Clinical pharmacological aspects of mitochondrial function in muscle
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CHAPTER III

MITOCHONDRIAL FUNCTION, GRIP STRENGTH AND ACTIVITY ARE RELATED TO RECOVERY AFTER A TOTAL KNEE ARTHROPLASTY

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ABSTRACT Low muscle quality and a sedentary lifestyle are indicators for a slow recovery after a total knee arthroplasty (TKA). Mitochondrial function is an important part of muscle quality and a key driver of sarcopenia. However, it is not known whether it relates to recovery. In this pilot study, we monitored activity after TKA using a wrist mounted activity tracker and assessed the relation of mitochondrial function on the rate of recovery after TKA. Additionally, we compared the increase in activity as a way to measure recovery to traditional outcome measures.

Patients were studied 2 weeks before TKA and up to 6 months after. Activity was monitored continuously. Baseline mitochondrial function (citrate synthase and complex 1-5 of the electron transport chain) was determined on muscle tissue taken during TKA. Traditional outcome measures (knee osteoarthritis observation score (KOOS), timed up-and-go (TUG) completion time, grip and quadriceps strength) were performed 2 weeks before, 6 weeks after and 6 months after TKA.

Using a multivariate regression model with various clinical baseline parameters, the following were significantly related to recovery: complex 5 abundance, grip strength and activity (regression weights 0.13, 0.02 and 2.89, respectively). During recovery, activity correlated to the KOOS-ADL score (r=0.55, p=0.009) and TUG completion time (r=-0.61, p=0.001).

Mitochondrial function seems to be related to recovery, but so are activity and grip strength, all indicators of sarcopenia. Using activity trackers before and after TKA might give the surgeon valuable information on the expected recovery and the opportunity to intervene if recovery is low.

INTRODUCTION

The total knee arthroplasty (TKA) procedure is the main treatment of end-stage osteoarthritis (OA) affecting the knee joint and one of the most successful orthopedic interventions to date. Worldwide, approximately 1.5 million TKAs are performed annually. In the Netherlands alone, 25.569 were performed in 2018, an increase of almost 40% compared to 2010.[1] The procedure has a 10-year survival of more than 90% and in most cases, patients return to their level of physical activity in 6 months' time.[2-3] However, despite advances in technology and patient care, an estimated 20-25% of procedures have unsatisfactory results, with 16-30% dissatisfaction in functional outcome.[4-6] Many factors have been proposed to predict outcome, including sarcopenia, the age-related decline in muscle quality.[7] It is estimated that up to 44% of TKA patients suffer from sarcopenia.[8] Sarcopenia is hypothesized to be driven partly by dysfunctional mitochondria, which in OA patients is induced by a sedentary lifestyle.[9-12] Muscle cells rely heavily on mitochondria to fulfill their high energy demand and are easily affected by a disturbance in mitochondrial function.[13] Recovery after a TKA procedure depends, amongst other factors, on muscle function, but it is currently not known if mitochondrial function can predict or relates to recovery after a TKA.[3] Traditionally, recovery after orthopedic procedures is evaluated with patient reported outcome measures (PROMS) and functional tests, such as the timed up-and-go test (TUG) or the measurement of quadriceps strength, at a very limited number of outpatient visits.[3] Although important, PROMS are subjective and functional tests, especially when only performed during the very limited number of outpatient visits, do not reflect the patient's activity outside the hospital.[14] With modern technology increasingly being a part of our lives, wearables, such as activity trackers, have become mainstream and widely used.[15] Measuring daily activity objectively and continuously during a period of time, without visiting the outpatient clinic, will not only monitor functional recovery in patients after orthopedic procedures, but will also give leads to be addressed if discrepancies exist with PROM data, which is often the case.[16] Moreover, it will allow the treating surgeon to monitor the recovery online and offer the possibility to adjust rehabilitation if deemed necessary. However, it is not known if activity trackers can accurately track recovery after a TKA and how activity correlates to PROM and other functional measurements.

The primary aim of this study was to assess the relation of mitochondrial function at baseline on the recovery after TKA. The secondary aim was to use an activity tracker to measure that recovery and to evaluate the association between the activity tracker and traditional outcome measures (PROM, TUG, grip strength and quadriceps strength) during the recovery period.

MATERIAL AND METHODS

Design and study schedule

This was an observational, prospective cohort, level 2 evidence study in patients with end-stage OA, who underwent a TKA. Two weeks prior to the TKA, screening for eligibility and baseline measurements were performed to determine the preoperative clinical function. After the TKA procedure, patients visited the outpatient clinic for follow-up visits at 6 weeks and 6 months. Functional measurements were performed during the outpatient clinic visits and activity was monitored continuously up to 6 months.

Participants

All patients were recruited from the TKA waiting list at the orthopedic department of the Alrijne Hospital (Leiden, The Netherlands), where the procedure and follow-up measurements took place. Inclusion criteria were a minimal age of 60 years; Indication for a unilateral, primary TKA, due to moderate to severe OA of the knee joint (grade 3-4 on the Kellgren and Lawrence scale); formerly able to walk independently; and ability to use a smartphone. Exclusion criteria were any planned surgery in the contralateral knee within 12 months after study enrollment; a history (within 3 months before screening) of alcohol consumption exceeding 2 standard drinks per day on average; and an underlying chronic disease, which would interfere with study participation or the validity of the measurements.

The study was approved by the independent ethics committee Stichting BEBO (Assen, the Netherlands) and conducted according to the principles of the Helsinki Declaration under registration number NL61972.056.17. Informed consent was obtained from all subjects prior to study enrollment.

Surgical technique

All TKAs were performed via medial parapatellar approach and with tourniquet application. Femoral and tibial components were cemented. Before closure, the knee capsule was locally infiltrated with lidocaine in order to facilitate immediate postoperative mobilization.[17]

Biopsy procedure

From each patient, two muscle tissue samples, 5×5×5mm each, were collected from the vastus lateralis muscle within 5 minutes after tourniquet application. Once collected, visible fat was removed and samples were put in two cryovials and immediately snap frozen in an ice bath of methanol and dry ice within 2 minutes and kept there until the end of the TKA procedure. Samples were transported on dry ice and stored at ≤ −80°C until analysis.

Mitochondrial enzyme assay

The mitochondrial enzyme assay was performed by Metabiolab (Lausanne, Switzerland). Muscle tissue was cut, weighed, crushed and sonicated in a dedicated buffer. Colorimetry to measure enzymatic activity was done on tissue homogenate using the Cobas Modular Analyzer Series (Roche Diagnostics, Basel, Switzerland). Citrate synthase (CS) abundancy was measured directly and used as reference value to calculate complex 1-5 activity. Complex 1 (NADH-ubiquinone reductase (CP1)) activity was measured following NADH's dizsappearance, using rotenone as a specific inhibitor to ensure specificity of the assay.[18] Complex 2 (succinate-ubiquinone reductase (CP2)) activity was measured through the reduction of 2,6-dichlorophenolindophenol, a final electron acceptor, after the addition of succinate.[18] The activity of complex 3 (ubiquinone-cytochrome C reductase (CP3)) was followed with the change of reduction of cytochrome c, whose absorbance is greater in its oxidized form than in its reduced form.[19] Complex 4 (cytochrome c oxidase (CP4)) activity assessment was based on the same assessment, with the use of potassium cyanide to inhibit the activity of the enzyme.[18] Complex 5 (ATP synthase (CP5)) activity was based on the regeneration of ATP through the action of pyruvate kinase and phosphoenolpyruvate carboxykinase.[20]

Knee injury and Osteoarthritis Outcome Score (KOOS)

The KOOS questionnaire evaluates the functional status and quality of life of patients with knee injury and is considered a valid and reliable outcome measure in TKA.[21] The Dutch translation of the questionnaire was used.[22] It was measured prior to surgery and 6 weeks and 6 months after surgery during outpatient visits. The ADL domain has shown best content validity for older patients and best represents functional disability.[23] Therefore, for this study, the total and ADL sub-scale score was used as outcome.

Timed up-and-go test

The TUG is a simple test to reliably assess mobility and balance, in TKA patients.[24] The test consists of measuring the time (in sec) it takes for an individual to get up from a standard chair, walk a distance of 3 m (marked on the floor), turn around, walk back to the chair, and sit down. Patients are not allowed to use their arms to get up from the chair.

Quadriceps strength

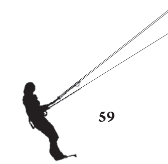
Maximal voluntary strength testing of the quadriceps muscle of the operated leg was assessed using a handheld dynamometer (CITEC, type CT 3001, C.I.T. Technics, Haren, The Netherlands). The subjects were positioned on an examining table in prone position with the right knee flexed to a 90° angle with the dynamometer placed against the instep. Maximal voluntary strength in Newton (N) in the quadriceps was exerted by extending the knee joint with the investigator keeping the position of the dynamometer fixed. Subjects were verbally motivated to apply maximal voluntary eccentric force, which was previously shown to produce reliable results.[25] Measurements were performed three times per occasion by the same investigator and the highest force was used for further analysis.

Grip strength

Grip strength has been used in geriatric studies as a measurement of overall physical condition and has shown to be associated with outcome after surgical procedures.[26] Handgrip strength was measured using the Jamar Plus dynamometer device (Patterson Medical, Nottinghamshire, United Kingdom). Each subject was positioned in a straight-backed chair with both feet placed flat on the floor. The force (in kg) was determined of the dominant hand. Subjects were instructed to keep an upright posture, with the elbow flexed at 90° and the forearm and wrist in neutral position. Subject were verbally motivated to provide maximum grip force. Out of three attempts, the highest force was used for further analysis.

Activity tracker

Consumer health devices have been evaluated in monitoring physical activity and show good reliability and validity in measuring parameters such as the daily number of steps.[27] The wrist mounted Nokia Go activity tracker was continuously



worn from 2 weeks before the TKA up to 6 months after. The Nokia Health platform is Android or IOS smartphone-based and the app, the Nokia Health Mate. The patient's own smartphone was used and set-up in such a way to contain no personal data other than height, weight and date of birth. An iPhone was supplied in case a patient did not own a smartphone. Via the app, data were automatically stored online on a secure Nokia server without any intervention required from the patient.

Definition of activity and recovery

Activity was defined as the mean daily number of steps, measured over the period of one week. Baseline activity was the mean number of daily steps over the 2 weeks before TKA. Recovery was defined as the weekly change of the mean daily number of steps over a period of 6 months, starting from the first week after TKA during which activity was down to a minimum and all patients were at home.

Power calculation

Based on the variability in electron transport chain complex IV activity in muscle tissue reported in a previous study with sedentary elderly (coefficient of variability = 60.8%), a sample size of 30 was found to be sufficient to detect an estimated correlation with clinical outcome variables of R = 0.4 with a power of 80% and a two-sided significance level of 0.05, taking into account possible drop-out of patients.[28]

Statistical method

Data were collected by printed data collection forms and entered into Promasys, an electronic data capturing system. Statistics were performed using SPSS v25 (IBM corp., Armonk, NY, USA). The significance of change of clinical measurements between 6 weeks and 6 months after TKA was determined by paired samples t-tests. Activity was correlated to clinical measurements with repeated measures (at 6 weeks and at 6 months after TKA), with a random intercept but no random slope. The relation of baseline predictors (activity, KOOS-A score, quadriceps strength, TUG completion time, grip strength, mitochondrial function, statin use, age, sex and BMI) on recovery was determined using a multivariate regression model with backwards elimination. Results are reported in the change of the number of steps increase per week (i.e. recovery) per unit of the predicting factor. Relation per predictor on recovery was depicted with scatter plots, showing the predicted recovery for minimum, mean and maximum predictor values. Significant predictors were then combined to formulate an algorithm to predict recovery. No correction for multiple testing was made, due to the exploratory nature of the study. Level of significance was p 0.05.

RESULTS

Demographics

A total of 30 patients (20 females and 10 males) were enrolled into the study with a median age of 71 years (range 60-83 years). All enrolled patients completed the required study procedures and were included in the analysis. Demographics are listed in Table 3.1.

Mitochondrial enzymes in muscle

CS and CP 1-5 abundancies at time of surgery are listed in Supplementary Table 3.4. Variability in mitochondrial function between patients was large with ranges of 166 to 558 (CS), 7.7 to 188.8 (CP1), 14.1 to 75.7 (CP2), 0.28 to 7.02 (CP3), 2.8 to 58.2 (CP4) and 229 to 1182 (CP5).

Clinical measurements

Clinical measurements before TKA, at 6 weeks after and 6 months after TKA are depicted in Figure 3.2A-D.

Knee injury and Osteoarthritis Outcome Score

After TKA, scores in all sub-scales were improved at 6 weeks, compared to preoperative, with a further improvement at the last follow-up at 6 months. On the ADL sub-scale, the group had a median score of 48.5 (range 20.6 to 89.7) prior to TKA, a median score of 80.9 (range 41.2 to 95.6,) at 6 weeks postoperatively and a median score of 86.0 (range 57.4 to 100,) at 6 months postoperatively (change from preoperative to 6 months after: CI95% -43 to -28; p<0.001).

Activity and recovery

Activity before surgery showed a group median of 4431 (range 1632 to 10340) daily steps. Directly after surgery, activity was decreased to a minimum of 1237 daily steps which increased during the 6 months thereafter to 4864 (Figure 3.1, change from pre-operative to 6 months after: CI95% -669 to 912; p=0.76). Graphs with individual activity data and a linear fit reflecting the recovery are depicted in Supplementary Figure 3.5. Recovery ranged from 32 to 392 steps per week with a median of 101.

Timed up-and-go test

Prior to surgery, the median TUG time to completion was 12.1 seconds (range 8.0 to 28.1 seconds). During the postoperative period, it decreased to 10.8 seconds (range 8.0 to 28.7) at 6 weeks and eventually to 8.3 seconds (range 6.1 to 26.3) at 6 months (change from pre-operative to 6 months after: CI95% 2.7 to 4.8; p<0.001).

Quadriceps strength

Quadriceps strength decreased after surgery and increased again over the follow-up period. Before surgery median strength was 149 N (range 48 to 265), deceased at 6 weeks to 119 N (range 51 to 245) and increased to 153 N (range 87 to 244) at 6 months (change from pre-operative to 6 months after: CI95% -23 to 9; p=0.39).

Grip strength

Grip strength before surgery (median 31.2, range 14.7 to 60.1) did not significantly change at 6 weeks (median 31.3, range 15.0 to 59.3) and 6 months after (median 32.3, range 14.8 to 57.5, change from pre-operative to 6 months after: CI95% -1.8 to 1.2; p=0.65).

Correlations between activity and clinical function measurements

Measured during the recovery period after TKA, Activity correlated significantly with KOOS ADL (r=0.55, p=0.009) and TUG (r=-0.61, p=0.001), but not to quadriceps strength and grip strength (Table 3.2).

Multivariate regression model to predict recovery

Through backward elimination, the following baseline predictors were significantly correlated with recovery: activity (r=0.51, p=0.004), grip strength (r=0.42, p=0.02) and CP5 abundancy (r=0.38, p=0.05). Separate association plots between predictors and recovery are displayed in Figure 3.3A-C. Combining the predictors, recovery can be estimated by the following algorithm:

$$\text{Recovery} = -111.92 + (0.02 \times [\text{activity before surgery}]) + (0.13 \times [\text{CP5 abundancy}]) + (2.89 \times [\text{grip strength}])$$

For every 1 unit of CP5 abundancy, recovery increases with 0.13 steps/week (p=0.04). For every 1 step of activity, recovery increases with 0.02 steps/week (p=0.005). For every 1 kg of grip strength, recovery increases with 2.89 steps/week (p=0.02). The relation of predictors on the recovery (regression weights) is listed in Table 3.3 and in depicted in Figure 3.4A-C (per predictor, the other two predictors are fixed to the median value).

DISCUSSION

We showed that mitochondrial function (CP5 abundancy), grip strength and activity (mean daily number of steps) before surgery were found to be significantly related to the postoperative recovery in daily number of steps, measured with an activity tracker. Additionally, activity during the recovery period correlated well with traditional patient reported and functional measurements after surgery (KOOS-ADL score, TUG completion score and quadriceps strength).

Age-related declines in walking speed are strongly associated with impairments in mitochondrial function and indices of mitochondrial biogenesis[29,30] and it is known that a sedentary lifestyle itself can reduce mitochondrial function in skeletal muscle.[28] Mitochondrial function, including CP5, was found to be decreased in sedentary, pre-frail elderly, when compared to age-matched active elderly.[28] CP5, or ATP synthase, is the final step in the oxidative phosphorylation process. Congenital deficiency of the enzyme causes severe neuromuscular impairment shortly after birth.[31] The other complexes were not correlated to recovery, but the correlation coefficients between the different complexes were all significant and ranged from 0.50 to 0.89. The exact mechanism is not fully understood, but it is thought that exercise increases mitophagy, which is the way for the cell to remove dysfunctional mitochondria to be replaced by healthy ones.[28] Although early mobilization after knee replacing surgery has proven to shorten hospital stay, increasing physical activity by exercise before surgery has not proven to significantly improve postoperative recovery.[32,33] Nonetheless, we showed that a higher activity before surgery was correlated to a faster recovery after surgery. The latter may indicate that keeping up a certain degree of mobility prevents sarcopenia. Additionally, adults with a sedentary lifestyle have a higher likelihood for smoking and living with a chronic disease,[34] which also relates to the recovery after surgery. Therefore, activity in terms of mobility might be more informative about outcome after surgery than the amount of exercise per se.

Grip strength reflects the general physical condition of an individual[35-37] and is an important tool in the assessment of frailty in elderly patients.[38] Additionally a low grip strength is associated to a higher mortality in the general population.[39] Grip strength in elderly patients before receiving surgery for a hip fracture correlates to walking recovery.[40] We showed that higher grip strength was correlated to a faster recovery. Grip strength is easy to measure in a clinical setting and could therefore be of value to predict recovery after a TKA.

Measuring mitochondrial function prior to surgery could be a way to select candidates for pre-surgery rehabilitation, but this is not possible in the routine clinical setting due to lack of reliable non-invasive measurements. Monitoring activity is easier and more realistic. Using wearable technology for this is not new and has been shown to be an objective method to measure postoperative recovery.[41] Nevertheless, it is rarely used in routine clinical practice. Due to the increasing availability of modern smartphones, monitoring a patient's activity as part of postoperative recovery is now readily available. The built-in accelerometer and GPS are able to measure not only activity, but also the traveled distance and quality of walking (e.g. slow, fast and sitting), accurately. The data can automatically be shared online with the treating surgeon, providing objective data on mobility and still minimizing patient burden. Knowing patient's activity might lead to a more personalized physiotherapy program early after surgery to have an optimal recovery after this extensive arthroplasty surgery.

Monitoring activity provides the physician with these additional patient data, other than PROMS or functional measurements. PROM outcomes are based on perceived patient satisfaction, which is a very important parameter after TKA, but lack objectivity.[42] It is known that patient satisfaction after a surgical intervention can be negatively influenced by unmet patient expectations[43] , but in our cohort the KOOS-ADL questionnaire correlated to activity. In practice, activity data could be used as a reference on progress to both patient as physician in addition to questionnaire data to gauge recovery after TKA.

Quadriceps strength and TUG completion time also provide objective data and both parameters correlated to activity. This confirms that a simple pedometer can be used to objectively measure recovery after TKA. The correlation to quadriceps strength was borderline moderate, which could be attributed to the fact that it is known to be negatively influenced by voluntary muscle activation [3]. The most important advantage of measuring activity instead of quadriceps strength and TUG completion time is that it can be done daily using just the patient's smartphone, instead of a visit to the outpatient clinic and that it is not affected by voluntary muscle activation. Also, the patient would be able to monitor his/her own recovery, which could work motivational.

Predicting recovery after TKA with an algorithm would provide surgeons in how to follow-up their patients after surgery. For instance, arrangements for intensified physiotherapy or additional visits to the outpatient clinic could be made beforehand. Note that the algorithm should be further validated in a large and independent (and ideally prospective) dataset. Improving these predictive factors prior to surgery might improve postoperative recovery. Although activity would be the easiest factor to measure clinically, multimorbidity or motivational issues may keep patients from improving their sedentary lifestyle.[44] Pharmacologically improving mitochondrial function prior to TKA and in the course of the recovery phase might therefore improve recovery. Several (pre)clinical trials with mitochondrial function enhancing compounds have already shown promising results in treating diseases, in which mitochondrial dysfunction plays a role (such as heart failure, chronic renal failure and myopathy) by protecting mitochondria from oxidation, inducing mitophagy or stabilizing the electron transport chain.[45-48] Clinical trials to improve muscle function by improving mitochondrial function with or without physical exercise in sedentary elderly are currently in the making.[49,50] A possible limitation of this study may be the relatively small number of patients. However, the outcome of this pilot study demonstrates that, contrary to traditional questionnaire based and intermittent, methods of evaluation wearable technology provides meaningful data on individual recovery. Additionally, correlations with measures of muscle strength and mitochondrial function were found in this study. Although our data have to be confirmed in larger studies we have demonstrated that wearable continuous measurements may allow conclusions drawn from smaller studies and determine the individual value of interventions rather than for groups.

In conclusion, the level of recovery after TKA was significantly related to the level of CP5 abundancy, grip strength and activity before surgery. Activity also strongly correlated to traditional measures for recovery, which could be considered to validate the outcome measure of the activity tracker. Pharmacologically improving mitochondrial function before surgery might be a potential way to improve recovery after TKA.

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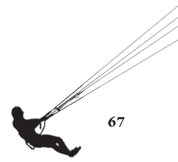

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TABLE 1 Demographics. Demographics of study patients (n=30)

Variable	Value
Age (years)	71 (60.0 – 83)
Female sex	20 of 30
Weight (kg)	87 (65 – 113)
BMI (kg/m^2)	29 (22 – 38)
Caucasian	30 of 30

TABLE 2 Correlations. Correlations between activity and clinical function measurements, using repeated measures correlation.

Variable	R	p-value
Activity vs KOOS-A	0.55	0.009
Activity vs TUG	-0.61	0.001
Activity vs quadriceps	0.40	0.07

TABLE 3 Regression weights. Regression weights per significant predictor, determined by the multivariate regression model.

Predictor	Regression weight	p-value
CP5 abundancy	0.13	0.04
Activity	0.02	0.005
Grip	2.89	0.02

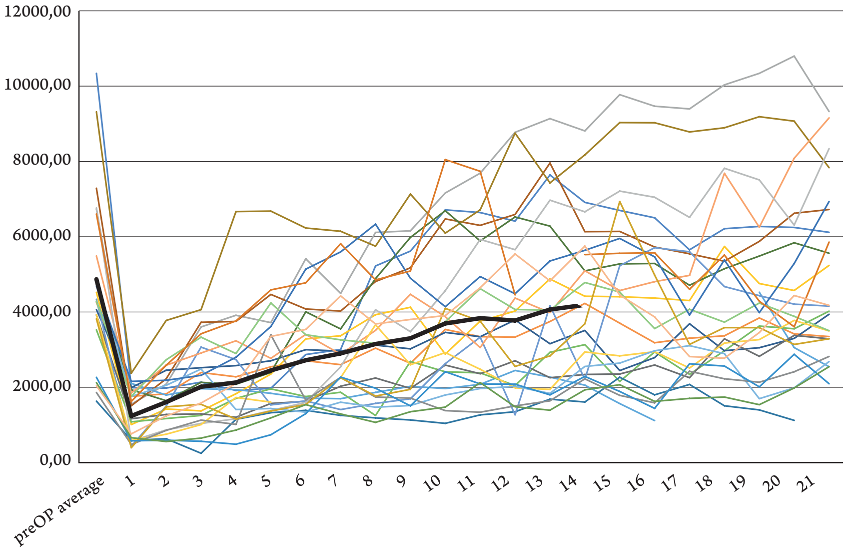
CP5 =complex 5.

TABLE 4 Mitochondrial enzymes. Listing of abundance of mitochondrial enzymes.

	Mean (SD)	Min, max
Citrate synthase abundance (U/g prot)	337 (± 111)	166, 558
Complex 1 abundance (U/g prot)	61.4 (± 49.2)	7.7, 188.8
Complex 2 abundance (U/g prot)	30.1 (± 16.0)	14.1, 75.7
Complex 3 abundance (U/g prot)	1.92 (± 1.64)	0.28, 7.02
Complex 4 abundance (U/g prot)	24.3 (± 13.3)	2.8, 58.2
Complex 5 abundance (U/g prot)	497 (± 196)	229, 1182

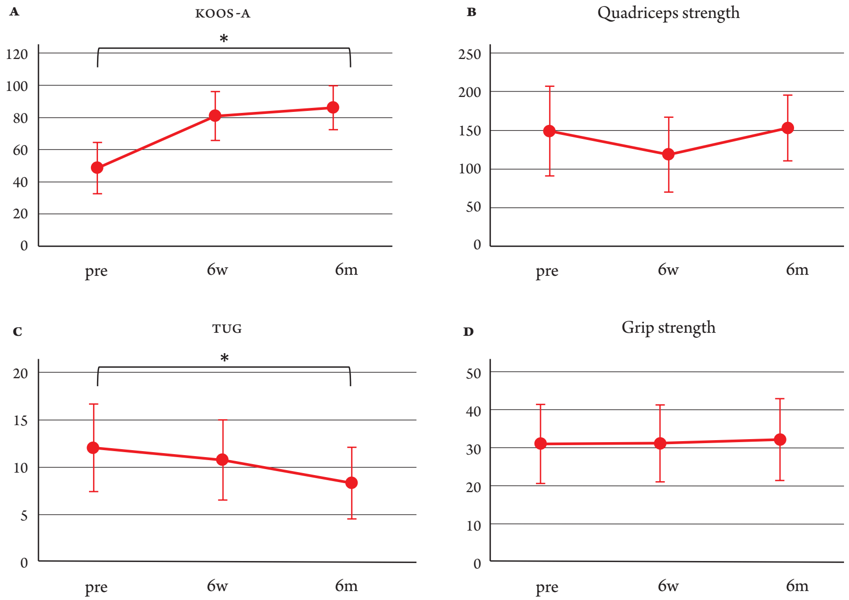
SD = standard deviation, U = unit, Prot = protein.

FIGURE 1 **Activity tracker.** Activity before surgery until 6 months after (separate line per patient). Activity before TKA was measured over a 2-week period. Activity dropped to a minimum after TKA for all patients.



The thick black line represents the group average.

FIGURE 2 A-D **Clinical measurements.** Clinical measurements over time (median values with SD). A. KOOS ADL, B. quadriceps strength, C. Timed up-and-go completion time and D. grip strength.



* = $p < 0.05$.

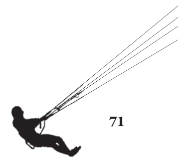
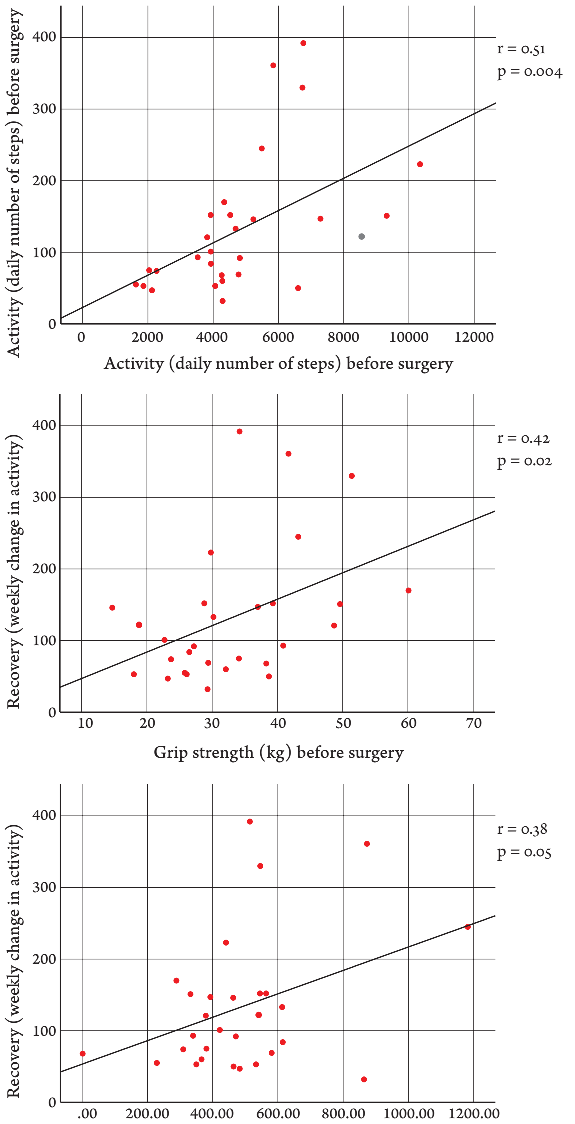
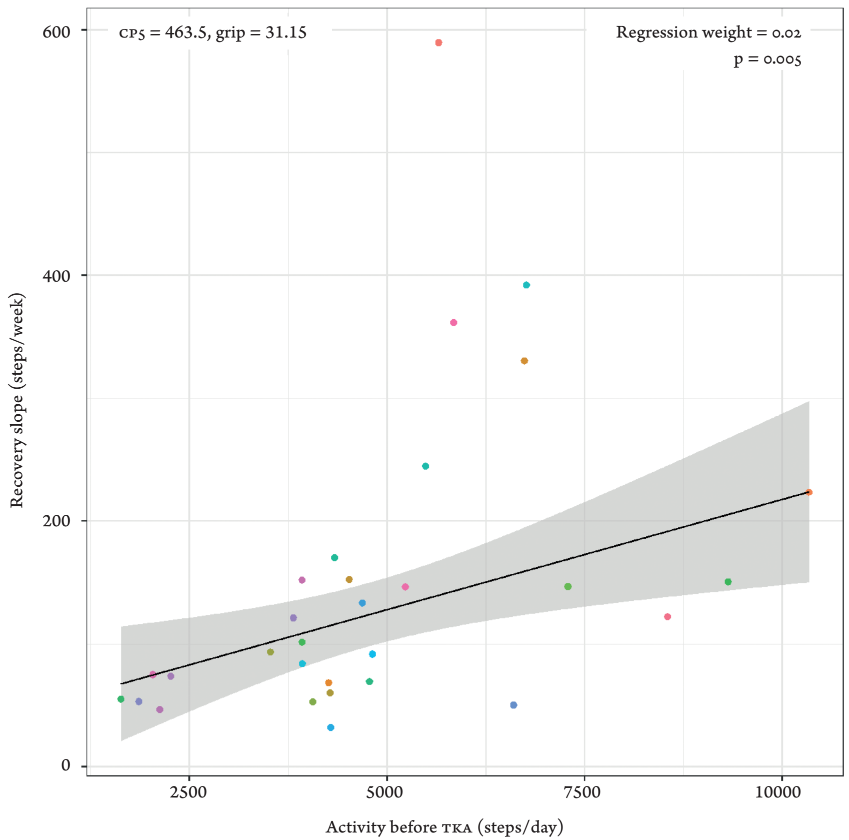


FIGURE 3 A-C **Correlations.** Pearson correlations between recovery (weekly change in activity) and predictors before surgery. Moderate associations with recovery were observed between A. activity; B. grip strength; and C. CP5 abundancy.



R=0.51, p=0.004. R= 0.42, p=0.02. R=0.38, p=0.05.

FIGURE 4 **Regression model.** Predicted recovery plots with regression weights for different values of correlating predictors. A. activity, B. grip strength and C. CP5 abundancy. 95% confidence intervals depicted as shaded area. Regression weights and p values in legend per graph.



CP5=463.5 , grip=31.15. Regression weight 0.02, p=0.005.

FIGURE 5 **Individual activity.** Individual step count data with linear fit reflecting recovery.