs but the technique must follow standard guidelines and fluoroscopic positioning with the beam parallel to the tibia and the components [18]. However, this is operator dependent, and it is difficult to ensure a reproducible technique was used in the analysed studies. Follow-up in most studies was at least 2 years but there was variation in this range and insufficient data to stratify risk of RLLs according to length of follow-up. Examination of earlier years of registry reports before the introduction of the modified tibial tray might have shed some light specifically into the revision rates of the original version of the ATTUNE, but this might be complicated by lower numbers of knees at risk of revision in earlier years.

The authors believe that despite our study limitations, the original design of the cemented ATTUNE® TKA system is associated with a high rate of RLLs both on the tibia and femur, but it remains unclear specifically which components or bearings are most at risk of this. Whilst we draw attention to this finding we are also unclear of its clinical significance. Longer follow-up studies and data are needed to determine the clinical relevance of the increased rate of RLLs with the original ATTUNE® implant and until such evidence is available, we recommend close surveillance for all patients with this implant.

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Table 1. Characteristics of all included studies in the systematic review.

Lead author (Year of publication)	**Study design (Level of Evidence, Country)**	**No. of patients (TKAs)**	**Patient groups (TKA designs, cement used)** **Group 1: ATTUNE** **Group 2: Control**	**Gender** (M:F)	**Age (years)** Mean (range)	**Follow-up (months)**
Kaptein (2020) [37]	RCT (I, Netherlands)	74 (74)	**Group 1** (n=38) ATTUNE® CR Fixed Palacos R+G **Group 2** (n=36) PFC Sigma® CR Fixed Palacos R+G	**Group 1**: 18M:20F **Group 2**: 11M:25F	**Group 1**: 69±9.5 **Group 2**: 68±8.2	ATTUNE 24 Control 24
Robinson (2021) [57]	Prospective cohort (II, UK)	192 (192)	**Group 1** (n=96) ATTUNE® CR Fixed **Group 2** (n=96) PFC Sigma® CR (n=41) Vanguard® CR (n=55) Fixed Palacos R+G	**Group 1**: 51M:45F **Group 2**: 34M:62F NSD	**Group 1**: 70.6 **Group 2**: 68.1 P=0.88	ATTUNE 24 Control 24
Ranawat (2017) [51]	Prospective cohort (II, USA)	200 (200)	**Group 1** (n=100) ATTUNE® PS 61 fixed / 39 RP **Group 2** (n=100) PFC Sigma PS 83 fixed / 17 RP Cement type not specified	**Group 1**: 33M:67F **Group 2**: 29M:71F P=0.54	**Group 1**: 71±7.3 **Group 2**: 70.1±7.4 P=0.4	ATTUNE Mean: 22.8 (95%CI: 21.6-22.8) Control Mean: 24 (95%CI: 21.6-22.8)
Lachiewicz (2021) [40]	Retrospetcive cohort (III, USA)	624 (677)	**Group 1** (n=154, 166 TKAs) ATTUNE® PS Fixed, cement: DePuy SmartSet HV: 71 (43%) DePuy SmartSet MV: 77 (46%) Simplex P MV: 18 (11%) **Group 2** (n=470, 511 TKAs) Various manufacturers DePuy SmartSet HV: 20 (4%) Simplex-P MV: 492 (96%)	**Group 1**: 135M:19F **Group 2**: 419M:51F P=0.784	**Group 1**: 63.8±8.2 (44-85) **Group 2**: 64.6±7.7 (43-88) P=0.271	ATTUNE Mean: 23.7±12.4 Range: 6-67 Control Mean: 25±16.8 Range: 10-75

Behrend (2020) [8]	Retrospective cohort (III, Switzerland)	291 (291)	**Group 1** (n=100) ATTUNE® CR **Group 2** (n=191) LCS® CR Mobile Palacos R+G	**Group 1**: 52M:48F **Group 2**: 85M:106F P=0.22	**Group 1**: 71±10 (45-89) **Group 2**: 70±10 (44-91) P=0.68	Both groups Mean: 13.5 Range: 10-21
Jin (2020) [36]	Retrospective cohort (III, Korea)	142 (142)	**Group 1** (n=68) ATTUNE® PS **Group 2** (n=74) PERSONA® PS Fixed Simplex P	**Group 1**: 9M:59F **Group 2**: 14M:60F P=0.36	**Group 1**: 69.7±5.9 **Group 2**: 67.9±7.3 P=0.44	ATTUNE Mean: 28.4±12.6 Control Mean: 29.1±13.2
Staats (2019) [60]	Retrospective cohort (III, Austria)	529 (529)	**Group 1** (n=276) ATTUNE® 22PS/254CR, 255 fixed / 21 mobile **Group 2** (n=253) PFC Sigma® 38PS/215CR Mobile Palacos R+G	**Group 1**: 103M:173F **Group 2**: 105M:148F p>0.05	**Group 1**: 69±9 **Group 2**: 68±10 p>0.05	ATTUNE Mean: 19±7 Control group Mean: 25±11
Torino (2022) [61]	Case-series (IV, USA)	668 (742)	ATTUNE® CR/PS Fixed or mobile Cement: various types	260M:408F	70.3±9.8	ATTUNE Mean: 42±16.8
van Loon (2021) [62]	Case-series (IV, USA)	200 (200)	ATTUNE® RP 115CR/85PS Cement type not specified	74M:126F	65.4±7.8 (41-78)	ATTUNE 24 months
Hoskins (2020) [32]	Case-series (IV, Australia)	112 (122)	ATTUNE® 121 fixed: 9PS/112CR, 1 RP	38M:74F	71.2 (44-89)	ATTUNE Mean: 21 Range: 3-51
Song (2020) [59]	Case-series (IV, Italy)	500 (500)	ATTUNE® PS Cement type not specified	32M:468F	71.3±7.3	ATTUNE Mean: 40.8±19.2
Giaretta (2019) [26]	Case-series (IV, Italy)	185 (192)	ATTUNE® PS Fixed Palacos R+G	89M:129F	70.3±6.52 (43-85)	ATTUNE Mean: 37.9±13.9 Range: 12-64.8

n: number of patients, **TKA**: total knee arthroplasty, **PS**: posterior-stabilised, **CR**: cruciate-retaining, **RP:** rotating-platform,
PFC: Press-Fit Condylar, **NR**: not reported, **NA**: not applicable,
UK: United Kingdom **ATTUNE®, PFC Sigma®, LCS®:** DePuy Synthes, Warsaw, IN, USA. **Vanguard®, PERSONA®**: Zimmer Biomet, Warsaw, IN, USA

Table 2. Definition of radiolucency lines (RLL) and radiographic evaluation system in all included studies.

Lead Author (Year)	Definition of RLL	System used for radiographic evaluation (number of assessors)
Kaptein (2020) [37]	RLL (tibia) at the implant-cement interface on AP/Lat long-leg standing radiographs.	MKSRESM (2)
	RLL (tibia) either at implant-cement or cement-bone interface on AP/Lat standing radiographs. Reported on both ≥ 2mm in depth or progressive pattern (significant) and on < 2mm in depth (non-significant). RLL at implant-cement interface included in analysis.	KSRESM (2)
Ranawat (2017) [51]	RLL (tibia and femur) at implant-cement interface on weight-bearing AP, Lat and 30° merchant view + AP long-leg standing view.	KSRESM (2)
Lachiewicz (2021)[40]	RLL (tibia) at implant-cement interface on AP/Lat standing radiographs	MKSRESM (2)
Behrend (2020) [8]	RLL (tibia and femur) at implant-cement interface on AP/Lat radiographs. Documented if ≥ 2mm in a progressive pattern	MKSRESM
Jin (2020) [36]	RLL (tibia and femur) at implant-cement interface on AP/Lat radiographs. Documented if ≥ 2mm or progressively enlarging RLL was found in any zone in AP/Lat views	KSRESM (2)
Staats (2019) [60]	RLL (tibia and femur) either at implant-cement or cement-bone interface on AP/Lat standing radiographs. Documented if detected on two serial radiographs	MKSRESM (2)
	RLL (tibia and femur) ≥ 2mm in depth on AP/Lat standing radiographs	No system reported
Hoskins (2020) [32]	RLL (tibia and femur) at implant-cement interface (AP/Lat radiographs). Classified as partial or complete.	MKSRESM
Song (2020) [59]	Medial tibial bone resorption was evaluated. Progression according to change in size of bone resorption area, defined as no progression when change in size was less than 2mm.	Own classification system of bone resorption (2)
Giaretta (2019) [26]	RLL (tibia and femur) at implant-cement interface on AP/Lat standing radiographs	MKSRESM

RLL: radiolucency lines, **AP:** anteroposterior view, **Lat:** lateral view, **KSRESM:** Knee Society Radiographic Evaluation System [23],
MKSRESM: Modern Knee Society Radiographic Evaluation System [44]

Table 3. Radiolucency lines reported post-operatively in all studies included in the systematic review.*

Lead author (Year)	Type of prosthesis Radiographic evaluation	Tibial RLL (knees) in ATTUNE®	Tibial RLL (knees) in Control	Femoral RLL in ATTUNE®	Femoral RLL in Control	Knees with RLL overall in ATTUNE	Knees with RLL overall in Control	Statistical analysis (ATTUNE vs Control)
Kaptein (2020) [37]	ATTUNE vs PFC CR MKSRESM	16 (16) AP Z1: 14 (42%) Z2: 2 (6%)	4 (3) AP Z1: 3 (8.6%) Z2: 1 (2.8%)	NR	NR	16/33 (48%)	3/35 (8.6%)	Tibial/Overall RLL: P=0.002
Robinson (2021) [57]	ATTUNE vs PFC or Vanguard CR KSRESM	28 (26) AP Z1: 6 (23%) Z4: 2 (7.7%) Lat view Z1: 2 (7.7%) Z2: 2 (7.7%) Z3: 16 (61.5%)	29 (20) AP Z1: 7 (24%) Z3: 1 (3%) Z4: 3 (10%) Lat Z1: 6 (21%) Z2: 2 (7%) Z3: 9 (31%)	NR	NR	26/96 (27%)	20/96 (21%)	Tibia/Overall RLL: P=0.42
Ranawat (2017) [51]	ATTUNE vs PFC PS KSRESM	0/100	0/100	0/100	0/100	0/100	0/100	No difference
Lachiewicz (2021) [40]	ATTUNE vs various PS MKSRESM	182 (110) AP Z1: 26 (16%) Z2: 14 (8%) Lat Z1: 1 (1%) Z2: 8 (5%) Z3: 3A: 49 (30%) 3P: 28 (17%) Z5: 26 (16%)	NR	NR	NR	110/166 (66%)	NR	NA
Behrend (2020) [8]	ATTUNE vs LCS CR MKSRESM	2 (1) AP Z1: 1 (1%) Z2: 1 (1%)	6 (5) AP Z1: 2 (1%) Z2: 4 (2.1%)	15 (14) Lat view: Z1: 1 (1%) Z2: 12 (12%) Z3A: 1 (1%) Z3P: 1 (1%)	22 (18) Lat view: Z1: 6 (3.1%) Z2: 15 (7.9%) Z3A: 0 Z3P: 1 (0.5%)	14/100 (14%)	18/191 (9.4%)	Tibial RLL: P=0.428 Femoral RLL: P=0.236 Overall RLL: NSD
Jin (2020) [36]	ATTUNE vs PERSONA PS KSRESM	8 (4) AP Z1: 4 (5.9%) Z2: 4 (5.9%)	8 (4) AP Z1: 4 (5.4%) Z2: 4 (5.4%)	6 (3) Lat view: Z1: 3 (4.4%) Z4: 3 (4.4%)	3 (2) Lat view: Z1: 2 (2.7%) Z4: 1 (1.4%)	5/68 (7%)	4/74 (5%)	Tibial RLL: p=0.98 Femoral RLL: p=0.99 Overall RLL: P=0.98

Staats (2019) [60]	ATTUNE (22PS/254CR) vs PFC (38PS/215CR) MKSRESM	AP 38 (37) Z1: 26 (9%) Z2: 6 (2%) Lat 68 in 56 knees (20.3%) Z1: 6 (2%) Z2: 3 (1%) Z3: 3A: 44 (16%) 3P: 12 (4%) Z5: 3 (1%)	AP 11 (10) Z1: 8 (3%) Z2: 3 (1%) Lat 6 in 6 knees (2.4%) Z1: 0 Z2: 0 Z3: 3A: 3 (1%) 3P: 0 Z5: 3 (1%)	40 (40) Lat view: Z1: 3 (1%) Z2: 33 (12%) Z3: 1	6 (5) Lat view: Z1: 0 Z2: 6 (2%) Z3: 0	97/276 (35%)	19/253 (7.5%)	Tibial RLL: P<0.001 Femoral RLL: P<0.001 Overall RLL: P<0.001
van Loon (2021) [62]	ATTUNE RP 115CR/85PS (no control)	0/191	NA	0/191	NA	0/191	NA	NA
Hoskins (2020) [32]	ATTUNE (9PS/112CR) (no control) MKSRESM	AP Z1: 28 (23%) Z2: 28 (23%) Lat Z1: 16 (13%) Z2: 14 (53.8%) Z3: 3A: 0 3P: 1 (3.4%)	NA	Lat view: Z1: 9 (7%) Z2: 0 Z3: 3A: 2 3P: 2 Z5: 17 (14%)	NA	29/122 (23.8%)	NA	NA
Song (2020) [59]	ATTUNE PS (no control)	21/500 (4.2%) Under medial tibial baseplate UT1: 31 (19.2%) UT2: 10 (2%)	NA	NA	NA	96/500 (19.2%)	NA	NA
Giaretta (2019) [26]	ATTUNE PS (no control) MKSRESM	25/192 (13%) AP Any zone: 25 (13%) Lat Any zone: 17 (8.8%)	NA	23/192 (12%) Lat Any zone: 23 (12%)	NA	43/192 (22.4%)	NS	NA

TKA= total knee arthroplasty, **PS**: posterior-stabilised, **CR**: cruciate-retaining, **RP:** rotating-platform, **PFC**: Press-Fit Condylar, **RLL**: radiolucency lines, **AP**: anteroposterior view, **Lat**: lateral view, **Z:** zone, **NA**: not applicable, **NR=**not reported, **NSD=**no significant difference, **p<0.05**: significant, **MKSRESM**: Modern Knee Society Radiographic Evaluation System [44], **KSRESM**: Knee Society Radiographic Evaluation System [23], **ATTUNE®, PFC Sigma®, LCS®**: DePuy Synthes, Warsaw, IN, USA. **PERSONA®**: Zimmer Biomet, Warsaw, IN, USA

*The numbers in total in each box refer to the numbers of knees which had at least one RLL.

Table 4. Prevalence (estimated rate) for any radiolucency lines in the ATTUNE® groups reported in medial tibia, tibia, femur and overall

RLL (TKA design)	No. of studies (TKAs)	Estimated rate - OR (95%CI)	Estimated rate - OR (95%CI) (excluding the 3 studies reporting on RLL ≥ 2mm) [8, 36, 62]	Heterogeneity			
				τ^2	I^2	Q value	P value
Tibia and/or femur overall (fixed)	6 (682)	29.9% (95%CI: 15.6-49.6%)	36.3% (19.6%-57.2%)	1.020	95.182	103.778	P<0.001
Tibia and/or femur overall (CR)	3 (234)	27.4% (13.4-47.9%)	NA	0.535	86.831	15.187	P=0.001
Tibia and/or femur overall (any)	10 (1,558)	21.4%% (95%CI: 12.7-33.7%)	31% (95%CI: 19.2-46%).	0.818	93.708	143.042	P<0.001
Tibia AP (fixed)	5 (560)	27.4% (95%CI: 10.1-55.8%)	36.1% (95%CI: 13.7%-66.8%)	1.794	96.650	119.392	P<0.001
Tibia AP (CR)	3 (234)	18.5% (5.1-49.2%)	NA	1..338	89.688	19.395	P<0.001
Tibia AP (PS)	4 (526)	11.7% (1.8-48.8%)	NA	3.623	97.593	124.653	P<0.001
Tibia AP (any)	9 (1,236)	11.3% (95%CI: 4.5-25.6%)	22.1% (95%CI: 8.7-45.9%)	1.913	95.913	195.721	P<0.001
Medial tibia AP (fixed)	5 (490)	15.8% (95%CI: 8.4-28%)	19% (95%CI: 10-33.1%)	0.562	85.953	28.476	P<0.001
Medial tibia AP (CR)	3 (234)	8.4% (95%CI: 1.0-45.4%)	NA	3.388	93.149	29.193	P<0.001
Medial tibia AP (PS)	4 (834)	8.4% (95%CI: 4.3-15.5%)	NA	0.313	77.971	13.618	P=0.003
Medial tibia AP* (any)	10 (1,666)	9.1% (5.4-15.1%)	12.8% (95%CI: 7.6-20.7)	0.586	86.737	67.859	P<0.001
Tibia Lat (any)	5 (838)	3.8% (95%CI: 1.1-12.1%	5.6% (95%CI: 1.7-16.7%)	1.447	88.923	36.110	P<0.001
Femur Lat (any)	6 (936)	8.9% (95%CI: 5.1-15%)	11.5% (95%CI: 6.6-19.5%)	0.295	72.982	18.506	P=0.002

RLL: radiolucency lines, **OR:** odds ratio, **95%CI:** 95% Confidence Interval, **p<0.05:** significant, **NA:** not applicable, **TKAs:** total knee arthroplasties, **AP:** anteroposterior view, **Lat:** lateral view**, PS:** Posterior-stabilised, **CR:** cruciate-retaining,

*Medial tibia (AP): included one study which defined as radiolucency any medial tibial bone resorption, but only radiolucencies reported for zones of medial tibial baseplate included [59]

Table 5. Demographics and outcomes (loosening and revision rates) from studies included in the systematic review.

Lead Author (Year)	TKA design	Follow-up (months) Mean (range)	Number of ATTUNE TKAs	Loosening	Revision overall	Revision due to loosening
Robinson (2021) [57]	Fixed CR	24	96	0	NR	NR
Lachiewicz (2021) [40]	Fixed PS	Mean: 23.7±12.4 (6-67)	166	27	31*	27*
Jin (2020) [36]	Fixed PS	Mean: 28.4±12.6	142	0	NR	NR
Staats (2019) [60]	Fixed + mobile CR/PS	Mean: 19±7	276	0	3	0
Van Loon (2021) [62]	Mobile-CR/PS	Mean: 24	200	NR	1	0
Song (2020) [59]	PS	Mean: 40.8 (2-5)	500	NR	2	0
Giaretta (2019) [26]	Fixed PS	Mean: 37.9 (12-64.8)	228	2	2	2
Torino (2022) [61]	Fixed + mobile	Mean: 42	742	10	17	10

TKA: total knee arthroplasty, **CR:** cruciate-retaining, **PS:** posterior-stabilised, **NR:** not reported
All were based on radiological findings, with one based on radiological and clinical characteristics [40].
*Including 12 TKAs awaiting revision.

Table 6. Overall revision rates of the ATTUNE TKA reported in National Joint Registries.

NJR (Year)	ATTUNE TKAs (n)	Revisions (n)	Reported revision	Revision rate 1 year (95%CI)	Revision rate 2 years (95%CI)	Revision rate 3 years (95%CI)	Revision rate 4 years (95%CI)	Revision rate 5 years (95%CI)	Revision rate 6 years (95%CI)
UK (2022) [48]	FB (all fix): 33,769 MB (all fix): 5770	NR	Cumulative	FB (all fix) 0.39 (0.32-0.46) MB (all fix) 0.26 (0.16-0.45)	NR	NR	NR	FB (all fix) 2.06 (1.88-2.27) MB (all fix) 1.37 (1.03-1.83)	NR
Australia (2022) [1]	Cement CR: 20,427 PS: 10,431	CR: 473 PS: 206	Cumulative	CR cement 0.9 (0.9-1.0) PS cement 0.9 (0.7-1.1)	NR	NR	NR	CR cement 3.1 (2.8-3.4) PS cement 2.6 (2.3-3.0)	NR
New Zealand (2022) [54]	All fix: 35,148	All fix: 193	Rate/100 component years	0.549 (0.474-0.632)	NR	NR	NR	NR	NR
Sweden (2020) [53]	All fix: 115	NR	Overall relative risk	0.88 (0.12-6.27)	NR	NR	NR	NR	NR
Germany (2021) [2]	CR FB cement 5,802 CR MB cement 1,417 PS FB cement 1,362 PS MB cement 417	NR	Revision probability	CR FB cement 1.6 (1.3-2.0) CR MB cement 1.4 (0.9-2.2) PS FB cement: 2.5 (1.7-3.6) PS MB cement: 1.0 (0.4-2.8)	NR	CR FB cement 3.1 (2.6-3.7) CR MB cement 2.8 (1.9-3.9) PS FB cement: 4.0 (3.0-5.5) PS MB cement: 1.4 (0.6-3.3)	CR FB cement 3.2 (2.7-3.8) CR MB cement 3.2 (2.2-4.6) PS FB cement: 5.6 (4.1-7.6) PS MB cement: 1.4 (0.6-3.3)	CR FB cement 3.6 (2.9-4.4) CR MB cement 3.6 (2.9-4.4) PS FB cement: 5.9 (4.3-8.1) PS MB cement: NR	CR FB cement 3.6 (2.9-4.4) CR MB cement 3.6 (2.9-4.4) PS FB cement: NR PS MB cement: NR
Netherlands (2022) [3]	Cement: 3,261	23	Cumulative	0.5 (0.2-0.8)	NR	2.4 (1.7-3.2)	NR	3.2 (2.2-4.1)	NR
Switzerland (2021) [6]	All fix: 18,286	NR	Cumulative	1.7 (1.5-1.9)	NR	NR	5.7 (5.3-6.1)	6.3 (5.9-6.8)	6.9 (6.3-7.4)

Switzerland (2022) [5]	All fix CR FB: 2,677 CR MB: 4,753 PS FB: 2,224 PS MB: 3,246	CR FB: 2,677 CR MB: 4,753 PS FB: 2,224 PS FB: 3,246	Adjusted revision rate	NR	CR FB: 2.8 (2.2-3.5) CR MB: 4.2 (3.7-4.9) PS FB: 2.9 (2.3-3.7) PS MB: 3.7 (3.1-4.4)	NR	NR	NR	NR

NJR: National Joint Registry, **TKA:** total knee arthroplasty, **n:** number, **UK:** United Kingdom, **CR:** cruciate-retaining, **PS:** posterior-stabilised, **FB:** fixed-bearing, **MB:** mobile-bearing, **fix:** fixation, **NR:** not reported.

***Rate/100 component years**: Equivalent to the yearly revision rate expressed as a percent and is derived by dividing the number of prostheses revised by the observed component years multiplied by 100.

****Adjusted revision rate**: Revision rate adjusted for effects of mortality and emigration.

Table 7. Risk of bias for prospective cohort studies using the Newcastle-Ottawa Scale (NOS) [64].

Lead author (Year)	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration of that outcome was not present at start of study	Comparability of cohorts	Assessment of outcome	Follow up long enough for outcomes to occur	Adequate of follow-up of cohorts	NOS score
Robinson (2021) [57]	Somewhat representative*	Drawn from same community as the exposed cohort*	Secure record*	Yes*	Study control for post-op radiolucencies* Study controls for gender, age, BMI, side, pre-op deformity*	Independent blind assessment*	Yes*	Subject lost to follow-up unlikely to introduce bias – small number lost*	9
Ranawat (2017) [51]	Somewhat representative*	Drawn from same community as the exposed cohort*	Secure record*	Yes*	Study control for post-op radiolucencies* Study controls for gender, age, BMI, side, clinical outcomes, ROM*	Record linkage*	Yes	Subject lost to follow-up unlikely to introduce bias – small number lost*	9

BMI: body mass index, **ROM:** range of motion

A study can be awarded a maximum of 1 star for each question and a maximum of 2 stars for comparability of cohorts. The more stars a study was awarded, the lower was the risk of bias.
Threshold for "Good quality": 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
The asterisks represent stars.

Table 8. Assessment of methodological quality of the non-randomised retrospective studies (MINORS criteria) [56].

Criteria	**Torino (2022)** [61]	**van Loon (2021)** [62]	**Behrend (2020)** [8]	**Jin (2020)** [36]	**van Loon (2021)** [62]	**Staats (2019)** [60]	**Hoskins (2020)** [32]	**Song (2020)** [59]	**Giaretta (2019)** [26]
A clearly stated aim	2	2	2	1	2	2	2	2	2
Inclusion of consecutive patients	0	0	0	0	0	0	0	2	2
Prospective data collection	0	2	2	0	2	0	2	2	0
Endpoints appropriate to the study aim	2	2	2	2	2	2	1	2	2
Unbiased assessment of the study endpoint	1	1	2	2	1	2	1	2	1
Follow-up period appropriate to the study aim	2	2	2	2	2	2	2	2	2
Loss to follow-up <5%	1	2	2	1	2	2	2	2	1
Prospective calculation of the study size	0	0	2	0	2	2	0	2	0
Adequate control group	0	0	2	2	0	2	0	0	0
Contemporary group	2	2	2	2	2	2	2	2	2
Baseline equivalence of groups	2	0	2	2	0	2	0	0	0
Adequate statistical analysis	2	2	2	2	2	2	1	2	1
TOTAL	**14**	**15**	**22**	**16**	**17**	**20**	**13**	**22**	**13**

MINORS, Methodological Index for Non-randomized Studies [56].
The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).
Maximum possible score being 24 for comparative studies.