Systematic Review

Time to Total Knee Arthroplasty after Intra-Articular Hyaluronic Acid or Platelet-Rich Plasma Injections: A Systematic Literature Review and Meta-Analysis

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Abstract: Intra-articular (IA) hyaluronic acid (HA) and platelet-rich plasma (PRP) injections are increasingly being prescribed for knee osteoarthritis (KOA). However, failure of the medical treatment may result in total knee arthroplasty (TKA). We wondered if IA HA or PRP injections (intervention) may delay the time to TKA (outcome) among KOA patients (population), compared to KOA patients not receiving these injections (comparator). For this systematic literature review (SLR) and meta-analysis, we selected observational studies with at least one group of patients receiving IA HA or PRP and with TKA data available. The main outcome was time from the diagnosis of KOA to TKA. We included 25 articles in the SLR (2,824,401 patients) and four in the meta-analysis. The mean strengthening the reporting of observational studies in epidemiology (STROBE) score was 63%. For patients receiving versus not receiving HA injections, the delay between a declared diagnosis of KOA to TKA was increased by 9.8 months (95% CI (8.2–11.4)). As compared with standard of care, the effect size of HA injections for this outcome was 0.57 (95% CI (0.36–0.76)). Only one study described a median time from PRP injections to TKA of 4.1 years (range 0.3–14.7). IA HA injections were associated with increased time to TKA. Causality cannot be concluded because of missing confounder factors as comorbidities. Data were insufficient to conclude any effect of PRP injections on TKA delay.

Keywords: knee osteoarthritis; hyaluronic acid; platelet-rich plasma; total knee arthroplasty; treatment

1. Introduction

Osteoarthritis (OA) is the most prevalent chronic joint disease, causing pain, disability and progressive joint destruction. Due to the sedentariness caused by the difficulty to walk, knee OA (KOA) is associated with mortality and cardiovascular diseases [1–4]. It is responsible for a substantial economic burden [5].

The management of OA is only symptomatic and should be individualized for each patient. It may use non-pharmacological (physiotherapy, exercise training, knee braces, etc.) [6,7] and pharmacological options (analgesic, non-steroidal anti-inflammatory, intra-articular [IA] injections of corticosteroids) [8,9]. Among pharmacological options, IA hyaluronic acid (HA) injections have been used for several years for symptom reduction, although controversial [10]. IA HA injections are recommended in the guidelines of the Osteoarthritis Research Society International (OARSI) and the French Society of Rheumatology [8,11], but conditionally not in the guidelines of the American College of Rheumatology (ACR) and the American Academy of Orthopaedic Surgeons [9,12].
The mechanism of action of HA injections remains unclear. IA HA injections may replace endogenous HA, stimulate endogenous HA synthesis by fibroblasts and inhibit cartilage degradation by aggrecanase [13–15]. The structural effects of HA on OA progression have not been demonstrated on X-ray images [16,17], but some studies have suggested a protective effect on cartilage by slowing down the cartilage volume loss and the aggravation of the cartilage defect score as compared with controls on magnetic resonance imaging (MRI) [18].

IA platelet-rich plasma (PRP) injections, which are increasingly being used in KOA [19], are based on the ability of platelets to release growth factors and many other beneficial mediators [20]. PRP injections may reduce pain and disability as compared with placebo [21,22], but their clinical efficacy has been challenged by recent negative studies [23]. The ACR and OARSI guidelines strongly recommend against their use because of lack of high-quality trials and lack of standardized preparation of PRP [9,11]. In a few studies, PRP injections have had positive effects on cartilage in animal models and slowed OA [24]. The growth factors released after platelet activation, including vascular endothelial growth factor, transforming growth factor beta and platelet-derived growth factor, may stimulate chondrocyte proliferation and mesenchymal stem cell differentiation and inhibit NF-κB [20,25,26].

Finally, total knee arthroplasty (TKA) is proposed in cases of failure of optimal well-conducted medical treatment. However, TKA may be responsible for serious adverse events (e.g., thrombosis or infection). Moreover, about 20% of patients continue to have chronic pain despite TKA [27].

As OA is a slowly progressive disease, long-term efficacy is difficult to assess. The outcome measures used in randomized clinical trials (RCTs) to estimate the efficacy of medical treatment in OA are symptoms (i.e., pain and function) and structural outcomes (by X-ray images or MRI). TKA has been recently considered one of the most clinically relevant hard endpoints for assessing the relevance of any knee OA treatment [28,29]. In one RCT with a small number of patients, more TKAs were performed in the placebo than HA group (OR = 0.41 95% CI (0.09–1.89)) [30]. Another RCT suggested that HA injection may delay the time to TKA but without reaching significance, with a mean difference in delay from IA HA injection to TKA of 3.8 months (p = 0.219) between the HA and placebo groups. However, such an endpoint requires several years of follow-up, which limits its use in pivotal trials.

Considering the possible protective effects on cartilage and long-term symptomatic efficacy of IA HA or PRP injections, we aimed to determine whether these treatments could increase the time to TKA in OA patients. For this, we performed a systematic literature review and meta-analysis of observational studies with the requirement of TKA as an outcome to investigate whether IA HA and PRP injections are associated with a delay in TKA.

2. Materials and Methods

2.1. Systematic Literature Search

We systematically reviewed the literature according to the Cochrane guidelines [31] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [32]. Relevant publications were selected from PubMed and Embase with no limit on time (up to 28 January 2022) or language. The Cochrane database was not consulted because it does not include observational studies. The systematic review was registered on PROSPERO (CRD42020166804).

The keywords for the PubMed research were (“OA, Knee” [Mesh]) AND (“Hyaluronic acid” OR “Viscosupplementation” OR “Viscosupplements” OR “Platelet-Rich Plasma” OR “Blood Platelets” [Mesh]) AND (“OA, Knee/surgery” [Mesh] OR “Arthroplasty, Replacement, Knee” [Mesh] OR “Knee Prosthesis” [Mesh] OR “KA” OR “Knee replacement”).

We also searched abstracts for the past 2 years (January 2020 to January 2022) from meetings of the ACR, European League Against Rheumatism, French Society of Rheumatology, American Academy of Orthopedic Surgeons, Société Française de Chirurgie Orthopédique et Traumatologique (SOFCOT), American Association of Hip and Knee Sur-
2.2. Study Selection

To assess the effect of IA HA or PRP injection (intervention) on TKA delay (outcome) among patients with KOA (population) compared to KOA patients not receiving these injections (comparator), French and English observational (cohort, case–control and cross-sectional) studies of humans were selected, with the following criteria: at least one group of patients had received IA HA or PRP injections for KOA, with TKA as an outcome. To compare IA injection and non-IA injection groups, three variables of interest were determined in both groups: time from diagnosis of KOA to TKA (in month or year), time from IA HA or PRP injection to TKA (in month or year) and prevalence of TKA. We excluded studies with IA injections performed during TKA surgery and interventional studies. Two independent readers (SB and KL) selected articles based on titles and abstracts, then on full texts. In case of doubt, JS has been consulted and KL performed the final decision.

2.3. Data Extraction

The participants were separated into two groups: patients who received IA injections and patients who did not. We extracted the following data: publication data (title of the article, first and last author, publication date), study design (type of study, year(s) of inclusion, name of the database of inclusion, study quality score), population (total number of patients included, mean age and sex of patients, associated comorbidities), data on KOA (Kellgren–Lawrence (KL) grade, visual analog scale (VAS) for pain), type of HA (brand name, number of courses), method to obtain PRP and data needed for statistical analysis (time from a declared diagnosis of KOA to TKA or from IA injection to TKA (mean, standard deviation [SD]; median (interquartile range [IQR]) or number of TKAs during the observation time).

The quality of publications was assessed by the strengthening the reporting of observational studies in epidemiology (STROBE) quality score for observational studies (total score 22 points, expressed in percentage) [34,35].

2.4. Statistical Analysis

To examine the delay to TKA, the primary outcome was time from a declared diagnosis of KOA to TKA. The secondary outcomes were time from IA HA or PRP injection to TKA and the prevalence of TKA at fixed endpoints from a declared diagnosis of KOA or from the first IA injection mentioned in the study. We performed separate analyses for HA and PRP injections.

For each outcome, the results were analyzed descriptively for each study with calculation of mean (+SD) and/or median (+IQR) time and/or mean prevalence (%). The outcomes were also described for each HA course when data were available. Then, for the primary outcome when we had enough data, we performed a pooled analysis to evaluate the association between IA injection and time to TKA: for continuous variables, we calculated an effect size (ES) by the Hedges’ formulations adjusted $g$, for IA HA products compared to a control group. The ES is the standard mean deviation: mean difference/standard deviation at baseline. If the ES is <0.2, the effect of treatment is considered trivial, >0.2 to 0.5 small, >0.5 to 0.8 moderate, >0.8 to 1.2 high and >1.2 very high [36]. For binary variables, we calculated the odds ratio (OR). The accuracy of the ES and the OR is expressed by the 95% confidence interval (CI). We pooled analyses for HA but not PRP injections because of a lack of available data.

We used Revman V.5.3 for the meta-analysis. Heterogeneity was assessed by the $I^2$ index; with $I^2 > 50\%$ (high heterogeneity), we used a random-effects model, and with $I^2 < 50\%$ (low heterogeneity), a fixed-effects model.
3. Results

3.1. Literature Search and Characteristics of Included Studies

A total of 25 studies met the selection criteria and were included in the descriptive analysis (Figure 1): 23 of HA injections, 1 of PRP injections and 1 of HA or PRP injections. The studies were from the United States [37–52], Spain [53,54], France [55–57], Turkey [58], Thailand [59], Finland [60] and Australia [61]. The mean STROBE quality score was 63% [34,35], but the results were heterogeneous ($I^2 = 99\%$). All the studies were retrospective except three of them [45,56,57]. Details about the studies are in Table 1.

Figure 1. Flow chart of included studies. HA = hyaluronic acid; TKA = total knee arthroplasty; KOA = knee osteoarthritis, PRP = platelet-rich plasma.

Ten studies were included for the primary outcome (9 retrospective [37–42,50,51,55] and 1 prospective [57]). The data from KHOALA cohort were obtained for an observational study [57] and directly from the cohort database [33].

3.2. Patient and Product Characteristics

In total, 2,824,401 patients were included; the mean age was $55.1 \pm 12.8$ years [58] to $70.5 \pm 9.2$ years [47] and the mean prevalence of women was $49.3\%$ [47] to $83\%$ [58]. In studies using a database, patients with a diagnosis of KOA were identified according to the International Classification of Diseases, 9th revision (ICD-9) or ICD-10 codes, and the comparison involved those receiving or not receiving IA HA or PRP injections [37–43,50,51,55]. In the other studies, in addition to the KOA diagnosis, IA injection was an inclusion criterion [43–49,52,53,56,58–62]. Pain VAS score, KL score and clinical severity were heterogeneous among studies.

The characteristics of studies and patients are in Table 2. Concerning comorbidities (which may influence the decision of knee joint replacement due to perioperative risk), in the study of Delbarre et al., the Charlson comorbidity index (CCI) did not differ between patients receiving and not receiving HA injections [55]. In the study by Altman et al., patients in the HA group were younger and the mean CCI was lower than in the other group ($0.6 \text{ vs. } 0.7, p < 0.001$) [38]. In another study, the prevalence of comorbidities was $61.6\%$ in the HA group versus $33\%$ in the PRP group [60]. Some studies mentioned body mass index (BMI): in the study by Annaniemi et al., the frequencies of obesity were $67\%$ and $45.3\%$ in the PRP and HA groups, respectively. However, again, there was no group without any treatment [60]. The other studies mentioning BMI did not have a control group. The injection products used and their controls are in Supplementary Materials (Table S1).
### Table 1. Characteristics of included studies.

| Author and Year of Publication | Quality Score STROBE (%) | Patients with IA Injection (n) (Population) | Injection Products (Intervention) | Patient without IA Injection (n) (Comparator) | Data of Interest Available (Outcome) | Time from KOA Diagnosis to TKA | Prevalence of TKA from Diagnosis | Time from IA Injection to TKA | Prevalence of TKA from IA Injection |
|-------------------------------|--------------------------|------------------------------------------|----------------------------------|-------------------------------------------|-----------------------------------|---------------------------------|-------------------------------|--------------------------------|---------------------------------|
| Altman-dasa, 2015 [38]       | 65%                      | 50,349 All HA                            | 131,673                          | Yes                                      | Yes                               | No                              | No                            | No                              | No                              |
| Delbarre, 2017 [55]          | 81%                      | 1296 All HA                              | 366                              | Yes                                      | Yes                               | No                              | No                            | No                              | No                              |
| Ong, 2016 [39]               | 76%                      | 9586 All HA                              | 25,560                           | Yes                                      | No                                | No                              | No                            | No                              | No                              |
| Altman-kim, 2015 [37]        | 76%                      | 8423 All HA                              | 14,132                           | Yes                                      | No                                | No                              | No                            | No                              | No                              |
| Ong, 2019a [41] *            | 66%                      | 88,501 All HA                            | 1,941,996                        | No                                       | Yes                               | No                              | No                            | No                              | No                              |
| Ong, 2019b [40] *            | 76%                      | 37,160 All HA                            | 104,145                          | Yes                                      | Yes                               | No                              | No                            | No                              | No                              |
| Etter, 2020 [42]             | 77%                      | 4376 HMW HA                              | 90,316                           | Yes                                      | No                                | No                              | No                            | No                              | No                              |
| Abbott, 2013 [51]            | Abstract                 | 6981 All HA                              | 19,627                           | Yes                                      | No                                | No                              | No                            | No                              | No                              |
| Malanga, 2020 [50]           | 68%                      | 45,801 HA                                | 229,455                          | Yes                                      | No                                | Yes                             | Yes                           | Yes                             | Yes                             |
| Latourte, 2022 [57]          | Cohort                   | 191 All HA                               | 465                              | Yes                                      | No                                | No                              | No                            | No                              | No                              |
| Korzmar, 2013 [58]           | 44%                      | 197 LMW HA                               | 487                              | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Jurado, 2012 [53]            | 61%                      | 202 HMW HA                               | 22                               | No                                       | No                                | Yes                             | No                            | No                              | No                              |
| Dasa, 2018 [39]              | 68%                      | 50,389 HA                                | 0                                | No                                       | No                                | Yes                             | No                            | Yes                             | Yes                             |
| Waddell, 2014 [44]           | 67%                      | 1342 HMW HA                              | 0                                | No                                       | No                                | Yes                             | No                            | Yes                             | Yes                             |
| Bowman, 2018 [45]            | 67%                      | 120 HMW HA                               | 0                                | No                                       | No                                | Yes                             | Yes                           | Yes                             | Yes                             |
| Miller, 2017 [47]            | 69%                      | 218 HMW HA                               | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Turajane, 2008 [59]          | 44%                      | 183 LMW HA                               | 0                                | No                                       | No                                | Yes                             | Yes                           | Yes                             | Yes                             |
| Lundstrom, 2019 [46]         | 53%                      | 1147 LMW HA                              | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Anand, 2018 [48]             | 55%                      | 130 HMW HA                               | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Barrett, 2002 [49]           | 67%                      | 176 LMW HA                               | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Whitman, 2010 [62]           | 27%                      | 220 HMW HA                               | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Campbell, 2004 [61]          | 29%                      | 61 HMW HA                                | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Evanich, 2001 [53]           | 67%                      | 70 HMW HA                                | 0                                | No                                       | No                                | Yes                             | Yes                           | Yes                             | Yes                             |
| Mazieres, 2007 [56]          | 67%                      | 296 HMW HA                               | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Annaniemi, 2019 [60]         | 59%                      | 8694 All HA PRP                          | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |
| Sanchez, 2020 [54]           | 67%                      | 186 PRP                                  | 0                                | No                                       | No                                | No                              | No                            | Yes                             | Yes                             |

* Same study with different analysis for each article. CS = corticosteroids; HA = hyaluronic acid; HMW = high molecular weight, IA = intra-articular; TKA = total knee arthroplasty; KOA = knee osteoarthritis; LMW = low molecular weight, PRP = platelet-rich plasma.
Table 2. Characteristics of studies and included patients.

| Author and Year of Publication | Patients (n) | Database/Years of Inclusion | OA Diagnostic Criteria | With TKA | Without TKA | Age (years), Mean ± SD | Female (%) | Mean BMI (kg/m²) |
|--------------------------------|-------------|----------------------------|------------------------|----------|-------------|------------------------|-----------|-----------------|
| Altman-dasa, 2015 [38]        | 182,022     | IMS Health Database/2007–2013 | Codes                  | Yes      | No          | 61 ± 8.9               | 58.7%     | -               |
| Delbarre, 2017 [55]           | 14,782      | French medical insurance/2006–2013 | X-ray images of the knee followed by an IA injection, prescribed by an OA specialist | Yes      | Yes         | 67.67 ± 10.41          | 66%       | -               |
| Ong, 2016 [39]                | 35,142      | 5% Medicare/2005–2012 | OA knee or osteoarthritis with pain leg codes | Yes      | No          | -                      | 61.2%     | -               |
| Altman-kim, 2015 [37]         | 22,555      | Truven market scan commercial/2006–2011 | Codes                  | Yes      | No          | -                      | 61.7%     | -               |
| Ong, 2019a [41]               | 2,030,497   | Optum informatics/2006–2016 | Codes                  | Yes      | Yes         | -                      | -         | -               |
| Ong, 2019b [40]               | 141,305     | Codes                  | Yes                    | Yes      | No          | -                      | -         | -               |
| Etter, 2020 [42]              | 30,028      | Truven market scan commercial/2008–2017 | Codes by an orthopedics | Yes      | No          | -                      | 58.2%     | -               |
| Abbott, 2013 [51]             | -           | Truven market scan commercial/2007–2011 | First visit to an OA specialist | Yes      | No          | -                      | -         | -               |
| Malanga, 2020 [50]            | 275,256     | 5% Medicare/2010–2015 | Codes                  | Yes      | Yes         | -                      | -         | -               |
| Latourte, 2022 [57]           | 656         | No/2013 | ACR                  | Yes      | Yes         | 62.21 ± 8.45          | 70.3%     | 30.3 ± 6.2 |
| Kozma, 2013 [58]              | 684         | No/2007–2009 | NA                   | Yes      | Yes         | 55.1 ± 12.8           | 83.6%     | -               |
| Jurado, 2012 [53]             | 224         | No/2006–2009 | Spanish recommendations | Yes      | Yes         | -                      | -         | 67.9%          |
| Dasa, 2018 [43]               | 50,389      | IMS Health Database/2007–2010 | First injection of HA | Yes      | No          | 57.5 ± 10.5           | 59.9%     | -               |
| Waddell, 2014 [44]            | 1342        | No/1997–2010 | -                   | Yes      | Yes         | 67.5 ± 10.1           | 60.2%     | 31.5 ± 7   |
| Bowman, 2018 [45]             | 102         | No/2013–2016 | -                   | Yes      | Yes         | 60.1 ± -              | 71.6%     | 33 ± -      |
| Miller, 2017 [47]             | 218         | No/NA   | ACR                  | Yes      | Yes         | 70.5 ± 9.2            | 46.3%     | 30.5 ± 6.9 |
| Turajane, 2008 [59]           | 183         | No/2001–2004 | ACR                  | Yes      | Yes         | 68.7 ± -              | 74.9%     | 25.1 ± -    |
| Lundstrom, 2019 [64]          | 1147        | No/2008–2014 | -                   | Yes      | Yes         | 62.2 ± 14             | 65.7%     | 25.21 ± -   |
| Anand, 2018 [48]              | 130         | No/1999–2003 | -                   | Yes      | Yes         | -                      | 57.7%     | -               |
| Barrett, 2002 [49]            | 376         | No/-    | ACR                  | Yes      | Yes         | 72 ± 11               | -         | -               |
| Whitman, 2010 [62]            | 220         | No/-    | -                   | Yes      | Yes         | -                      | 74.5%     | -               |
| Campbell, 2004 [61]           | 61          | No/-    | X-ray images or arthroscopy | Yes      | Yes         | 62.2 ± -              | 44.3%     | 55.7%          |
| Evanhich, 2001 [52]           | 70          | No/1997 | X-ray images         | Yes      | Yes         | 66 ± 14               | 61%       | -               |
| Annaniemi, 2019 [60]          | 180         | No/2014–2017 | Radiography         | Yes      | Yes         | 61.3 ± 8.8            | 60.3%     | 29.8 ± 4.8 |
| Mazieres, 2007 [56]           | 296         | No/2003–2004 | ACR                  | Yes      | Yes         | 69 ± 10               | 65%       | 28 ± 5       |
| Sanchez, 2020 [54]            | 481         | No/2014–2019 | Radiography         | Yes      | Yes         | 63.9 ± -              | 49.3%     | -               |

ACR = American College of Rheumatology; BMI = body mass index; IA = intra-articular; OA = osteoarthritis; SD = standard deviation; TKA = total knee arthroplasty; - = not applicable.

### 3.3. Primary Outcome: Time from KOA Declared Diagnosis in the Database to TKA (HA Injection)

#### 3.3.1. Descriptive Delay from Each Study

In the 10 studies included [37–42,51,55,57], 418,266 patients underwent TKA (Table 2); 142,210 (34%) had received HA injections.

In seven studies giving appropriate data for such analyses [37–40,42,50,55], the median time from a KOA diagnosis to TKA was significantly longer for patients receiving (range 15.8 months [38] to 29.8 months [37]) than not receiving HA injections (3.7 [38] to
12 months [40,42,55], \( p < 0.001 \), and the mean time was significantly longer for patients receiving injections (19.7 ± 14.2 [38] to 39.4 months (SD unknown) [42] vs. 8.9 ± 11.6 [38] to 27.4 months (SD unknown) [42]). Only in the French cohort KHOALA did the mean time from a declared diagnosis of KOA to TKA not significantly differ between the HA injection and control group: 9.67 ± 6.77 and 10.56 ± 9.14 years (\( p = 0.58 \)) [57].

3.3.2. Pooled Mean Delay and ES

In the pooled analyses, we excluded six articles (mean time unavailable [40,51], lacking SD [37,39,42] or from redundant databases [39]). Then, for four observational studies, the mean time from a declared diagnosis of KOA to TKA for patients receiving than not receiving HA injections was 614 ± 456 days (20 months) versus 234 ± 377 days (7.7 months). The mean difference was 299 days (95% CI (250–348)) (i.e., 9.8 months (95% CI [8.2–11.4])) between the two groups and the ES for HA injections was 0.57 (95% CI (0.38–0.76)) (Figure 2) [38,50,55,57].

3.3.3. Multiple Courses of HA Injections

The mean and median times to TKA increased with each additional HA session in two studies [37,38]. The difference in median time between one and two courses was 262 or 409 days in two different studies, and between three and four courses was 227 or 317 days [37,38]. Additionally, in the study of Abott et al., each treatment increased the mean gap by 202 days on average [51]. In the study of Ong et al., the median time to TKA increased from approximately 20 months for one course to almost 5 years for five or more courses [40].

3.4. Secondary Outcomes: Time from IA Injection to TKA (HA Injection)

Seven studies mentioned time from IA injection to TKA [43–45,50,52,53,59], ranging from 6.7 [52] to almost 36 months [53]. The pooled mean time from IA HA injection to TKA was 14.3 ± 11.1 months [43–45,50,52,59]. Only one study (\( n = 20 \)) had a control group: TKA was 14 months later for patients who received than did not receive HA injections (\( p < 0.001 \)) [53].

3.5. Secondary Outcomes: Prevalence of TKA at 2 Years after a Declared Diagnosis of KOA

From the results of two studies with a total of 2,045,279 patients, the prevalence of TKA at 2 years after declared diagnosis of KOA in the database did not differ between patients receiving or not receiving HA injections: OR = 3.07 (95% CI (0.60–15.74)) [41,55].

3.6. Secondary Outcomes: Prevalence of TKA at Different Times after IA HA Injection

We extracted the reported prevalence of TKA after IA HA injections (Table 3). At 1 year after IA HA injection, the mean TKA prevalence was 5.2% (95% CI 3.7–6.7) for 877 patients [47,58,62] and at 2 years was 8.2% (95% CI (5.8–10.6)) for 520 patients [47,62].
### Table 3. Prevalence of TKA after IA injection.

| Time     | After IA HA Injection | After PRP Injection |
|----------|-----------------------|---------------------|
| 6 months | Barett, 2002 [49]    | 20.3%               |
|          | Mazieres, 2007 [56]  | 0.7%                |
| 8 months | Campbell, 2004 [61]  | 11.4% *             |
| 10 months| Evanich, 2001 [52]   | 28.6% *             |
| 1 year   | Whitman, 2010 [62]   | 1%                  |
|          | Korkmaz, 2013 [58]   | 3.2%                |
|          | Miller, 2017 [47]    | 10.4%               |
| 17 months| Annaniemi, 2019 [60] | 36% *               |
| 2 years  | Miller, 2017 [47]    | 18%                 |
| 27 months| Bowman, 2018 [45]    | 19.6%               |
| 3 years  | Dasa, 2018 [43]      | 25.7%               |
| 3.5 years| Turajane, 2008 [59]  | 25%                 |
|          | Miller, 2017 [47]    | 37.2% *             |
| 5 years  | Latouste, 2022 [57]  | 25.7%               |
| 6 years  | Sanchez, 2020 [54]   | -                   |
| 6.5/7 years| Lundstrom, 2019 [46]| 50%                 |
| 7.3 years| Sanchez, 2020 [54]   | -                   |
| 8 years  | Waddell, 2014 [44]   | 25%                 |

* = Prevalence on mean follow-up. HA = hyaluronic acid; IA = intra-articular; PRP = platelet-rich plasma; TKA = total knee arthroplasty; - = not applicable.

### 3.7. PRP Injections

We included two studies with a group of patients who underwent IA PRP injections [54,60], but only one had a control group [60]. The characteristics of patients are in Table 2. We extracted the prevalence of TKA after PRP injections (Table 3).

Annaniemi et al. retrospectively compared patients who received HA or PRP injections, with a mean follow-up of 17 months after PRP injections. The groups were not comparable at baseline: as compared with the HA group, the PRP group was younger, the prevalence of comorbidities and diabetes was lower and the prevalence of obesity was higher. During follow-up, 5 patients in the PRP group and 31 in the HA group underwent TKA (p < 0.001) [60].

The study of Sanchez et al. was an observational retrospective cohort of patients receiving PRP injections, with no control group. The median time from IA PRP injection to TKA was 4.1 years (range 0.3–14.7) for 186 patients [54].

### 4. Discussion

This study aimed to determine whether IA HA or PRP injections may delay the requirement for TKA for patients with KOA. In studies using a database, the median and mean times from diagnosis of KOA to TKA were significantly longer for patients receiving IA HA injections: TKA occurred almost 10 months later for HA than no-HA injection groups. The ES for IA HA injections from KOA declared diagnosis in the database to TKA compared to usual care was moderate (0.57) [38,50,55,57]. The pooled mean time from IA HA injection to TKA was 14.3 ± 11.1 months [43–45,50,59]. For this analysis, only one study had a control group. For PRP injections, only one study described a median time from PRP injection to TKA of 4.1 years (range 0.3–14.7) but without any comparator [54].

The time from IA HA injection to TKA may be considered “earned time” without TKA. Delaying TKA by 1 year seems achievable with HA injections. However, it does not necessarily reflect a structural effect of HA. Indeed, a treatment may delay TKA by reducing the pain [55,63,64]. Miller et al. showed a 20% reduction in VAS knee pain with
intra-articular sodium hyaluronate injection in most patients who chose to delay TKA [47]. HA could allow for modulating the time for the TKA decision according to the patient’s needs, for example, to manage a comorbidity that may interfere with the surgery, to lose body mass, to start a muscular strengthening program against sarcopenia or to align with the personal will.

Delaying a TKA is cost-effective. Ong et al. followed patients for 2 years after KOA diagnosis according to the database and calculated healthcare costs. In all, 96.8% of patients did not undergo TKA, but 69% of the healthcare costs were attributed to surgical care in the United States. The total savings for patients who received IA HA injections and did not undergo TKA would have been up to US 1.84 billion dollars [41]. In another study, HA injections represented only a small fraction (3%) of the overall costs [65].

These results should be interpreted with caution because the common slow evolution of KOA can lead to repeated HA injections. In other words, the more patients want to delay surgery, the more they are prompted to receive multiple IA HA courses, even if the reduction in pain may not be sufficient as compared with what early TKA would achieve. The increased time from declared diagnosis of KOA to TKA observed for patients receiving IA HA injections might thus reflect not only a pharmacological effect of HA, but also the preferences of patients and/or physicians.

Among limitations, few publications reported confounding factors that could modify time to TKA, such as KOA severity, psycho-social context and comorbidities. The CCI did not differ in the study of Delbarre et al. [55]. In the study of Altman et al., it was significantly lower but not clinically relevant in the HA group compared to the control group (0.6 vs. 0.7, p < 0.001). In another study, the prevalences of a comorbidity were 61.6% and 33% in the HA and PRP groups, but both types of injections may be used to avoid TKA in patients with comorbidities, and the study had no group of patients without HA or PRP injections [60]. The other studies had no data on comorbidities or no group without any injection. These may be factors of the surgical decision as absolute or relative contraindications that may delay the surgical procedure. It could constitute a bias of indication for IA injections in the studies. In addition, the CCI does not include BMI or body mass, which are important factors to consider for TKA indication. Risk of surgical revision increases with BMI [66]: with BMI > 30 kg/m², surgical complications increase 3% [67]. In the meta-analysis, unfortunately only a few studies mentioned BMI.

Second, the results were heterogeneous, reflecting the lack of consensus in the use of IA HA injections and practices among countries. For example, studies included patients with different clinical or structural disease severity (different VAS pain, KL stage, function score). The onset of KOA symptoms or KOA diagnosis (especially based on codes) is not necessarily the disease onset. However, the research was exhaustive by including all articles reporting a delay to TKA. There is also a lack of data for statistical analyses. Results of some studies were not pooled in the meta-analysis because the results overlapped with those of other studies in that they used the same database [39,50], or because the studies lacked quantitative data (number of patients, mean delay, SD, control group, data on TKA, etc.). However, the data available were used maximally for the analyses, and authors of selected studies were contacted (without success) to obtain supplementary data. Despite a growing interest in PRP injection use in OA, data on PRP injection and the TKA requirement remain scarce. Another limitation is the possible publication bias, which could not be analyzed by a funnel plot.

Despite these limitations, the study has several strengths. This is the first meta-analysis on the effect of IA HA or PRP injection on time to TKA. The research has been exhaustive and included good-quality studies (mean STROBE score 63%) with more than 2,820,000 patients. All possible time outcomes (mean delay, prevalence) and all possible time points (from KOA diagnosis in the database and from IA injection to TKA) were evaluated to fully exploit the data. The main outcome is original.

In conclusion, the results suggest that IA HA injections are associated with a 10-month delay in TKA in KOA. Causality cannot be concluded because of confounding factors and
indication bias. Data were insufficient to conclude on any effect of PRP injections on TKA delay. Further research is needed to address this critical issue in the management of KOA.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11143985/s1. Table S1: Characteristics of injection products and control care for knee osteoarthritis.

Author Contributions: Conceptualization, S.B., J.S. and K.L.; methodology, S.B. and K.L.; software, S.B.; validation, S.B., J.S. and K.L.; formal analysis, S.B. and K.L.; investigation, S.B. and K.L.; resources, (embase, pubmed), S.B. and (Khoala cohort), A.L.; data curation, S.B. and K.L.; writing—original draft preparation, S.B. and K.L.; writing—review and editing, S.B., A.C., F.E., A.L., P.R., F.B., J.S. and K.L.; visualization, S.B., A.C., F.E., A.L., P.R., F.B., J.S. and K.L.; supervision, J.S. and K.L.; project administration, S.B., J.S. and K.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data may be obtained upon request to corresponding author.

Acknowledgments: The authors thank Francis Guillemin and the KHOALA Study group for providing the data from the KHOALA cohort.

Conflicts of Interest: Berkani, Courties and Louati have no relevant financial or non-financial interests to disclose. Eymard reports personal fees and non-financial support from RegenLab and personal fees from Pfizer outside the submitted work. Latourte reports personal fees from Pfizer, Aryslab and Medac outside the submitted work. Richette reports personal fees from Expanscience, Pierre Fabre, Ferring, Sanofi and Genevieve. Berenbaum reports other support from 4MOVING BIOTECH and personal fees from 4P PHARMA, during the writing of this study; personal fees from Boehringer, Bone Therapeutics, CellProthera, Expanscience, Galapagos, Gilead, GSK, Lilly, Merck Sereno, MSD, Nordic, Novartis, Pfizer, Regulaxis, Roche, Sandoz, Sanofi, Servier, UCB and Peptinov, and grants from TRB Cheledica outside the submitted work. In addition, Berenbaum has a patent WO2020104833A1 (co-inventors: R Rattenbach and Francis Berenbaum): Composition and methods for regulating chondrocyte proliferation and increasing of cartilage matrix production issued. Sellam reports grants and personal fees from Pfizer, grants and personal fees from MSD, and personal fees from Fresenius Kabi, Novartis, Janssen, Roche, Galapagos and Sanofi outside the submitted work.

References

1. Swain, S.; Sarmanova, A.; Coupland, C.; Doherty, M.; Zhang, W. Comorbidities in Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies. Arthritis Care Res. 2020, 72, 991–1000. [CrossRef] [PubMed]
2. Louati, K.; Vidal, C.; Berenbaum, F.; Sellam, J. Association between diabetes mellitus and osteoarthritis: Systematic literature review and meta-analysis. RMD Open 2015, 1, e000077. [CrossRef] [PubMed]
3. Baudart, P.; Louati, K.; Marcelli, C.; Berenbaum, F.; Sellam, J. Association between osteoarthritis and dyslipidaemia: A systematic literature review and meta-analysis. RMD Open 2017, 3, e000442. [CrossRef] [PubMed]
4. Nüesch, E.; Dieppe, P.; Reichenbach, S.; Williams, S.; Hf, S.; Jüni, P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: Population based cohort study. BMJ 2011, 342, d1165. [CrossRef]
5. The Burden of Musculoskeletal Diseases in the United States. Available online: https://www.boneandjointburden.org/ (accessed on 19 July 2020).
6. Ornetti, P.; Fortunet, C.; Morisset, C.; Gremeaux, V.; Maillere, J.; Casillas, J.; Laroche, D. Clinical effectiveness and safety of a distraction-rotation knee brace for medial knee osteoarthritis. Ann. Phys. Rehabil. Med. 2015, 58, 20–313. [CrossRef]
7. Zeng, C.-Y.; Zhang, Z.-R.; Tang, Z.-M.; Hua, F.-Z. Benefits and Mechanisms of Exercise Training for Knee Osteoarthritis. Front. Physiol. 2021, 12, 794062. [CrossRef]
8. Sellam, J.; Courties, A.; Eymard, F.; Ferrero, S.; Latourte, A.; Ornetti, P.; Bannwarth, B.; Baumann, L.; Berenbaum, F.; Chevalier, X.; et al. Recommandations de la Société française de rhumatologie sur la prise en charge pharmacologique de la gonarthrose. Rev. Rhum. 2020, 87, 439–446. [CrossRef]
9. Kolasinski, S.L.; Kolasinski, S.L.; Neogi, T.; Neogi, T.; Hochberg, M.C.; Hochberg, M.C.; Oatis, C.; Oatis, C.; Guyatt, G.; Guyatt, G.; et al. 2019 American College of Rheumatology / Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res. 2020, 72, 149–162. [CrossRef]
10. Richette, P. Hyaluronic acid: Still useful in knee osteoarthritis? *J. Bone Spine* **2017**, *84*, 655–656. [CrossRef]

11. Bannuru, R.R.; Osani, M.C.; Vaysbrot, E.E.; Arden, N.K.; Bennell, K.; Bierma-Zeinstra, S.M.A.; Kraus, V.B.; Lohmander, L.S.; Abbott, J.H.; Bhandari, M.; et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr. Cartil.* **2019**, *27*, 1578–1589. [CrossRef]

12. Brophy, R.H.; Fillingham, Y.A. A AOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. *J. Am. Acad. Orthop. Surg.* **2022**, *30*, e721–e729. [PubMed]

13. Pozo, M.A.; Balazs, E.A.; Belmonte, C. Reduction of sensory responses to passive movements of inflamed knee joints by hylan, a hyaluronan derivative. *Exp. Brain Res.* **1997**, *116*, 3–9. [CrossRef] [PubMed]

14. Smith, M.M.; Ghosh, P. The synthesis of hyaluronic acid by human synovial fibroblasts is influenced by the nature of the hyaluronate in the extracellular environment. *Rheumatol. Int.* **1987**, *7*, 113–122. [CrossRef] [PubMed]

15. Yatabe, T.; Mochizuki, S.; Takizawa, M.; Chijiwa, M.; Okada, A.; Kimura, T.; Fujita, Y.; Matsumoto, H.; Toyama, Y.; Okada, Y. Hyaluronan inhibits expression of ADAMTS4 (aggrecanase-1) in human osteoarthritic chondrocytes. *Ann. Rheum. Dis.* **2009**, *68*, 1051–1058. [CrossRef]

16. Listrat, V.; Ayral, X.; Patarnello, F.; Bonvarlet, J.-P.; Simonnet, J.; Amor, B.; Dougados, M. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan®) in osteoarthritis of the knee. *Osteoarthr. Cartil.* **1997**, *5*, 153–160. [CrossRef]

17. Pham, T.; Le Henaff, A.; Ravaud, P.; Dieppe, P.; Paolozzi, L.; Dougados, M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NDR101, in comparison with diclofenac and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. *Ann. Rheum. Dis.* **2004**, *63*, 1611–1617. [CrossRef]

18. Wang, Y.; Hall, S.; Hanna, F.; Wuka, E.A.; Grant, G.; Marks, P.; Feletar, M.; Cicuttini, F.M. Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: A two-year single-blind clinical trial. *BMJ Musculoskelet. Disord.* **2011**, *12*, 195. [CrossRef]

19. Eymard, F.; Ornetti, P.; Maillet, J.; Noel, É.; Adam, P.; Legré-Boyer, V.; Boyer, T.; Allali, F.; Gremeaux, V.; Kaux, J.-F.; et al. Intra-articular injections of platelet-rich plasma in symptomatic knee osteoarthritis: A consensus statement from French-speaking experts. *Knee Surg. Sports Traumatol. Arthrosc.* **2020**, *29*, 3195–3210. [CrossRef]

20. Andia, I.; Maffulli, N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat. Rev. Rheumatol.* **2013**, *9*, 721–730. [CrossRef]

21. Patel, S.; Dhillon, M.S.; Aggarwal, S.; Marwaha, N.; Jain, A. Treatment with Platelet-Rich Plasma Is More Effective than Placebo for Knee Osteoarthritis. *Am. J. Sports Med.* **2013**, *41*, 356–364. [CrossRef]

22. Smith, P.A. Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis. *Am. J. Sports Med.* **2016**, *44*, 884–891. [CrossRef] [PubMed]

23. Bennell, K.L.; Paterson, K.L.; Metcalf, B.R.; Duong, V.; Eyles, J.; Kasza, J.; Wang, Y.; Cicuttini, F.; Buchbinder, R.; Forbes, A.; et al. Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients with Knee Osteoarthritis. *JAMA J. Am. Med. Assoc.* **2021**, *326*, 2021–2030. [CrossRef] [PubMed]

24. Fice, M.P.; Miller, J.; Christian, R.; Hannon, C.P.; Smyth, N.; Murawski, C.D.; Cole, B.J.; Kennedy, J.G. The Role of Platelet-Rich Plasma in Cartilage Pathology: An Updated Systematic Review of the Basic Science Evidence. *Arthrosc. J. Arthrosc. Relat. Surg.* **2019**, *35*, 961–976.e3. [CrossRef]

25. Ornetti, P.; Nourissat, G.; Berenbaum, F.; Sellam, J.; Richette, P.; Chevalier, X. Does platelet-rich plasma have a role in the treatment of osteoarthritis? *Jt. Bone Spine* **2016**, *83*, 31–36. [PubMed]

26. Fuggle, N.R.; Cooper, C.; Oreffo, R.O.C.; Price, A.J.; Kaux, J.F.; Maheu, E.; Cutolo, M.; Honvo, G.; Conaghan, P.G.; Berenbaum, F.; et al. Alternative and complementary therapies in osteoarthritis and cartilage repair. *Aging* **2020**, *32*, 547–560. [CrossRef] [PubMed]

27. Beswick, A.D.; Wylie, V.; Gooberman-Hill, R.; Blom, A.; Dieppe, P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis: A systematic review of prospective studies in unselected patients. *BMJ Open* **2012**, *2*, e000435. [CrossRef] [PubMed]

28. Kim, Y.; Levin, G.; Nikolov, N.P.; Abugov, R.; Rothwell, R. Concept End Points Informing Design Considerations for Confirmatory Clinical Trials in Osteoarthritis. *Arthritis Care Res.* **2020**, *74*, 1154–1162. [CrossRef]

29. McAlindon, T.; Driban, J.; Henrotin, Y.; Hunter, D.; Jiang, G.-L.; Skou, S.; Wang, S.; Schnitzer, T. OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthr. Cartil.* **2015**, *23*, 747–760. [CrossRef]

30. Dougados, M.; Nguyen, M.; Listrat, V.; Amor, B. High molecular weight sodium hyaluronate (hyalactin) in osteoarthritis of the knee: A 1 year placebo-controlled trial. *Osteoarthr. Cartil.* **1993**, *1*, 97–103. [CrossRef]

31. Cochrane Handbook for Systematic Reviews of Interventions. Available online: https://training.cochrane.org/handbook/current (accessed on 1 June 2020).

32. PRISMA. Available online: http://prisma-statement.org/PRISMAStatement/Checklist (accessed on 3 February 2022).

33. Guillemin, F.; Rat, A.-C.; Roux, C.H.; Fautrel, B.; Mazieres, B.; Chevalier, X.; Euler-Ziegler, L.; Fardellone, P.; Verrouil, E.; Morvan, J.; et al. The KOHAAL cohort of knee and hip osteoarthritis in France. *J. Bone Spine* **2012**, *79*, 597–603. [CrossRef]

34. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J. Clin. Epidemiol.* **2008**, *61*, 344–349. [CrossRef] [PubMed]
35. Benchimol, E.I.; Smeeth, L.; Gottmann, A.; Harron, K.; Moher, D.; Petersen, I.; Sørensen, H.T.; von Elm, E.; Langan, S.M. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med.* 2015, 12, e1001885. [CrossRef] [PubMed]

36. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed.; Lawrence Erlbaum Associates: Hillsdale, NJ, USA, 1988; ISBN 978-0-8058-0283-2.

37. Altman, R.; Fredericson, M.; Bhattacharyya, S.K.; Bisson, B.; Abbott, T.; Yadalam, S.; Kim, M. Association between Hyaluronic Acid Injections and Time-to-Total Knee Replacement Surgery. *J. Knee Surg.* 2016, 29, 564–570. [CrossRef] [PubMed]

38. Altman, R.D.; Lim, S.; Steen, R.G.; Dasa, V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database. *PLoS ONE* 2015, 10, e0145776. [CrossRef] [PubMed]

39. Ong, K.L.; Anderson, A.F.; Niazi, F.; Fierlinger, A.L.; Kurtz, S.M.; Altman, R.D. Hyaluronic Acid Injections in Medicare Knee Osteoarthritis Patients Are Associated with Longer Time to Knee Arthroplasty. *J. Arthroplast.* 2016, 31, 1667–1673. [CrossRef]

40. Ong, K.L.; Runa, M.; Lau, E.; Altman, R. Is Intra-Articular Injection of Synvisc Associated with a Delay to Knee Arthroplasty in Patients with Knee Osteoarthritis? *Cartilage* 2018, 10, 423–431. [CrossRef] [PubMed]

41. Ong, K.L.; Runa, M.; Lau, E.; Altman, R.D. Cost-of-illness of knee osteoarthritis: Potential cost savings by not undergoing arthroplasty with the first 2 years. *Clin. Outcomes Res.* 2019, 11, 245–255. [CrossRef]

42. Etter, K.; Chitnis, A.S.; Holy, E.C.; Gray, F.S.; Manalac, F.J.; Bisson, B.; Bhattacharyya, S.K. High-concentration nonavian high-molecular weight hyaluronic injections and time-to-total knee replacement surgery. *J. Comp. Eff. Res.* 2020, 9, 795–805. [CrossRef]

43. Dasa, V.; Lim, S.; Heeckt, P. Real-World Evidence for Safety and Effectiveness of Repeated Courses of Hyaluronic Acid Injections on the Time to Knee Replacement Surgery. *Am. J. Orthop.* 2018, 47, 58. [CrossRef]

44. Joseph, B.; Waddell, D.D. Delayed Total Knee Replacement with Hylan G-F 20. *J. Knee Surg.* 2014, 29, 159–168. [CrossRef]

45. Bowman, E.N.; Hallock, J.D.; Throckmorton, T.W.; Azar, F.M. Hyaluronic acid injections for osteoarthritis of the knee: Predictors of successful treatment. *Int. Orthop.* 2018, 42, 733–740. [CrossRef] [PubMed]

46. Lundstrom, Z.T.; Sjytma, T.T.; Greenlund, L.S. Rethinking Viscosupplementation: Ultrasound- Versus Landmark-Guided Injection for Knee Osteoarthritis. *J. Ultrasonar Med.* 2020, 39, 113–117. [CrossRef] [PubMed]

47. Miller, E.L.; Sloniewsky, M.J.; Gibbons, E.T.; Johnston, J.G.; Vosler, K.D.; Nasir, S. Long-term clinical benefit and cost-effectiveness of an 8-week multimodal osteoarthritis management program incorporating intra-articular sodium hyaluronate (Hyalgan®) injections. *J. Pain Res.* 2017, 10, 1045–1054. [CrossRef] [PubMed]

48. Anand, A.; Balduini, F.; Rogers, K. Hyaluronic acid in management of advanced osteoarthritis of the knee: Retrospective analysis. *Eur. J. Orthop. Surg. Traumatol.* 2010, 20, 645–649. [CrossRef]

49. Barrett, J.P.; Siviero, P.; Barrett, J.P. Retrospective Study of Outcomes in Hylan®-Treated Patients with Osteoarthritis of the Knee. *Clin. Drug Investig.* 2002, 22, 87–97. [CrossRef]

50. Malanga, G.; Niazi, F.; Kidd, V.D.; Lau, E.; Kurtz, S.M.; Ong, K.L.; Concoff, A.L. Knee Osteoarthritis Treatment Costs in the Medicare Patient Population. *Am. Health Drug Benefits* 2020, 222–226. [CrossRef] [PubMed]

51. Ong, K.L.; Runa, M.; Lau, E.; Altman, R. Is Intra-Articular Injection of Synvisc Associated with a Delay to Knee Arthroplasty in Patients with Knee Osteoarthritis? *Cartilage* 2018, 10, 423–431. [CrossRef] [PubMed]

52. Evanich, J.D.; Evanich, C.J.; Wright, M.B.; Rydlewicz, J.A. Efficacy of Intraarticular Hyaluronic Acid Injections in Knee Osteoarthritis Patients—A Cox model analysis. *PLoS ONE* 2017, 12, e0187227. [CrossRef] [PubMed]

53. Jurado, M.R.; Fidalgo, A.E.; Villar, V.R.; Medina, J.M.; López, B.S. Factores que influyen sobre el tiempo hasta la necesidad de intervenir a un paciente en la lista de espera para prótesis de rodilla. *Reumatol. Clin.* 2013, 9, 148–155. [CrossRef]

54. Sánchez, M.; Torquera, C.; Sánchez, P.; Beitia, M.; García-Cano, B.; Guadilla, J.; Delgado, D. Platelet-rich plasma injections delay the need for knee arthroplasty: A retrospective study and survival analysis. *Int. Orthop.* 2020, 45, 401–410. [CrossRef]

55. Delbarre, A.; Amor, B.; Bardoulat, I.; Tetafort, A.; Pelletier-Fleury, N. Do intra-articular hyaluronic acid injections delay total knee replacement in patients with osteoarthritis—A Cox model analysis. *PLoS ONE* 2017, 12, e0187227. [CrossRef] [PubMed]

56. Mazieres, B.; Bard, H.; Ligier, M.; Bru, L; D’Orsay, G.G.; Le Pen, C. Medicoeconomic evaluation of hyaluronic acid for knee osteoarthritis in everyday practice: The MESSAGE study. *It. Bone Spine* 2007, 74, 453–460. [CrossRef] [PubMed]

57. Latourte, A.; Rat, A.; Omorou, A.; Ngueyom-Sime, W.; Eymard, F.; Sellam, J.; Roux, C.; Ea, H.; Cohen-Solal, M.; Bardin, T.; et al. Do Glucocorticoid Injections Increase the Risk of Knee Osteoarthritis Progression Over 5 Years? *Arthritis Rheumatol.* 2022; ahead of print. [CrossRef]

58. Korkmaz, M.; Erdogan, Y.; Okur, A.; Göçmen, A.Y.; Güneydinc, I. Comparison of the Effects of Intraarticular Hyaluronic Acid and AntiInflammatory Drug Treatments on the Surgical Intervention Rates in Patients with Gonarthritis. *Turk. J. Med. Sci.* 2013, 43, 222–226. [CrossRef]

59. Turajane, T.; Amphansap, T.; Labpiboonpong, V.; Maungsiri, S. Total knee replacement following repeated cycles of intra-articular sodium hyaluronate (500-730 Kda) in failed conservative treatment of knee osteoarthritis: A 54-month follow-up. *J. Med. Assoc. Thail.* 2009, 92, S63–S68.

60. Annanieri, J.A.; Pere, J.; Giordano, S. Platelet-rich plasma versus hyaluronic acid injections for knee osteoarthritis: A propensity-score analysis. *Scand. J. Surg.* 2018, 108, 329–337. [CrossRef]
61. Campbell, D.; Angel, K.R.; Dobson, P.J.; Lewis, P.; Tandon, S. Experiences of viscosupplementation for knee osteoarthritis. *Aust. Fam. Physician* 2004, 33, 863–864.

62. Whitman, C.S.; Allen, D.; Comadoll, J.L.; Thomason, H.C.; Oweida, S.D. A Retrospective Study of SUPARTZ® and Repeat Treatment for Osteoarthritis Pain in the Knee. *J. Manag. Care Med.* 2010, 13, 43–47.

63. McHugh, G.A.; Luker, K.A. Influences on individuals with osteoarthritis in deciding to undergo a hip or knee joint replacement: A qualitative study. *Disabil. Rehabil.* 2009, 31, 1257–1266. [CrossRef]

64. Tang, A.; Almetwali, O.; Zak, S.G.; Bernstein, J.A.; Schwarzkopf, R.; Aggarwal, V.K. Do preoperative intra-articular corticosteroid and hyaluronic acid injections affect time to total joint arthroplasty? *J. Clin. Orthop. Trauma* 2020, 16, 49–57. [CrossRef]

65. Ong, K.L.; Niazi, F.; Lau, E.; Mont, M.A.; Concoff, A.; Shaw, P.; Kurtz, S.M. Knee OA cost comparison for hyaluronic acid and knee arthroplasty. *J. Orthop. Surg. Res.* 2020, 15, 305. [CrossRef] [PubMed]

66. Electricwala, A.J.; Jethanandani, R.G.; Narkbunnam, R.; Huddleston, J.I.; Maloney, W.J.; Goodman, S.B.; Amanatullah, D.F. Elevated Body Mass Index Is Associated with Early Total Knee Revision for Infection. *J. Arthroplast.* 2017, 32, 252–255. [CrossRef] [PubMed]

67. Ward, D.T.; Metz, L.N.; Horst, P.K.; Kim, H.T.; Kuo, A.C. Complications of Morbid Obesity in Total Joint Arthroplasty: Risk Stratification Based on BMI. *J. Arthroplast.* 2015, 30, 42–46. [CrossRef] [PubMed]