applied sciences

MDPI

Review

Potential New Treatments for Knee OA: A Prospective Review of Registered Trials

Marius Ioniţescu [1], Dinu Vermeşan [1], Bogdan Andor [1,*], Cristian Dumitrascu [2], Musab Al-Qatawneh [1], Vlad Bloanca [2], Andrei Dumitrascu [3] and Radu Prejbeanu [1]

[1] Department of Orthopedics, "Victor Babes" University of Medicine and Pharmacy of Timisoara, Eftimie Murgu Square No 2, 300041 Timisoara, Romania; mariusionitescu@gmail.com (M.I.); dinu@vermesan.ro (D.V.); msb898@gmail.com (M.A.-Q.); raduprejbeanu@gmail.com (R.P.)
[2] Department of Plastic Surgery, "Victor Babes" University of Medicine and Pharmacy of Timisoara, Eftimie Murgu Square No 2, 300041 Timisoara, Romania; d.victorcristian@yahoo.com (C.D.); vlad.bloanca@gmail.com (V.B.)
[3] Faculty of Medicine, "Victor Babes" University of Medicine and Pharmacy of Timisoara, Eftimie Murgu Square No 2, 300041 Timisoara, Romania; andrei.dumitrascu@student.umft.ro
* Correspondence: andor.bogdan@umft.ro

Abstract: We aimed to evaluate potential new treatments for knee osteoarthritis (OA). The National Institute of Health ClinicalTrials.gov database was searched for "Osteoarthritis, Knee". We found 565 ongoing interventional studies with a total planned enrollment of 111,276 subjects. Ongoing studies for knee OA represent a very small fraction of the registered clinical trials, but they are over a quarter of all knee trials and over two thirds of all OA studies. The most researched topic was arthroplasty, with aspects such as implant design changes, cementless fixation, robotic guidance, pain management, and fast track recovery. Intraarticular injections focused on cell therapies with mesenchymal stem cells sourced from adipose tissue, bone marrow, or umbilical cord. We could see the introduction of the first disease modifying drugs with an impact on knee OA, as well as new procedures such as geniculate artery embolization and geniculate nerve ablation.

Keywords: osteoarthritis; knee; arthroplasty; intraarticular injections; mesenchymal stem cells; platelet rich plasma; clinical trials; pain

Citation: Ioniţescu, M.; Vermeşan, D.; Andor, B.; Dumitrascu, C.; Al-Qatawneh, M.; Bloanca, V.; Dumitrascu, A.; Prejbeanu, R. Potential New Treatments for Knee OA: A Prospective Review of Registered Trials. *Appl. Sci.* **2021**, *11*, 11049. https://doi.org/10.3390/app112211049

Academic Editor: Claudio Belvedere

Received: 14 October 2021
Accepted: 19 November 2021
Published: 22 November 2021

1. Introduction

Osteoarthritis (OA) is the end stage degeneration of synovial joints and the knee is the most common location, with a high prevalence especially in the elderly [1]. The pooled global prevalence of knee OA is thought to be 22.9% in individuals over 40 years old and it is higher in females than males [1,2]. Over 1 million joint replacements are performed each year in the Unites States of America (USA) alone, and the predictions are that this will continue to increase [1,2].

The pathogenesis involves a complex interplay between genetics, trauma, and inflammation but it is not fully understood [1,3–6]. OA affects the entire joint. Cartilage degradation starts before it is macroscopically evident and progresses until it is completely lost. The subchondral bone remodels and forms osteophytes and the synovium maintains a chronic inflammation [1,3–6]. In the OA knees, the infrapatellar fat pad has been shown to be inflamed, fibrotic, and more vascularized, and it secretes inflammatory molecules [5,6]. Symptoms begin early in the adult life and continue to aggravate. Pain is the most common reason for seeking medical advice [1,4,7]. Patients experience cartilage thinning, recurrent joint effusions aggravated by physical activity, synovial hypertrophy, degenerative meniscal tears, and bone edema [1,4,7]. These changes may only be evident initially on magnetic resonance imaging (MRI), but as they progress, they can also be observed on plain radiographs [1,4,7,8]. End stages lead to limb deformity especially in the coronal

plane (varus), incomplete extension, decreased range of motion, instability, constant pain, and serious disability [1,4,7,8].

Current treatments include lifestyle changes, physical therapy, walking aids, non steroidal anti-inflammatory drugs (NSAIDs), and intraarticular injections (IA). Surgical procedures are aimed at restoring limb alignment (high tibial osteotomy) or entirely replacing the diseased joint (arthroplasty) [3,7,9–12]. The surgical management for OA of the knee guideline was developed in 2015. It summarizes the current knowledge and is endorsed by several societies [9]. Obese patients and those with chronic pain have less improvement in outcomes with total knee arthroplasty (TKA). Patients with diabetes are at higher risk for complications after TKA [9]. Peri-articular local anesthetic infiltration, peripheral nerve blockade, decrease postoperative pain and opioid requirements. Neuraxial anesthesia may improve selected perioperative outcomes and decrease some complications [9]. Tourniquet decreases blood loss but increases short term postoperative pain. Tranexamic acid, as with virtually all major surgeries, significantly reduces blood loss [9]. There appears to be no difference in outcome, function, or complications between cruciate retaining and posterior stabilized implants, all-polyethylene or modular tibial components cemented or cementless fixation, especially on the femur, as well as patellar resurfacing. For OA predominantly of the medial compartment, unicompartmental arthroplasty has similar outcomes compared to high tibial osteotomy but more revisions versus total knee replacement [9]. Navigation and patient specific instrumentation do not improve pain, function, revisions, and perioperative complications in knee arthroplasty. Early postoperative mobilization and supervised exercise program improve pain, function, and reduce hospital length of stay [9].

The 2021 AAOS guideline for non-arthroplasty management of knee OA found moderate or strong evidence that patient education, self-management, weight loss, exercise, neuromuscular training, canes and braces, oral and topical NSAIDs and acetaminophen are adequate and efficient noninvasive treatments [10]. IA corticosteroids offer short term relief and arthroscopic partial meniscectomy has good outcomes for pain and mechanical symptoms. For IA HA there is moderate evidence against their utility but this point is debated [10].

Despite recent progress, there are no disease modifying drugs. Present therapies alleviate symptoms with variable efficacy [3,7,10–12]. Future treatments that will impact knee OA undergo several regulatory approvals before market use [3,7,10–12]. ClinicalTrials.gov is the largest clinical trials database, run by the United States National Library of Medicine at the National Institutes of Health [13].

We aimed to evaluate the potential new treatments for knee OA by performing a prospective review of currently registered trials.

2. Materials and Methods

The National Institute of Health U.S. National Library of Medicine ClinicalTrials.gov data base was searched on 23 September 2021. We found 2777 registered studies for "Osteoarthritis, Knee" (Figure 1) with the following current status:

1. Not yet recruiting 156.
2. Recruiting 377.
3. Enrolling by invitation 19.
4. Active, not recruiting 151.
5. Suspended 13.
6. Terminated 129.
7. Completed 1488.
8. Withdrawn 72.
9. Unknown status 364.

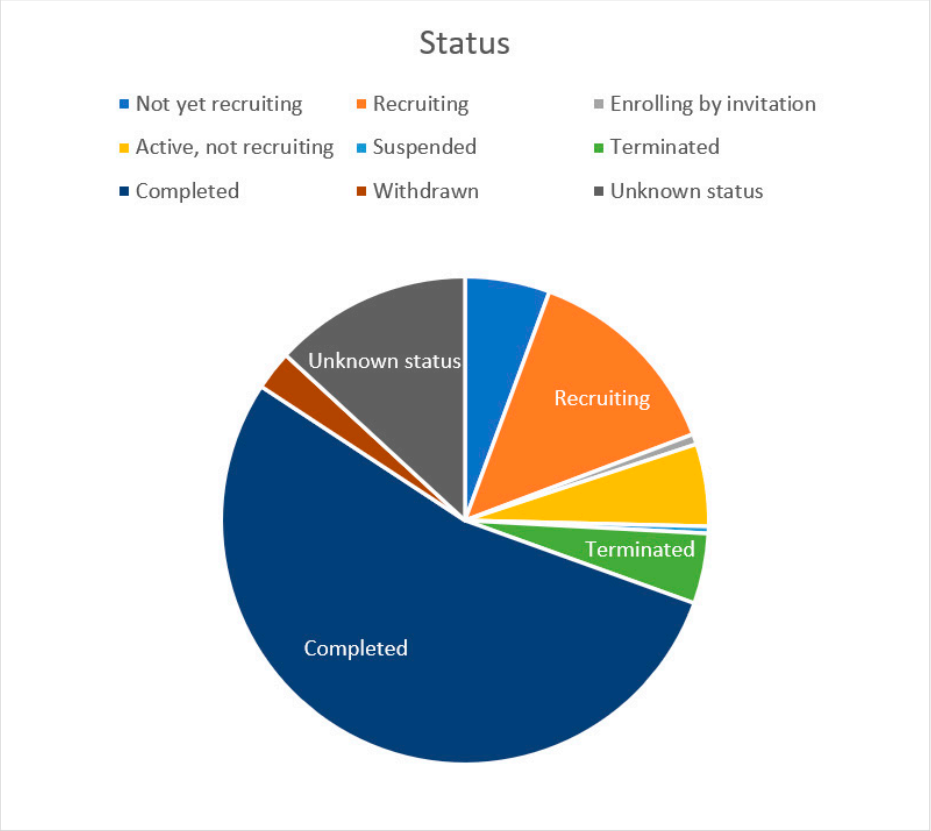

Figure 1. Status of registered studies for "Osteoarthritis, Knee".

We excluded trials that were either finished or with an uncertain status (5–9), a total of 2066. We further excluded observational studies and those that started for more than 10 years (2007–2012), a total of 146. Trials were then grouped according to the targeted clinical applicability. We followed the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist and the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) guidelines [14]. Descriptive statistics were presented using Microsoft Excel (Microsoft, Redmond, WA, USA).

3. Results

There were 565 studies with a total planned enrollment of 111,276 subjects, which represented 0.5% out of 71,280 interventional studies started on or after 1 January 2013 and listed as recruiting, not yet recruiting, active not recruiting or enrolling by invitation. For the same criteria, this was 25.6% of the 2049 knee trials and 68.1% of the 830 OA studies. Most were from USA and Western Europe, categorized by subject as (Figures 2 and 3):

- Behavioral 53.
- Biological 62.
- Combination product 6.
- Device 185.
- Diagnostic test 7.
- Dietary supplement 13.
- Drug 112.
- Other 121.
- Genetic 1.
- Procedure 95.
- No specification 26.

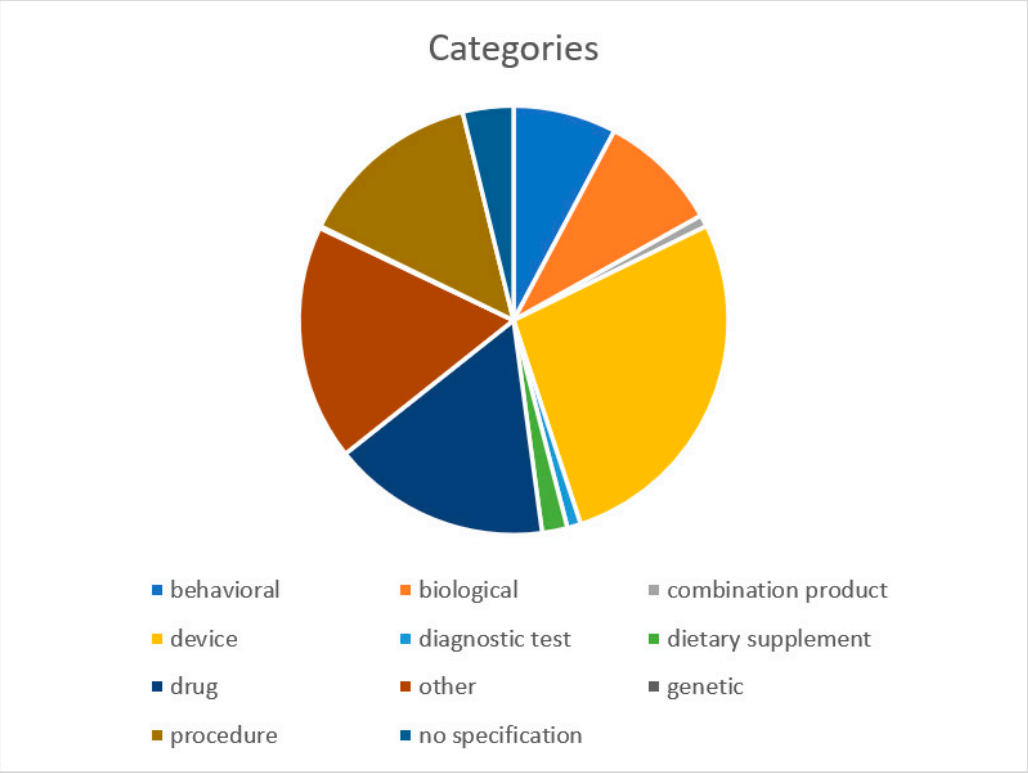

Figure 2. Interventional trials categories.

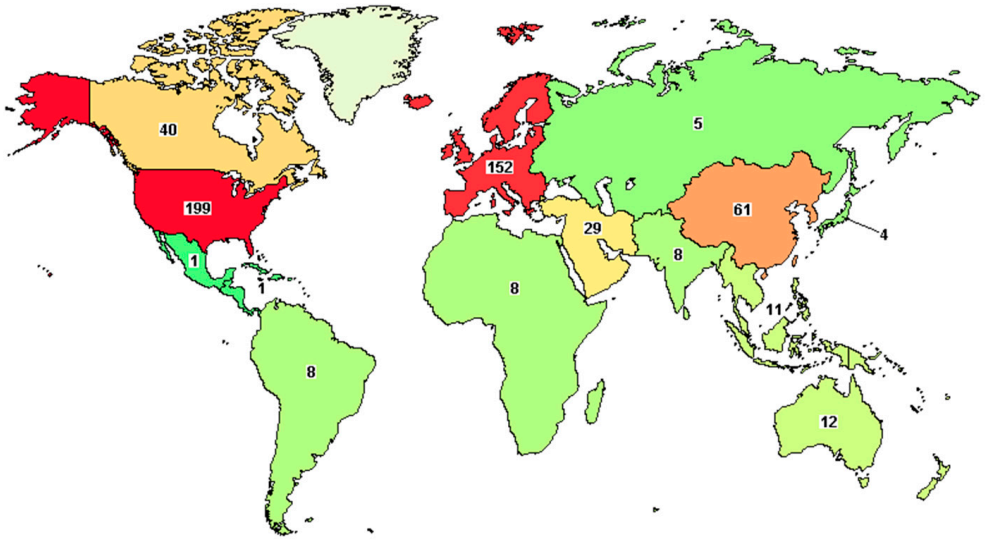

Figure 3. *Cont*.

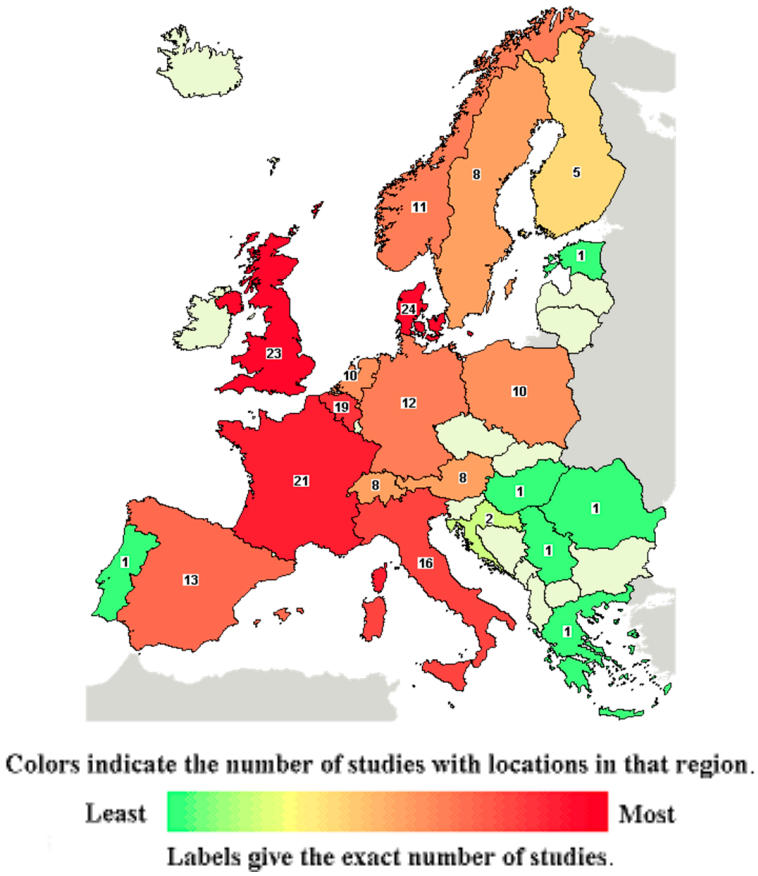

Figure 3. Geographic distribution of interventional trials (green low–red high).

The trials distribution based on starting year is presented in Figure 4. The majority of the interventional trials (75%) had a randomized allocation design (Figure 5).

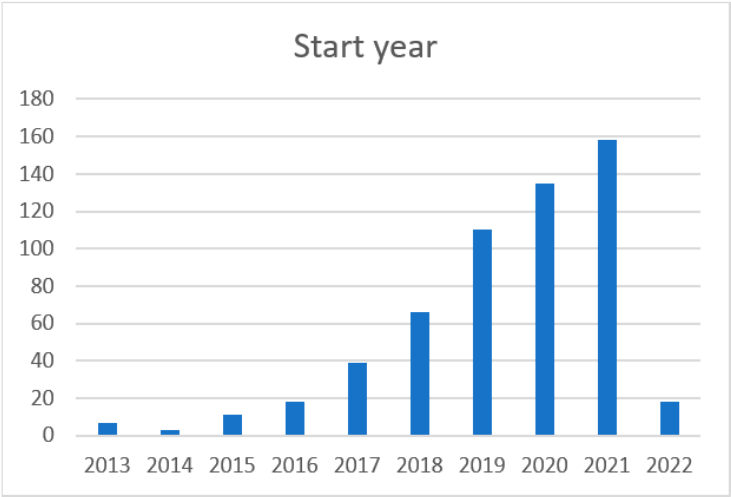

Figure 4. Starting year.

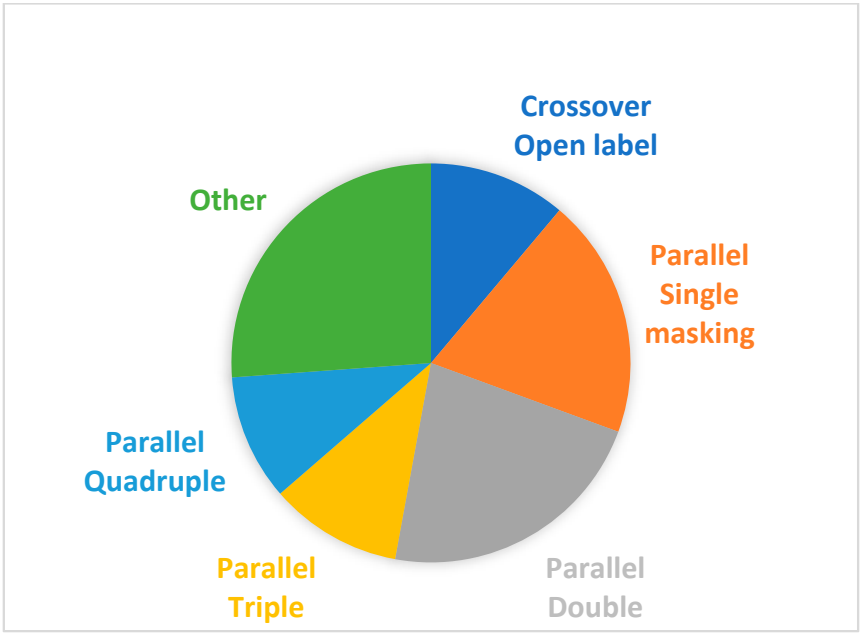

Figure 5. Study design.

Based on potential clinical applicability, the trials can be grouped in (Figure 6, Table 1, Supplemental Materials):

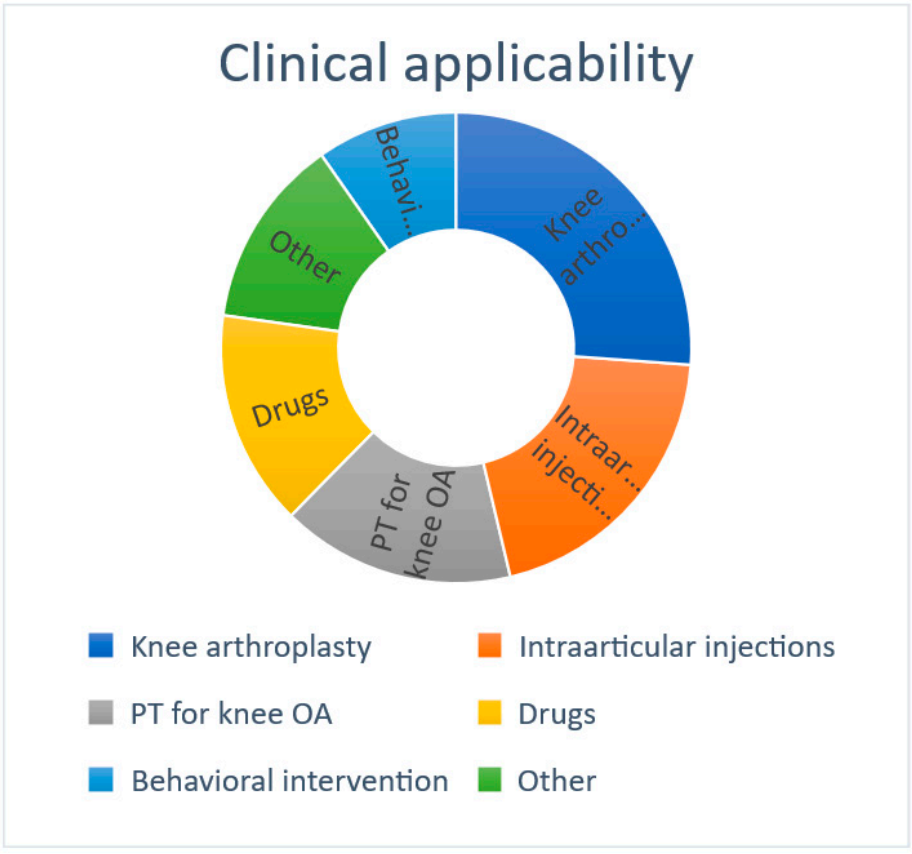

Figure 6. Clinical applicability distribution.

Table 1. Clinical trials categorized based on clinical applicability.

Clinical Applicability	Number of Studies	% of Total Analyzed	Number of Subjects
Knee arthroplasty	148	26.2	28,915
Intraarticular injections	114	20.2	15,269
Physical therapy	91	16.1	18,260
Drugs	84	14.9	18,608
Behavioral intervention	55	9.7	7804
Other	74	13.1	24,432

Knee replacement was the most investigated topic. Studies focused on new knee systems with single radius or anatomic femoral component designs, cementless fixation, robotic guidance, postoperative pain management using peripheral nerve blocks (adductor canal). or dexamethasone and outpatient rehabilitation, under the categories:

✓ 79 device.
✓ 18 drug.
✓ 45 procedure.
✓ 6 other.

Intraarticular injections were very well represented. Most trials were for cell therapies, using mesenchymal stem cells (MSCs), sourced from adipose tissue, bone marrow, or umbilical cord. Platelet rich plasma (PRP) and hyaluronic acid (HA) were much less studies, as well as several experimental products, under the following categories:

✓ 59 biological.
✓ 4 combination.
✓ 18 device.
✓ 21 drug.
✓ 9 procedure.
✓ 1 other.

Physical therapy included devices for electro stimulation and exercise regimens some performed under blood flow restriction, under the categories:

✓ 1 combination.
✓ 37 device.
✓ 51 other.
✓ 2 procedure.

Drugs. This topic had many items under investigation: Anakinra, Bone Morphogenetic Protein 7, Cathepsin K inhibitor, Fasinumab, Lorecivivint, Sprifermin, Tanezumab and several experimental products (such as adeno-associated virus carrying IL-1 receptor antagonist):

✓ 2 biological.
✓ 13 dietary supplement.
✓ 67 drug.
✓ 1 genetic.

Behavioral interventions focused on promoting healthy lifestyle and diet, cognitive behavioral education, mindfulness, and meditation:

✓ 50 behavioral.
✓ 1 device.
✓ 4 other.

Other. Some trials were difficult to classify as a group. They mainly included genicular artery embolization, genicular nerve ablation but also high tibial osteotomy, ozone therapy, spa, and footwear modifications:

- ✓ 1 biological.
- ✓ 18 device..
- ✓ 2 diagnostic test
- ✓ 3 drug.
- ✓ 26 other.
- ✓ 22 procedure.
- ✓ 2 radiation.

4. Discussion

In this review, we found that ongoing studies for knee OA represent a very small fraction of the registered clinical trials but they are over a quarter of all knee trials and over two thirds of all OA studies. The most researched topic was arthroplasty, with aspects such as minor implant design changes, a more biologic cementless fixation, robotic guidance, pain management, and fast track recovery. IA injections research focused on cell therapies with MSCs sourced from adipose tissue, bone marrow, or umbilical cord. We could see the introduction of the first disease modifying drugs with an impact on knee OA, as well as various interesting procedures such as blood flow restriction exercises, geniculate artery embolization, and geniculate nerve ablation.

4.1. Knee Replacement

In our analysis, knee arthroplasty was the most investigated topic. There were several trials investigating the differences between single and multi radius femoral component designs. Current designs have matured over many years with minor adjustments. They produce 90–95% survival at 15–20% and good clinical outcomes measured by patient reported outcomes for the majority of the patients (approximately 85%) [15–17]. The multi radius was introduced many years ago and aims to restore the natural "J" shape of the femoral condyles. In the normal knee, this functions in synergy with the femoral roll-back to offer stability, strength, and improved flexion. The single radius places the center of rotation more distal and posterior. It attempts, at least in theory, to provide more lever arm for the extensor mechanism and thus improve strength. Current evidence did not show any significant differences between these two femoral component designs regarding functional outcomes [18].

Another studied topic was the medial congruence. The natural knee has a stable medial compartment and a more mobile lateral. Some new implants attempt to replicate this by using a modified polyethylene design and studies are under way to evaluate possible benefits.

Cementless fixation lost in popularity, but in our analysis we found a renewed interest. This is probably generated by younger patients receiving knee replacements and improved implant manufacturing. Current knee arthroplasty systems use cemented fixation as golden standard. There is an ongoing debate over the superiority of cementless fixation. There are many aspects of arthroplasty which contribute towards outcomes and survival in very large cohorts such as national registries [19,20]. In theory, the roughened, porous surface of the knee implants may provide optimal bone ingrowth which in turn will produce a durable fixation. Unfortunately, early cementless implants had many issues which led to early loss of fixation and subsidence, especially on the tibia, due to poor geometry and ineffective osteoinductive surfaces [19,20]. A recent meta-analysis found no difference in revisions and function between cemented and cementless knee replacements up to 16.6-year follow-up, based on current literature [20].

Knee arthroplasty addresses pain, restores range of motion, and corrects limb deformity. The primary prosthetic implants are stabilized by the knee's envelope of ligaments and mobilized by the extensor mechanism. Accurate positioning of the implant will lead to improved function and longer survival [7,9,17]. Classic systems use anatomic guides and surgeon experience. Navigation and patient specific cutting guides were later introduced but failed to prove their utility. We now can use 3D preoperative planning, integrate it

together with intraoperative mapping of the bone contours and have the surgeons assisted by a robotic arm to make the bone cuts and establish ligamentous balance [9,17]. Several points have impaired the expansion of robotic surgery in knee arthroplasty. Robotics are at the beginning but have not significantly improved these numbers. They may improve rotational and coronal alignment but with added hassle of having the cumbersome robot in the room, maybe a technician, additional steps for referencing the robot to the patient and most importantly added costs [17,21–23].

Partial (unicondylar) knee replacements replace just the medial compartment, which is more often damaged by OA. These prostheses are less invasive to implant and produce comparable outcomes to total knee replacements in selected patients [9,17]. However, they were plagued by higher revision rates compared to total knee designs. It may be that by only partially replacing the joint through a limited approach, the positioning of the components is not optimal. This is where robotic assistance already shows fewer complications (RR: 0.52, $p = 0.036$) and lower revision rates (RR: 0.42, $p = 0.017$) [17,24]. An alternative to unicondylar knee replacement is the high tibial osteotomy. Total knee replacements are successful for advanced disease, suitable for the elderly population. For younger patients and those with mild articular destruction but aggravating pain and disfunction the current treatment options are less successful [25–27]. This leaves a significant segment of the population with serious disability and discomfort during physical activities and daily living routine.

Pain management and regional anesthesia for knee arthroplasty are an integral part of the fast-track recovery trend [9,10,17]. A combination of local infiltration analgesia (performed by the surgeon) and adductor canal peripheral nerve block (done by the anesthesiologist) reduce pain and in the early postoperative period and aid functional recovery initiation. Systemic dexamethasone and local anesthetic infiltration between popliteal artery and capsule of knee can also contribute [28].

4.2. Intraarticular Injections

IA were very well represented among the future trials. There are several benefits of IA administration: decreased systemic effects, high local concentrations, ease of access to the knee, proven placebo effect and very rare adverse events [29]. We found that most trials were for cell therapies, using MSCs. Orthobiologic products already in clinical practice include bone marrow aspirates, adipose derived stem cells and PRP (platelet rich plasma). Ideal candidates should have normal lower limb alignment and no major mechanical disturbances [30]. Nevertheless, current evidence suggests that progenitor cells relieve pain by activating mu-opioid receptors and that they have anti inflammatory properties. It is less likely that they can rebuild tissue [31].

Bone marrow aspirate is harvested from the iliac crest and concentrated by centrifugation. It contains hematopoietic stem cells which stimulate the regeneration process and promote wound healing, MSCs and endothelial progenitor cells which support vascularization. It has higher concentration of interleukin 1 receptor antagonist (IL-1ra) compared to PRP [29–34]. In the USA, bone marrow aspirate concentrate is preferred as opposed to culture-expanded MSCs because it meets the FDA (Food and drug administration) standards as a minimally manipulated autologous source MSCs [29,31]. MSCs injection obtained from bone marrow concentrate may also improve posttraumatic shoulder osteonecrosis compared to simple core decompression [31].

Adipose derived products use micro fragmented adipose tissue, stromal vascular fraction, and cultured adipose derived stem cells. The rationale for using adipose tissue is mainly that it contains up to 500 MSCs per milliliter than bone marrow concentrate [29,31]. Adipose autograft is harvested in the operating room or less commonly in the office from the abdomen using a large syringe. Micronized fat only minimally manipulates the tissues and thus does not separate cells from clusters [29,32]. It is currently the only FDA approved adipose tissue therapy. A step further is syringe emulsification which uses pressure and a dense mesh filter. Adipose tissue derived MSCs and stromal vascular fraction improve WOMAC (Western Ontario and McMaster Universities Arthritic Index) scores, reduce

pain and improve function in old adults with symptomatic knee OA [33]. Gobbi et al. administered a single injection of autologous microfragmented adipose tissue to 120 knees (75 patients) with a mean age of 69.6 years, BMI 28.4 and Kellgren Lawrence grades 2 to 4. They found grade 2 disease had the best results in KOOS—Pain up to 24 months. Functional and quality of life success was seen in 88.3%, (66 patients) at all follow-up time points [34].

Umbilical cord products are harvested at birth and saved as potential adjuvants for future disease such as cancer. It is a highly valuable source of stem cells in general, also known as Wharton Jelly MSCs [3,7,10,11,29]. There is currently very little data available, but many clinical trials are under way. Umbilical cord MSCs have shown WOMAC improvements up to 1 year in patients with diffuse knee pain due to OA. The effect was superior to HA [35]. For patients receiving high tibial osteotomy, the intraarticular addition of bone marrow aspirate concentrate or human umbilical cord blood-derived MSCs provided similar, outcomes in terms of pain relief, functional scores, and quality of life at a mean follow-up of 33 months [36].

PRP is obtained by collecting peripheral blood and processing it by centrifugation (usually 5 min at 1500 rpm). It contains platelets, growth factors, white blood cells, and red blood cells [3,7,10,11,29,37]. Growth factors which promote cartilage healing are transforming growth factor (TGFB-1), insulin like growth factor (IGF-1), fibroblast growth factor (bFGF), and bone morphogenic proteins (BMP-2). Those which deter are, among others, vascular epithelial growth factor (VEGF), insulin like growth factor binding protein (IGFBP-2 and 3), platelet derived growth factor PDGF-AA, AB, and BB, and endothelial growth factor (EGF) [3,7,10,11,29,37]. PRPs can be leucocyte rich (pro inflammatory, used for tendinitis) or poor (anti-inflammatory) which have better results in OA with an inflammatory component (morning stiffness, effusion with physical activity) [3,7,10,11,29,37]. Currently there are many products on the market, all of which differ regarding centrifugation parameters, platelet and white cells count, and growth factor concentration. The efficacy of PRP remains controversial. The major issues are come from the experimental methods, confusing nomenclature, non standardized preparation methods and lack of in-depth understanding of mechanisms of action [37].

Treatment of knee OA with PRP may improve clinical outcomes when compared with HA. HA is a component of normal synovial fluid. In knee OA patients, it contributes to viscosuplementation and pain relief. In our analysis of prospective studies, HA research was much less represented [38].

4.3. Physical Therapy

We found ongoing studies on blood flow restriction exercises as well as devices such as electro stimulation and smart phone applications [39]. People with knee OA have quadriceps atrophy. Regaining strength and endurance improves function and pain but is many times difficult because joint damage impedes adequate physical training. Blood flow restriction exercises are performed using restrictive straps or cuffs similar to Tourniquets on the proximal thigh [40]. These are used to partially restrict arterial inflow and completely block venous return. It is unclear what mechanism is triggered by this hypoxic environment. It may induce quadriceps angiogenesis and hypertrophy. The benefit is that increased strength and exercise tolerance are obtained more efficiently and with less joint stress compared to regular exercise [40,41]. Electrical stimulation can also be added. Efficient neuromuscular electrical stimulation protocols use a frequency between 50 and 75 Hz, a pulse duration between 200 and 400 μs and a treatment duration of at least 20 min [41].

4.4. Drugs

Disease modifying drugs are currently lacking. The present knowledge on OA pathophysiology is growing and has created new possibilities for potential therapeutic targets currently being investigated in randomized controlled trials [3,7,10–12]. Emerging solutions target matrix-degrading proteases, cartilage metabolism, bone remodeling, inflamma-

tion and Wnt signaling. Furthermore, nerve growth factor inhibitors could address OA pain [11,12,42].

Inhibition of specific cytokines may slow OA progression. Anakinra inhibits IL-1 had encouraging results in animal models and is currently investigated on humans [3,7,10–12,42]. Bone Morphogenetic Protein 7 is a growth factor which also has an anabolic effect on cartilage. Cathepsin K inhibitor slows down bone degradation [3,7,10–12,42]. Lorecivivint modulates Wnt signaling which induces cartilage breakdown and osteophyte formation. Preclinical development produced encouraging results of chondrocyte regeneration, cartilage protection, anti-inflammatory activity and improved joint health. It could be a first disease modifying agent for OA [11,42]. IA Sprifermin (Human-Recombinant Fibroblast Growth Factor 18) may support chondrocyte proliferation, collagen expression and matrix production. It is currently investigated for IA injection [11,42]. Monoclonal antibodies have improved receptor selectivity and are already being used in several diseases. Subcutaneous Tanezumab and Fasinumab have shown improvements in pain and patient reported outcomes in patients with knee OA. Gene therapy includes IA administration of adeno-associated virus carrying IL-1 receptor antagonist [3,11,42].

4.5. Behavioral Interventions

These aim to reshape the patients' lifestyle by using aerobic exercise, pain education, dietary changes, gait retraining, and meditation. An integral part is cognitive behavioral therapy, an intervention which addresses pain, depression, and insomnia. It targets specific individual needs to encourage social engagement and reduce chronic fatigue and pain catastrophizing [43].

4.6. Other

Genicular artery embolization is a novel strategy for addressing knee OA pain. The inflammatory component in the pathogenesis is associated with increased angiogenesis [44]. Small vessels can be temporarily or permanently obliterated by interventional radiology embolization. Several embolic particles can be used, and the palliative procedure appears safe and efficient as measured by patient reported outcome scores [44].

Nerve ablation uses radiofrequency (heat) to damage sensory nerves and interrupt transmission of pain signals. Radiofrequency energy causes oscillation of ions in the tissues and the resulting friction creates heat [45,46]. Lesions begin at 43 degrees C, but the target temperature is 80. Cooled probes circulate water to dissipate heat at the tip of the probe and thus allow for more energy to be transferred beyond the tissue tip interface [45,46]. This in turn will produce more volume in which nerves can be damaged. Anatomical studies have identified key geniculate sensory nerves which innervate the joint capsule and transmit pain in osteoarthritic patients. These branches have high variability but are concentrated in specific regions. These are identified using radioscopy or ultrasound guidance [45,46].

Our research has several shortcomings. Literature reviews generally have a retrospective design and perform a systematic analysis of completed studies with reported results. We performed a prospective review of ongoing trials. This enabled us to overview what is currently being investigated. Unfortunately, many of these projects have incomplete public data, lack details of investigational products and do not have results. In addition, we included trials from a single registry. By using a relatively broad topic—Knee OA, the collected data was difficult to structure because of the high number of studies and their heterogeneity. Our analysis aimed to provide a perspective of future directions on knee OA, a subject with potentially great impact on aging populations worldwide.

Knee OA is a topic of interest among orthopedic ongoing trials. Arthroplasty topics are implant design, cementless fixation, robotic assistance, or pain management. Intraarticular injections focus on cell therapies with mesenchymal stem cells sourced from adipose tissue, bone marrow, or umbilical cord. Future research includes disease modifying drugs, as well as various procedures such as blood flow restriction exercises, geniculate artery embolization, and geniculate nerve ablation.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app112211049/s1.

Author Contributions: Conceptualization, M.I. and B.A.; methodology, D.V.; software, C.D.; validation, M.I.; B.A. and R.P.; formal analysis, M.A.-Q.; investigation, V.B.; resources, A.D.; data curation, M.A.-Q.; writing—original draft preparation, M.I.; writing—review and editing, C.D.; visualization, D.V.; supervision, R.P.; project administration, R.P.; funding acquisition, B.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. The APC was funded by the "Victor Babes" University of Medicine and Pharmacy of Timisoara.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Stefania Onea.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sharma, L. Osteoarthritis of the Knee. *N. Engl. J. Med.* **2021**, *384*, 51–59. [CrossRef]
2. Cui, A.; Li, H.; Wang, D.; Zhong, J.; Chen, Y.; Lu, H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine* **2020**, *29–30*, 100587. [CrossRef]
3. Primorac, D.; Molnar, V.; Rod, E.; Jeleč, Ž.; Čukelj, F.; Matišić, V.; Vrdoljak, T.; Hudetz, D.; Hajsok, H.; Borić, I. Knee Osteoarthritis: A Review of Pathogenesis and State-Of-The-Art Non-Operative Therapeutic Considerations. *Genes* **2020**, *11*, 854. [CrossRef] [PubMed]
4. Khella, C.M.; Asgarian, R.; Horvath, J.M.; Rolauffs, B.; Hart, M.L. An Evidence-Based Systematic Review of Human Knee Post-Traumatic Osteoarthritis (PTOA): Timeline of Clinical Presentation and Disease Markers, Comparison of Knee Joint PTOA Models and Early Disease Implications. *Int. J. Mol. Sci.* **2021**, *22*, 1996. [CrossRef]
5. Belluzzi, E.; Macchi, V.; Fontanella, C.G.; Carniel, E.L.; Olivotto, E.; Filardo, G.; Sarasin, G.; Porzionato, A.; Granzotto, M.; Pozzuoli, A.; et al. Infrapatellar Fat Pad Gene Expression and Protein Production in Patients with and without Osteoarthritis. *Int. J. Mol. Sci.* **2020**, *21*, 6016. [CrossRef]
6. Rim, Y.A.; Ju, J.H. The Role of Fibrosis in Osteoarthritis Progression. *Life* **2021**, *11*, 3. [CrossRef]
7. Katz, J.N.; Arant, K.R.; Loeser, R.F. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *JAMA* **2021**, *9*, 568–578. [CrossRef]
8. Biehl, C.; Heinrich, M.; Biehl, L.; Knapp, G.; Heiss, C.; Thormann, U. Biomechanical Particularities in the Therapy of the Rheumatic Knee. *Appl. Sci.* **2020**, *10*, 8600. [CrossRef]
9. American Academy of Orthopaedic Surgeons Surgical Management of the Knee Evidence-Based Clinical Practice Guideline. Published 4 September 2015. Available online: https://www.aaos.org/globalassets/quality-and-practice-resources/surgical-management-knee/smoak-cpg_4.22.2016.pdf (accessed on 14 October 2021).
10. American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline (3rd ed.). Published 31 August 2021. Available online: https://www.aaos.org/oak3cpg (accessed on 14 October 2021).
11. Grässel, S.; Muschter, D. Recent advances in the treatment of osteoarthritis. *F1000Research* **2020**, *9*, F1000. [CrossRef] [PubMed]
12. Zhang, W.; Robertson, W.B.; Zhao, J.; Chen, W.; Xu, J. Emerging Trend in the Pharmacotherapy of Osteoarthritis. *Front. Endocrinol.* **2019**, *10*, 431. [CrossRef]
13. Available online: https://clinicaltrials.gov/ct2/results?cond=Osteoarthritis%2C+Knee&flds=bgijkopv&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=&Search=Apply (accessed on 23 September 2021).
14. Tricco, A.C.; Lillie, E.; Zarin, W.; O'Brien, K.K.; Colquhoun, H.; Levac, D.; Moher, D.; Peters, M.D.J.; Horsley, T.; Weeks, L.; et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Intern. Med.* **2018**, *169*, 467–473. [CrossRef]
15. Sun, J.; Mavrogenis, A.F.; Scarlat, M.M. The growth of scientific publications in 2020: A bibliometric analysis based on the number of publications, keywords, and citations in orthopaedic surgery. *Int. Orthop.* **2021**, *45*, 1905–1910. [CrossRef] [PubMed]
16. Todor, A.; Vermesan, D.; Haragus, H.; Patrascu, J.M., Jr.; Timar, B.; Cosma, D.I. Cross-cultural adaptation and validation of the Romanian International Knee Documentation Committee-subjective knee form. *PeerJ* **2020**, *8*, e8448. [CrossRef] [PubMed]
17. Batailler, C.; Swan, J.; Sappey Marinier, E.; Servien, E.; Lustig, S. New Technologies in Knee Arthroplasty: Current Concepts. *J. Clin. Med.* **2020**, *10*, 47. [CrossRef]

18. Kim, J.; Min, K.D.; Lee, B.I.; Kim, J.B.; Kwon, S.W.; Chun, D.I.; Kim, Y.B.; Seo, G.W.; Lee, J.S.; Park, S.; et al. Comparison of functional outcomes between single-radius and multi-radius femoral components in primary total knee arthroplasty: A meta-analysis of randomized controlled trials. *Knee Surg. Relat. Res.* **2020**, *32*, 1–12. [CrossRef]
19. Ene, R.; Nica, M.; Ene, D.; Cursaru, A.; Cirstoiu, C. Review of calcium-sulphate-based ceramics and synthetic bone substitutes used for antibiotic delivery in PJI and osteomyelitis treatment. *EFORT Open Rev.* **2021**, *6*, 297–304. [CrossRef]
20. Prasad, A.K.; Tan, J.H.S.; Bedair, H.S.; Dawson-Bowling, S.; Hanna, S.A. Cemented vs. cementless fixation in primary total knee arthroplasty: A systematic review and meta-analysis. *EFORT Open Rev.* **2020**, *5*, 793–798. [CrossRef]
21. Siddiqi, A.; Mont, M.A.; Krebs, V.; Piuzzi, N.S. Not All Robotic-assisted Total Knee Arthroplasty Are the Same. *J. Am. Acad. Orthop. Surg.* **2021**, *29*, 45–59. [CrossRef]
22. Tandogan, R.N.; Kort, N.P.; Ercin, E.; van Rooij, F.; Nover, L.; Saffarini, M.; Hirschmann, M.T.; Becker, R.; Dejour, D. European Knee Associates (EKA). Computer-assisted surgery and patient-specific instrumentation improve the accuracy of tibial baseplate rotation in total knee arthroplasty compared to conventional instrumentation: A systematic review and meta-analysis. *Knee Surg. Sports Traumatol. Arthrosc.* **2021**. epub ahead of print. [CrossRef] [PubMed]
23. Boia, E.S.; David, V.L. The Financial Burden of Setting up a Pediatric Robotic Surgery Program. *Medicina* **2019**, *55*, 739. [CrossRef]
24. Sun, Y.; Liu, W.; Hou, J.; Hu, X.; Zhang, W. Does robotic-assisted unicompartmental knee arthroplasty have lower complication and revision rates than the conventional procedure? A systematic review and meta-analysis. *BMJ Open* **2021**, *11*, e044778. [CrossRef]
25. Predescu, V.; Grosu, A.M.; Gherman, I.; Prescura, C.; Hiohi, V.; Deleanu, B. Early experience using patient-specific instrumentation in opening wedge high tibial osteotomy. *Int. Orthop.* **2021**, *45*, 1509–1515. [CrossRef]
26. Kon, E.; Di Matteo, B.; Verdonk, P.; Drobnic, M.; Dulic, O.; Gavrilovic, G.; Patrascu, J.M.; Zaslav, K.; Kwiatkowski, G.; Altschuler, N.; et al. Aragonite-Based Scaffold for the Treatment of Joint Surface Lesions in Mild to Moderate Osteoarthritic Knees: Results of a 2-Year Multicenter Prospective Study. *Am. J. Sports Med.* **2021**, *49*, 588–598. [CrossRef]
27. Cofaru, N.F.; Roman, M.D.; Cofaru, I.I.; Oleksik, V.S.; Fleaca, S.R. Medial Opening Wedge High Tibial Osteotomy in Knee Osteoarthritis—A Biomechanical Approach. *Appl. Sci.* **2020**, *10*, 8972. [CrossRef]
28. Hussain, N.; Brull, R.; Sheehy, B.; Dasu, M.; Weaver, T.; Abdallah, F.W. Does the addition of iPACK to adductor canal block in the presence or absence of periarticular local anesthetic infiltration improve analgesic and functional outcomes following total knee arthroplasty? A systematic review and meta-analysis. *Reg. Anesth. Pain Med.* **2021**, *46*, 713–721. [CrossRef]
29. Levy, D.M.; Petersen, K.A.; Scalley Vaught, M.; Christian, D.R.; Cole, B.J. Injections for Knee Osteoarthritis: Corticosteroids, Viscosupplementation, Platelet-Rich Plasma, and Autologous Stem Cells. *Arthrosc. J. Arthrosc. Relat. Surg.* **2018**, *34*, 1730–1743. [CrossRef] [PubMed]
30. Radu, F.; Valentin, O.; Adrian, P.; Mihaela, C.M.; Mihai, R. Properties and Behaviour of Distal Femur to Axial Loading in Osteochondral Autologous Transplantation. *Rom. Biotechnol. Lett.* **2014**, *2*, 9141–9147.
31. Chu, C.R.; Rodeo, S.; Bhutani, N.; Goodrich, L.R.; Huard, J.; Irrgang, J.; LaPrade, R.F.; Lattermann, C.; Lu, Y.; Mandelbaum, B.; et al. Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference. *J. Am. Acad Orthop. Surg.* **2019**, *27*, e50–e63. [CrossRef] [PubMed]
32. Hernigou, P.; Hernigou, J.; Scarlat, M. Mesenchymal stem cell therapy improved outcome of early post-traumatic shoulder osteonecrosis: A prospective randomized clinical study of fifty patients with over ten year follow-up. *Int. Orthop.* **2021**, *45*, 2643–2652, epub ahead of print. [CrossRef] [PubMed]
33. Agarwal, N.; Mak, C.; Bojanic, C.; To, K.; Khan, W. Meta-Analysis of Adipose Tissue Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis. *Cells* **2021**, *10*, 1365. [CrossRef]
34. Gobbi, A.; Dallo, I.; Rogers, C.; Striano, R.D.; Mautner, K.; Bowers, R.; Rozak, M.; Bilbool, N.; Murrell, W.D. Two-year clinical outcomes of autologous microfragmented adipose tissue in elderly patients with knee osteoarthritis: A multi-centric, international study. *Int. Orthop.* **2021**, *45*, 1179–1188. [CrossRef] [PubMed]
35. Matas, J.; Orrego, M.; Amenabar, D.; Infante, C.; Tapia-Limonchi, R.; Cadiz, M.I.; Alcayaga-Miranda, F.; González, P.L.; Muse, E.; Khoury, M.; et al. Umbilical Cord-Derived Mesenchymal Stromal Cells (MSCs) for Knee Osteoarthritis: Repeated MSC Dosing Is Superior to a Single MSC Dose and to Hyaluronic Acid in a Controlled Randomized Phase I/II Trial. *Stem Cells Transl. Med.* **2019**, *8*, 215–224. [CrossRef]
36. Yang, H.Y.; Song, E.K.; Kang, S.J.; Kwak, W.K.; Kang, J.K.; Seon, J.K. Allogenic umbilical cord blood-derived mesenchymal stromal cell implantation was superior to bone marrow aspirate concentrate augmentation for cartilage regeneration despite similar clinical outcomes. *Knee Surg. Sports Traumatol. Arthrosc.* **2021**, *25*, 1–11, epub ahead of print. [CrossRef] [PubMed]
37. Ren, B.; Lv, X.; Tu, C.; Li, Z. Research trends of platelet-rich plasma application in orthopaedics from 2002 to 2020: A bibliometric analysis. *Int. Orthop.* **2021**, *45*, 2773–2790. [CrossRef] [PubMed]
38. Belk, J.W.; Kraeutler, M.J.; Houck, D.A.; Goodrich, J.A.; Dragoo, J.L.; McCarty, E.C. Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Am. J. Sports Med.* **2021**, *49*, 249–260. [CrossRef]
39. Onofrei, R.R.; Amaricai, E.; Suciu, O.; David, V.L.; Rata, A.L.; Hogea, E. Smartphone Use and Postural Balance in Healthy Young Adults. *Int. J. Environ. Res. Public Health* **2020**, *17*, 3307. [CrossRef]

40. Bobes Álvarez, C.; Issa-Khozouz Santamaría, P.; Fernández-Matías, R.; Pecos-Martín, D.; Achalandabaso-Ochoa, A.; Fernández-Carnero, S.; Martínez-Amat, A.; Gallego-Izquierdo, T. Comparison of Blood Flow Restriction Training versus Non-Occlusive Training in Patients with Anterior Cruciate Ligament Reconstruction or Knee Osteoarthritis: A Systematic Review. *J. Clin. Med.* **2021**, *10*, 68. [CrossRef] [PubMed]
41. Novak, S.; Guerron, G.; Zou, Z.; Cheung, G.; Berteau, J.P. New Guidelines for Electrical Stimulation Parameters in Adult Patients With Knee Osteoarthritis Based on a Systematic Review of the Current Literature. *Am. J. Phys. Med. Rehabil.* **2020**, *99*, 682–688. [CrossRef]
42. Latourte, A.; Kloppenburg, M.; Richette, P. Emerging pharmaceutical therapies for osteoarthritis. *Nat. Rev. Rheumatol.* **2020**, *16*, 673–688. [CrossRef]
43. Rice, D.; McNair, P.; Huysmans, E.; Letzen, J.; Finan, P. Best Evidence Rehabilitation for Chronic Pain Part 5: Osteoarthritis. *J. Clin. Med.* **2019**, *8*, 1769. [CrossRef]
44. Torkian, P.; Golzarian, J.; Chalian, M.; Clayton, A.; Rahimi-Dehgolan, S.; Tabibian, E.; Talaie, R. Osteoarthritis-Related Knee Pain Treated With Genicular Artery Embolization: A Systematic Review and Meta-analysis. *Orthop. J. Sports Med.* **2021**, *9*, 23259671211021356. [CrossRef]
45. Chen, A.F.; Mullen, K.; Casambre, F.; Visvabharathy, V.; Brown, G.A. Thermal Nerve Radiofrequency Ablation for the Nonsurgical Treatment of Knee Osteoarthritis: A Systematic Literature Review. *J. Am. Acad. Orthop Surg.* **2021**, *29*, 387–396. [CrossRef] [PubMed]
46. Chou, S.H.; Shen, P.C.; Lu, C.C.; Liu, Z.M.; Tien, Y.C.; Huang, P.J.; Chou, C.M.; Shih, C.L. Comparison of Efficacy among Three Radiofrequency Ablation Techniques for Treating Knee Osteoarthritis: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7424. [CrossRef] [PubMed]