STUDY PROTOCOL AND STATISTICAL ANALISYS PLAN

TELEMEDICINE IN PERSONALIZED HOME-BASED REHABILITATIVE TREATMENT AFTER TOTAL KNEE REPLACEMENT (TKA): PILOT STUDY

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Title of the study: Telemedicine in personalized home-based rehabilitative treatment after total knee replacement (TKA): pilot study.

Introduction: Knee osteoarthritis (OA) is the most common form of diagnosed arthritis, with increasing incidence due to its association with aging and obesity in the general population. [1] The percentage of affected individuals reaches approximately 40% in populations over 70 years old. [1] The prevalence is higher among women. [1] Common symptoms include, besides pain, reduced range of motion (ROM) or joint locking, crepitus or noises during movement, decreased strength, swelling, and instability, which also lead to negative psychological impacts, contributing to decreased daily activity, mobility, and an overall reduction in quality of life. [2] In the pathogenesis of OA, proteolytic enzymes (matrix metalloproteinases, MMPs) are involved, with increased production caused by various factors. Initially, chondrocytes can partially compensate by increasing proteoglycan production and tissue inhibitors of metalloproteinases (TIMPs). Unfortunately, when the direct cause cannot be addressed, this compensation is insufficient to restore the balance between cartilage synthesis and degradation. Consequently, proteoglycan levels decrease, the collagen structure becomes brittle, and degenerative phenomena such as fissuring or tearing of the cartilage layer, as well as subchondral cartilage damage, begin to occur. Although these features are typically used to quantify disease severity, OA affects almost all other components of the knee, including ligaments, menisci, nerves, and muscles acting on the joint. [3] Based on etiology, two categories of OA exist: primary, non-traumatic or idiopathic; and secondary, mainly due to mechanical misalignment or trauma.

Treatment options for knee OA include conservative or surgical approaches. Non-surgical treatments can be pharmacological or non-pharmacological. Non-pharmacological therapies often start with weight loss, followed by physical activity, which alone can reduce pain and improve quality of life. [4] [5] Strengthening exercises targeting stabilizer muscles of the knee (particularly the quadriceps) aim to reduce the load transferred directly onto the joint during movement, thereby decreasing joint stress. [6] A recent review demonstrated that physical exercise is an effective therapy for individuals with early-stage knee OA. [7] [8] Despite the importance of non-pharmacological strategies, less than 40% of patients with knee OA receive such approaches. [9] One reason for this low utilization is limited access to rehabilitation, especially when in-person attendance is challenging. Therefore, the World Health Organization recommends digital interventions to complement traditional healthcare, aiming to improve access for broader populations. [10] Recent literature shows that both in-person and digital treatments can lead to clinically significant improvements in pain. [11] OA is a leading cause of disability and has a high economic impact, both in direct costs (medications, surgeries) and indirect costs (lost income, increased expenses). [12] [13] Advances in digital health technologies through digital platforms can enable the delivery of primary care interventions aligned with global guidelines, potentially at reduced costs compared to traditional care models. [14]

Another challenge limiting the use of this effective therapeutic strategy is inconsistent adherence to treatment plans. Factors influencing poor adherence include fluctuating symptoms, comorbidities, personal motivation, and individual goals, which need to be explored to incorporate patient-centered objectives into personalized rehabilitation programs. [14] In addition to psychological and emotional factors, clinical examinations and posturography analysis are recommended for planning conservative interventions in OA patients. [15] [16] [17] Limited access to early treatments, combined with their proven effectiveness in pain reduction and optimal recovery of activities of daily living (e.g., walking), contributes to the increasing number of total knee arthroplasties (TKA) performed annually. [18] [19] Postoperative deficits in balance components, such as reduced proprioception, decreased postural control, and slower muscle activation, have been documented. [20] [21] A recent study highlights the utility of posturographic assessment in developing targeted rehabilitation programs to compensate for postural deficits and improve gait performance. [22] Tele-rehabilitation has been shown to be as effective as face-to-face therapy in controlling pain and improving functional recovery after TKA. [23]

Study Objectives: The primary aim is to demonstrate that adherence and, consequently, functional outcomes (pain reduction and limitations) at short- and long-term follow-up improve with a personalized exercise program that includes psychological-motivational assessment and development of personalized exercises based on posturographic analysis. This program is supported via digital therapy through tele-rehabilitation, leading to pain reduction and decreased medication use (project: Sy-Di-DOA).

Materials and Methods: To ensure quality and ethical standards in the design and implementation of our randomized controlled trial (RCT), we will adhere to the Helsinki criteria and the CONSORT checklist. All patients admitted for rehabilitation following Total Knee Arthroplasty (TKA) at the San Giovanni di Dio Rehabilitation Center in Adelfia (BA) will be evaluated for eligibility to participate in an RCT for primary symptomatic osteoarthritis (OA) of the knee between October-November 2024 and March 2025.

Inclusion criteria:

Age between 50 and 75 years;

Recent unilateral total knee arthroplasty;

Body Mass Index (BMI) < 35 [24];

Ability to stand on one leg;

Absence of known active neurological or oncological diseases.

Exclusion criteria:

Traumatic or inflammatory knee OA;

Valgus/varus deformity (hip-knee-ankle angle > or < 10°).

The control group, after medical and physiotherapeutic assessment, will undergo a posturographic examination and then receive a personalized treatment aimed at strengthening the specific muscles of the lower limbs, improving the range of motion of the joint, and enhancing balance and gait in two physiotherapy sessions per day, each lasting 45 minutes, during the 22-25 days of hospitalization. This will be followed post-discharge by an outpatient standard treatment consisting of two sessions per week, each lasting 45 minutes, for the subsequent weeks up to three months from T0 at a physiotherapy outpatient clinic [25].

The study group, in addition to the aforementioned assessments, will receive a personalized treatment aimed at specifically strengthening the muscles of the lower limbs, improving the range of motion of the joint, enhancing balance, and optimizing gait in the same manner and for the same duration. At the end of the hospitalization, continuation of the outpatient rehabilitation treatment is planned with a personalized program of two sessions per week, each lasting 45 minutes, for the following weeks up to three months from T0, supervised at home by a physiotherapist via telemedicine (a video call using Zoom as the videoconferencing software with encryption). [25]

Sample Size Calculation: A target sample size of 40 patients (20 in each group) has been calculated to achieve at least 90% power to detect a difference of 1.7 points with a standard deviation of 1.3 in the VAS score between the study and control groups. This calculation assumes a bilateral test and an alpha level (α) of 0.01, accounting for a 20% dropout rate. The calculation references a previous study.

Statistical Analysis: The primary outcome will be the difference in improvement of function as measured by the WOMAC and KOOS tests, as well as the assessment of reduction in resting pain intensity measured with the VAS scale before total knee arthroplasty (TKA) and at 12 weeks in both the study and control groups. Secondary outcomes will include the improvement in independence in activities of daily living before and after the therapeutic intervention in both groups, assessed using the Barthel index and the mRS; the psychobehavioral assessment at the time of recruitment using the CEQ, COP-NIV, PAM13, CG-PAM scales; and attitudes towards technology recorded with the TAM scale at recruitment.

An additional evaluation will examine analgesic consumption throughout the study duration in both groups and the time to discontinuation of any prescribed mobility aids.

Patient characteristics and outcome measures will be reported in aggregated form: mean ± standard deviation for continuous variables and absolute frequencies (percentages) for categorical variables. The statistical analysis of outcomes will assess the significance of differences between groups and within groups over time. Initial characteristics and changes in outcomes will be examined and compared.

The Wilcoxon signed-rank test for paired samples will be used to evaluate intra-group differences and the effect of the physiotherapy program. The Mann-Whitney U test for two independent samples will assess the significance of differences between groups and evaluate the inter-group effect of telerehabilitation. The χ^2 test will be employed to verify the homogeneity of categorical variable distributions across the two arms.

Statistical significance will be set at $p < 0.05$. The effect size (ES) for the Mann-Whitney U test will be calculated in the case of inter-group comparisons.

Each patient will only participate in the study after signing the informed consent form for participation. Each participant will be invited to complete a diary in which they will record their daily consumption of any analgesic medications taken for knee pain during the study period, from start to finish. They will report the total weekly and monthly consumption (12 weeks / 3 months), specifying the type of drug (paracetamol/NSAIDs/corticosteroids/opioids/myorelaxants). Additionally, the complete discontinuation of any prescribed mobility aids will be recorded.

At evaluation times T0 (study admission), T1 (1.5 months), and T2 (3 months), both groups will be assessed on the following aspects:

Pain intensity using the Visual Analog Scale (VAS), which is a unidimensional psychometric scale for self-assessment of pain intensity. It consists of a 10 cm horizontal line marked with two verbal descriptors: one indicating the absence of pain perception, and the other representing the maximum pain intensity experienced. The patient marks on the line the point that reflects the intensity of the symptom perceived at the time of assessment [26].

Using the same evaluation times, the following tests will be administered:

- The Western Ontario and McMaster Universities Arthritis Index (WOMAC): a patient-reported outcome measure (PRO) designed to identify changes in symptoms and activity limitations in individuals with hip or knee osteoarthritis, even after joint replacement surgery. It has demonstrated strong psychometric properties. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items assessing pain intensity related to various activities or positions), Stiffness (2 items evaluating stiffness in different circumstances), and Physical Function (17 items assessing difficulty experienced during specific activities). All items are rated on a Likert scale from 0 (no symptoms) to 4 (high intensity or difficulty) [27].
- The Knee Injury and Osteoarthritis Outcome Score (KOOS): a self-administered questionnaire designed to evaluate symptoms related to knee joint injuries or osteoarthritis. It is also valid for patients who have undergone total knee arthroplasty. KOOS is considered a reliable tool for assessing the impact of knee conditions on daily life and overall function. The scale comprises 42 items across 5 subscales: Symptoms (7 items, 2 related to stiffness), Pain (9 items), Function in daily living (17 items), Sport and recreation (5 items), and Quality of life related to the knee (4 items). All items use

the same response format, employing a 5-point Likert scale from 0 (no problems/difficulties) to 4 (severe problems/difficulties) [28].

- The Barthel Index for Activities of Daily Living (BI): an ordinal scale measuring a person's ability to complete daily activities through 10 items. Each item is evaluated by the operator based on the individual's capacity to perform a task independently, with assistance, or not at all. The assessment is as follows: 0 = unable, 1 = needs assistance, 2 = independent. The scores from the ten items are summed and multiplied by 5 to obtain a total score out of 100. The interpretative guidelines for Barthel scores are: 0-20 indicates "total dependence"; 21-60 "severe dependence"; 61-90 "moderate dependence"; 91-99 "slight dependence" [29] [30].
- The Modified Rankin Scale (mRS): used to measure the degree of disability, typically in patients with neurological conditions. The scale is constructed as a variable from 0 to 6: 0 = No symptoms; 1 = No significant disability despite symptoms; able to perform all usual duties and activities; 2 = Slight disability; unable to perform all previous activities but able to handle own affairs without assistance; 3 = Moderate disability; requires help but can walk without assistance; 4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = Severe disability; bedridden, incontinent, and requiring constant care; 6 = Dead. Recently, several tools have been developed for a more systematic assessment of mRS, such as mRS-9Q. Free online calculators are available [31] [32].

At time T0, characteristics such as age, sex, level of education, marital status, employment, and presence of a caregiver were investigated. Additionally, during the same period, the willingness to participate in digital treatment was assessed using the Technology Acceptance Model (TAM). Patients' credibility and expectations were evaluated through the Credibility/Expectancy Questionnaire (CEQ). The activation of the patient regarding their own care was measured using the Patient Activation Measure (PAM13), and similar areas of interest within the caregiver were identified using the caregiver version of the Patient Activation Measure (GC-PAM). To understand how individuals respond when facing difficult or stressful events in life, the "Coping Orientation to Problems Experienced-New Italian Version" (COP-NIV) scale was employed.

- The Credibility/Expectancy Questionnaire (CEQ): is a quick and easily administered scale used to measure treatment expectancy and the rationale credibility for use in clinical outcome studies. It has demonstrated results not only in reducing depressive, anxious, and general symptoms but also in increasing therapeutic alliance in physiotherapy [33] [34].

  This is a self-report questionnaire composed of 6 items grouped into two subscales: i) credibility (cognitive focus) and ii) outcome expectation (focus on emotional process). The credibility assesses the reliability of the treatment according to the subject, specifically how much they believe they can

trust the treatment to benefit from it and how useful it will be, closely related to the therapeutic relationship. The expectation refers to the improvement that the subject believes they can achieve from the treatment. The expectation precedes any contact with the therapist and is related to the belief about how much improvement they will experience with that particular treatment, considering their perceptions before starting the treatment.[35]

- The Patient Activation Measure (PAM13): evaluates the patient's knowledge, skills, and confidence in managing their condition. Activation data provide information for designing personalized care strategies and interventions (e.g., additional supports or resources).[36] It consists of 13 items on a Likert scale. Each item has five response categories with scores ranging from 1 to 5: (1) "Strongly disagree," (2) "Disagree," (3) "Agree," (4) "Strongly agree," and (5) "Not applicable." It produces a summed score, normalized to 100. The corresponding interpretation is as follows: Level 1 (patients feel their role is important: items 1 and 2), Level 2 (patients have the confidence and knowledge to act: items 3–8), Level 3 (acting: items 9–11), and Level 4 (maintaining the course under stress: items 12 and 13).[36]
- The Caregiver/Assistant Activation Scale (CG-PAM): It is a 13-item instrument that addresses the same concepts as the PAM, through almost identical questions but from the caregiver's perspective, and produces a summed score normalized to 100. The score can fall into one of four levels. The result is divided into four levels interpreted similarly to the PAM, but in relation to the caregiver. [37]
- The Coping Orientation to Problems Experienced-New Italian Version (COP-NIV): It is a self-administered questionnaire that considers different coping modalities. It investigates five main independent dimensions (social support, avoidance, positive attitude, problem orientation, and transcendental orientation). It is composed of 60 items that assess how individuals respond to stressful events. For each statement, respondents must indicate how frequently they use that particular "strategy" on a 4-point Likert scale. [38]
- The Technology Acceptance Model (TAM): consists of 12 items, with six items measuring Perceived Usefulness (PU) and six items measuring Perceived Ease of Use (PEU). PU reflects the extent to which a person believes that a technology will improve their work performance, while PEU measures how easy a person believes it will be to use the technology. The questions are measured on a scale similar to a Likert scale. [39]

Statistical analysis: The characteristics of the patients and the outcome measures will be reported in aggregate form as mean ± standard deviation for continuous variables and absolute frequencies (percentages) for categorical variables.

The statistical analysis of outcomes will include the significance of differences. The initial characteristics and changes in outcomes between the two groups will be examined and compared. The Wilcoxon signed-rank test will be used to assess intra-group differences and the effect of the physiotherapy program. The Mann-Whitney U test for independent samples will be used to detect the significance of differences between groups and to evaluate the inter-group difference and the effect of tele-rehabilitation. The χ^2 test will be used to verify the homogeneity of the distribution of categorical variables across the two arms. Statistical significance will be set at $p < 0.05$, and the Effect Size (ES) for the Mann-Whitney U test will be calculated in the case of inter-group comparisons.

Expected results: We anticipate that the collected data will enhance our understanding of patients with recent total knee arthroplasty (TKA) due to osteoarthritis (OA), from both structural and behavioral perspectives. This knowledge will allow us to adapt more effective rehabilitative strategies at the time of discharge from dedicated centers, utilizing telemedicine to improve interventions and further reduce costs.

Study location: Presidio territoriale di recupero e riabilitazione funzionale "San Giovanni di Dio" ex art. 26 L. n. 833/1978, operational headquarters: trav. di via Fieno, 5 Adelfia (Ba) (Territorial rehabilitation and recovery center for individuals with physical, psychological, sensory, or mixed disabilities "San Giovanni di Dio", authorized to operate and with institutional accreditation from ASL Bari, equipped with 60 beds for intensive rehabilitation for adults).

Type of study: randomized controlled trial (RCT).

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