

Activity level and quality of life among patients before and after total knee
replacement surgery

Ph.D. Thesis

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List of Abbreviations:

Body Mass Index: BMI

Cochrane Central Register of Controlled Trials: CENTRAL

Confidence Intervals: CIs

Controlled Clinical trials: CCTs

Female: F

Kellgren-Lawrence grade: KL

Knee injury and Osteoarthritis Outcome Score: KOOS

Knee Society Score: KSS

Male: M

Multivariate Analysis of Variance: MANOVA

National Institutes of Health: NIH

Non-Steroidal Anti-Inflammatory Drugs: NSAIDs

Not Applicable: NA

Osteoarthritis: OA

Osteoarthritis Research Society International: OARSI

Osteoarthritis-specific Quality of Life scale: OAQoL

Oxford Knee Score: OKS

Physical Activity: PA

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: PRISMA

Quality of Life: QoL

Randomized Controlled Trials: RCTs

Risk Of Bias In Nonrandomized Studies: ROBINS-I

Short Form 36: SF-36

Strengthening the Reporting of observational studies in Epidemiology: STROBE

Total Knee Replacement: TKR

Visual Analog Score: VAS

Weighted Mean Differences: WMDs

Western Ontario and McMaster Universities Osteoarthritis Index: WOMAC

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1. Introduction and aims

1.1 Definition of Osteoarthritis (OA)

Osteoarthritis (OA) is a progressive musculoskeletal disorder that is associated with bone enlargement, changes in the joint margin, and cartilage denegation (Glyn-Jones et al., 2015). This injury is one of the most common age-related injuries that leads to chronic disability and health burden (Glyn-Jones et al., 2015). OA is more commonly seen in weight-bearing joints, such as the hip and knee joints, than in non-weight bearing joints, such as hand joints (Glyn-Jones et al., 2015, Felson et al., 2000, Felson, 2006). Knee OA is a very common type of osteoarthritis that is associated with cartilage breakdown, meniscus damage, new bone growth at the joint margin, and biomechanical changes. The incidence of OA in the knee joint is the greatest (up to 30%) compared with other joints (Glyn-Jones et al., 2015, Felson et al., 2000, Felson, 2006). Knee OA is becoming the leading cause of disability among elderly individuals, as it is the 11th highest contributor to global disability (Cross et al., 2014). Knee OA is joined with high mortality, cardiovascular problems, and low quality of life (QoL) (Hawker et al., 2014, Felson, 2006, Felson et al., 2000, Glyn-Jones et al., 2015).

1.2 Risk factors for knee OA

Various risk factors are associated with knee OA, such as age, genetic factors, gender, body weight, muscle weakness, and knee joint alignment deformities (Felson, 2006, Felson et al., 2000, Felson et al., 1988, Felson et al., 1991). The age factor is strongly associated with knee OA. It is suggested that the thickness of cartilage decreases and its ability to absorb shocks during daily activity decreases with age. These changes lead to a breakdown of cartilage cells and new bone growth (osteophytes) (Felson, 2006, Felson et al., 2000, Felson et al., 1997). It has been estimated that the risk of developing knee OA with osteophytes increases by 20% per five years of age after the age of 54 years old (Hart et al., 1999).

The second important risk factor is gender. Knee OA is more common among women (11%) than men (7%), particularly after the age of 50 years old (Felson et al., 2000, Felson et al., 1997).

Women after 50 years old have low levels of estrogen, which leads to cartilage breakdown and low metabolism (Felson et al., 2000, Beaupre et al., 2000). These changes make women have a higher prevalence of knee OA than men. In the Netherlands, women have a relative risk of two (95% CI: 1.74–2.31) to develop radiological knee OA compared with men (Szilagyi et al., 2022). Furthermore, the risk of knee OA among the obese population is higher than that among the average-weight population. Obesity, however, not only increases the risk of developing knee OA three times but also increases the progression of knee OA (Murphy et al., 2008, Felson et al., 2000). It has been suggested that women with body mass index more than 26.4 kg/m² had a significant risk of developing knee osteophytes (Spector et al., 1994). Moreover, women with obesity have a significantly higher incidence (incidence rate 3.3% per year) of osteophytes than non-obese women (Hart et al., 1999). Additionally, it has been estimated that each five kg increase in weight over the average weight will increase the incidence of osteophytes by 30% (Hart et al., 1999).

1.3 Symptoms of knee OA

Knee OA is associated with clinical symptoms and/or radiological symptoms. The clinical symptoms based on the American College of Rheumatology include pain, crepitus, morning stiffness, low physical activity level, joint instability, swelling, gait deformity, joint effusion, and local inflammation (Suter et al., 2017, Hunter et al., 2008, Altman et al., 1991). Mainly, pain and low physical activity level are the leading causes of disability among patients with knee OA (Suter et al., 2017, Hunter et al., 2008, Altman et al., 1991).

The radiological symptoms based on X-ray are characterized by inflammation, new bone growth (osteophytes), cartilage breakdown, debris in the synovial fluid, and subchondral cysts (Jacobson, 1996, Kellgren and Lawrence, 1957). The Kellgren and Lawrence (K-L) scale is used to assess knee OA by measuring space narrowing and osteophyte appearance (Kellgren and Lawrence, 1957). Based on this scale, knee OA has five grades: zero (no OA), grade K-L1 (doubtful of having knee OA), grade K-L2 (mild knee OA), K-L3 (moderate knee OA), and K-L4 (severe knee OA) (Kellgren and Lawrence, 1957, Ryu et al., 2012) (Figure 1).



Figure 1: Knee OA grades (Ryu et al., 2012).

1.4 Prevalence of knee OA

In Hungary, it was estimated that 17% of the Hungarian population had OA based on the European Health Interview Survey 2014 (Fekete et al., 2020). In addition, Fekete et al., 2020 found that 15.15% of the patients had knee OA (15 out of 99 patients) for more than ten years. This study found that women are more affected by knee OA than men (12.4% and 9.9%, respectively) (Fekete et al., 2020). Furthermore, Horváth et al., 2011 found that 111 patients (out of 672, 16.5%, 70 women and 41 men) had radiographic knee OA and 2.9% of them had severe knee OA ($K-L \geq 3$) in the south-western part of Hungary (Horváth et al., 2011). Most of these patients were elderly with a high body mass index (more than 30 kg/m^2), but there were no differences in prevalence between women and men (Horváth et al., 2011). Another study for Horváth in 2010 found that 91 of of 676 (13.3%) participants had radiographic knee OA and 20 (2.9%) participants had severe knee OA (Horváth et al., 2010).

The quality of life among Hungarian patients with knee OA was the worst compared to other patients from Germany, Spain, and Italy based on the osteoarthritis-specific quality of life scale (OAQoL), which could be related to differences in culture, the provided health services, and duration of illness (Wilburn et al., 2017).

1.5 Knee OA treatments

Various treatments are currently available to address knee OA that could be conservative or surgical interventions. The suitable interventions are chosen based on the grade of knee OA, the severity of pain, and activity level limitations (Beswick et al., 2019, Smith et al., 2016, Robert-Lachaine et al., 2020). Nevertheless, all of the interventions aim to reduce pain, improve the physical activity level, enhance the quality of life, and reduce OA progression (Beswick et al., 2019, Smith et al., 2016, Robert-Lachaine et al., 2020).

1.5.1 Conservative interventions

Different conservative interventions are being prescribed for patients with knee OA, namely, education, weight management, pharmacology treatments, physiotherapy sessions, and orthotics interventions (Lim and Al-Dadah, 2022). The pharmacological treatments included non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, or corticosteroid injections. In general, pharmacological treatments are used to reduce pain in mild knee OA. However, pharmacological treatments cannot be used for the long-term because they are associated with side effects such as bone degeneration, gastrointestinal problems, and peptic ulcer development (Rannou et al., 2016, Crofford, 2013).

Physical therapy is also used with patients with knee OA as an effective intervention. The therapists provide different interventions for patients with knee OA, including manual therapy, electrical stimulation, thermotherapy, balance exercises, knee taping, posture correction exercises, massage therapy, joint manipulation, and functional training (Bosomworth, 2009, Anwer et al., 2018, Wang et al., 2012, Whittaker et al., 2021). Each type of physical intervention

has benefits and considerable limitations in dealing with pain, disabilities, knee OA progression, and quality of life improvement (Whittaker et al., 2021, Lim and Al-Dadah, 2022).

Furthermore, various orthotic interventions also show satisfactory outcomes among patients with knee OA, such as foot insole, knee brace, and knee-ankle-foot orthoses (Alfatafta, 2015, Whittaker et al., 2021, Lim and Al-Dadah, 2022, Alfatafta et al., 2021, Alfatafta et al., 2016). Orthotic interventions aim to reduce the load on the affected side to reduce pain during daily activities and enhance the quality of life (Alfatafta, 2015, Whittaker et al., 2021, Lim and Al-Dadah, 2022). Among the available conservative interventions (nonsurgical), using knee braces to treat patients with knee OA is one of the recommendations. More details were discussed in the next chapter.

Knee brace for knee OA

The knee brace is a common conservative treatment for patients with knee OA for improving the quality of life and reducing pain (Schmalz et al., 2010, Hjartarson and Toksvig-Larsen, 2018, Ornetti et al., 2015, Adhikari, 2016, Richards et al., 2005, Jones et al., 2013, Thoumie et al., 2018, Alfatafta et al., 2021). The unloader (off-loader) knee brace is widely prescribed for patients with either medial tibiofemoral compartment OA, lateral tibiofemoral compartment OA, patellofemoral knee OA, bi-compartmental knee OA, or tri-compartmental knee OA (McGibbon et al., 2021). This brace focused on load distribution away from the affected compartment and correcting the knee alignment to reduce pain, enhance the quality of life, and delay disease progression (McGibbon et al., 2021, Moller et al., 2021). It was suggested that the knee brace could decrease the force over the knee compartment between 5.5% and 30%, which helps in OA progression and soft tissue repairs (McGibbon et al., 2021, Deie et al., 2013). The main difference between the knee brace and other orthotics interventions is that the knee brace applies the force directly to femur and tibia bones to correct alignment, reduce the load over the knee joint, and enhance symmetry walking with less anxiety and pain (Draper et al., 2000).

Using the knee brace is associated with biomechanical and clinical benefits based on both subjective and objective assessment tools. Various studies assessed the biomechanical benefits (walking speeds, joint angle, joint space, pressure, joint moments, etc) of knee brace using gait

analysis (McGibbon et al., 2021, Deie et al., 2013, Yan et al., 2022, Khosravi et al., 2021). The outcomes of these studies found that the knee brace is an effective intervention to reduce the load over the knee joint, increase walking speeds, and decrease the knee varus or valgus moment (McGibbon et al., 2021, Deie et al., 2013, Yan et al., 2022, Khosravi et al., 2021). In addition, it was found that the knee valgus brace reduced the knee valgus (adduction) angle among patients with medial compartment knee OA, which led to a significant decrease ($P < 0.05$) in the mediolateral load transmitted through the medial compartment (Esrafilian et al., 2012).

Furthermore, a knee brace has positive impacts on the clinical symptoms of knee OA including pain and activity level based on subjective assessment tools. The latest systematic review by Alfatafta in 2021 (Alfatafta et al., 2021) about the effects of knee braces on pain and activity levels among patients with medial compartment knee OA stated that the knee brace is an effective conservative treatment to reduce pain and enhance the quality of life based on subjective assessment tools. The next chapter will discuss this study in depth.

However using the knee brace has biomechanical and clinical benefits, some patients did not accept using the knee brace for a long-term. For instance, some patients stopped using the knee brace because they had fitting problems, skin problems, knee pain, and walking difficulties (Deie et al., 2013, Briggs et al., 2012, Fu et al., 2015). Moreover, some patients complained of a heavy feeling of the brace or slipping down feeling or anxiety with using the knee brace (Schmalz et al., 2010, Thoumie et al., 2018, van Egmond, 2017). Hence, here are some tips to consider before using the knee brace: (a) the knee brace is more recommended for patients with body mass less than 30 kg/m^2 and with a low Kellgren-Lawrence scale, (b) it is recommended for relatively young patients, (c) it is recommended to be worn for at least six months for better outcomes, (d) and it is recommended to choose the right size (Moller et al., 2021, Draper et al., 2000, Alfatafta et al., 2021). In summary, using a knee brace is associated with biomechanical benefits, clinical benefits, and quality of life benefits. However, the knee brace should be prescribed for suitable patients to obtain the maximum benefits. The patients' criteria that could fit properly with the knee brace were discussed in chapter two.

1.5.2 Surgical interventions

There are several choices for surgical interventions, such as arthroscopy, high-tibia osteotomy, and arthroplasty (uni-compartment or total compartment) (Katz et al., 2014, Lespasio et al., 2017). Arthroscopy is a minor surgery and the simplest method, as there are no surgical tools left in the joint (Katz et al., 2014). This method is performed to remove the inflammatory debris and damaged cartilage. Compared with other surgical interventions, this method has a lower postoperative risk of inflammation, pain, and swelling (Katz et al., 2014). High-tibia osteotomy aims to reduce the load from the affected side and transfer it to the non-affected side. This surgery is suitable for young active patients with uni-compartment medial knee OA (Lespasio et al., 2017). For patients with severe and advanced knee OA, arthroplasty is the only surgical option to reduce pain and enhance the quality of life (Ferket et al., 2017a, Skou et al., 2018, Skou et al., 2016, Skou et al., 2015, Arendt-Nielsen et al., 2018, Lespasio et al., 2017).

Total knee replacement

Total knee replacement (TKR) is the most commonly used intervention for late-stage and severe knee osteoarthritis. TKR is considered a gold-standard treatment when pain is intolerable; the other treatments no longer relieve pain (Ferket et al., 2017a, Skou et al., 2018, Skou et al., 2016, Skou et al., 2015, Arendt-Nielsen et al., 2018, Lespasio et al., 2017). The core outcomes of this surgery are reducing pain and enhancing the quality of life during daily activities (Ferket et al., 2017a, Lespasio et al., 2017). It has been stated that TKR is the only option for severe knee OA to reduce pain and restore the activity level since pain could be reduced between 90-95% with up to a 2% complication rate (Lespasio et al., 2017). Additionally, more than 90% of patients who had TKR reported satisfactory outcomes that could last for 20 years after the surgery (Lespasio et al., 2017).

Various studies evaluated the effect of TKR on pain and activity level using subjective assessment tools such as questionnaires. Skou et al., 2016 evaluated the effects of TKR on pain among patients with severe knee OA in Denmark (Skou et al., 2016). This study included 100 patients with knee OA (K-L ≥ 2) from two different hospitals in Denmark. The participants were randomly divided into two groups: a TKR group and a nonsurgical group. The severity and threshold of pain were assessed using a visual analog scale questionnaire (VAS pain) and a

handheld algometer, respectively. The outcomes were measured at baseline and three months after the surgery. The patients in the TKR group underwent knee surgery followed by education, pain medication, exercises, and diet. The patients in the nonsurgical group had only education, pain medication, exercises, and diet. This study found that pain severity was reduced among both groups; however, the patients in the TKR group had less pain severity ($P= 0.20$) and had a higher pressure-pain threshold ($P<0.05$) than the control group after three months of the intervention (Skou et al., 2016).

Another study evaluated pain and activity levels among 22 patients (average age 63.7 years old, body mass index 32.9 kg/m^2) with severe knee OA in the USA before TKR and six months after surgery (Mandeville et al., 2008). After the surgery, the patients received standard rehabilitation follow-up at the hospital, but no constant rehabilitation follow-up was performed thereafter. The outcomes of this study were measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire two weeks before the surgery and six months after the surgery. The outcomes of this study found that pain based on WOMAC before the surgery was $46.69 (\pm 22.32)$. After six months of the surgery, pain was significantly reduced to $14.74 (\pm 15.12)$. Furthermore, the activity level also significantly improved from $46.90 (23.42 \pm)$ to $15.44 (\pm 12.14)$ six months after surgery (Mandeville et al., 2008).

The effect of TKR on pain and activity level was also evaluated using objective assessment tools such as accelerometers. A study by Harding et al., 2014 (Harding et al., 2014) evaluated the effect of TKR on activity level using ActiGraph. The ActiGraph is a small uniaxial accelerometer that is worn on the waist. The ActiGraph measures the activity level as physical activity counts only. During this study 25 patients with severe knee OA in Australia were recruited. After the surgery, the patients received standard postoperative care at and out of the hospital. The outcomes were evaluated before the surgery and six months after the surgery. The results of this study found that the activity level six months after surgery did not significantly change. Additionally, the patients did not meet the physical activity guideline (150 minutes of activities per week), as they spent 83% of their time on sedentary activity after the surgery compared with 82% preoperatively (Harding et al., 2014).

Another study by Frimpong et al., 2019 (Frimpong et al., 2019) also evaluated the effects of TKR on activity level using ActiGraph. This study recruited 89 patients with severe knee OA in South Africa. The activity level was examined before the surgery and six months after the surgery. This study found that sedentary time decreased by 64% ($P= 0.00$) after six months of surgery compared with preoperative sedentary time. Moreover, the spent time on light activities also significantly increased by 34.8% ($P= 0.00$) six months after the surgery (Frimpong et al., 2019).

Nevertheless, after reviewing the available studies in this field, it has been found that there is insufficient information that covers the effect of TKR on activity level using high reliability accelerometers such as ActivPAL. Thus, the missing information will be discussed in depth in chapter three.

1.6 Conclusion

Knee OA is a serious musculoskeletal injury and the leading cause of disability, low activity level, and low quality of life in Hungary and worldwide. Various treatments are currently available to address knee OA that could be conservative or surgical interventions. The suitable interventions are chosen based on the grade of knee OA, the severity of pain, and activity level limitations. Nevertheless, all of the interventions aim to reduce pain, improve the physical activity level, enhance the quality of life, and reduce OA progression. The knee brace is the most commonly used conservative intervention for mild and moderate knee OA. Total knee replacement (TKR) is the most commonly used surgical intervention for severe knee OA. The two different interventions aim to reduce pain and increase the activity level to enhance the quality of life.

1.7 Aims

The effects of the knee brace and TKR on pain and activity level are generally measured by both subjective and objective assessment tools. Nevertheless, some questions are still poorly addressed, or insufficient information is available about these two types of interventions (knee brace and total knee replacement surgery). For instance, in Hungary, there are no databases about the activity level of Hungarian patients before and after total knee replacement surgery based on objective assessment tools, as subjective assessment tools (questionnaires) were mainly used to assess pain and activity levels. Therefore, during my Ph.D study, I found gaps in the available information about the knee valgus brace and total knee surgery, and I worked to answer the following aspects with different research methodologies:

1- The effect of knee valgus brace on pain and activity level over different time intervals among patients with medial knee OA. The aim of this study was critically evaluating the studies that only assessed the effect of knee valgus brace on pain and activity level among medial knee OA participants in the last 20 years (from 2000-2020).

2-The effect of total knee replacement surgery on activity level based on ActivPAL. The aim of this study was to understand the objective improvement after total knee replacement surgery to

find out if this surgery could significantly enhance the quality of life or not, based on a high-quality accelerometer.

3-The activity level improvement after total knee replacement surgery among patients with severe knee OA using the ActivPAL and SF-36. The aim of this study was to evaluate the improvement in quality of life pre-post TKR surgery among patients using subjective and objective assessment tools

4- Quality of life of patients with severe knee osteoarthritis who were on the waiting list for total knee replacement surgery in Hungary. The aims of this study were providing clear information about quality of life for patients with severe knee OA, identifying the most challenging activities for patients with severe knee OA, and identifying whether there were differences in quality of life across the included women and men.

2. Effect of using knee valgus brace on pain and activity level over different time intervals among patients with medial knee OA: A systematic review ¹

2.1 Introduction

Knee osteoarthritis is the most common reason for disability, pain, and limited activity level among the elderly. The medial compartment of the knee joint is 10 times more likely to be affected by osteoarthritis (OA) than the lateral compartment because it receives almost 70% of the total joint load during walking (Haladik et al., 2014, Schipplein and Andriacchi, 1991, Birmingham et al., 2001). In the UK and Netherlands, it has been seen that 25% of elderly over 50 years have severe knee OA yearly (Peat et al., 2001), and women are more affected than men (6.6% vs. 4.9%, women vs. men, respectively) (Guillemin et al., 2011). During medial knee OA, the medial space of the knee joint is narrowing due to cartilage degeneration that leads to a high varus moment (Birmingham et al., 2001, Haladik et al., 2014, Jones et al., 2013). This high varus moment generates pain during daily activity and sometimes during rest in severe cases. Moreover, it has been suggested that patients with knee OA complain of knee instability during daily activities which is correlated with knee pain and low quality of life (Ramsey et al., 2007).

The primary questionnaires that are used to evaluate pain and activity level among patients with knee OA are the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analogue pain score (VAS), the short form 36 (SF-36), and the Knee injury and Osteoarthritis Outcome Score (KOOS). Those questionnaires have high validity and reliability (Bellamy et al., 1988, Collins et al., 2016, Hawker et al., 2011, Ware and Sherbourne, 1992), and examine pain and activity in the last previous weeks; hence, the patients can remember their experiences with pain and their daily activities (Bellamy et al., 1988, Hawker et al., 2011, Hjartarson and Toksvig-Larsen, 2018, Roos et al., 1998).

¹ Reference: Alfatafta, H., Onchonga, D., Alfatafta, M., Boncz, I., Lohner, S., & Molics, B. (2021). Effect of using knee valgus brace on pain and activity level over different time intervals among patients with medial knee OA: systematic review. *BMC musculoskeletal disorders*, 22(1), 1-9.

Various interventions (surgical and non-surgical) are recommended based on the Osteoarthritis Research Society International (OARSI) guidelines such as surgical interventions, physiotherapy, orthotics (foot orthoses, knee braces), pain killers, and self-managements. Those interventions aim to reduce pain, improve activity level, and slow disease progressions (Bannuru et al., 2019, Pham et al., 2003).

The Knee valgus brace is one of the accepted conservative interventions for patients with medial compartment knee OA to improve quality of life and reduce the load on the medial compartment of the knee joint (Haladik et al., 2014, Jones et al., 2013). This brace is used to correct the knee varus by applying valgus force with two methods: bending system (three-point pressure system) directly to the knee joint or by applying valgus force and external rotation of the leg (Gaasbeek et al., 2007, Haladik et al., 2014, Jones et al., 2013, Robert-Lachaine et al., 2020). Both designs aim to reduce the knee varus alignment, unload the medial compartment of the knee, and decrease the symptoms (Gaasbeek et al., 2007, Haladik et al., 2014, Jones et al., 2013). Thus, using the knee valgus brace could increase the knee's mediolateral stability and reduce pain (Ramsey et al., 2007). The knee valgus brace could be an off-the-shelf or custom-made brace. Most of the studies recommend using the custom-made knee valgus brace because it shows better fitting, better knee varus correction, and better activity level improvement (Birmingham et al., 2001, Draganich et al., 2006, Jones et al., 2013).

The available systematic review and meta-analysis studies evaluated all kinds of knee braces (such as soft, dynamic, valgus, and others) that are used for patients with medial compartment knee OA, but there is no study has evaluated the effect of knee valgus brace over a different time interval. Thus, the aim of this study is critically evaluating the studies that only assessed the effect of knee valgus brace on pain and activity level among medial knee OA participants in the last 20 years (from 2000-2020). The time interval of using a knee valgus brace was determined as short-term use (up to 3 months), moderate-term use (more than 3 months and up to 6 months), and long-term use (more than 6 months).

2.2 Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were used to report the methodology and the results of the systematic review.

2.2.1 Search strategy

Two independent reviewers searched the following electronic databases from January 2000 until the end of November 2020: Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PubMed, Web of Science, and Scopus. The used search strategy is available in Appendix 1 and the search strategy was adapted for the different databases as required.

2.2.2 Study screening

Two reviewers independently selected studies based on predefined inclusion criteria. The titles and abstracts were reviewed first, and irrelevant references were excluded. Then full-text publications of potentially relevant studies were obtained and checked for final inclusion. The references and related articles of the selected studies were screened for more suitable studies. Any disagreement was resolved by discussion between the two reviewers. If they could not reach an agreement, the third reviewer was consulted and a decision was made by a discussion and majority vote. Authors were contacted if the data were not clear or further information was required.

2.2.3 Eligibility criteria

All studies (randomized-controlled-trials (RCTs), controlled clinical trials (CCTs), and other study designs, such as cohort studies and case-control studies) that evaluated the effects of knee valgus brace on pain and functional activities were included and they had to be written in English. Also, they had to meet all of the following criteria:(a) adult participants with medial compartment knee osteoarthritis, (b) participants with pain, morning stiffness, and activity level limitations, (c) the outcomes of pain and/or activity level are measured using WOMAC, SF36, KOOS, or VAS, (d) and publication between January 2000-end of November 2020.

The study was excluded if it (a) looked at evaluating the knee valgus brace combined with another treatment or medication, (b) had children participants, (c) evaluated pain and activity level with other questionnaires, (d) used different kinds of knee orthoses instead of knee valgus brace, (e) had patients with lateral compartment knee OA or had OA in other joints such as hip or ankle joints. No restrictions if the knee OA was with clinical or/and radiological symptoms.

2.2.4 Data extraction and risk-of-bias assessment

Two reviewers independently extracted data from the selected studies or reports according to a fixed protocol (screening strategy). The following information was extracted: study design, number of participants, patients' demographic, the health status of participants, type of knee brace, duration, pain score, activity level scores, and funding resources.

The risk of bias in each study was assessed by two reviewers independently according to the Strengthening the Reporting of Observational Studies in Epidemiology tool (STROBE) for non-randomized studies and the Cochrane risk-of-bias tool for randomized controlled studies. STROBE evaluates the good reporting of the observational studies and has 22 items to assess the reporting quality of title and abstract, introduction, methods, results, and discussion sections (Vandenbroucke et al., 2014, Vandenbroucke et al., 2007).

The Cochrane risk-of-bias tool evaluates six items: random sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each item is judged as being in one of three categories: low (low risk of bias), high (high risk of bias), and unclear (lack of information or uncertainty about the potential for bias). 'Low' indicates a superior quality study, whereas 'high' indicates methodology of inferior quality.

2.3 Results

A total of 986 potentially relevant records were identified through the systematic literature search of electronic databases. After removing duplicates, 806 unique records were assessed for eligibility (Figure 2). From these, 770 records were excluded after the title and abstract screening, and another 12 were excluded after full-text screening. Finally, 24 records fulfilled the inclusion criteria (579 participants, with an average age of 57 ± 5.5 years, and with an average body mass index of 26 ± 2.1 kg/m²).

Only seven of them are randomized control studies and the rest are either crossover studies or prospective studies (Table 1). Those studies evaluated the effect of knee valgus brace on pain and/or activity level over different time intervals: short-term use (up to three months), moderate-term use (up to six months), and long-term use (more than six months) among participants with medial compartment knee OA (Table 1).

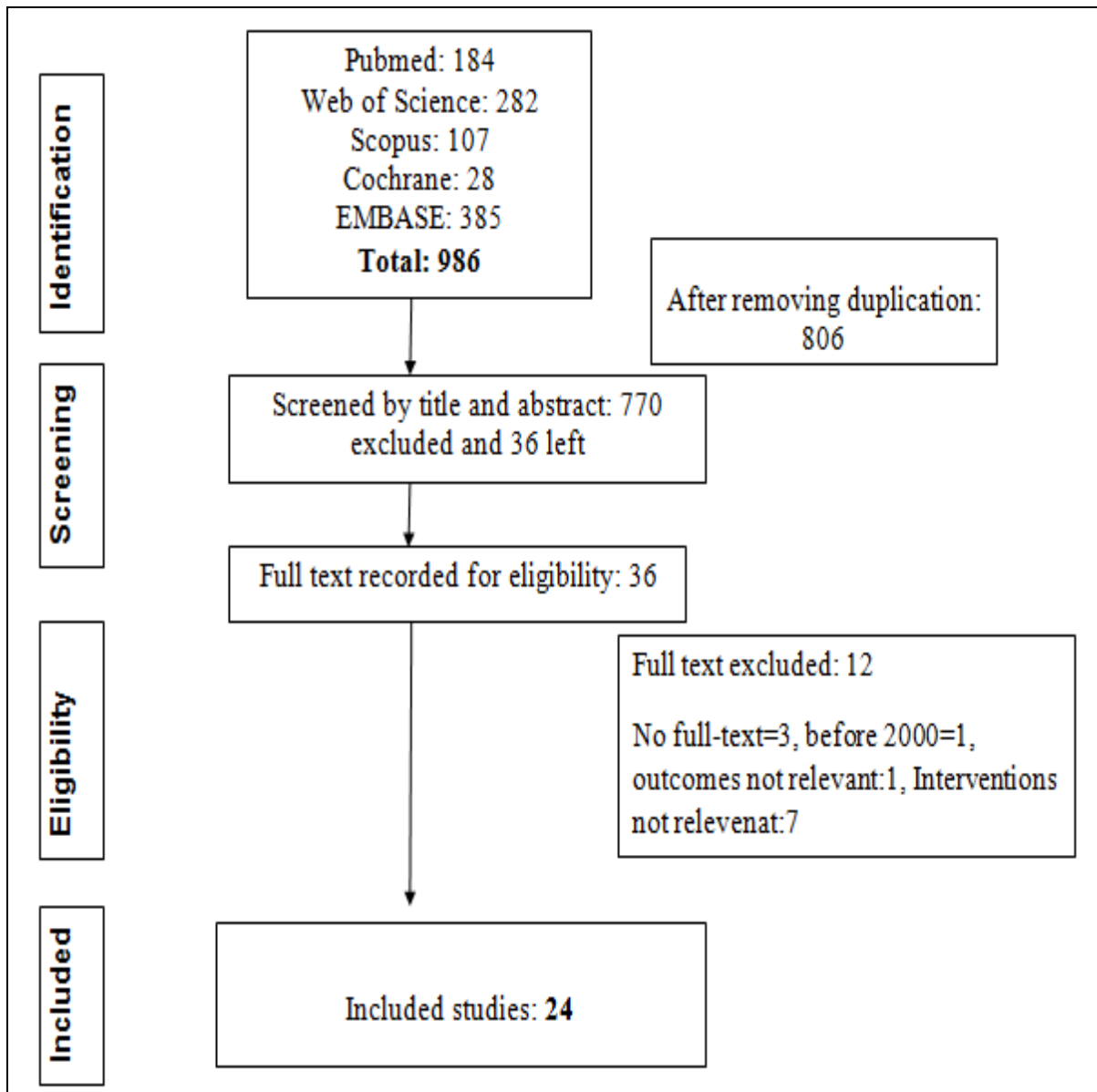


Figure 2: PRISMA flowchart of information through the different phases of a systematic review.

First author, publication year (reference no).	Study design	Number of participants	Intervention duration	Type of the knee valgus brace	Used-questionnaire	The direction of effect
1. (Jones et al., 2013)	crossover randomized	28 (12F, 16M)	2 weeks	Donjoy-OA Adjuster, DJO, Vista, USA)	WOMAC VAS pain	↑
2. (Haladik et al., 2014)	Prospective cohort	10 (1F, 9M)	2 weeks	OA Adjuster	WOMAC	↑
3. (Fu et al., 2015)	Prospective cohort	10 (4F, 6M)	4 weeks	Unloader valgus knee braces (Ossurhf, Reykjavik, Iceland)	WOMAC VAS pain	↑
4. (Pollo et al., 2002)	Prospective cohort	11 (1F, 10M)	2 weeks	Generation II Un-loader ADJ brace, Generation II US	VAS pain	↑
5. (Schmalz et al., 2010)	Prospective cohort	16 (8F, 8M)	4 weeks	Genu Arthro knee brace	VAS pain	↑
6. (Ramsey et al., 2007)	Prospective cohort	16 (not available)	2 weeks	GenerationII Unloader Select, Generation II USA, Inc., Bothell, Washington	KOOS	—

7. (Hsieh et al., 2020)	Comparative study	20 (13F, 7M)	1 month and 3 months	Thruster Legacy OA brace	WOMAC VAS pain	↑
8. (Briggs et al., 2012)	Prospective cohort	39 (16F,23M)	3 week, 6 weeks, and 6 months	Unloader brace	WOMAC SF-36	↑
9. (van Egmond, 2017)	Randomized controlled trial	100. In Bledsoe Thruster group 50 (20F, 30M). In SofTec group 50 (22F, 28M)	2 weeks and 12 weeks	The Bledsoe Thrusterbrace (B&Co Inc. N.V., Sint-Antelinks, Belgium) and the SofTec OA Brace (Bauerfeind AG, Zeulenroda-Triebes, Germany)	VAS pain WOMAC SF-36	↑
10. (Barnes et al., 2002)	Prospective cohort	30 (12F, 18M)	8 weeks	Counterforce brace (breg, calif)	SF-36	↑
11. (Thoumie et al., 2018)	Randomized controlled trial	32 (24F, 8M)	6 weeks	The rebel reliever unloading knee brace	VAS pain (100mm)	↑
12. (Gaasbeek et al., 2007)	Prospective cohort	15 (3F, 12M)	6 weeks	The SofTec OA valgus brace	WOMAC VAS pain	↑

13. (Laroche et al., 2014)	Prospective cohort	20 (16F, 4M)	5 weeks	PROTEOR (France)/ ODRA® brace	WOMAC	↑
14. (Draganich et al., 2006)	Crossover	10 (not available)	5 weeks	Adjustable OA Defiance; dj Orthopedics)	WOMAC	↑
15. (Ornetti et al., 2015)	Prospective cohort	20 (16F, 4M)	6 weeks and 52 weeks	OdrA brace	KOOS VAS pain	↑
16. (Arazpour et al., 2013)	Randomized prospective cohort	12 (8F, 4M)	6 weeks	Custom-made knee valgus brace	VAS pain	↑
17. (Robert-Lachaine et al., 2020)	Randomized crossover	24 (10F, 14M)	3 months	Valgus three-point bending system brace (V3Pbrace), an unloader brace with valgus and external rotation functions (VERbrace) and a stabilizing brace	WOMAC KOOS	↑
18. (Hurley et al., 2012)	Prospective cohort	24 (4F, 20M)	6 months	Breg Fusion valgus unloader braces (custom-made)	WOMAC SF-36	—
19. (Iqbal, 2014)	Randomized controlled trial	60 (24F, 36M)	6 months	Custom-made off-loading knee braces	VAS pain (mm) VAS activity (%)	↑
20. (Richards et al., 2005)	Crossover study	12 (5F, 7M)	6 months	GII Orthotics-Europe, Eindhoven, The Netherlands	VAS pain	↑

21. (van Raaij et al., 2010)	Randomized controlled trial	46 (35F, 11M)	6 months	The MOS Genu1 knee brace	WOMAC Function VAS pain	-
22. (Ostrander et al., 2016)	Randomized controlled trial	16 (8F,8M)	6 months	A medial-unloader brace (Fusion OA; Breg, Inc)	KOOS VAS pain	↑
23. (Hjartarson and Toksvig-Larsen, 2018)	Randomized controlled trial	52 out 74 finished one year study	12 months	Unloader One® Knee Brace (Ossur,Iceland)	KOOS	↑
24. (Sattari and Ashraf, 2011)	Randomized controlled trial	20 (63%F, 37%M)	9 months	The generation II of knee orthosis	VAS pain	↑

Table 1: Observational and randomized studies on the association of using knee valgus brace and questionnaires (WOMAC, VAS, SF-36, KOOS). ↑ means that a positive, significant change was described in the manuscript between before and after values; – means that the outcomes improved but not significantly; ↓ means that a significant negative change was described in the publications. F: means female, M: means male.

2.3.1 Short-term use (up to three months)

Most of the available studies evaluated the effect of using the knee brace on pain and activity level for up to three months (two of them are randomized controlled studies) (Table 1). All of them support using the knee valgus brace as a conservative intervention for patients with medial knee OA to reduce pain and increase activity level (Arazpour et al., 2013, Briggs et al., 2012, Draganich et al., 2006, Fu et al., 2015, Gaasbeek et al., 2007, Haladik et al., 2014, Hsieh et al., 2020, Jones et al., 2013, Laroche et al., 2014, Ornetti et al., 2015, Ramsey et al., 2007, Robert-Lachaine et al., 2020, Schmalz et al., 2010, Thoumie et al., 2018, van Egmond, 2017, Pollo et al., 2002, Barnes et al., 2002).

Within one month, Jones et al., 2013 (Jones et al., 2013) evaluated 28 participants with knee valgus brace and lateral wedge insole. Each condition was used for two weeks with two weeks washout between the two conditions. The results show that a knee valgus brace with a 6-degree knee valgus sitting reduces pain and improves the activity level significantly ($P= 0.00$) compared to the baseline (no interventions). Fu et al., 2015 (Fu et al., 2015) also evaluated 10 participants with six different interventions for four-weeks with no wash-out period. The knee valgus brace significantly reduced pain by 20% in WOMAC and 15.5% in VAS compared to the baseline. Barnes et al., 2002 examined 30 patients with medial knee OA for 8 weeks with knee valgus brace and indicated pain and activity also improved significantly based on the SF-36 questionnaire. Furthermore, 41% of them still use the brace after the investigation, while 35% of them stopped using the brace because of poor fitting or discomfort. After 5 weeks, Briggs et al., 2012, Draganich et al., 2006, and Laroche et al., 2014 (Briggs et al., 2012, Draganich et al., 2006, Laroche et al., 2014) studies indicated that pain and activity significantly improved based on WOMAC and SF-36 questionnaire in comparison with the no-brace condition. After three months of using the knee valgus brace, both WOMAC and KOOS scores improved 10-40% on average (Robert-Lachaine et al., 2020).

In contrast, among these studies, some patients had controversial responses with using the knee valgus brace. In 2007, Ramsey et al. (Ramsey et al., 2007) evaluated 16 patients with a neutral brace and a 4-degree knee valgus brace. Each condition was used for two weeks (with two weeks

wash-out period between the two conditions). Pain and activity level were measured using KOOS questionnaire. The results show that the knee valgus brace could improve pain and activity level but not significantly. This result could be due to the knee valgus bracing order was not randomized. Moreover, 6 participants (out of 16 participants) complained of a feeling of slipping down the brace (Schmalz et al., 2010), and 25% of the participants stop using the brace because they had minor compliance such as redness, blisters, poor fitting, and pain (van Egmond, 2017). Furthermore, some users complain from knee flexion limitation during walking with the knee valgus brace which is not very comfortable for them (Arazpour et al., 2013, Fu et al., 2015, Hsieh et al., 2020, Jones et al., 2013).

2.3.2 Moderate-term use (up to six months)

After six months of using the knee valgus brace, positive results were also suggested by six studies (three of them are randomized controlled studies). Briggs et al., 2012 (Briggs et al., 2012) study showed that 25% of medial knee OA participants have less pain and only 12 patients had knee surgery after six months of using the knee valgus brace. Moreover, Iqbal, 2014 (Iqbal, 2014) study assessed Mistry Pakistani patients with medial knee OA for six months with knee valgus brace and found that both pain and function were improved significantly ($P= 0.00$). However knee valgus brace is effective to improve pain and function, five participants out of 120 had poor fitting and swelling (Iqbal, 2014). Similarly, Richards et al., 2005 and Ostrander et al., 2016 (Richards et al., 2005, Ostrander et al., 2016) showed that the knee valgus brace is an effective conservative intervention for carefully selected patients.

In contrast, Hurley et al., 2012 (Hurley et al., 2012) stated that using a knee valgus brace could improve pain and activity level but not significantly ($P= 0.05$ and $P= 0.08$, respectively) based on WOMAC. This result could be explained by the high body mass index of the participant in that study ($31.8 \pm 5.2 \text{ kg/m}^2$) and a short average brace wearing duration (average of 4.7 hours per day). In further, van Raaij, et al (2010) (van Raaij et al., 2010) also found that patients with knee OA wear the knee valgus brace for few hours per day due to feeling less comfortable.

2.3.3 Long-term use (more than six months)

Only three studies (two of them are randomized controlled trials) evaluated the long-term benefits of using the knee valgus brace between 2000-2020 and their results also support using the knee valgus brace (Table 1). Hjartarson and Toksvig-Larsen, 2018 (Hjartarson and Toksvig-Larsen, 2018) evaluated 149 patients with unilateral knee OA who were randomly divided into a brace group (n=74) and a placebo group (n=75). After one year, both groups show improvement in pain and function, but the improvement among the brace group was more significantly based on KOOS (P= 0.00). Only 25 participants dropped out from the brace group because they underwent knee surgery or had problems with using the brace.

Sattari and Ashraf, (2011) (Sattari and Ashraf, 2011) ran a randomized controlled study on unilateral knee OA. The participants were randomly divided into three groups: a brace group, an insole group, and a control group. After nine months, the brace group had pain relief compared to the control group (P= 0.02). Furthermore, Ornetti et al., 2015 (Ornetti et al., 2015) also evaluated their participants after one year of using the knee valgus brace and suggested that 76% of them had significant improvement in pain and activity level (effect size more than 0.8).

2.3.4 Reporting quality assessment

The Strengthening the Reporting of Observational Studies in Epidemiology tool (STROBE) was used to evaluate the quality of non-randomized articles. Concerning the title and abstract, all the accepted studies have informative abstracts that were well reported, except for some studies (Barnes et al., 2002, Gaasbeek et al., 2007, Laroche et al., 2014, Ramsey et al., 2007, Richards et al., 2005, Schmalz et al., 2010) the abstracts were very brief and did not provide enough information about the results. Regarding the introduction, all of the accepted articles explained the background and the object of the study, except for two studies (Draganich et al., 2006, Fu et al., 2015), the background was brief. In the method section, the study design, participants' criteria, and data collection process were clearly identified. In the result section, the results were well reported in all studies except for two studies (Ramsey et al., 2007, Draganich et al., 2006) they did not mention the details about the recruited participants such as gender or age.

In the discussion, all studies indicated and discussed the key points of the findings. Concerning limitations, all studies stated the limitations, except for the following studies (Ramsey et al., 2007, Barnes et al., 2002, Gaasbeek et al., 2007, Richards et al., 2005, Schmalz et al., 2010). Regarding the source of funding, the following studies received external grant and fund and reported the source of the fund and the role of the funders (Ornetti et al., 2015, Ramsey et al., 2007, Draganich et al., 2006, Barnes et al., 2002, Gaasbeek et al., 2007, Briggs et al., 2012, Laroche et al., 2014, Pollo et al., 2002, Haladik et al., 2014, Hsieh et al., 2020).

For the seven randomized controlled studies, the Cochrane risk-of-bias tool was used (Appendix 2). The overall biases associated with these results were high especially the performance bias and detection bias as neither the researchers nor the participants were blind about the given interventions.

2.4 Discussion

The available knee orthoses for medial compartment knee OA are various. The knee valgus brace is one of the used interventions for patients with medial knee OA to reduce pain and improve activities. This type of brace is designed to reduce the knee varus moment through two different mechanisms: applying a three-point pressure system (bending system) to femur and tibia bones or applying valgus force and external rotation. This kind of brace shows better clinical outcomes than soft brace and rest sleeve because of moderate-term reduction of pain and disabilities (Feehan, 2012). However, the potential benefits of using this brace are still not clear with a low level of evidence. Thus, this study aims to extensively cover the available publications (in the last 20 years) that evaluate the effects of using the knee valgus brace on pain and activity level.

After systematically reviewing the available studies, the outcomes of this study found that the majority of the available studies agree that using a knee valgus brace but with some side effects and fair complications. For instance, Ornetti et al., 2015 (Ornetti et al., 2015) study found that patients used to wear the brace for more than 8 hours per day initially, but then the time of wearing reduced to almost 6 hours per day after one year due to discomfort, skin problems, or

excessive pressure and pain at the front of the tibia. However, 98.6% of patients had pain relief by using a knee valgus brace (Feehan, 2012), some patients stopped using the brace due to discomfort, skin irritation, poor fitting, poor appearance, or had severe pain that the brace cannot reduce (Ornetti et al., 2015, Fu et al., 2015, Hsieh et al., 2020, Jones et al., 2013, Ostrander et al., 2016, van Egmond, 2017).

Moreover, the finding of this investigation noticed that the knee valgus brace could be suitable for some patients more than others. For instance, Barnes et al., 2002 (Barnes et al., 2002) suggested that patients who have severe Kellgren-Lawrence grade (KL) grade and higher body mass index 28-30 kg/m² stopped using the knee valgus brace, whereas patients with lower KL grade (grade II) and BMI between 20-24 kg/m² still use the brace. Obese participants complain of rotation and skin irritation due to poor fitting. Participants with severe knee OA (KL grade IV) were less satisfied with using the knee valgus brace and found it less effective (Hsieh et al., 2020, Jones et al., 2013). Thus, using the knee valgus brace could be more recommended and suitable for the patients who have less than 8 degrees of knee varus, less than 20 degrees of knee flexion contracture, mild to moderate knee OA level (KL grade II and III), and their body mass index less than 30 kg/m² (Barnes et al., 2002, Jones et al., 2013, Ostrander et al., 2016).

As a result, it is still important to provide a guideline for orthotists and therapists about the patients' criteria that could fit properly with the knee valgus brace (such as body mass index, pain level, knee varus angle, and other factors). Moreover, it is critical to provide clear information for patients about the duration of wearing and how to deal with related complications. Besides, it is necessary to try the brace on before buying for a few days to avoid disappointment as it is not a cheap intervention.

2.4.1 The limitations

The included studies for this study have some limitations. Most of the studies had short-term follow-up, a small sample, no control group, and a low level of evidence. Few of them are randomized control studies with a moderate level of evidence. Therefore, it is important to investigate the long-term effect of knee valgus braces with randomized-control studies with high

validity questionnaires and high-quality methodology. Additionally, further research is required to identify the optimal patients who can get the maximum benefit from wearing the knee valgus brace (such as age, gender, BMI, knee varus angle, KL grade, pain level, and brace wearing duration).

The limitation of this study was including both randomized and non-randomized studies. The decision to include all types of studies was due to the limited number of randomized studies that focus on the effect of the knee valgus brace on pain and activity level. Also, it was difficult to include only randomized studies as they have some dissimilarities in terms of control group features, the used questionnaire, the study procedure, and the duration of using the brace. In further, this study focused on evaluating activity level through questionnaires (the self-reported) not by objective methods, such as activity monitors, because mainly using questionnaires is faster, cheaper, and easier for researchers than using activity monitors. However, future studies could be run and include activity level that are evaluated by objective methods.

2.5 Conclusion

To sum up, the results of this study found that knee valgus brace could be an effective intervention for specific patients to reduce pain and improve activity level but with fair compliance. However, the long-term effect is still not clear, and further research is needed to fill the gaps. This finding could be important for specialists who work with patients with medial compartment knee OA to provide sufficient information about the knee valgus brace for the patients before recommending the knee valgus brace to ensure the best quality of life and pain management.

3. Effect of the knee replacement surgery on activity level based on ActivPAL: A systematic review and meta-analysis study ²

3.1 Introduction

Total knee replacement surgery (TKR) is the last surgical intervention to deal with severe knee injuries such as severe knee osteoarthritis (Tambascia et al., 2016, Lingard et al., 2006). The main outcomes of this surgery are reducing pain and increasing the quality of life and the physical activity (PA) level of the patients with severe knee OA (Lingard et al., 2006). The success of this surgery depends on the patients' self-satisfaction in terms of quality of life improvement after the surgery including physical improvement (Ferket et al., 2017b, Lingard et al., 2006). Physical improvement is not only important to increase self-satisfaction but also to enhance musculoskeletal and cardio-respiratory functions, reduce the risk of falls, improve physical function, and reduce the risk of death (Hoorntje et al., 2020).

Most of the available studies that evaluated the PA level after the surgery used subjective methods only such as questionnaires (Nutton et al., 2008, Nutton et al., 2012, Nutton et al., 2014). The mainly used questionnaires that evaluate the quality of life and the PA level improvements are the 36-item Short-Form health survey (SF-36), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Knee injury and Osteoarthritis Outcome Score (KOOS), and the Oxford Knee Score (OKS) (Collins and Roos, 2012). However, those questionnaires are subjective evaluation methods and are associated with limited reliability and recall bias (Collins et al., 2016, Collins and Roos, 2012). Therefore, PA after knee OA surgery evaluated with precise methods such as ActivPAL remains unclear.

Several studies have relied on different types of objective monitors (accelerometer or pedometer); however, most of these monitors have low validity and reliability (Arnold et al.,

²Reference: Alfatafta, H., Alfatafta, M., Onchonga, D., Hammoud, S., Khatatbeh, H., Zhang, L., ... & Molics, B. (2022). Effect of the knee replacement surgery on activity level based on ActivPAL: a systematic review and meta-analysis study. *BMC musculoskeletal disorders*, 23(1), 1-9.

2016, Almeida et al., 2018, Hammett et al., 2018). On the other hand, few studies have used high validity and reliability objective monitors to measure PA level among elderly population. To our knowledge, no systematic review and meta-analysis studies have focused on evaluating the PA level after the surgery based on only high validity and reliability objective monitors such as ActivPAL (PAL Technologies, Glasgow, UK).

ActivPAL is a light-weight (20g) subjective uniaxial accelerometer that is used widely to evaluate the PA level. This monitor detects the inclination of the thigh to determine body movement (Edwardson et al., 2017, Grant et al., 2008, Grant et al., 2006, Yang and Hsu, 2010). The ActivPAL is a valid and reliable device to measure the time spent in sedentary, standing, and stepping states and the number of steps per day. The reliability of the ActivPAL is considerably high (between 0.97-0.99) (Grant et al., 2006, Grant et al., 2008). It is valid to evaluate children, adults, and the elderly. Additionally, it is valid to assess the slow walking population with less than 1% absolute misclassification error (Grant et al., 2006, Grant et al., 2008, Godfrey et al., 2007, Aminian and Hinckson, 2012, Blackwood et al., 2022).

Compared with other accelerometers, using hip/thigh-worn accelerometers and wrist-worn accelerometers cannot distinguish between walking and stair climbing activities; besides, they cannot distinguish between sitting and lying down positions (Blackwood et al., 2022). Therefore, the ActivPAL is more recommended to be used with the elderly population than other monitors to evaluate slow walking and distinguish between different activities and postures (Kim et al., 2015, Blackwood et al., 2022). For the previously mentioned criteria of the ActivPAL, this study focused on evaluating the studies that used the ActivPAL as a monitor for data collection.

The patients who decided to make TKR surgery are expecting to reach the outcomes of the surgery. However, the outcomes of the surgery are still doubtful as some patients feel that their activity level after the surgery did not change significantly, while only less than 5% of them had restored their activity level after 1-2 years of the surgery (Arnold et al., 2013, Kahn and Schwarzkopf, 2015). Additionally, their activity level after the surgery still does not meet the recommended guidelines of the activity level of 150 minutes per week of moderate-intensity

physical activities (Granat et al., 2020, Haskell et al., 2007). Thus, it is critical to identify the activity level enhancement after TKR surgery using high validity monitor.

To date, no systematic review is available to determine the PA level improvement using the ActivPAL. Hence, this study aims to understand the objective improvement after TKR surgery to find out if this surgery could significantly enhance the quality of life or not, based on a high-quality accelerometer.

3.2 Methods

This meta-analysis study is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Page et al., 2021) (Appendix 5).

3.2.1 Search strategy

Five electronic databases including Cochrane Central Register of Controlled Trials, EMBASE, PubMed, Web of Science, and Scopus were searched for relevant studies. Two independent reviewers conducted a research based on the search strategy. This strategy was adapted for the different databases as required (Appendix 4). The search was performed from January 2000 until the end of October 2021.

3.2.2 Study screening

Two reviewers independently selected studies based on predefined inclusion criteria. The titles and abstracts were reviewed first, and irrelevant references were excluded. Then, the reviewers screened the full-text publications of potentially relevant studies. The references and related articles of the selected studies were screened for more suitable studies. Any disagreement was resolved by discussion among the two reviewers with the possibility to involve a third author as a consultant to make a final decision. Authors were contacted for more information or clarifications if needed.

3.2.3 Eligibility criteria

All English language published studies that evaluated the PA level improvement before and after total knee replacement surgery using the ActivPAL included regardless of the study designs. Moreover, the included articles must meet the following criteria: (a) adult participants with severe knee OA who received TKR surgery, (b) minimum follow-up time was six months, and (c) the PA level was measured by the ActivPAL only. The study was excluded if (a) it combined total knee replacement surgery with any other interventions, or (b) used another accelerometer.

3.2.4 Data extraction and risk-of-bias assessment

The two reviewers used the same data extracted sheet to report the following aspects: study information (author, year), study design, number of participants, patients' demographic, preoperative activity level, postoperative activity level, main findings, and funding resources.

The reviewers evaluated the quality of reporting according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) tool for non-randomized studies which has 22 items to assess the reporting quality of title and abstract, introduction, methods, results, and discussion sections (Vandenbroucke et al., 2014, Vandenbroucke et al., 2007). Moreover, the Risk Of Bias In Non-randomized Studies (ROBINS-I) tool was used to evaluate the risk of bias in non-randomized controlled studies by evaluating seven domains of bias (confounding, selection, measurement of interventions, missing data, measurement of outcomes, and reporting) (Sterne et al., 2016). For non-randomized uncontrolled studies, the National Institutes of Health (NIH) quality assessment tool was used to evaluate the quality of pre-post studies without a control group (National Heart and Institute).

3.2.5 Statistical analysis

The Cochrane Collaboration's Review Manager Program (RevMan version 5.3, Cochrane Collaboration, Oxford, UK) was used for data analysis. Weighted mean differences (WMDs) and corresponding 95% confidence intervals (CIs) were estimated by Fixed-effect meta-analysis. The chi-square test for Q and the I^2 quantity were used to test heterogeneity between studies.

Significant results were considered if a p-value for the chi-square test ≤ 0.1 and $I^2 \geq 50\%$ (Page et al., 2021).

3.3 Results

A total of 4427 relevant studies was found initially. After removing duplicated articles and reviewing the title and the abstract, 395 articles remained. Then, four articles met the inclusion criteria after the full-text examination (Pellegrini et al., 2021, Granat et al., 2020, Lützner et al., 2014, Frimpong et al., 2020) (Figure 3). Later, one of them was excluded because it was only a protocol study (Pellegrini et al., 2021). Finally, three studies were included (two of them were uncontrolled studies). From forward citation searches, 71 articles were assessed, but none of them met the inclusion criteria.

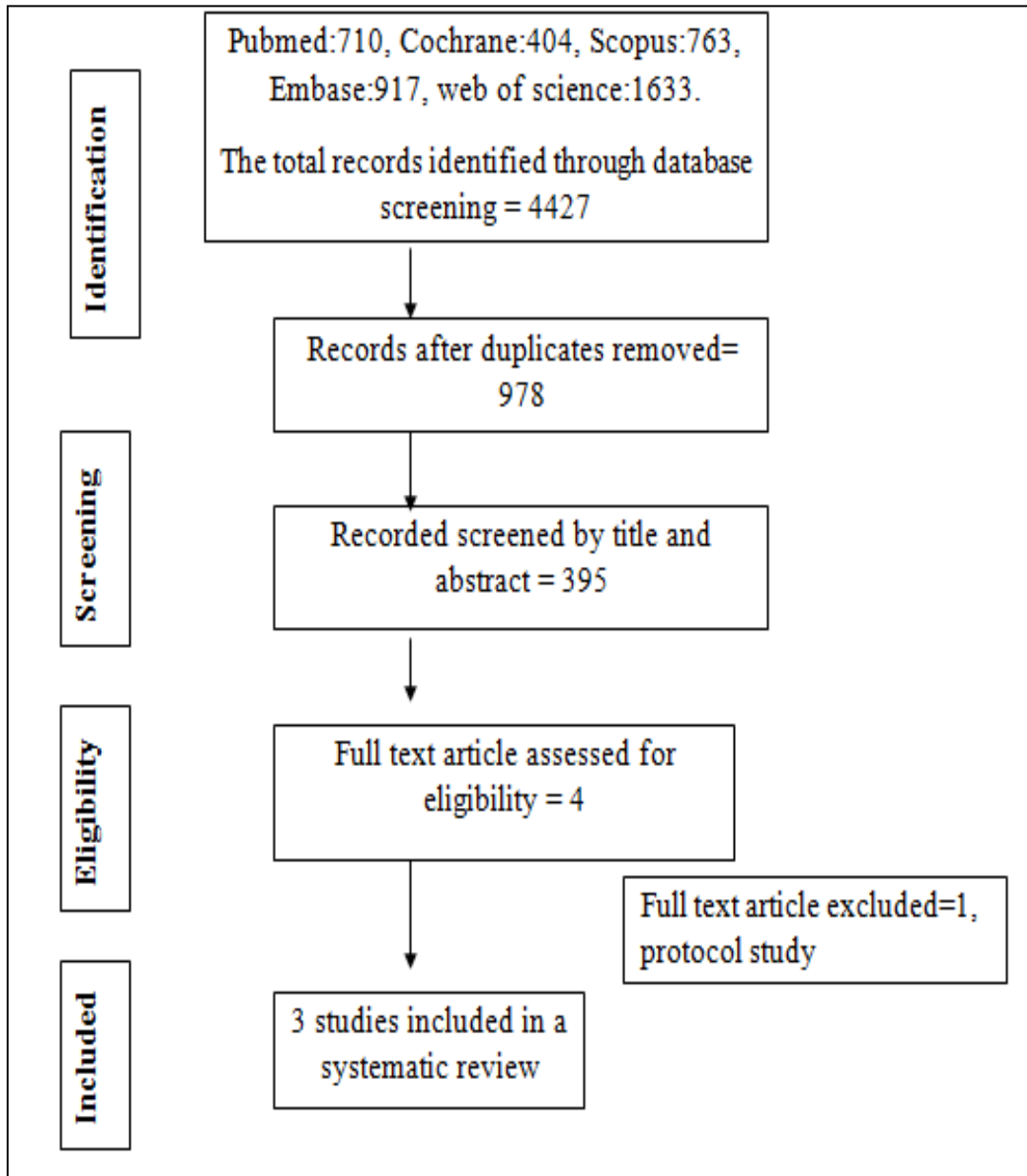


Figure 3: PRISMA flow chart of the study identification.

3.3.1 Systematic review

The three included studies were prospective and only one of them included a control group (Table 2 and 3). The total number of patients was 173 participants with an average age of 63.3 years and an average of 33.2 kg/m² body mass index (Table 2).

Authors	Type of study	Follow up	Number of participants (M/F)	Average age (years)	Average BMI(kg/m ²)
Granat et al., 2020	Uncontrolled before-after study	6 months and 12 months	33 (6M, 27F)	59±6	37.21±7.65 for females, 32.38±2.01 for males
Lützner et al., 2014	Controlled before-after study	12 months	97 (52M, 45F)	68.9	31.3 (30.3–32.3)
Frimpong et al., 2020	Uncontrolled before-after study	6 months	43 (NA)	62.8±8.6	33.8 (±7.1)

Table 2: Summary of the included studies. M: male. F: female. NA: not applicable.

Variables	Granat et al., 2020	Lützner et al., 2014	Frimpong et al., 2020
Before the surgery			
Sedentary time (hour/day)	19.48	12.2	9.8
Standing time(hour/day)	3.47	10.8	5.3
Stepping time(hour/day)	0.98*	1.4	1.31*
Steps (number/day)	4240*	5278*	2559*
After 6 months of the surgery			
Sedentary time (hour/day)	19.27	NA	8.48
Standing time(hour/day)	3.64	NA	5.35
Stepping time(hour/day)	1.17*	NA	1.68*
Steps (number/day)	4853*	NA	3515*
After 12 months of the surgery			
Sedentary time (hour/day)	19.08	12.2	NA
Standing time(hour/day)	3.54	10.3	NA
Stepping time(hour/day)	1.36*	1.5	NA
Steps (number/day)	6174*	6473*	NA

Table 3: Summary of results of the included studies. The highlighted results (*) are with significant changes. (NA = not available).

Granat et al., 2020 (Granat et al., 2020) evaluated 33 participants after six-months and one year of total knee replacement surgery. The patients used the ActivPAL for seven consecutive days at each stage. The monitor was attached over the mid-thigh. The results found that the stepping time and steps' number after six-months and one year of having the surgery significantly improved compared to pre-surgery. The number of steps significantly improved by 14.4% and 45.6% after six-month and one year, respectively. Moreover, the stepping time significantly improved by 11.48 ± 2.05 (19.38%) min/day and by 22.66 ± 2.24 (38.77%) min/day after six-

months and one year, respectively. However, the changes in stepping time and the number of steps did not meet the PA guideline of 150 minutes of activity per week. Whilst no significant differences were seen in sedentary time and standing time.

Lützner et al.,2014 (Lützner et al., 2014) assessed 97 patients after one year of total knee replacement surgery. The patients used the ActivPAL for four consecutive days. The monitor was attached over the anterolateral tibia. This study found that the number of steps increased from 5278 ± 2999 to 6473 ± 3654 steps/day one year after the surgery. However, no significant changes in sedentary, stepping, and standing times were demonstrated. Furthermore, only 16 participants met the PA guidelines.

Frimpong et al., 2020 (Frimpong et al., 2020) examined 43 participants after six-months of unilateral total knee replacement surgery. The patients used the ActivPAL for seven consecutive days. The monitor was attached over mid-thigh. The results found that the number of steps significantly improved (with an average of 2559 to 3515 steps/day, $P= 0.001$, 37.35%) and the stepping time significantly increased (with an average of 79 to 101 minutes/day, $P= 0.006$, 28.2%) after six-months of the surgery. Nevertheless, no significant changes in sedentary and sitting times were reported.

3.3.2 Meta-analysis results

The meta-analysis was used to evaluate the activity level enhancement after six months and one year. The results revealed that the heterogeneity of the activity level after six months and one year is low to moderate (Figure 4-6). After six months of the surgery, the number of steps (two studies, 76 participants) improved (95% CI 0.11, 0.76; $P= 0.38$; $I^2=0\%$) with small heterogeneity. Based on the same two studies, the sedentary time, stepping time, and standing time improved but insignificantly (Figure 4). After one year of the surgery, the number of steps (two studies, 130 participants) enhanced (95% CI 0.22, 0.71, $P= 0.10$; $I^2=63\%$) with moderate heterogeneity (Figure 4). The sedentary time, stepping time, and standing time (two studies, 130 participants) also insignificantly improved (Figure 5). However, the overall heterogeneity after six months and one year was low and up to $I^2= 45\%$, $P= 0.11$ (Figure 4-6).

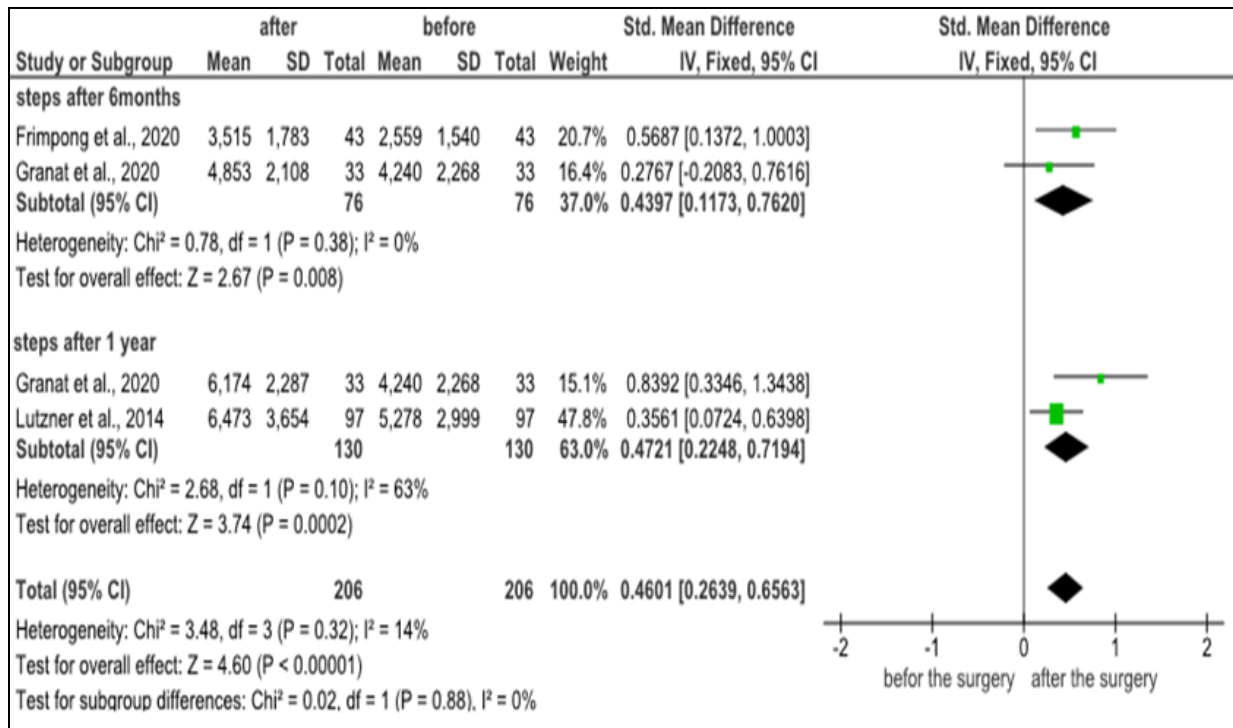


Figure 4: Meta-analysis of number of steps (average number/day) after six months and one year of the surgery.

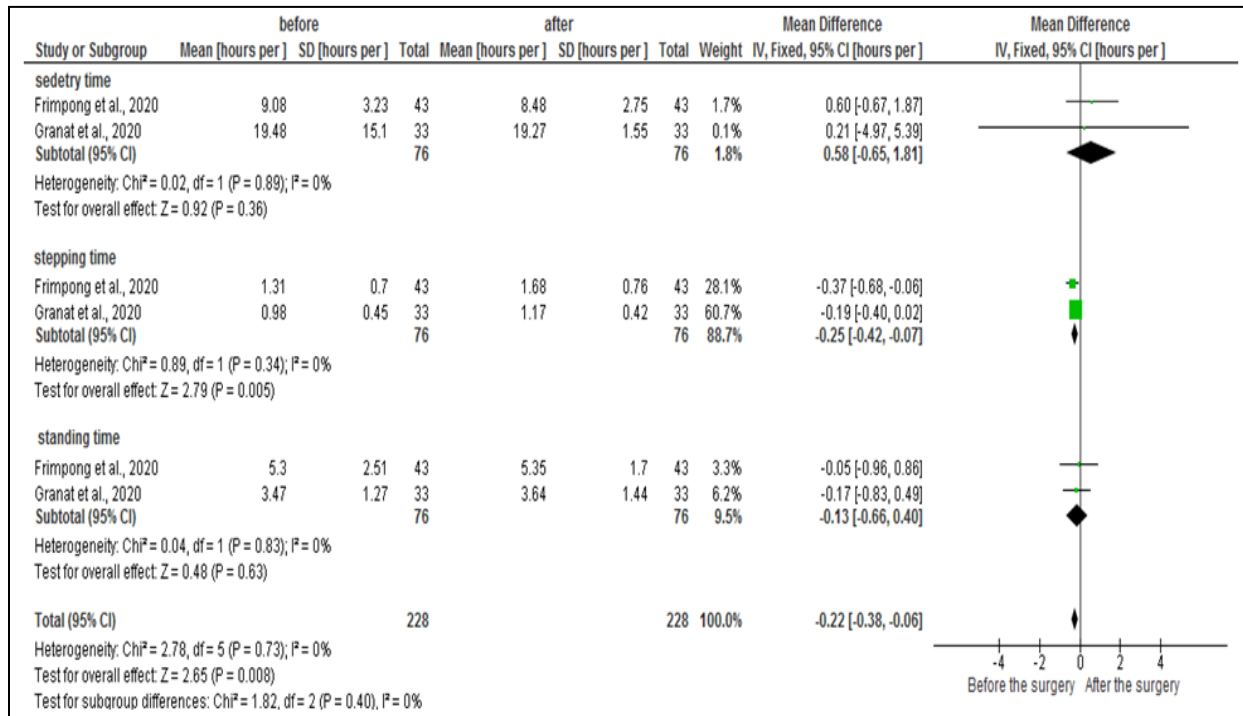
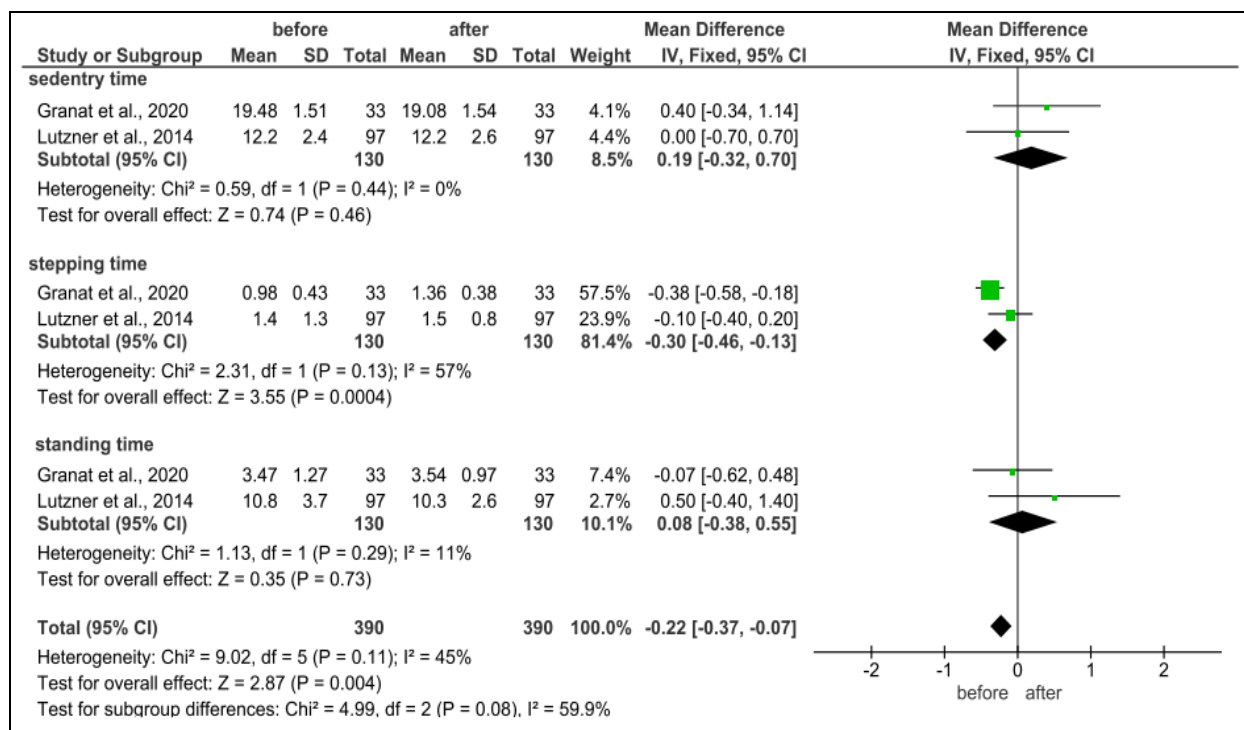


Figure 5: Meta-analysis results of sedentary time, stepping time, and standing time (hour/day) after six months of the surgery.



6: Meta-analysis results of sedentary time, stepping time, and standing time (hour/day) after one year of the surgery.

3.3.3 Reporting quality and Risk of bias assessments

The accepted articles were non-randomized studies; thus, the STROBE tool was used to assess the study's generalizability. In terms of title and abstract, the three accepted studies had a clear informative abstract. For the introduction, also all the three included studies provided critical background with specified objectives. In terms of methods and results, all of them clearly described the study design, data collection, recruitment process, participants' criteria, the main measurable variables, and the main outcomes. For the discussion, all studies revealed the main key points, compared their findings with other studies, and stated the associated limitations. For funding, two studies reported their source of funding (Granat et al., 2020, Lütznner et al., 2014).

ROBINS-I tool was used to evaluate the risk of bias in the controlled study, Lütznner et al., 2014 (Lütznner et al., 2014) (Appendix 3). That study was associated with selection bias and performance bias. The researchers attached the ActivPAL on the tibia which is not a

recommended location; besides, it collected the data of four days which is not very enough to evaluate the PA. These findings might reduce the generalization of the results.

For studies without a control group, Granat et al., 2020 (Granat et al., 2020) and Frimpong et al., 2020 (Frimpong et al., 2020), the NIH quality assessment was used to evaluate the quality and risk of bias (Appendix 6). The two included studies were incorporated with risk of bias, such as selection bias, unblinded participants, and the statistical analysis did not take into account the use of individual-level data to determine effects at the group level. These findings might reduce the quality of the results, and reduce the internal validity.

3.4 Discussion

Total knee replacement is not an easy decision-making intervention to cope with severe knee injuries. The patients expect that TKR surgery will help them to restore their physical activity, be more active, and to be more independent. Hence, a systematic review study was conducted to evaluate the PA improvement after the surgery using the ActivPAL. This study focused on the PA that was examined with the ActivPAL as it is a very accurate monitor, suitable to evaluate the sedentary time of the elderly population, and more recommended to be used than the ActiGraph (Kim et al., 2015). The main finding of this study is only the number of steps was significantly improved after the surgery among most of the patients (Granat et al., 2020, Lützner et al., 2014, Frimpong et al., 2020). Nevertheless, this improvement is still not enough to restore their normal activity level as it did not reach to recommended activity level guideline. Moreover, the sedentary time did not significantly reduce after the surgery which could decrease the effectiveness of TKR surgery.

It is expected that the outcomes of the included studies are associated with participant's health status before the surgery. For instance, the average age of the included participants in Granat et al., 2020 study (Granat et al., 2020) was considerably low (59 ± 6 years old, range: 49–76 years old). In Lützner et al., 2014 study (Lützner et al., 2014), the participants had a high number of steps (with an average of 5000 steps/day) before the surgery. Similarly, Frimpong et al., 2020 study (Frimpong et al., 2020) found significant differences in the number of steps after six

months and that could be related to include some patients with a body mass index less than 30 kg/m². Therefore, the age, body mass index, and activity level of the patients before the surgery could be correlated with the outcomes of TKR surgery.

Other factors also could have impacts on the outcomes of TKR surgery. It has been suggested that TKR surgery could increase the movement-related activity and number of sit-to-stand movements by 0.7% and 9.7% respectively after six-months and that depends on the body mass of the patients and the physical treatment after the surgery (de Groot et al., 2008). Another study found that male and young age (<65 years old) patients show better PA levels after the surgery than women and elderly participants (Kersten et al., 2012). Furthermore, the emotional state of the patients and their partners has an influence on the PA recovery after the surgery (Kalisch et al., 2021). Therefore, more research is required to understand the impact of these factors and find other factors.

The results that have been reviewed in this study match with other studies which evaluated the PA level after at least six-months of having TKR surgery using other types of activity monitors. These studies also found small changes in the AP after six-months of the surgery as patients were still inactive and had high sedentary time after the surgery (de Groot et al., 2008, Kersten et al., 2012, Kalisch et al., 2021, Harding et al., 2014, Moellenbeck et al., 2021). Similarly, the available systematic review studies that reported the PA after TKR surgery using other types of activity monitors found that the changes in the AP after six-month of the surgery, and only moderate changes could be seen in the PA after one year of the surgery but still insufficient (Arnold et al., 2016, Almeida et al., 2018, Hammett et al., 2018).

To sum up, even the subjective measures such as pain, function, and stiffness might improve after the surgery, not all aspects of the activity level based on the objective tools significantly increased. So far, no enough evidences about the benefit of this surgery on the PA level are available. Hence, better physical capability after the surgery does not mean a better PA level.

3.4.1 The limitations

This study is engaged with limitations. Few studies met the inclusion criteria and none of them is a randomized controlled study; therefore, the results of the included studies could be associated with a high risk of bias such as selection bias and performance bias. Also, this study included only studies that used the ActivPAL and excluded studies with any other interventions with the surgery which limit the results' generalizability.

3.5 Conclusions

Total knee replacement surgery is an effective treatment to improve the quality of life among patients with severe knee injuries. Based on the high validity monitor, the number of steps significantly improved, but the sedentary time did not change. To increase the maximum benefits of the surgery, the sedentary time should be decreased. Hence, long-term follow-ups, rehabilitation programs, and physical interventions are important to enhance the physical outcomes and reduce the sedentary time after the surgery. This finding could be important for specialists who work with TKR patients to restore their activity level after the surgery and make them more satisfied by implementing activities that help them to reduce their sedentary time. The patients' expectations after the surgery should be discussed with the patients before the surgery.

4. Activity level and quality of life among patients before and after knee replacement surgery: A case-series study

4.1 Introduction

Knee osteoarthritis (OA) is one of the most common diseases among the elderly population globally as it is associated with age and obesity (Cross et al., 2009, Cross et al., 2014, Horváth et al., 2011). In Hungary, the prevalence of knee osteoarthritis was 16.5% in 2011. A total of 2.9% of them had severe osteoarthritis in a group aged 20–67 years (Horváth et al., 2011). The core symptoms associated with knee OA are pain, low physical activity (PA) level, and disabilities (Horváth et al., 2011, Cross et al., 2009, Cross et al., 2014).

Conservative treatments such as pharmacological treatment, orthotics, physiotherapy sessions, and others could be effective for mild-moderate knee OA (Alfatafta et al., 2016, Alfatafta et al., 2021, Crawford et al., 2013). Total knee replacement (TKR) surgery is the gold-standard treatment to deal with severe knee OA when pain is no longer relieved by conservative treatments (Malviya et al., 2009, Ferket et al., 2017a). Thus, the expected goals of TKR surgery are reducing pain and improving the quality of life (Malviya et al., 2009, Ferket et al., 2017a, Tambascia et al., 2016).

In Hungary, pain and PA after TKR were evaluated only once using the SF-36 questionnaire (Rádler et al., 2018). In general, the questionnaires used to assess the PA of patients with knee OA are associated with recall bias and have low-moderate reliability and validity (Collins and Roos, 2012, Collins et al., 2016). Hence, it was necessary to evaluate the PA of Hungarian patients with severe knee OA using high validity and reliability objective tools, as no databases are available in this field in Hungary. To our knowledge, no prior study has explored the PA level of Hungarian patients before and after surgery using objective tools or has explored the PA level of Hungarian patients before and after surgery in terms of the number of steps, sedentary time, standing time, and stepping time using a high validity and reliability accelerometer such as

ActivPAL. This information is important to understand the physical activity level and physical behaviour of patients with severe knee OA before and after surgery using objective tools.

Therefore, the aims of this case-series were (a) to understand the activity level of the included Hungarian patients with severe knee OA, and (b) to evaluate the activity level of the included Hungarian patients one year after TKR surgery. The measured variables were evaluated with both objective and subjective monitoring tools.

4.2 Methods

4.2.1 Study design and population

This study evaluated the quality of life (QoL) and activity level one month before the surgery and one year after the surgery among eight Hungarian patients (four females, four males) with an average age of 70.8 ± 4.5 years old and 30.7 ± 4.3 kg/m² (Table 4).

Domains	Total (n=8)
Age (y)	70.8±4.5
Gender	4 males, 4 females
BMI (kg/m²)	30.7±4.3
Smoking	0
Heart problems	3 (2 males, 1 female)
Diabetes	2 (1 male, 1 female)
Hypertension	6 (2 males, 4 females)

Table 4: Demographic data of the participants.

The inclusion criteria were the presence of a clinical and radiological diagnosis of osteoarthritis that required TKR surgery. The confirmation of radiological diagnosis was performed by the orthopedic surgeon at the orthopedic clinic, the University of Pécs, to ensure that participants

needed TKR surgery. Participants were excluded if they had hip and ankle injuries in the last five years or if they had co-morbidities or medical conditions that affected physical activity such as congestive heart failure or cognitive impairment. Ethical approval was obtained from the University of Pécs, and a consent form was initially collected from the participants.

4.2.2 Physical activity measurement tools

The activity level was evaluated with ActivPAL and the short form (SF-36) questionnaire. ActivPAL (PAL Technologies, Glasgow, UK) is a uniaxial accelerometer (20g) that calculates the time spent in sedentary, standing, and stepping, and the number of steps per day for up to 14 days (Edwardson et al., 2017, Lyden et al., 2017, Dahlgren et al., 2010, Taraldsen et al., 2011, Ryan et al., 2006). The ActivPAL is recommended to be used with the elderly more than other monitors such as ActiGraph because it has a higher validity and reliability to detect body movement at different speeds than ActiGraph (Kim et al., 2015, Ryan et al., 2006). Before use, the monitor was charged and activated with ActivPAL3™ (version 8.11.9.100).

Moreover, the Hungarian version of the short form (SF-36) was used to assess QoL. This form is composed of 36 items about eight domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Each domain is scaled between zero (poor health status) and 100 (no problem at all) (Ware Jr and Gandek, 1998, Kalantar-Zadeh et al., 2001, Czimbalmos et al., 1999).

4.2.3 Intervention and total knee replacement surgery

All of the participants underwent the operation with the medial parapatellar approach that was performed by the orthopedic surgeon. Various prosthetic knee types were used such as S and N Genesis II, Johnson and Johnson PFC sigma, and Zimmer Nexgen. No compliances were reported after the surgery. The patients stayed five to six days at the hospital after the surgery. Physiotherapy sessions were standardized according to hospital protocols to minimize confounding factors for both inpatient and outpatient periods (for three months only).

4.2.4 Data collection procedure

One month before the surgery, all participants were briefed about the study first and signed the consent form. Each participant was asked to complete the Hungarian language SF-36 questionnaire before the surgery. Then, they were instructed to wear the ActivPAL for seven days most of the time (removed it during shower time or water activities). The instructions were given written and verbally to ensure they understood the instructions. The ActivPAL was attached at mid-thigh with self-adhesive tape under the clothes. The participants were asked to return the monitor on the day of the surgery.

One year after the surgery, the participants were asked to visit the clinic for follow-up, fill out the SF-36, and use the ActivPAL for one week. The same previously mentioned instructions were given again to each patient. Then, the participants were asked to return the monitor after one week of usage by post.

4.2.5 Data analysis

For data from the SF-36 questionnaire, the average (\pm SD) of physical functioning, physical role, pain, general health, and the overall QoL score were calculated for each participant at all assessment time points as these aspects are the most relevant aspects with the study's goal. The data from the ActivPAL were extracted from the monitor using the software. Then, the downloaded files were imported into Excel. The average (\pm SD) of sedentary time, standing time, stepping time, and the number of steps were calculated for each participant at all assessment time points during the testing period (seven days). A valid day is defined as 10 hours of continuous activity with less than three hours of interruptions. All data were analyzed by SPSS (SPSS Inc., Chicago, IL, USA) using a paired sample test. Significant results were considered if the significance (2-tailed) value was less than 0.05 (Ross and Willson, 2017). Only eight patients were included in the paired sample t-tests. The data were normally distributed based on the Kolmogorov-Smirnov test (Lilliefors, 1967).

4.3 Results

Ten participants initially participated in this study. After one year, one participant was not available for the final study, and the ActivPAL data of one participant were not included in the presurgery data because his data were not valid. Thus, ten participants completed the SF-36 questionnaire and had valid ActivPAL data before the surgery. One year after surgery, eight participants completed the SF-36 questionnaire and had valid ActivPAL data (Table 5).

Variables	Pre-surgery	One year post-surgery	Significant (P value)	95% Confidence interval for differences (IC)	
				Low	High
The SF-36 score (pre-surgery n=8, post-surgery n=8)					
Overall score	50.0±26.7	75.0±23.1	0.050	-49.9	-0.19
Physical functioning	58.1±20.8	61.2±21.5	0.582	-15.5	9.6
Role limitations due to physical health	46.8±41.0	43.7±7.4	0.89	-50.9	57.2
Bodily Pain	41.8±23.5	51.8±25.1	0.32	-32.3	12.7
General health	52.5±11.6	56.2±20.6	0.704	-26.1	18.6
ActivPAL data (pre-surgery n=8, post-surgery n=8)					
Time of sedentary	18.3±1.9	16.1±3.1	0.033	0.24	4.1
Time of standing (hour)	3.5±1.4	5.8±2.7	0.030	-4.22	-0.11
Time of stepping (hour)	1.5±0.6	2.2±0.9	0.046	-1.2	-0.01
Number of steps (number)	6270±2754	7344±3331	0.11	-2507.04	358.0

Table 5: The average (\pm SD) of the activity level before and one year after total knee replacement surgery. The number of the paired sample is eight.

4.3.1 ActivPAL results

The physical activity level was enhanced after one year of total knee replacement surgery based on an objective monitor (Table 5). Standing time significantly improved from 3.5 ± 1.4 to 8 ± 2.2 hours per day (65.7%, $P= 0.030$) one year after surgery. The stepping time also improved by 46.6% ($P= 0.046$) after one year of the surgery. Furthermore, the number of steps enhanced from 6270 ± 2754 to 7344 ± 3331 (17.1%, $P= 0.11$). One year after surgery, patients spent 2.2 hours per day (12%, $P= 0.033$) on sedentary activity less than before the surgery.

4.3.2 The SF-36 questionnaire results

The total QoL score of the patients was 50.0 ± 26.7 before the surgery and improved to 75.0 ± 23.1 one year after surgery ($P= 0.05$) (Table 5). The bodily pain based on this questionnaire improved from 41.8 ± 23.5 to 51.8 ± 25.1 (23.9%, $P= 0.32$). Furthermore, role limitations due to physical health enhanced by 6.6% ($P= 0.89$). In addition, physical functioning and general health one year after total knee replacement surgery improved by 5.3% ($P= 0.58$) and 7.0% ($P= 0.70$), respectively.

4.4 Discussion

This study measured the activity level before and one year after total knee replacement surgery among patients with severe knee OA. To our knowledge, this study is the first study in Hungary that used a highly valid objective accelerometer to understand the physical activity level of patients with severe knee OA and their physical activity improvement one year after TKR. This study found that the included Hungarian patients with severe knee osteoarthritis spend most of their daily time with sedentary activities (with an average of 18.3 ± 1.9 hours per day), and they only spend almost 1.5 ± 0.6 hours per day walking with an average of 6270 ± 2754 steps per day.

One year after TKR, the included Hungarian patients have better physical activity levels and less pain (less pain or a better QoL in general) based on both objective and subjective tools. The activity level increased between 65.7%-12% based on the ActivPAL and between 50%-5.3%

based on the SF-36 questionnaire after one year of the surgery. However the sedentary time decreased from 18.3 ± 1.9 to 16.1 ± 3.1 hours per day, these changes are still not enough to allow the included Hungarian patients to meet the general physical activity guidelines (Haskell et al., 2007).

Few studies evaluated the PA using the same accelerometer with a one-year follow-up (Granat et al., 2020, Lützner et al., 2014, Alfatafta et al., 2022). Granat et al., 2020 evaluated the physical activity of 33 patients before and one year after surgery. This study found that the number of steps significantly improved by 45.6% (from 4240 to 6174 steps/day) one year after TKR. Moreover, Lützner et al., 2014 also evaluated the physical activity level of 97 patients before and one year after one year of TKR with ActivPAL. This study found that the number of steps significantly improved by 22.6% (from 5278 ± 2999 to 6473 ± 3654 steps/day). This current study also found that the number of steps improved by 17% (from 6270 ± 2754 to 7344 ± 3331). In terms of stepping time, it was significantly improved based on Granat et al., 2020 by 38.77%. However, the stepping time insignificantly improved by 28.2% based on Lützner et al., 2014 study. This finding could be due to applying the ActivPAL over the tibia, which is a less reliable position, and the monitor was used only for four days (Lützner et al., 2014). In terms of sedentary times, all of the available studies and this current study stated that the sedentary time did not significantly reduce after one year of TKR.

Furthermore, this study found that the PA of the included Hungarian patients was improved based on the SF-36 questionnaire. The total score of the SF-36 questionnaire significantly improved by 50% ($P= 0.050$) one year after TKR. Similarly, among Greek elderly women, the total score of the SF-36 questionnaire significantly improved from 29.33 ± 11.3 before surgery to 62.35 ± 2.7 six months after TKR (Tsonga et al., 2011). Other studies used different types of questionnaires. For instance, Granat et al., 2020 (Granat et al., 2020) found that physical activity based on the Oxford knee score (OKS) significantly increased by 142% ($P= 0.00$) one year after TKR. Also, the OKS score improved six months after TKR from 12 points to 42 points (Frimpong et al., 2020).

In summary, the activity level and pain among the included Hungarian patients with severe knee osteoarthritis improved after TKR. However, long follow-up and staying active after surgery are still necessary to obtain better outcomes. These findings could be important for therapists who care for Hungarian patients with severe knee osteoarthritis in order to understand their physical limitations before and after the surgery. Additionally, they should be helped by focusing on how to enhance the outcomes of TKR to reach the maximum activity level improvement.

4.4.1 The limitations

Although the sample size was small, the participants were recruited from a large hospital that came from different places in Hungary. Thus, the results might reflect the general population. Unfortunately, due to the COVID-19 epidemic only few patients were able to visit the hospital and participate in this study. Furthermore, a one-year follow-up could not be sufficient time to assess the effect of the surgery; however, this is the first study in Hungary that evaluated the PA one year after TKR using an objective monitor. Moreover, this study emphasizes the importance of evaluating outcomes using objective tools not only subjective tools. Further studies are recommended with longer follow-up and more participants.

4.5 Conclusion

Based on both subjective and objective assessment tools, the recruited Hungarian patients had better physical activity levels and QoL after TKR. However, the objective assessment tool, ActivPAL, is more sensitive and reliable than the subjective assessment tools. Thus, it is important to include objective assessment tools in the evaluation to reduce recall bias and represent more information about the physical activity level. Moreover, the sedentary time among the recruited Hungarian patients after TKR surgery was still high and might have reduced the efficiency of TKR surgery. Hence, long-term follow-up and rehabilitation sessions could be required to reduce the sedentary time and increase the efficiency of TKR surgery.

5. Quality of life of patients with severe knee osteoarthritis in Hungary: A cross-sectional study³

5.1 Introduction

Knee osteoarthritis (OA) is a very common chronic degenerative musculoskeletal disease (Felson et al., 2000, Midgley, 2021). The incidence of knee OA is increasing with age, obesity, occupation, gender (women are more affected than men) (Cui et al., 2020, Felson et al., 2000, Felson, 2006, Felson et al., 1988). Knee OA is characterized by cartilage breakdown, osteophyte formation, and joint space loss. Therefore, it increases the risk of knee pain, low quality of life (QoL), disability, and mortality (Felson et al., 2000, Felson, 2006). It has been found that 80% of patients with knee OA had movement limitation, and 25% of them were unable to achieve their daily life activities that negatively impacted their psychological status (Mahir et al., 2016).

It has been reported that the global prevalence of knee OA was 22.4% among the 40 and over age group, while the global incidence of knee OA was 203 per 10,000 person-years among the 20 and over age group in 2020 (Cui et al., 2020). The prevalence and incidence were significantly higher among females than males (1.69 vs. 1.39, $P < 0.001$, respectively) (Cui et al., 2020). In 2010, 185 of the examined knees in the southwestern part of Hungary had Kellgren-Lawrence ≥ 2 (16.5%), and 20 of the examined knees had Kellgren-Lawrence ≥ 3 (2.9%) (Horváth et al., 2011). Another study found that the prevalence of knee OA in Hungary was 13.3% in 2010, where 2.9% of them had severe knee OA (Horváth et al., 2010).

Patients with severe knee OA have severe clinical and/or radiological symptoms, such as severe pain during activities and rest, depression, low activity level, low quality of life, stiffness, gait deformities, large osteophytes, joint enlargement, and joint space narrowing (Felson et al., 2000, Felson, 2006, Midgley, 2021, Berger et al., 2012, Hall et al., 2017, Rathbun et al., 2017). For severe knee OA, total knee replacement surgery is the optimal treatment to reduce pain and

³ Reference: **Alfatafta, H**, Alfatafta, M, Amer, F, Hammoud, S, Zhang, L, Molics, B, Boncz, I. (2022). Quality Of Life Of Patients With Severe Knee Osteoarthritis In Hungary: Cross-Sectional. Study Studia Universitatis Babes-Bolyai Educatio Artis Gymnasticae. 67(2), 5-15

enhance the quality of life (Ferket et al., 2017a, Dieppe et al., 2011, Biggs et al., 2019, Escobar et al., 2017, Nunez et al., 2009).

In Hungary, the quality of life of patients with severe knee OA has not sufficiently investigated. One conference paper reported the quality of life (QoL) among Hungarian patients with severe knee OA before total knee replacement surgery using four different questionnaires, including a homemade questionnaire, the Knee Society Score (KSS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the short form (SF-36) questionnaire (Busa et al., 2019). However, the number of participants was not mentioned, and the reported results and methods were not well presented as it was a conference paper. As a result, insufficient data are available about the activity level of Hungarian patients with severe knee OA. Therefore, more information is required in this field to have clear information about their QoL, to identify the most challenging activities for patients with severe knee OA, and to identify whether there are differences in QoL across women and men.

This cross-sectional study aimed to report QoL of patients with severe knee OA who planned to have total knee replacement surgery after one month. Additionally, this study aimed to evaluate the gender differences in terms of QoL. The results of this study could be important to therapists who work with patients with severe knee OA.

5.2 Methods

This is a cross-sectional study and part of a case series study that was conducted between 2020 and 2021. The included participants had to continue the main study with a one-year follow-up.

5.2.1 Participants

Ten participants (four males, six females) on the waiting list for total knee replacement surgery were included in this study, with an average age of 70.6 ± 4.0 years and an average body mass index (BMI) of 30.7 ± 3.4 kg/m² (Table 6).

Domains	Total N=10
Age (year)	70.6 ±4.0
Body mass index (BMI) (kg/m²)	30.7±3.4
Knee OA duration	More than four years
Using walking assistance	3 (1 male, 2 females)
Hypertension	8 (2 males, 6 females)
Diabetes	3 (1 male, 2 females)
Smoking	None
Employment	2 (1 male, 1 female)
Marital-status	5 Married (3 males, 2 females) 5 Non-married (2 Divorced, 3 Widow)

Table 6: Demographic data of the participants.

The participants were recruited from the Department of Orthopedics (Clinical Center, University of Pécs, Hungary). The inclusion criteria were the presence of radiological and clinical symptoms of knee osteoarthritis, the Kellgren-Lawrence (K-L) scale score ≥ 3 (Kohn et al., 2016), and pain during daily activities. Furthermore, the included participants had to be scheduled for total knee replacement surgery within a month. The radiological symptoms were confirmed by the orthopedic surgeon at the orthopedic clinic. The exclusion criteria were to have one or more of the following: osteoarthritis in the hip or ankle, knee replacement before, knee surgery in the last five years, hip and ankle injuries in the last five years, and cognitive problems. Ethical approval from the University of Pécs was granted and the consent form was signed by all participants before participation.

5.2.2 Procedure

The patients who met the inclusion criteria were invited to participate in the study. Ten patients agreed to participate in this study. All the included participants were briefed about the study, and they were asked to sign the consent form. Then, each participant was asked to complete the Hungarian language SF-36 questionnaire one month before the surgery. The eight domains of the short form (SF-36) were reported, including physical functioning, physical role, bodily pain,

general health, vitality, social functioning, emotional role, and mental health (Brazier et al., 1992, Hayes et al., 1995, Ware Jr, 2000, Ko et al., 2013). It is scored from zero to 100. A low score indicates poor health status and a high score shows better health status (Brazier et al., 1992, Hayes et al., 1995, Ware Jr, 2000, Ko et al., 2013).

5.2.3 Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, USA, version 24) was used to calculate descriptive statistics and the Multivariate Analysis of Variance (MANOVA). In the multivariate analysis, all eight domains were dependent variables, and gender was an independent variable. The results were considered significant if the P value was less than 0.05. Other factors such as using walking assistance, diabetes, hypertension, smoking, employment, and marital-status were not recorded because the outcomes were insignificant. The scoring was performed online via the online software Orthotool-kit (<https://www.orthotoolkit.com/sf-36/>).

5.3 Results

Ten patients had severe knee OA with a minimum of four years of knee OA and were ready for total knee replacement surgery and completed the SF-36 questionnaire. The average of eight domains with standard deviation were calculated (Table 7). Based on the mean of the eight domains of the SF-36, the results show that three domains were less than 50%, including pain, role limitation due to physical activity, and role limitation due to emotional problems. The average reported pain was 40.95%, which was the lowest among the domains. The role limitation due to physical activity was the second lowest domain, with an average of 42.5%. In contrast, the overall mean of social functioning and emotional well-being were the higher domains.

In addition, the comparison of the eight domains according to gender showed that there were significant differences between women and men in two domains: physical functioning and role limitations due to emotional problems. Women had significantly lower physical functioning and role limitations due to emotional problems than men by 42.8% (P= 0.03) and 73.3% (P= 0.005), respectively. Other differences were seen between women and men but the differences were

insignificant. For instance, women reported lower role limitations due to physical activity than men by 53.44%. In addition, women had lower average energy and emotional well-being domains than men by 24.46% and 22.5%, respectively.

Domains	Overall Outcomes, N=10 (\pm SD)	Outcomes of males, N=4 (\pm SD)	Outcomes of females, N=6 (\pm SD)	P value
1) Physical functioning	52% (22.75)	70% (15.8)	40% (17.5)	0.03*
2) Role limitations due to physical health	42.5% (37.36)	62.5% (47.8)	29.1% (34.9)	0.180
3) Role limitations due to emotional problems	46.71% (39.11)	83.3% (33.2)	22.2% (33.3)	0.005*
4) Energy/fatigue	55.5% (13.63)	65% (11.54)	49.1% (10.8)	0.067
5) Emotional well-being	69.2% (16.34)	80% (18.18)	62% (10.5)	0.086
6) Social functioning	71.25% (27.67)	75% (28.8)	68.7% (27.6)	0.74
7) Pain	40.95% (23.94)	47.3% (26.2)	36.6% (21.9)	0.62
8) General health	52.5% (13.18)	52.5% (13.2)	52.5% (13.18)	1.00

Table 7: Mean and standard deviation of the SF-36 domains in the included participants with comparison between the eight domains according to gender.

* Significant results.

5.4 Discussion

This cross-sectional study aimed to report the quality of life among patients with severe knee OA who were ready for total knee replacement surgery and the gender differences in terms of QoL. This study is part of another study that evaluated the activity level before and one year after total knee replacement surgery. The outcomes of this study found that there were significant impairments in some of the sub-scores of QoL. The included Hungarian patients had low physical function and a high pain level, which reduced their ability to freely achieve their daily activities. However, the overall scores of social functioning and emotional well-being among participants were the highest in domains with less struggle.

The results of this study are similar to those of other studies that reported OoL using the SF-36 questionnaire since these articles showed that OoL is impaired due to knee OA and that functional and pain scores were the lowest (Mahir et al., 2016, Alkan et al., 2014, Saeed et al., 2021). The impairment of quality of life could be correlated with pain severity and radiological severity (Alkan et al., 2014, Hannan et al., 2000, Muraki et al., 2012).

Furthermore, this study found differences in pain and emotional status in terms of gender. The included Hungarian women with severe knee OA had more severe pain and more functional limitations due to emotional problems than the included Hungarian men patients. Similar results were found in other published articles that showed that women with knee OA had higher pain and lower QoL than men with knee OA (Muhammad et al., 2018, Alkan et al., 2014, Muraki et al., 2012, Cui et al., 2020, Tonelli et al., 2011). Therefore, gender was a risk factor for the incidence and severity of knee OA.

For emotional status, this study found that the included Hungarian women with severe knee OA had lower emotional well-being and lower functional activity due to emotional problems than men. Similarly, other studies found that women with knee OA were more likely to have negative mood, anxiety, and depression than men with knee OA (Cui et al., 2020, Keefe et al., 2004, Tonelli et al., 2011). This could be due to the higher pain intensity and low activity level of women with knee OA (Tonelli et al., 2011). Another study conducted in Pakistan found that the role limitation due to emotional problems had a poor score (with an average response of 30%), which could be due to participant characteristics since most of the participants were overweight (Saeed et al., 2021). Hence, it is suggested that obesity could reduce QoL by more than 70% (Saeed et al., 2021, Cui et al., 2020) and increase the risk of disabilities (Batsis et al., 2014). As a result, obesity among patients with severe knee OA should be controlled, as it also reduces the QoL and physical activity level.

5.4.1 The limitations

This cross-sectional study is a part of a case-series study with a small sample size. The data collection process was performed through the COVID-19 pandemic, and it was difficult to get in touch with more elderly individuals due to difficulties in reaching the hospital and putting their lives at risk. Furthermore, the included participants had to continue the main study with one-year follow-up; hence, the number of participants was low. Nevertheless, the outcomes of this study could help therapists in Hungary understand OoL and the most challenging activities among patients with severe knee OA. In addition, the results could be a basic for further studies regarding knee OA to be conducted in Hungary with a larger sample size.

5.5 Conclusion

Knee OA is a global disabling disease that is associated with pain and low quality of life. Patients with severe knee OA complain mainly of pain and role limitations due to physical health and emotional problems. Additionally, the included Hungarian women with severe knee OA had significantly lower physical functioning and role limitations due to emotional problems than the included Hungarian men. Hence, it is necessary to include intensive emotional health care in the treatment strategy for women with severe knee OA in Hungary. Further studies with larger sample sizes are needed.

6. Novel findings and practical application

6.1 Novel findings

- The systematic- review study aimed to provide a comprehensive overview of the effects of using the knee valgus brace on self-reported pain and activity levels over three different time intervals: short-term, moderate-term, and long-term among patients with medial compartment knee osteoarthritis. This study found that most of the included studies recommended using the knee valgus brace to reduce pain and enhance the quality of life. However, most of them are short-term studies, and more information about the long-term effects is needed.
- Using the knee valgus brace could be more recommended and suitable for patients who have less than 8 degrees of knee varus, less than 20 degrees of knee flexion contracture, mild to moderate knee OA level (KL grade II and III), and their body mass index less than 30 kg/m². Patients with severe knee OA and higher body mass (more than 30 kg/m²) index are less satisfied with using knee valgus brace due to poor fitting.
- The meta-analysis study aimed to address the activity level improvement after at least six months of total knee replacement based on the high validity and reliability accelerometer ActivPAL. This study found that the number of steps significantly increased after surgery; however, the sedentary time after surgery was still high and could reduce the efficiency of surgery. Therefore, to increase the efficiency of TKR surgery, it is important to reduce sedentary time.
- Moreover, the meta-analysis study suggested that the health status of the patients before the surgery is associated with the outcomes of the surgery. Patients with high activity level before the surgery are more likely to have better physical activity level after the surgery.
- The case-series study is the primary study for my Ph.D. This study aimed to assess the activity level behavior of patients with severe knee OA and to evaluate the quality of life improvement after one year of total knee surgery. Additionally, we addressed whether the activity level improvement after total knee replacement surgery is sufficient to restore normal activity levels.

The results of this study found that the activity level and pain were enhanced one year after surgery; however, the sedentary time after surgery should be reduced more to reach the maximum benefits of surgery. Hence, to enhance the efficiency of the surgery, it is recommended to try to reduce the sedentary time and join a long-term rehabilitation follow-up.

- To the best of our knowledge, the main study of the thesis was the first in Hungary which gave details about the number of steps, stepping time, and sedentary time among patients with severe knee OA using activPAL. Using a high avidity objective assessment tool is important to evaluate the PA among patients with knee OA in order to understand their physical activity behaviour.
- The last study in my thesis was a cross-sectional study that aimed to report the quality of life among the recruited Hungarian patients with severe knee OA and to assess the differences in quality of life based on gender differences. The results of this study found that the included Hungarian patients with severe knee OA had low activity levels and high pain level. Furthermore, the included Hungarian women with severe knee OA had lower functional levels due to emotional problems than the included Hungarian men.
- It is important to include intensive emotional treatment in the rehabilitation strategy for patients with severe knee OA in Hungary to enhance their quality of life.

6.2 Practical application

This thesis discussed four studies. The systematic review study found that most of the included studies found using a knee valgus brace effective in reducing pain and improving activity level over different time intervals. In addition, patients with less severe knee OA and with BMI less than 30 kg/m² were more satisfied with using knee valgus brace and found it more effective than patients with severe knee OA and BMI more than 30 kg/m². Obese patients complained of rotation and skin irritation due to poor fitting. Hence, specific patients' criteria could fit properly with the knee valgus brace. These criteria should be checked before description the knee valgus brace for patients with medial compartment knee OA patients in order to reach the maximum benefits and to avoid any further pain and discomfort.

The meta-analysis study found that total knee replacement surgery is an effective treatment for improving patients' quality of life with severe knee injuries. Based on the high validity monitor, the number of steps significantly improved, but the sedentary time did not change significantly. Therefore, it is important to decrease sedentary time for patients after total knee replacement surgery in order to restore their activity level, decrease their sedentary time, and increase their satisfactory outcomes after surgery. This could be done by implementing rehabilitation program with long-term follow-up sessions to enhance the physical outcomes and reduce the sedentary time after the surgery.

The case-series study found that the included Hungarian patients have better physical activity levels and less pain (less pain or a better QoL in general) based on both objective and subjective tools after total knee replacement surgery. The activity level based on activPAL and SF-36 questionnaire enhanced after one year of the surgery. However, the changes in sedentary time are still not enough to allow the included Hungarian patients to meet the general physical activity guidelines which could reduce the efficiency of TKR surgery. Therefore, implementing long-term follow-up and rehabilitation sessions could be required to reduce the sedentary time and increase the efficiency of TKR surgery in Hungary.

The cross-sectional study found that there were significant impairments in some of the sub-scores of QoL. The patients with severe knee osteoarthritis had a low quality of life and severe pain during daily activities which reduced their ability to freely achieve their daily activities. However, the overall scores of social functioning and emotional well-being among participants were the highest in domains with less struggle. Furthermore, women with severe knee OA had significantly higher pain and lower quality. The findings of this study emphasize the importance of including intensive emotional health care in the treatment strategy for women with severe knee OA. Moreover, the findings of this study help the for specialists who work with Hungarian patients with severe knee OA to understand their quality of life impermanent.

7. Summary

Osteoarthritis (OA) is a degenerative musculoskeletal joint disease that is correlated with age, gender, and body weight (Glyn-Jones et al., 2015, Felson et al., 2000, Felson, 2006). Knee OA is a very common type of osteoarthritis which is associated with various changes such as cartilage breakdown, meniscus damage, new bone growth at the joint margin, and biomechanical changes (Hawker et al., 2014, Felson, 2006, Felson et al., 2000, Glyn-Jones et al., 2015). Knee OA has different stages depending on the degenerative severity and new bone formation based on the Kellgren and Lawrence (K-L) (Kellgren and Lawrence, 1957). The core signs and symptoms of knee OA are pain during daily activities, low physical level, disabilities, and mortalities (Hawker et al., 2014, Felson, 2006, Felson et al., 2000, Glyn-Jones et al., 2015). In Hungary, the prevalence of advanced and severe knee OA is increasing yearly (Horváth et al., 2011, Fekete et al., 2020). Moreover, the quality of life Hungarian patients with knee OA was less than other European patients with knee OA which could be related to differences in culture, the provided health services, and duration of illness (Wilburn et al., 2017).

The treatments for knee OA could be conservative interventions or surgical interventions depending on pain severity and disease progression such as education, weight management, pharmacology treatments, physiotherapy sessions, orthotics interventions, arthroscopy, high-tibia osteotomy, and arthroplasty (Alfatafta et al., 2021, Alfatafta et al., 2016, Alfatafta, 2015, Lim and Al-Dadah, 2022, Arendt-Nielsen et al., 2018, Lespasio et al., 2017). All of the available interventions aim to reduce pain, increase activity level, and enhance the quality of life for patients with knee OA (Alfatafta et al., 2021, Alfatafta et al., 2016, Alfatafta, 2015, Lim and Al-Dadah, 2022, Arendt-Nielsen et al., 2018, Lespasio et al., 2017, Jones et al., 2013, Thoumie et al., 2018, Ornetti et al., 2015).

Generally, the knee brace is the main conservative option used for mild and moderate knee OA (Schmalz et al., 2010, Hjartarson and Toksvig-Larsen, 2018, Ornetti et al., 2015, Adhikari, 2016, Richards et al., 2005, Jones et al., 2013, Thoumie et al., 2018, Alfatafta et al., 2021). While total knee replacement surgery is the surgical option that is mainly prescribed for severe knee OA (Ferket et al., 2017a, Skou et al., 2018, Skou et al., 2016, Skou et al., 2015, Arendt-Nielsen et al.,

2018, Lespasio et al., 2017). However, some questions are not well addressed in terms of knee valgus brace and total knee replacement surgery. Hence, during my Ph.D. journal, I investigated four research studies in order to fill the missing information about the effects of knee valgus brace over different time intervals, the effects of total knee replacement surgery, the activity level of patients before and after total knee replacement surgery, and the quality of life among Hungarian patients with severe knee OA. Here is the main summary for the four research studies:

1- The effect of knee valgus brace on pain and activity levels over different time intervals among patients with medial knee OA (Alfatafta et al., 2021). This study aimed to provide a comprehensive overview of the effects of using the knee valgus brace on self-reported pain and activity levels over three different time intervals: short-term, moderate-term, and long-term among patients with medial compartment knee osteoarthritis. Two independent reviewers searched the following electronic databases from January 2000 until the end of November 2020: Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PubMed, Web of Science, and Scopus to find relevant articles. This study found 24 studies that met the inclusion criteria. Most of the included studies recommended using the knee valgus brace to reduce pain and enhance the quality of life.

Moreover, the included studies found that some patients stopped using the brace due to different reasons such as discomfort, skin irritation, poor fitting, poor appearance, or pain (Ornetti et al., 2015, Fu et al., 2015, Hsieh et al., 2020, Jones et al., 2013, Ostrander et al., 2016, van Egmond, 2017). As a result, the knee valgus brace could be effective for specific patients more than others (Barnes et al., 2002, Hsieh et al., 2020, Jones et al., 2013, Ostrander et al., 2016). Knee OA patients with less than 8 degrees of knee varus, less than 20 degrees of knee flexion contracture, mild to moderate knee OA level (KL grade II and III), and their body mass index less than 30 kg/m² were more satisfied with using knee valgus brace than other patients (Barnes et al., 2002, Hsieh et al., 2020, Jones et al., 2013, Ostrander et al., 2016). However, most of the included studies are short-term studies, and more information about the long-term effects is needed to find out other side effects of using a knee valgus brace or other recommendations before using a knee valgus brace.

The findings of this study help specialists who work with patients with medial compartment knee OA to provide sufficient information about the knee valgus brace before recommending the knee valgus brace to ensure the best quality of life and pain management.

2-The effect of total knee surgery on activity level based on ActivPAL. This study aimed to address the activity level improvement after at least six months of total knee replacement based on the high validity and reliability accelerometer ActivPAL. Five electronic databases including Cochrane Central Register of Controlled Trials, EMBASE, PubMed, Web of Science, and Scopus were searched for relevant studies by two independent reviewers based on the search strategy. Three studies were included (Alfatafta et al., 2022). This study found that the number of steps significantly increased after surgery; however, the sedentary time after surgery was still high and could reduce the efficiency of surgery (Granat et al., 2020, Lützner et al., 2014, Frimpong et al., 2020). Other studies reported similar results based on using other activity monitors (Arnold et al., 2016, Almeida et al., 2018, Hammett et al., 2018). The sedentary time should be reduced to increase the quality of life.

In addition, it is expected that different factors could have impacts on the outcomes of total knee replacement surgery such as age, body mass index, and activity level of the patients before the surgery (de Groot et al., 2008, Kersten et al., 2012, Granat et al., 2020, Lützner et al., 2014, Frimpong et al., 2020). Hence, this study suggested that the health status of the patients before the surgery is associated with the outcomes of the surgery.

The results of this study will help specialists who work with patients undergoing total knee replacement surgery to restore their activity level, decrease their sedentary time, and increase their satisfactory outcomes after surgery.

3- The activity level and quality of life before and after total knee replacement surgery among patients with severe knee OA. This is the primary study for my Ph.D. This study aimed to assess the activity level behavior of patients with severe knee OA and to evaluate the quality of life improvement after one year of total knee surgery. Additionally, we addressed whether the

activity level improvement after total knee replacement surgery is sufficient to restore normal activity levels. The activity level and quality of life were evaluated with ActivPAL and SF-36 questionnaire. ActivPAL (PAL Technologies, Glasgow, UK) is a uniaxial accelerometer that calculates activity level including the time spent in sedentary, standing, and stepping, and the number of steps per day for up to 14 days (Edwardson et al., 2017, Lyden et al., 2017, Dahlgren et al., 2010, Taraldsen et al., 2011, Ryan et al., 2006). This accelerometer has a higher validity and reliability to detect body movement with different walking speeds, and it is suitable to be used with the elderly (Kim et al., 2015, Ryan et al., 2006). This was the first time this accelerometer was used among patients with knee OA in Hungary to evaluate their activity level before and after total knee replacement surgery.

The results of this study found that the activity level and pain were enhanced one year after surgery based on ActivPAL and SF-36 questionnaire; however, the sedentary time after surgery should be reduced more to reach the maximum benefits of total knee replacement surgery. Hence, to enhance the efficiency of the surgery, it is recommended to try to reduce the sedentary time and join a long-term rehabilitation follow-up (Granat et al., 2020, Lützner et al., 2014, Alfatafta et al., 2022). Moreover, objective assessment tools are important to be implemented in the evaluation to reduce recall bias and represent more information about the physical activity level of patients with knee OA in Hungary.

To the best of our knowledge, the main study of the thesis was the first study in Hungary which gave details about the number of steps, stepping time, and sedentary time among patients with severe knee OA using activPAL. Using a high avidity objective assessment tool is important to evaluate the physical activity among patients with knee OA in order to understand their physical activity behaviour. The results of this study are crucial for specialists who work with Hungarian patients with severe knee OA to understand their activity level limitations and how to enhance their activity level after surgery.

4- The last study in my thesis was a cross-sectional study that aimed to report the quality of life among the recruited Hungarian patients with severe knee OA and to assess the differences in quality of life based on gender differences. Insufficient data are available about the activity level

of Hungarian patients with severe knee as only one conference paper (Busa et al., 2019) reported the quality of life (QoL) among Hungarian patients with severe knee OA before total knee replacement surgery using four different questionnaires, including a homemade questionnaire, the Knee Society Score (KSS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the short form (SF-36) questionnaire. The number of participants was not mentioned, and the reported results and methods were not well presented as it was a conference paper (Busa et al., 2019). Therefore, this study aimed to report quality of life of patients with severe knee OA who planned to have total knee replacement surgery after one month. Additionally, this study aimed to evaluate gender differences in terms of the quality of life.

The SF-36 questionnaire (Hungarian version) was used to assess the quality of life of the patients one month before total knee replacement surgery. The participants were recruited from the Department of Orthopedics (Clinical Center, University of Pécs, Hungary). The results of this study found that the included Hungarian patients with severe knee OA had low activity level and high pain level. Furthermore, the included Hungarian women with severe knee OA had lower functional level due to emotional problems than the included Hungarian men. Similar results were reported by (Cui et al., 2020, Keefe et al., 2004, Tonelli et al., 2011) as women with knee OA were more likely to have negative mood, anxiety, and depression than men with knee OA. Women with knee OA have a higher pain intensity than men (Tonelli et al., 2011). As a result, it is recommended to include intensive emotional health care in the treatment strategy for women with severe knee OA in Hungary.

8. List of publications

1. **Alfatafta, H.**, Alfatafta, M., Onchonga, D., Hammoud, S., Khatatbeh, H., Zhang, L., ... & Molics, B. (2022). Effect of the knee replacement surgery on activity level based on ActivPAL: a systematic review and meta-analysis study. *BMC musculoskeletal disorders*, 23(1), 1-9.
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11. Király, B., Varga, D., Fekete, H., **Alfatafta, H.**, Mazzag, K., Ács, P., ... & Molics, B. (2022). POSB331 The Examination of Effectiveness of the Education of Exercise Techniques and Training Methods: in Weight Training. *Value in Health*, 25(1), S224-S225.
12. **Alfatafta, H.**, Onchonga, D., Alfatafta, M., Boncz, I., Lohner, S., & Molics, B. (2021). Effect of using knee valgus brace on pain and activity level over different time intervals among patients with medial knee OA: systematic review. *BMC Musculoskeletal Disorders*, 22(1), 1-9.
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List of Appendixes

Appendix 1: Searching Protocol

- #1 osteoarthritis[Title/Abstract] OR osteoarthrosis[[Title/Abstract]
- #2 degenerative joint disease[Title/Abstract]
- #3 osteoarthritis, knee[MeSHTerms]
- #4 #1 OR #2 OR#3
- #5 knee[Title/Abstract]
- #6 knee joint[MeSHTerms]
- #7 #5 OR #6
- #8 brace*[Title/Abstract] OR bracing[Title/Abstract]
- #9 orthotic devices[MeSHTerms]
- #10 #8 OR #9
- #11 #4 AND #7 AND #10

Appendix 2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hjartarson & Toksvig-Larsen, 2018	?	+	-	-		+	+
Iqbal, 2014	+	-	-	-	-	-	+
Ostrander et al., 2016	+	+	-		+	-	+
Sattari & Ashraf, 2011	+	+	-		+		+
Thoumie et al., 2018	+	+	-		+	+	+
van Egmond et al., 2017	+	+	+	+	+	+	+
van Raaij et al., 2010	+	+	-		+	+	+

Appendix 3: PRISMA check list

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (line 1)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 (line 19)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Appendix 4: Search strategy for Pubmed (filter is date of publication:1/1/2000-31/10/2021, language is English)

- 1 Arthroplasty, Replacement, Knee/ mesh term
- 2 Knee Prosthesis/ mesh term
- 3 knee replacement. Title/Abstract
- 4 tkr. Title/Abstract.
- 5 or/1-4
- 6 Knee/
- 7 knee. Title/Abstract
- 8 or/6-7
- 9 Arthroplasty/ mesh term
- 10 Joint Prosthesis/ mesh term
- 11 (arthroplast* or prosthe* or replace*). Title/Abstract
- 12 or/9-11
- 13 8 and 12
- 14 5 or 13
- 15 activPal. Title/Abstract
- 16 function*. Title/Abstract
- 17 (activity or activities). Title/Abstract
- 18 (lying or sitting or standing or stepping). Title/Abstract
- 19 position. Title/Abstract
- 20 sedentary time. Title/Abstract
- 21 16 or 17 or 18 or 19 or 20
- 22 device. Title/Abstract.
- 23 monitor. Title/Abstract.
- 24 accelerometer. Title/Abstract.
- 25 22 or 23 or 24
- 26 21 and 25
- 27 15 or 26
- 28 14 and 27

Search strategy for Cochrane (filter is date of publication:1/1/2000-31/10/2021)

- 1 Arthroplasty, Replacement, Knee. Mesh term
- 2 Knee Prosthesis. Mesh term
- 3 knee replacement. Title, abstract, keyword
- 4 tkr. Title, abstract, keyword
- 5 or/1-4
- 6 Knee. Mesh term

7 knee. Title, abstract, keyword
8 or/6-7
9 Arthroplasty. Mesh term
10 Joint Prosthesis. Mesh term
11 (arthroplast* or prosth* or replace*). Title, abstract, keyword
12 or/9-11
13 8 and 12
14 5 or 13
15 activPal. Title, abstract, keyword
16 function*. Title, abstract, keyword
17 (activity or activities). Title, abstract, keyword
18 (lying or sitting or standing or stepping). Title, abstract, keyword
19 position. Title, abstract, keyword
20 sedentary time. Title, abstract, keyword
21 16 or 17 or 18 or 19 or 20
22 device. Title, abstract, keyword
23 monitor. Title, abstract, keyword
24 accelerometer. Title, abstract, keyword
25 22 or 23 or 24
26 21 and 25
27 15 or 26
28 14 and 27

Search strategy for Embase (filter is date of publication: 2000-2021, and language is English)

- 1 Arthroplasty, Replacement, Knee. Emtree exploded
- 2 Knee Prosthesis. Emtree exploded
- 3 knee replacement. Title, abstract, keyword
- 4 tkr. Title, abstract, keyword
- 5 or/1-4
- 6 Knee. Emtree exploded
- 7 knee. Title, abstract, keyword
- 8 or/6-7
- 9 Arthroplasty. Emtree exploded
- 10 Joint Prosthesis. Emtree exploded
- 11 (arthroplast* or prosthe* or replace*). Title, abstract, keyword
- 12 or/9-11
- 13 8 and 12
- 14 5 or 13
- 15 activPal. Title, abstract, keyword
- 16 function*. Title, abstract, keyword
- 17 (activity or activities). Title, abstract, keyword
- 18 (lying or sitting or standing or stepping). Title, abstract, keyword
- 19 position. Title, abstract, keyword
- 20 sedentary time. Title, abstract, keyword
- 21 16 or 17 or 18 or 19 or 20
- 22 device. Title, abstract, keyword
- 23 monitor. Title, abstract, keyword
- 24 accelerometer. Title, abstract, keyword
- 25 22 or 23 or 24
- 26 21 and 25
- 27 15 or 26

Search strategy for Web of science (filter is date of publication: 2000-2021, and language is English)

- 1 Arthroplasty, Replacement, Knee. Keyword Plus
- 2 Knee Prosthesis. Keyword Plus
- 3 knee replacement. Topic
- 4 tkr. Topic
- 5 or/1-4
- 6 Knee. Keyword Plus
- 7 knee. Topic
- 8 or/6-7
- 9 Arthroplasty. Keyword Plus
- 10 Joint Prosthesis. Keyword Plus
- 11 (arthroplast* or prosthe* or replace*). Topic
- 12 or/9-11
- 13 8 and 12
- 14 5 or 13
- 15 activPal. Topic
- 16 function*. Topic
- 17 (activity or activities). Topic
- 18 (lying or sitting or standing or stepping). Topic
- 19 position. Topic
- 20 sedentary time. Topic
- 21 16 or 17 or 18 or 19 or 20
- 22 device. Topic
- 23 monitor. Topic
- 24 accelerometer. Topic
- 25 22 or 23 or 24
- 26 21 and 25
- 27 15 or 26
- 28 14 and 27

***Search strategy for Scopus (filter is date of publication: 2000-2021, and language is English)**

- 1 Arthroplasty, Replacement, Knee. Keyword
- 2 Knee Prosthesis. Keyword
- 3 knee replacement. title, abstract, keyword
- 4 tkr. title, abstract, keyword
- 5 or/1-4 Keyword
- 6 Knee. Keyword Plus
- 7 knee. title, abstract, keyword
- 8 or/6-7. Keyword
- 9 Arthroplasty. Keyword
- 10 Joint Prosthesis. Keyword
- 11 (arthroplast* or prosth* or replace*). title, abstract, keyword
- 12 or/9-11. Keyword
- 13 8 and 12. Keyword
- 14 5 or 13. Keyword
- 15 activPal. title, abstract, keyword
- 16 function*. title, abstract, keyword
- 17 (activity or activities). title, abstract, keyword
- 18 (lying or sitting or standing or stepping). title, abstract, keyword
- 19 position. title, abstract, keyword
- 20 sedentary time. title, abstract, keyword
- 21 16 or 17 or 18 or 19 or 20. Keyword
- 22 device. title, abstract, keyword
- 23 monitor. title, abstract, keyword
- 24 accelerometer. title, abstract, keyword
- 25 22 or 23 or 24. Keyword
- 26 21 and 25. Keyword
- 27 15 or 26. Keyword
- 28 14 and 27. Keyword

Appendix 5: The risk of bias in the included articles based on ROBINS-I tool for before-after study with control group.

	Lützner et al., 2014
Confounding	Moderate
Selection	Moderate
Measurements of interventions	High
Missing data	Low
Measurements of outcomes	High
Reporting	Low
Overall	High

Appendix 6: The NIH quality assessment for Before-After (Pre-Post) studies with no control group.

	Granat et al., 2020	Frimpong et al., 2020
1. Was the research question or objective in this paper clearly stated?	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	Yes
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes
10. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	No
11. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	No	No
12. Summary Quality	Good	Good

Ethical Approval



UNIVERSITY OF PÉCS
Regional Research Ethic Committee of
Medical Center, Pécs, Hungary

Certificate

Pécs, 26. June 2020.

To Whom It May Concern,

Principal Investigator: Huda Alfatafta PhD student
Doctoral School of Health Sciences,
Faculty of Health Sciences, Medical School, University of Pécs, Hungary

Supervisors:

dr. Bálint Molics, First Assistant Professor, Institute of Physiotherapy and Sport Sciences, Faculty of Health Sciences, University of Pécs.
prof. dr. Imre Boncz, Institute of Health Insurance, Faculty of Health Sciences,
prof. dr. Péter Than, Orthopaedic Clinic, Clinical Center, University of Pécs

Title: Evaluation the physical activity level before and after the knee replacement surgery using ActivPAL and SF-36 Hungary

Aim: Topic of PhD Thesis, data collection for PhD thesis


Supplements:

- (1.) letter to the head of Regional Research Ethical Committee;
- (2.) letter to dr. Andor Sebestyén, head of Clinical Center Pécs, for data collection approval
- (3.) Scientific and literal background;
- (4.) Protocol: 1. – 4. visits;
- (5.) benefits of study; English and Hungarian forms;
- (6.) Participant's Information Sheet; (7.) Informed Consent Form;
- (8.) Patient Demographic Form; (9.) SF-36 Survey
- (10.) recommendation letter from prof. dr. András Vereczkei / prof. dr. Péter Than;
- (11.) recommendation letter from prof. dr. Endre Sulyok Endre, secretary of Doctoral School of Health Sciences;
- (12.) recommendation letters from supervisors;
- (13.) data collection approval supplement number 10.

Decision: The Ethics Committee as the Institutional Review Board **discussed** your application on its meeting held on 26th of June 2020. and **we took notice** of execution of clinical investigation after its protocol. At last we ask the principal investigator to send a summary of results for our Committee after he finished the investigation.

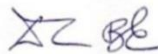
Record number: 8343/2020.

Yours sincerely


Samuel Komoly

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Appendix 7:

Submission of the doctoral dissertation and declaration of the originality of the dissertation

The undersigned,

Name: Huda Alfatafta

Maiden name: Huda Alfatafta

Mother's maiden name: Olfat Alfatafta

Place and time of birth: Amman, Jordan, 1989/10/14

on this day submitted my doctoral dissertation entitled: Activity level and quality of life among patients before and after total knee replacement surgery to the

PR-1 , frontiers of health sciences Programme of the Doctoral School of Health Sciences, Faculty of Health Sciences, University of Pécs.

Names of the supervisor(s): Dr. habil Molics Balint, Prof.Dr. Boncz Imre

At the same time, I declare that

- I have not submitted my doctoral dissertation to any other Doctoral School (neither in this country nor abroad),
- my application for degree earning has not been rejected in the past two years,
- in the past two years I have not had unsuccessful doctoral procedures,
- my doctoral degree has not been withdrawn in the past five years,
- my dissertation is independent work, I have not presented others' intellectual work as mine, the references are definite and full, on preparation of the dissertation I have not used false or falsified data.

Dated:

signed by Candidate

Supervisor

Co-supervisor

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Submission of the doctoral dissertation and declaration of the originality of the dissertation

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Names of the supervisor(s): Dr. Habil. Molics Bálint, Prof. Dr. Boncz Imre

At the same time, I declare that

- I have not submitted my doctoral dissertation to any other Doctoral School (neither in this country nor abroad),
- my application for degree earning has not been rejected in the past two years,
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Dated: 20 June 2023



signed by Candidate



Supervisor



Co-supervisor