Osteoarthritis and Cartilage Open 2 (2020) 100114

Contents lists available at ScienceDirect

Osteoarthritis and Cartilage Open

journal homepage: www.elsevier.com/journals/osteoarthritis-and-cartilage-open/2665-9131

Review

Effects of exercise therapy on joint instability in patients with osteoarthritis of the knee: A systematic review

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ARTICLE INFO

Keywords:
Knee osteoarthritis
Exercise therapy
Joint instability
Systematic review

SUMMARY

Objective: Abnormal load stress caused by joint instability has been reported to be one of the factors responsible for the development of osteoarthritis (OA). However, few studies have investigated the efficacy of exercise therapy for patients with knee instability-induced OA, and there are no specific treatment guidelines or effects for this form of OA. Therefore, the purpose of this study was to examine the effect of exercise treatments for joint instability in patients with knee OA by a systematic review.
Design: Systematic review.
Results: Searches in three databases, PubMed, Cochrane, and the Physiotherapy Evidence Database, yielded 14 articles that were scrutinized, and 6 articles that met the inclusion criteria were selected.
Conclusions: Exercise therapy focusing on joint instability, including muscle maintenance and strength training, and specific training targeting knee instability have no additional beneficial effects on knee joint instability. However, because of the benefits of treatment protocols based on patient attributes in exercise treatment focused on joint instability, it is necessary to investigate the effects in more detail in the future.

1. Introduction

Knee osteoarthritis (OA) is a common disease that causes pain and functional impairment, which can eventually lead to limitations in activities of daily living. Although the pathogenesis of knee OA has been reported to be related to various factors, the abnormal mechanical stress caused by joint instability is one of the key factors contributing to the development and progression of knee OA [1]. In addition, animal studies have validated that joint instability is a factor involved in the progression of OA [2] and that factors associated with joint instability, such as chronic synovitis [3], increased expression of proteolytic enzymes [4], osteophyte formation [5], and changes in the transforming growth factor-β1/Smad cascade [6], induce structural and molecular biological changes in OA.

Human clinical studies showed that, in terms of the relationship between knee OA and joint instability, many patients with knee OA experience joint instability [7,8], and joint instability may be a potential target for knee OA treatment. The knee joint is anatomically unstable on the tibial and femoral articular surfaces, and stability is maintained by the surrounding ligaments and the menisci. In general, functional abnormalities in these tissues induce joint instability. For the general treatment of OA, range of motion exercises, muscle strengthening, and lifestyle guidance for weight loss are important options [9]. Exercise treatment for OA must target instability by including exercises involving lateral thrusts, and provide physical and exercise therapies. However, continuing to exercise in an unstable knee condition might cause OA progression. Oka et al. reported that exercises on anterior cruciate ligament tear rat models resulted in anterior tibia instability, which further progressed to early OA compared to exercises with reduced forward instability [10].

Thus, the condition of knee joint stability/instability is an important focus for OA prevention. However, few studies have investigated the

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https://doi.org/10.1016/j.ocarto.2020.100114
Received 22 July 2020; Accepted 26 October 2020

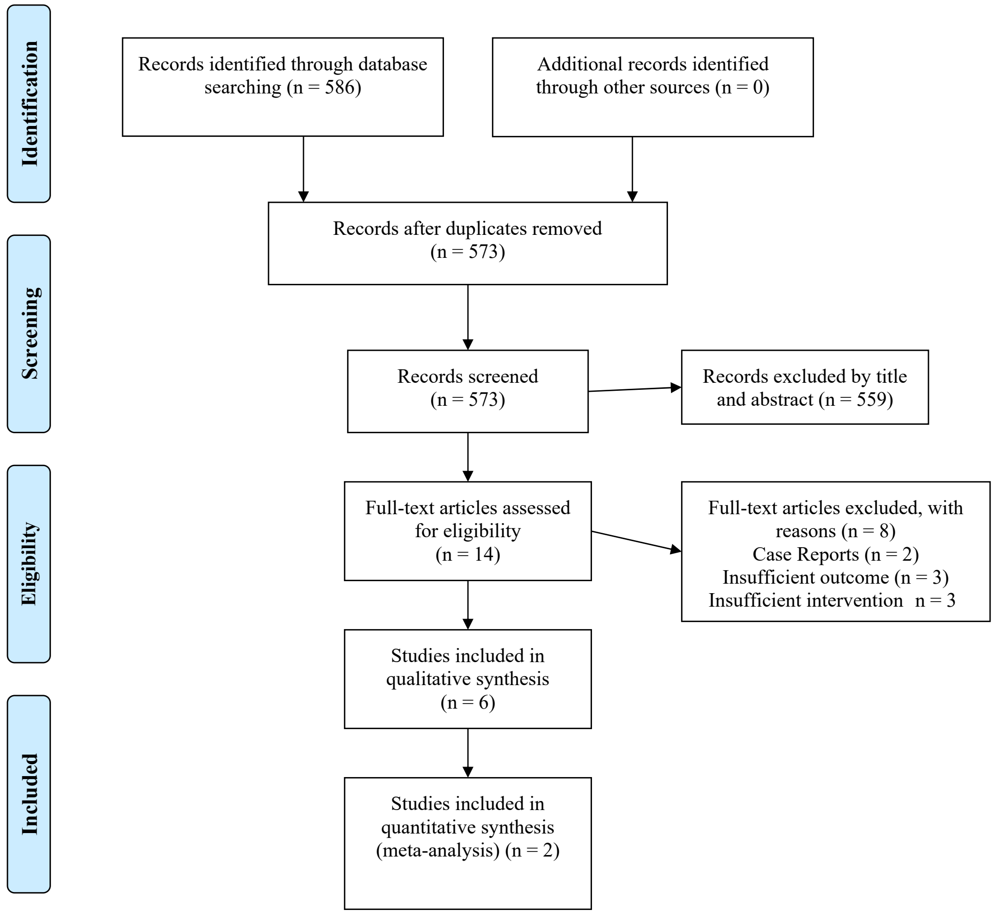

Figure 1. Search formula for target articles. The search formula for the systematic review of the effect of conservative therapy on joint instability in patients with osteoarthritis of the knee. MESH: Medical Subject Headings (Medical Terms Headings).

efficacy of exercise therapy for patients with knee instability-induced OA, and no specific treatment guidelines or effects have been reported to date. Therefore, the purpose of this study was to examine the effects of exercise treatment for joint instability in patients with knee OA through a systematic review and meta-analysis. The specific objectives were as follows:

1) To investigate previous research on how to assess joint instability in patients with OA of the knee.
2) To examine, through a meta-analysis, joint instability in patients with OA of the knee.

2. Method

This study was validated by a literature review; therefore, no ethical review was conducted. This review followed the recommendation and guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses [11,12]. The protocol was registered with PROSPERO (CRD42020194103).

2.1. Literature search

To examine the effect of rehabilitation on joint instability in patients with knee OA, we searched three databases: MEDLINE, Cochrane, and Physiotherapy Evidence Database (PEDro). The article search was performed up to June 2020, and the search included a combination of keywords to test the effect of exercise therapy on knee OA and joint instability. The specific searches were as follows:

MEDLINE Search.

#1 “Osteoarthritis, Knee” [Mesh]
#2 “Joint Instability” [Mesh])
#3 “laxity”
#4 “Exercise” [Mesh]
#5 “Exercise Therapy” [Mesh]
#6 “physical therapy”
#7 #3 OR #4
#8 #5 OR #6 OR #7
#9 #1 AND #7 AND #8

Cochrane.

#1 (“knee-joint”):ti,ab, kw OR (knee):ti,ab,kw
#2 MeSH descriptor:[Joint Instability]explode all trees
#3 (physical therapy):ti,ab, kw OR (conservative therapy):ti,ab,kw
#4 (“knee osteoarthritis”):ti,ab, kw OR (knee OA):ti,ab,kw
#5 #1 and #2 and #3 and #4
ti: title, ab: abstract, kw: keyword

PEDro.

#1 knee, osteoarthritis, instability

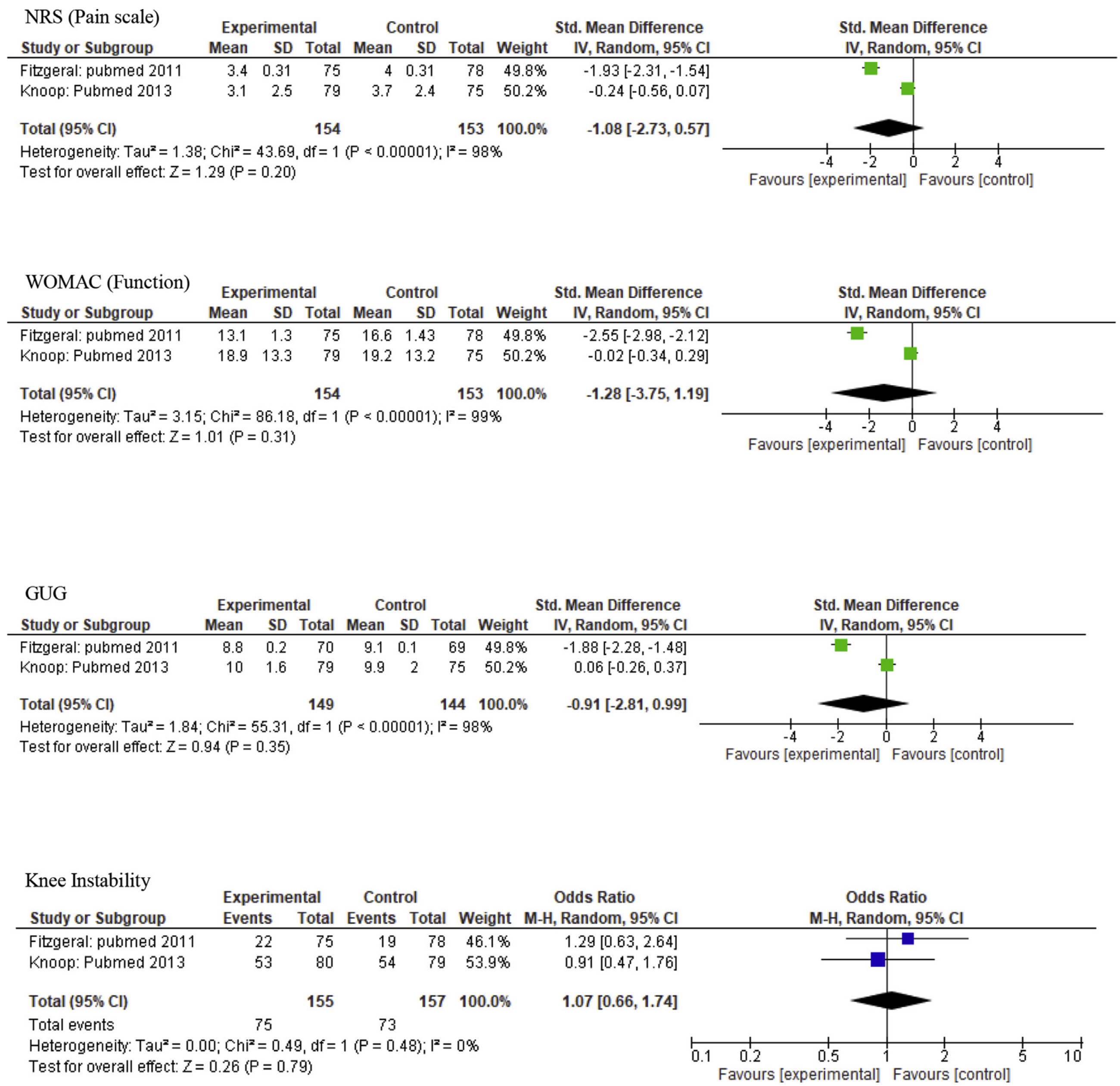

Figure 2. Results of meta-analysis. The black diamond indicates the amount of effect of the data; if the value of the SMD overlaps with 0, no effect is recognized.

#2 knee, osteoarthritis, laxity

2.2. Study selection

A study design focused on joint instability in patients with knee OA was selected. From the retrieved literature, we excluded duplicate articles, or those not in English. In addition, non-peer-reviewed papers, meeting minutes, reviews, or letters to the editor were excluded. The extraction was performed by three authors (SK, KN, and KM). The corresponding authors evaluated all papers, and a difference of opinion was resolved by a discussion held among the three authors.

2.3. Data extraction

Authors, year of publication, research design, patient attributes, OA severity, target population and comparison group (including rehabilitation interventions), outcome measures, and main results were extracted from the results of the articles.

2.4. Risk of bias assessments

The assessment of the risk of bias depended on the study design. For randomized trials, the risk of bias assessment was performed at the study level using the Cochrane risk of bias tool [13]. Cross-sectional studies were evaluated by the Appraisal tool for Cross-Sectional Studies (AXIS) [14]. The AXIS tool comprises 20 items evaluating various aspects of methodological quality. In addition, the quality of evidence of systematic reviews was evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE was designed to evaluate the quality of evidence for each outcome measure across studies. The scores were evaluated by two authors, and the overall quality of evidence was judged as “high,” “moderate,” “low,” or “very

Table 1
Summary of studies providing overview.

Author and year	Design	Patient & Group	Intervention	OA baseline	Main Evaluation	Primary outcome	Conclusion
Cudejko,2017 [16]	Single arm clinical trial (A within-subject design)	i-1) soft brace with no brace i-2) a non-tight with a tight soft brace. Age of 65.7 ± 9.3 years BMI of 29.8 ± 5.5 kg/m2 Male/Female 15/29	**Knee brace**	Radiographic severity of knee Kellgren/ Lawrence grade 0: n = 3 (7.0%) Kellgren/ Lawrence grade 1: n = 16 (37.2%) Kellgren/ Lawrence grade 2: n = 9 (20.9%) Kellgren/ Lawrence grade 3: n = 10 (23.3%) Kellgren/ Lawrence grade 4: n = 5 (11.6%)	i) The Western Ontario and McMaster Universities (WOMAC) ii) Numeric rating scale (NRS) iii) Get Up and Go (GUG) iv) 10m walk test v) Level walk vi) Self-reported knee confidence vii) Self-reported knee instability viii) Body mass index (BMI) ix) Radiographic knee OA severity [Kellgren/ Lawrence grade] x) Knee injury and Osteoarthritis Outcome Score (KOOS) xi) Perturbed walk	**Brace vs. no brace** Knee instability, level walk **OR** (95% CI): 0.41 (0.23 to 0.66), p= 0.002 Knee instability, perturbed walk **OR** (95% CI): 0.36(0.23 to 0.59), p< 0.001	The soft brace is an efficacious intervention self-reported knee instability
Gustafson JA, 2016 [17]	Cross-sectional study	i) knee unstable (n = 17) Age of 61.3 ± 6.5 years BMI of 30.6 ± 4.8kg/m^2 Male/ Female 6/11 ii) knee stable (n = 35) Age of 63.2 ± 7.5 years BMI of 28.7 ± 5.5kg/m^2 Male/ Female 22/13	N/A	All patients had to have at least a grade 2 Kellgren/ Lawrence grade 2: n = 8 Kellgren/ Lawrence grade 3: n = 30 Kellgren/ Lawrence grade 4: n = 14	i) Gait analysis (walking knee joint stiffness, knee angles, knee moment, gait speed)	N/A	Patients with self-reported instability appear to walk with lower knee joint stiffness compared to without instability
J. Knoop, 2014 [20]	Randomized controlled trial	i) Experimental group (n = 80) Age of 62.1 ± 7.6 years BMI of 28.8 ± 4.8kg/m^2 Male/Female 27/53 ii) Control group (n = 79) Age of 61.8 ± 6.6 years BMI of 28.3 ± 4.5kg/m^2 Male/ Female 35/44	Specific knee joint stabilization training	Radiographic severity of knee Kellgren/ Lawrence grade > 2 experimental group: n = 59 (61%) control group: n = 54 (68%)	i) The Western Ontario and McMaster Universities (WOMAC) ii) Numeric rating scale (NRS) iii) Get Up and Go (GUG) iv) Isovelocity muscle strength of the thigh v) Accuracy of inherent sense vi) Intra- and extra-axial laxity of the knee joint vii) Self-reported knee instability viii) Body mass index (BMI) ix) Radiographic knee OA severity [Kellgren/Lawrence grade] x) Knee joint alignment	**Experimental vs. Control** NRS, pain **B** (95% CI): 0.95 (−1.92 to 0.01), p = 0.05 GUG test **B** (95% CI): 0.58 (−1.13 to −0.02), p = 0.04	Knee stabilization therapy in the intervention may have added value for patients with knee instability and high muscle strength
Skou, 2014 [18]	Cross-sectional study	knee OA patient (n = 100) Age of 62.4 ± 7.3 years BMI of 29.6 ± 4.1kg/m^2 Male/ Female 48/52	N/A	All patients had to have at least a grade 2 knee OA to be included in the study. Kellgren/ Lawrence grade 2: n = 22 Kellgren/ Lawrence grade 3: n = 43 Kellgren/ Lawrence grade 4: n = 35	i) Radiographic knee alignment ii) Self-reported knee confidence iii) Walking pain (VAS) iv) Self-reported knee instability v) Quadriceps muscle strength using KinCom vi) Dynamic varus–valgus joint motion using Vicon	N/A	Worse self-reported knee confidence is associated with higher pain, worse self-reported knee instability, lower quadriceps muscle strength, and greater dynamic varus-valgus motion during walking.

(*continued on next page*)

Table 1 (*continued*)

Author and year	Design	Patient & Group	Intervention	OA baseline	Main Evaluation	Primary outcome	Conclusion
J. Knoop, 2013 [21]	Randomized controlled trial	i) Experimental group (n = 80) Age of 62.1 ± 7.6 years BMI of 28.8 ± 4.8kg/m^2 Male/Female 27/53 ii) Control group (n = 79) Age of 61.8 ± 6.6 years BMI of 28.3 ± 4.5kg/m^2 Male/Female 35/44	Specific knee joint stabilization training	**Experimental group**: Kellgren/Lawrence grade 0/1: n = 31 (39%) Kellgren/Lawrence grade 2: n = 23 (29%) Kellgren/Lawrence grade 3: n = 18 (23%) Kellgren/Lawrence grade 4: n = 8 (10%) **Control group**: Kellgren/Lawrence grade 0/1: n = 25 (32%) Kellgren/Lawrence grade 2: n = 21 (27%) Kellgren/Lawrence grade 3: n = 23 (29%) Kellgren/Lawrence grade 4: n = 10 (13%)	i) The Western Ontario and McMaster Universities (WOMAC) ii) Numeric rating scale (NRS) iii) Get Up and Go (GUG) iv) Isovelocity muscle strength of the thigh v) Accuracy of inherent sense vi) Intra- and extra-axial laxity of the knee joint vii) Self-reported knee instability viii) Body mass index (BMI) ix) Radiographic knee OA severity [Kellgren/Lawrence grade] x) Knee joint alignment	**Experimental vs. Control** Self-reported knee instability: >one episode in past 6 weeks (n/%) **B** (95% CI): 1.07 (0.64–1.67), p = 0.80 WOMAC (physical function, 0–68) **B** (95% CI): 0.01 (−2.58 to 2.571.67), p = 0.99	There was no effect on knee instability
G. Kelley Fitzgerald, 2012 [19]	Cross-sectional study	i) Nonresponders group (n = 99) Age of 65.1 ± 8.4 years BMI of 30.1 ± 5.8kg/m^2 Male/Female 32/67 ii) Responders group (n = 53) Age of 62.6 ± 9.0 years BMI of 30.2 ± 6.9kg/m^2 Male/Female 21/32	N/A	**Nonresponders group** Kellgren/Lawrence grade 0: n = 3 (0.0%) Kellgren/Lawrence grade 1: n = 1 (1.0%) Kellgren/Lawrence grade 2: n = 14 (14.1%) Kellgren/Lawrence grade 3: n = 45 (45.6%) Kellgren/Lawrence grade 4: n = 39 (39.4%) **Responders group** Kellgren/Lawrence grade 0: n = 1 (1.9%) Kellgren/Lawrence grade 1: n = 1 (1.9%) Kellgren/Lawrence grade 2: n = 7 (13.2%) Kellgren/Lawrence grade 3: n = 29 (54.7%) Kellgren/Lawrence grade 4: n = 15 (28.3%)	i) Self-reported knee instability ii) Quadriceps strength using BIODEX iii) Knee flexion and extension ROM iv) Ankle dorsiflexion ROM v) Hip flexibility (Thomas test), Hamstring and Gastrocnemius flexibility. vi) Fear-Avoidance Beliefs Questionnaire (FABQ) vii) Beck Anxiety Inventory viii) Depression	**Responders patients** Change variables: Joint instability Pain and function **OR** (95% CI): 1.67 (1.13–2.47), p < 0.01 Function only **OR** (95% CI): 1.61 (1.13–2.29), p < 0.01 Pain only **OR** (95% CI): 1.59 (1.13–2.23), p < 0.01	The results indicate improvement in self-reported knee instability and fear of physical activity are associated with treatment response to the therapeutic exercise programs
G. Kelley Fitzgerald, 2011 [22]	Randomized controlled trial	i) Basic exercise (n = 92) Age of 64.6 ± 8.4 years BMI of 30.2 ± 6.1kg/m^2 Male/Female 30/62 ii) Basic exercise + Agility-	Agility-Perturbation training	Kellgren/Lawrence grade 2 or higher (100%)	i) The Western Ontario and McMaster Universities (WOMAC) ii) Self-reported knee instability.	Intention-to-treat analysis **Basic exercise vs. Agility-Perturbation training** knee instability, p = 0.032	There was no effect on knee instability

(continued on next page)

Table 1 (*continued*)

Author and year	Design	Patient & Group	Intervention	OA baseline	Main Evaluation	Primary outcome	Conclusion
		Perturbation training (n = 91) Age of 63.3 ± 8.9 years BMI of 30.8 ± 6.8kg/m^2 Male/Female 31/60			iii) Numeric rating scale (NRS) iv) Global rating of change (GRC) score v) Get Up and Go (GUG) vi) Muscle Strength (Quadriceps, Hamstring) vii) Knee ROM (hyperextension/neutral/flexion) viii) Knee Outcome Survey-Activities of Daily Living Scale		

Table 2
Detailed assessment of joint instability.

Author and year	Main reference	Main outcome	Evaluation	Group
Gustafson Jam, 2016[17]	Fitzgerald, 2004[24] Irrgang JJ, 1998[23]	Knee Outcome Survey-Activities of Daily Living Scale 0 The symptom prevents me from all daily activity 1 The symptom affects my activity severely 2 The symptom affects my activity moderately 3 The symptom affects my activity slightly 4 I have the symptom but it does not affect my activity 5 I do not have giving way, buckling, or shifting of the knee	N/A	N/A
J. Knoop, 2014[20]	Fitzgerald, 2004[24] Irrgang JJ, 1998[23] J Knoop, 2012[7]	Yes or No assessed by questionnaire. 1) Self-reported knee joint instability 2) This knee instability resulted in activity limitations	The number of episodes of bucking, shifting, or giving way of the knee in the past 6 weeks.	None [0 episodes] Seldom [1–2 episodes] Regularly [3–5 episodes] Very often [>5 episodes]
Skou, 2014[18]	N/A	Knee instability 5 point Likert scale 0 knee does not give way, buckle, or shift 1 Strenuous activities like heavy physical work, skiing, or tennis 2 Moderate activities like moderate physical work, running, or jogging 3 Activities of daily living/light activities like walking or housework 4 Unable to perform any of the above activities due to giving way of the knee	N/A	N/A
J. Knoop, 2013[21]	Fitzgerald, 2004[24] Irrgang JJ, 1998[23]	Yes or No assessed by questionnaire. 1) Self-reported knee joint instability 2) This knee instability resulted in activity limitations	The number of episodes of bucking, shifting, or giving way of the knee in the past 6 weeks.	N/A
G. Kelley Fitzgerald, 2012[19]	Irrgang JJ, 1998[23]	Knee Outcome Survey-Activities of Daily Living Scale 0 The symptom prevents me from all daily activity 1 The symptom affects my activity severely 2 The symptom affects my activity moderately 3 The symptom affects my activity slightly 4 I have the symptom but it does not affect my activity 5 I do not have giving way, buckling, or shifting of the knee	N/A	N/A
G. Kelley Fitzgerald, 2011[22]	Irrgang JJ, 1998[23]	Knee Outcome Survey-Activities of Daily Living Scale 0 The symptom prevents me from all daily activity 1 The symptom affects my activity severely 2 The symptom affects my activity moderately 3 The symptom affects my activity slightly 4 I have the symptom but it does not affect my activity 5 I do not have giving way, buckling, or shifting of the knee	N/A	N/A

An assessment of joint instability in all the articles is presented.

Table 3
Details of exercise interventions for joint instability.

Author, year	Control group intervention	Experimental group intervention for joint instability
J. Knoop, 2014	1) Weeks 1–8: Strengthening of muscles 2) Weeks 9–12: 1) + daily activities	1) Weeks 1–4: Knee stability training (intrinsic sensation, neuromuscular control) 2) Weeks 5–8: (1) + muscle strengthening (endurance) 3) Weeks 9–12: (1) + muscle strengthening (power) + activities of daily living
J. Knoop, 2013	1) Weeks 1–8: Strengthening of muscles 2) Weeks 9–12: 1) + daily activities	1) Weeks 1–4: Knee stability training (intrinsic sensation, neuromuscular control) 2) Weeks 5–8: (1) + muscle strengthening (endurance) 3) Weeks 9–12: (1) + muscle strengthening (power) + activities of daily living)
G. Kelley Fitzgerald, 2011	i) Group 1: basic exercise 1) Stretch: Quadriceps, Hamstring, Triceps, Leg 2) Muscle strengthening: Quad set, SLR, supine hip extension, seated knee extension, single leg press, standing hamstring curls, heel lift, long sitting hip flexion and extension, ROMex, treadmill walking	ii) Group 2: i) + Agility-Perturbation training 1) Agility training: Side step, braiding (a side step that combines forward and backward crossover steps), forward crossover step during walking, backward crossover step during backward walking, shuttle walking, and multi-directional steps as directed by the therapist during walking. 2) Perturbation training: Form surface, tilt board, instability that incorporates the use of roller board exercise

Quad: quadriceps, SLR: straight-leg raising, ROM: range of motion.

low.” Detailed scores were related to five points: the risk of bias, inconsistency, indirectness, imprecision, and publication bias [15,16]. Three reviewers (KN, SK, and KM) independently evaluated the methodological quality of the included studies.

2.5. Meta-analysis

The studies that reported the course of treatment for patients with knee OA with a focus on exercise therapy and evaluated the function of the knee joint and joint instability were the subject of the secondary study. For each major outcome, data for means and standard deviation (SD) or 95% confidence intervals were obtained. Integrated estimates and 95% confidence intervals at standardized means were calculated with a random-effects model using Review Manager (RevMan) 5.3 (Nordic Cochran Center, Cochrane Collaboration, Copenhagen, Denmark) for Numerical Rating Scale (NRS) (pain) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, both of which were integrable data. The 95% confidence intervals were converted to SDs and a meta-analysis was performed. The corresponding authors contacted the authors of the covered studies to obtain additional newly accepted papers and detailed data. In the evaluation of each selected study, the meta-analysis was performed at common time points (6 months) for data integration.

3. Results

3.1. Papers analyzed and characteristics of the included studies

Fig. 1 shows the flowchart of the study selection process. The keyword search results in MEDLINE, Cochrane, and PEDro revealed 586 papers, including 13 duplicates. After title and abstract screening of 573 remaining papers, 31 full-texts were evaluated, and 14 articles were included. Thus, 14 papers were scrutinized and seven papers that met the inclusion criteria were finally selected, including, three cross-sectional studies [17–19] and three Random Control Trials (RCTs) [20–22]. The effect size of RCTs was analyzed using meta-analysis. Exercise therapy interventions focusing on joint instability in patients with OA of the knee was present in three of six articles. Three articles were RCTs that focused on exercise therapy interventions [20–22] and the other three were cross-sectional studies (Table 1) [17–19] (see Table 2) (see Table 3).

3.2. Outcome characteristics for knee joint instability

The assessment of knee instability in clinical trials is based on dynamic rather than static instability. The dynamic knee instability outcome was assessed by self-reporting past episodes of “buckling, shifting, or giving way of the knee” due to the difficulty of quantifying knee instability during movement. After an interview-based measure of knee instability was reported by Irrgang et al. [23], and Fitzgerald et al. [24], researchers have modified and used it. The characteristics of the self-reporting instability assessment include Yes/No or classifying the number of episodes (“buckling, shifting, or giving way”) in daily living.

3.3. Intervention characteristics for knee joint instability

Three papers [20–22] were extracted, each investigating the effects of exercise treatment on function, including joint instability, in patients with OA (Table 4) [20,21]. Knoop et al. reported that specific exercise therapy, which consists of three phases, resulted in functional recovery, but a similar effect was also found for general exercise therapy. The following phases were described: first phase (weeks 1–4) targeting knee joint stabilization; second phase (weeks 5–8) targeting muscle strength (i.e., muscle endurance) in addition to knee joint stabilization; and third

Table 4
Cochrane risk of bias tool.

Author, year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall Bias
J. Knoop, 2014[20]	Low	Low	Low	Some concerns	High	High
J. Knoop, 2013[21]	Low	Low	Low	Some concerns	High	High
G. Kelley Fitzgerald, 2011[22]	Low	Low	Low	Some concerns	High	High

Assessment of risk of bias for randomized trials.
Low: Low risk of bias is present.
Some concerns: Some concerns of risk of bias are present.
High: High risk of bias is present.
NI: No information is present.

Table 5
Appraisal tool for cross-sectional studies.

Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Gustafson JA, 2016[17]	Y	Y	Don't know	Y	Y	Y	Y	Y	Y	Y	Don't know	Y	N	N	Y	Y	Y	Y	N	Y
Skou, 2014[18]	Y	Y	Don't know	Y	Y	Y	N	Y	N	Y	Don't know	Y	Don't know	N	Y	Y	Y	Y	N	Y
G. Kelley Fitzgerald, 2012[19]	Y	Y	Don't know	Y	Y	Y	N	Y	Y	N	Don't know	Y	N	N	Y	Y	Y	Y	N	Y

Y = Yes, N = No, Don't know.
1) Were the aims/objectives of the study clear?.
2) Was the study design appropriate for the stated aim(s)?.
3) Was the sample size justified?.
4) Was the target/reference population clearly defined? (is it clear who the research was about?).
5) Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?.
6) Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?.
7) Were measure undertaken to address and categorize non-responders?.
8) Were the risk factor and outcome variables measured appropriate to the aims of the study?.
9) Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted or published previously?.
10) Is it clear what was used to determine statistical significance and/or precision estimates? (e.g., p-values, confidence intervals).
11) Were the methods (including statistical methods) sufficiently described to enable them to be rejected?.
12) Were the basic data adequately described?.
13) Does the response rate raise concerns about non-response bias?.
14) If appropriate, was information about non-responders described?.
15) Were the results internally consistent?.
16) Were the results presented for all the analyses described in the methods?.
17) Were the authors' discussions and conclusions justified by the results?.
18) Were the limitations of the study discussed?.
19) Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?.
20) Was ethical approval or consent of participants attained?.

Table 6
GRADE scale.

Author and year	Design	Number of participants	Limitation	Inconsistency	Indirectness for PICO	Imprecision	Publication bias	GRADE
J. Knoop, 2014[20]	Randomized controlled trial	n = 159	↓	–	–	–	–	⊕⊕⊕◯
J. Knoop, 2013[21]	Randomized controlled trial	n = 159	–	–	–	–	–	⊕⊕⊕⊕
G. Kelley Fitzgerald, 2011[22]	Randomized controlled trial	n = 183	↓	–	–	–	–	⊕⊕⊕◯

GRADE Score.
- : no problem
↓: one level down.
↓↓: two levels downpresent.

phase (weeks 9–12) targeting performance of daily activities in addition to knee joint stabilization and muscle strength (i.e., maximal muscle power). It was also shown that exercise therapy focusing on knee joint stabilization was more effective for patients with good muscle strength and minimal instability. On the other hand, in a study by Fitzgerald et al. [22] comparing exercise therapy focused on knee agility and perturbation with exercises consisting only of stretching and strengthening of the lower extremity muscles, both exercise therapies improved function, but had no effect on knee joint instability.

3.4. *Risk of bias assessments*

Two of the three RCTs assessed by Cochrane's Risk of Bias were rated as high quality (Table 4). One RCT did not provide a detailed methodology. Cross-sectional studies were graded by AXIS as follows: One study met 16 out of 20 criteria and three studies met 13–15 assessment criteria (Table 5). Moreover, we assessed the certainty of evidence for each outcome for exercise therapy compared with controls using the GRADE approach. Our findings largely revealed with “moderate” to “high” quality of evidence.Two papers were one level down due to the research limitations. Table 6 summarizes the findings for all exercise therapy outcomes assessed in this review for RCT.

3.5. *Meta-analysis*

Meta-analysis data from the two papers [21,22] were combined (Fig. 2). The standardized mean difference (SMD) of the integrated data according to Cohen's interpretation showed no effect sizes for pain: NRS (WMD: 1.08; 95% CI: 2.73, 0.57; $p = 0.200$; P for heterogeneity < 0.001; $I2 = 98\%$), WOMAC scores (WMD: 1.28; 95% CI: 3.75, 1.19; $p = 0.310$; P for heterogeneity < 0.001; $I2 = 99\%$), and GUG (WMD: 0.91; 95% CI: 2.81, 0.99; $p = 0.350$; P for heterogeneity < 0.001; $I2 = 98\%$). Therefore, the results showed that exercise therapy focusing on knee stabilization had no effect on pain or WOMAC scores. Heterogeneity was high in all obtained results (NRS, WOMAC, and GUG). Furthermore, the meta-analysis for self-reported instability did not differ from the normal group; heterogeneity did not differ either. Moreover, in joint instability, there was no statistically significant difference between the experimental and control groups (RR: 1.00; 95% CI: 0.82, 1.22; $p = 1.00$; p for heterogeneity $= 0.42$; $I2 = 0\%$).

4. Discussion

This study examined the impact of exercise therapy on joint instability in patients with knee OA through a systematic review. Six papers

[17–22] that met the inclusion criteria were eventually selected, and two papers [21,22] were analyzed for meta-analysis. Unfortunately, the effect of exercise therapy focusing on knee joint stabilization for patients with knee OA was limited for patients with early OA. General exercise therapy also yielded similar functional recovery as exercise therapy focused on knee stabilization, and there was no specific effect of exercise therapy that focused on knee joint stabilization.

Only six papers [17–22] were selected for exercise interventions focusing on joint instability in patients with knee OA. There were only three RCTs and four cohorts or case control trials. This suggests that, despite the large number of patients with knee OA, joint instability [24, 25], a recognized factor in the development of knee OA, has not been the focus of research as a clinically important exercise interventional component. One reason is that surgical therapy is often chosen for joint instability caused by ligament tears. In fact, many of the excluded papers assessed the effects of interventions on patients who had undergone reconstructive surgery after anterior cruciate ligament injury [26–37] or total knee arthroplasty [38–46]. Joint instability associated with ligament and meniscus injuries is the first option for treatment, and few papers on joint instability in age-related knee OA have been published. It was inferred that this makes it difficult to assess joint instability both statically and dynamically. Objective measures were scarce due to the lack of established methods for assessing dynamic knee instability, and dynamic knee instability was assessed based on the self-reported number of episodes of knee instability within the previous 6 weeks. This subjective evaluation method does not quantify dynamic knee instability; therefore, these results are difficult to compare with those of other papers. To prove that joint instability is one of the causes of human, as well as animal knee OA, it is necessary to confirm the changes before and after exercise treatment by an established quantitative evaluation method. In addition, since most forms of exercise therapy for knee instability are aimed at stabilizing the knee joint during movement (i.e. knee joint control), establishing a quantitative evaluation method is more sought after.

Exercise therapy focusing on joint instability was investigated by three RCTs [20–22]: two of them focused on stabilization of the knee joint early in the intervention [20,21] and one focused on agility and perturbation of the knee joint [22]. All three papers had one thing in common, strength maintenance training of the knee, which resulted in an improvement in the WOMAC physical function score after treatment in both the experimental and control groups. In general, previous reports of common exercise treatment of age-related OA led to functional improvements [47]. This is consistent with the results of previous reports showing that exercise treatment of OA led to functional improvements.

However, the meta-analysis focusing on joint instability did not show any effect on post-treatment knee instability compared to the control group without exercise therapy. Whether these differences in muscular endurance and strength training modalities resulted in differences in the effects on knee instability is not known, and future research should aim to elucidate this aspect. In addition, training added to muscle maintenance and strength training included intrinsic sensory receptivity and a neuromuscular approach. Specifically, training focused on knee stabilization involved the perception of knee position and movement in relation to the intrinsic sensory reception, and the maintenance of static or dynamic control of the knee in relation to the neuromuscular system. In the training focused on agility and perturbation, agility training was used primarily as a neuromuscular approach, and perturbation training as an intrinsic sensory receptivity approach. However, the fact that there was no difference in knee instability ratings compared to the control group did not indicate whether this was an important difference for knee instability, since this training did not add knee stabilization value to muscle maintenance and strength training.

On the other hand, exercise therapy focusing on knee joint stabilization tended to be effective for patients with knee OA and many instability episodes. Specifically, Knoop et al. concluded that initial knee stabilization therapy may have added value in patients with knee instability and strong muscles [20,21]. Therefore, prior to exercise therapy for knee joint instability, evaluation of physical functions, such as muscle strength and knee joint instability, and appropriate treatment protocols, may improve the treatment for knee joint instability in comparison with muscle strength and enhancement training for inherent sensation and neuromuscular training.

There are some caveats to the interpretation of this review. Publication bias could not be verified due to the limited number of published papers on joint instability and knee OA, and further verification is essential. Also, the influence of fear, varus-valgus alignment (lateral thrust), and bilateral vs. unilateral joint involvement on the joint instability has not been verified. Finally, there was a small gap between the intervention periods of the two studies in the integration of meta-analysis.

In conclusion, the selected studies showed no beneficial results of exercise therapy focused on knee joint instability, including muscle maintenance and strength training, or specific training targeting knee instability. However, because of the benefits of treatment protocols based on patient attributes in exercise treatment focused on joint instability, it is necessary to investigate the effects in more detail in the future. Therefore, this systematic review offers two practical recommendations for exercise treatment of joint instability and OA. The first is to establish a method for dynamic and static assessment of joint instability. Dynamic joint instability has been fine-tuned by the patient's subjectivity through interviews. As reported by Skou et al., it is possible to quantify joint instability with a three-dimensional analysis device, and these longitudinal examinations are necessary. Secondly, further details (such as the severity of OA, the degree of instability, and muscle weakness) are needed for exercise therapy focusing on joint instability. Further graded studies on knee OA, in which various factors are involved, are urgently needed.

Lastly, the purpose of this study was to examine the effect of exercise therapy on joint instability in patients with knee OA through a systematic review and meta-analysis. The results show that exercise therapy for knee OA influences muscle strength and pain; the effects of specific training targeting joint instability are not different from those of general exercise therapy; for patients with weak muscle strength, muscle strengthening prior to stabilization therapy may provide added value.

Contributions

All authors have read and approved the final submitted manuscript.
Study design: S. Kawabata, K. Nakao, and K. Murata.
Article collection: Y. Morishita and K. Murata.
Main reviewer: S. Kawabata, K. Nakao, and K. Murata.
Sub reviewer: Y. Oka, K. Arakawa, S. Kita, A. Kuroo, S. Nakagaki, and K. Kubita.
Meta-analysis: M. Sono and K. Murata.
Manuscript composition: K. Murata, T. Kokubun, and N. Kanemura.

Role of funding source

This study was supported by Japan Society for the Promotion of Science KAKENHI (20K19417) Grant-in-Aid for Young Scientists.

Declaration of competing interest

The authors have no conflicts of interest to report.

Acknowledgements

The authors thank Takuma Kojima, Chiharu Takasu, Takuma

Sakakida, and Tomonori Terada (students at Saitama Prefectural University) for their assistance with the review.

References

[1] D. Blalock, A. Miller, M. Tilley, J. Wang, Joint instability and osteoarthritis, Clin. Med. Insights Arthritis Musculoskelet. Disord. 8 (2015) 15–23. https://doi:10.4137/CMAMD.S22147.
[2] K. Murata, N. Kanemura, T. Kokubun, T. Fujino, Y. Morishita, K. Onitsuka, S. Fujiwara, A. Nakajima, D. Shimizu, K. Takayanagi, Controlling joint instability delays the degeneration of articular cartilage in a rat model, Osteoarthr. Cartil. 25 (2017) 297–308. https://doi:10.1016/j.joca.2016.10.011.
[3] K. Murata, T. Kokubun, K. Takayanagi, N. Kanemura, Restoring knee joint kinematics after anterior cruciate ligament injury might inhibit synovial membrane inflammation, Sport Sci. Health 15 (2019) 249–253. https://doi:10.1007/s11332-018-0481-y.
[4] K. Onitsuka, K. Murata, T. Kokubun, S. Fujiwara, A. Nakajima, Y. Morishita, N. Kanemura, Effects of controlling abnormal joint movement on expression of MMP13 and TIMP-1 in osteoarthritis, Cartilage 11 (2020) 98–107. https://doi:10.1177/1947603518783449.
[5] K. Murata, T. Kokubun, Y. Morishita, K. Onitsuka, S. Fujiwara, A. Nakajima, T. Fujino, K. Takayanagi, N. Kanemura, Controlling abnormal joint movement inhibits response of osteophyte formation, Cartilage 9 (2018) 391–401. https://doi:10.1177/1947603517700955.
[6] K. Murata, T. Kokubun, K. Onitsuka, Y. Oka, T. Kano, Y. Morishita, K. Ozone, N. Kuwabara, J. Nishimoto, T. Isho, K. Takayanagi, N. Kanemura, Controlling joint instability after anterior cruciate ligament transection inhibits transforming growth factor-beta-mediated osteophyte formation, Osteoarthr. Cartil. 27 (2019) 1185–1196. https://doi:10.1016/j.joca.2019.03.008.
[7] J. Knoop, M. van der Leeden, M. van der Esch, C.A. Thorstensson, M. Gerritsen, R.E. Voorneman, W.F. Lems, L.D. Roorda, J. Dekker, M. Steultjens, Association of lower muscle strength with self-reported knee instability in osteoarthritis of the knee: results from the Amsterdam osteoarthritis Cohort, Arthritis Care Res. 64 (2012) 38–45. https://doi:10.1002/acr.20597.
[8] J.A. Gustafson, S. Gorman, G.K. Fitzgerald, S. Farrokhi, Alterations in walking knee joint stiffness in individuals with knee osteoarthritis and self-reported knee instability, Gait Posture 43 (2016) 210–215. https://doi:10.1016/j.gaitpost.2015.09.025.
[9] Japan Physical Therapists Association, Physical Therapy Guidelines, 2011, Version 1. http://jspt.japanpt.or.jp/upload/jspt/obj/files/guideline/00_ver_all.pdf. (Accessed 20 June 2020).
[10] Y. Oka, K. Murata, T. Kano, K. Ozone, K. Arakawa, T. Kokubun, N. Kanemura, Impact of controlling abnormal joint movement on the effectiveness of subsequent exercise intervention in mouse models of early knee, Osteoarthr. Cartil. 13 (2019), 1947603519885007. https://doi:10.1177/1947603519885007.
[11] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, BMJ 339 (2009), https://doi.org/10.1136/bmj.b2535.
[12] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P.A. Loannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, Ann. BMJ 339 (2009), https://doi.org/10.1136/bmj.b2700.
[13] Cochrane. https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2, 2019. (Accessed 20 June 2020).
[14] M.J. Downes, M.L. Brennan, H.C. Williams, R.S. Dean, Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS), BMJ 6 (2016), e011458. https://doi:10.1136/bmjopen-2016-011458.
[15] GRADE Working Group, Grading quality of evidence and strength of recommendations, BMJ 328 (2004) 1490, https://doi.org/10.1136/bmj.328.7454.1490.
[16] G.H. Guyatt, A.D. Oxman, H.J. Schünemann, P. Tugwell, A. Knottnerus, GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology, J. Clin. Epidemiol. 64 (2011) 380–382, https://doi.org/10.1016/j.jclinepi.2010.09.011.
[17] J.A. Gustafson, S. Gorman, G.K. Fitzgerald, S. Farrokhi, Alterations in walking knee joint stiffness in individuals with knee osteoarthritis and self-reported knee instability, Gait Posture 43 (2016) 210–215. https://doi:10.1016/j.gaitpost.2015.09.025.
[18] S.T. Skou, T.V. Wrigley, B.R. Metcalf, R.S. Hinman, K.L. Bennell, Association of knee confidence with pain, knee instability, muscle strength, and dynamic varus-valgus joint motion in knee osteoarthritis, Arthritis Care Res. 66 (2014) 695–701. https://doi:10.1002/acr.22208.
[19] G.K. Fitzgerald, D.K. White, S.R. Piva, Associations for change in physical and psychological factors and treatment response following exercise in knee osteoarthritis: an exploratory study, Arthritis Care Res. 64 (2012) 1673–1680. https://doi:10.1002/acr.21751.
[20] J. Knoop, M. van der Leeden, L.D. Roorda, C.A. Thorstensson, M. van der Esch, W.F. Peter, M. de Rooij, W.F. Lems, J. Dekker, M.P. Steultjens, Knee joint stabilization therapy in patients with osteoarthritis of the knee and knee instability: subgroup analyses in a randomized, controlled trial, J. Rehabil. Med. 46 (2014) 703–707. https://doi:10.2340/16501977-1809.
[21] J. Knoop, J. Dekker, M. van der Leeden, M. van der Esch, C.A. Thorstensson, M. Gerritsen, R.E. Voorneman, W.F. Peter, M. de Rooij, S. Romviel, W.F. Lems, L.D. Roorda, M.P. Steultjens, Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial, Osteoarthr. Cartil. 21 (2013) 1025–1034. https://doi:10.1016/j.joca.2013.05.012.
[22] G.K. Fitzgerald, S.R. Piva, A.B. Gil, S.R. Wisniewski, C.V. Oddis, J.J. Irrgang, Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial, Phys. Ther. 91 (2011) 452–469. https://doi:10.2522/ptj.20100188.
[23] J.J. Irrgang, L. Snyder-Mackler, R.S. Wainner, F.H. Fu, C.D. Harner, Development of a patient-reported measure of function of the knee, J. Bone Joint Surg. Am. 80 (1998) 1132–1145. https://doi:10.2106/00004623-199808000-00006.
[24] G.K. Fitzgerald, S.R. Piva, J.J. Irrgang, Reports of joint instability in knee osteoarthritis: its prevalence and relationship to physical function, Arthritis Rheum. 51 (2004) 941–946. https://doi:10.1002/art.20825.
[25] D.T. Wallace, P.E. Riches, F. Picard, The assessment of instability in the osteoarthritic knee, EFORT Open Rev 4 (2019) 70–76. https://doi:10.1302/2058-5241.4.170079.
[26] P. Kouloumentas, E. Kavroudakis, E. Charalampidis, D. Kavroudakis, G.K. Triantafyllopoulos, Superior knee flexor strength at 2 years with all-inside short-graft anterior cruciate ligament reconstruction vs a conventional hamstring technique, Knee Surg. Sports Traumatol. 7 (2019) 3592–3598. https://doi:10.1007/s00167-019-05456-9.
[27] K.E. Webster, J.A. Feller, N. Hartnett, W.B. Leigh, A.K. Richmond, Comparison of patellar tendon and hamstring tendon anterior cruciate ligament reconstruction: a 15-year follow-up of a randomized controlled trial, Am. J. Sports Med. 44 (2016) 83–90. https://doi:10.1177/0363546515611886.
[28] D. Tsoukas, V. Fotopoulos, G. Basdekis, K.G. Makridis, No difference in osteoarthritis after surgical and non-surgical treatment of ACL-injured knees after 10 years, Knee Surg. Sports Traumatol. Arthrosc. 24 (2016) 2953–2959. https://doi:10.1007/s00167-015-3593-9.
[29] R. Sun, B.C. Chen, F. Wang, X.F. Wang, J.Q. Chen, Prospective randomized comparison of knee stability and joint degeneration for double-and single-bundle ACL reconstruction, Knee Surg. Sports Traumatol. Arthrosc. 23 (2015) 1171–1178. https://doi:10.1007/s00167-014-2934-4.
[30] P. Swärd, T. Fridén, T. Boegård, I. Kostogiannis, P. Neuman, H. Roos, Association between varus alignment and post-traumatic osteoarthritis after anterior cruciate ligament injury, Knee Surg. Sports Traumatol. Arthrosc. 21 (2013) 2040–2047. https://doi:10.1007/s00167-013-2550-8.
[31] R.B. Frobell, H.P. Roos, E.M. Roos, F.W. Roemer, J. Ranstam, L.S. Lohmander, Treatment for acute anterior cruciate ligament tear: five year outcome of randomized trial, BMJ 346 (2013). https://doi:10.1136/bmj.f232.
[32] B.C. Fleming, P.D. Fadale, M.J. Hulstyn, R.M. Shalvoy, H.L. Oksendahl, G.J. Badger, G.A. Tung, The effect of initial graft tension after anterior cruciate ligament reconstruction: a randomized clinical trial with 36-month follow-up, Am. J. Sports Med. 41 (2013) 25–34. https://doi:10.1177/0363546512464200.
[33] P. Suomalainen, T. Järvelä, A. Paakkala, P. Kannus, M. Järvinen, Double-bundle versus single-bundle anterior cruciate ligament reconstruction: a prospective randomized study with 5-year results, Am. J. Sports Med. 40 (2012) 1511–1518. https://doi:10.1177/0363546512448177.
[34] K. Sun, J. Zhang, Y. Wang, C. Zhang, C. Xia, T. Yu, S. Tian, A prospective randomized comparison of irradiated and non-irradiated hamstring tendon allograft for ACL reconstruction, Knee Surg. Sports Traumatol. Arthrosc. 20 (2012) 187–194. https://doi:10.1007/s00167-010-1393-9.
[35] I. Holm, B.E. Oiestad, M.A. Risberg, A.K. Aune, No difference in knee function or prevalence of osteoarthritis after reconstruction of the anterior cruciate ligament with 4-strand hamstring autograft versus patellar tendon-bone autograft: a randomized study with 10-year follow-up, Am. J. Sports Med. 38 (2010) 448–454. https://doi:10.1177/0363546509350301.
[36] A. Meunier, M. Odensten, L. Good, Long-term results after primary repair or non-surgical treatment of anterior cruciate ligament rupture: a randomized study with a 15-year follow-up, Scand. J. Med. Sci. Sports 17 (2007) 230–237. https://doi:10.1111/j.1600-0838.2006.00547.x.
[37] L.R. Swirtun, A. Jansson, P. Renström, The effects of a functional knee brace during early treatment of patients with a nonoperated acute anterior cruciate ligament tear: a prospective randomized study, Clin. J. Sport Med. 15 (2005) 299–304. https://doi:10.1097/01.jsm.0000180018.14394.7e.
[38] N.M. Kosse, P.J.C. Heesterbeek, J.J.P. Schimmel, G.G. van Hellemondt, A.B. Wymenga, K.C. Defoort, Stability and alignment do not improve by using patient-specific instrumentation in total knee arthroplasty: a randomized controlled trial, Knee Surg. Sports Traumatol. Arthrosc. 26 (2018) 1792–1799. https://doi:10.1007/s00167-017-4792-3.
[39] H. Hommel, K. Wilke, D. Kunze, P. Hommel, P. Fennema, Constraint choice knee arthroplasty: study protocol of a randomised controlled trial assessing the effect of level of constraint on postoperative outcome, BMJ (Open) 7 (2017), e012964. https://doi:10.1136/bmjopen-2016-012964.
[40] C. Baier, W. Fitz, B. Craiovan, A. Keshmiri, S. Winkler, R. Springorum, J. Grifka, J. Beckmann, Improved kinematics of total knee replacement following partially navigated modified gap-balancing technique, Int. Orthop. 38 (2014) 243–249. https://doi:10.1007/s00264-013-2140-x.
[41] M. Takeda, Y. Ishii, H. Noguchi, Y. Matsuda, J. Sato, Changes in varus-valgus laxity after total knee arthroplasty over time, Knee Surg. Sports Traumatol. Arthrosc. 20 (2012) 1988–1993. https://doi:10.1007/s00167-011-1783-7.
[42] C.O. Tibesku, K. Daniilidis, V. Vieth, A. Skwara, W. Heindel, S. Fuchs-Winkelmann, Sagittal plane kinematics of fixed- and mobile-bearing total knee replacements, Knee Surg. Sports Traumatol. Arthrosc. 19 (2011) 1488–1495. https://doi:10.1007/s00167-011-1462-8.
[43] T. Matsumoto, H. Muratsu, S. Kubo, K. Mizuno, K. Kinoshita, K. Ishida, T. Matsushita, K. Sasaki, K. Tei, K. Takayama, H. Sasaki, S. Oka, M. Kurosaka,

R. Kuroda, Soft tissue balance measurement in minimal incision surgery compared to conventional total knee arthroplasty, Knee Surg. Sports Traumatol. Arthrosc. 19 (2011) 880–886. https://doi:10.1007/s00167-010-1224-z.
[44] M. Hilding, P. Aspenberg, Local perioperative treatment with a bisphosphonate improves the fixation of total knee prostheses: a randomized, double-blind radiostereometric study of 50 patients, Acta Orthop. 78 (2007) 795–799. https://doi:10.1080/17453670710014572.
[45] Y.H. Kim, D.Y. Kim, J.S. Kim, Simultaneous mobile- and fixed-bearing total knee replacement in the same patients. A prospective comparison of mid-term outcome using a similar design of prosthesis, J. Bone Joint Surg. Br. 89 (2007) 904–910. https://doi:10.1302/0301-620X.89B7.18635.
[46] R. Straw, S. Kulkarni, S. Attfield, T.J. Wilton, Posterior cruciate ligament at total knee replacement. Essential, beneficial or a hindrance? J. Bone Joint Surg. Br. 85 (2003) 671–674. https://doi:10.1302/0301-620x.85b5.13812.
[47] A.K. Lange, B. Vanwanseele, M.A. Fiatarone Singh, Strength training for treatment of osteoarthritis of the knee: a systematic review, Arthritis Rheum. 59 (2008) 1488–1494. https://doi:10.1002/art.24118.