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ARTICLE

Mitochondrial function, grip strength, and activity are related to recovery of mobility 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 [CP] 1–5 abundance of the electron transport chain) was determined on muscle tissue taken during TKA. Traditional outcome measures (Knee Injury and Osteoarthritis Outcome 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: CP5 abundance, grip strength, and activity (regression weights 0.13, 0.02, and 2.89, respectively). During recovery, activity correlated to the KOOS-activities of daily living (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.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Sarcopenia, the age-related decline in muscle mass, poses a large burden to the health of elderly and healthcare spending. Sarcopenia has been correlated to mitochondrial dysfunction through impaired bioenergetics in muscle tissue of affected patients, but studies showing clinical importance of mitochondrial dysfunction and muscle functioning are lacking.

WHAT QUESTION DID THIS STUDY ADDRESS?

The primary aim of this study was to assess the relation of mitochondrial function at baseline on the recovery of mobility after total knee arthroplasty (TKA).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Mitochondrial function (complex 5 abundancy), alongside grip strength and activity significantly correlated to recovery in mobility after TKA. Mitochondrial function is therefore an important factor in muscle function.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Improving mitochondrial function is gaining interest as a way to pharmacologically treat sarcopenia. This study provides evidence for this rational in a clinical population.

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, ~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%[2] and, in most cases, patients return to their level of physical activity in 6 months' time.[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 patients who undergo TKA suffer from sarcopenia.[8] Sarcopenia is hypothesized to be driven partly by dysfunctional mitochondria, which in patients with OA 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, among other factors, on muscle function,[3] but it is currently not known if mitochondrial function can predict or relates to recovery after a TKA.

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.

MATERIALS AND METHODS

Design and study schedule

This was an observational, prospective cohort, level II 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 pre-operative 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. All patients had access to physiotherapy during and after hospitalization until 6 months postoperatively.

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 (grades 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 two 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 the 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 × 5 mm each, were collected from the vastus lateralis muscle within 5 min 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 min 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. 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). 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 disappearance, 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

The Knee Injury and Osteoarthritis Outcome Score (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 activities of daily living (ADL) domain has shown the best content validity for older patients and best represents functional disability.[23] Therefore, for this study, the total and ADL subscale score was used as outcome.

Timed up-and-go test

The TUG is a simple test to reliably assess mobility and balance, in patients who undergo TKA.[24] The test consists of measuring the time (in seconds) it takes for an individual to get up from a standard chair, walk a distance of 3 meters (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). The subjects were positioned on an examining table in the prone position with the right knee flexed to a 90 degree 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). Each subject was positioned in a straight-backed chair with both feet placed flat on the floor. The force (in kilograms) was determined of the dominant hand. Subjects were instructed to keep an upright posture, with the elbow flexed at 90 degrees and the forearm and wrist in the 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 setup 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. The app was password protected and in order to minimize bias the patients could not access it to view their performance.

Definition of activity and recovery

Activity was defined as the mean daily number of steps, measured over the period of 1 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%),[28] 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 dropout of patients.

Statistical method

Data were collected by printed data collection forms and entered into Promasys, an electronic data capturing system. Statistics were performed using SPSS version 25 (IBM). 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 body mass index) 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 women and 10 men) 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 1.

Mitochondrial enzymes in muscle

The CS and CP 1–5 abundancies at the time of surgery are listed in Table S1. 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 1a-d.

Knee Injury and Osteoarthritis Outcome Score

After TKA, scores in all subscales were improved at 6 weeks, compared to pre-operative, with a further improvement at the last follow-up at 6 months. On the ADL subscale, the group had a median score of 48.5 (range 20.6–89.7) prior to TKA, a median score of 80.9 (range 41.2–95.6) at 6 weeks postoperatively, and a median score of 86.0 (range 57.4–100), at 6 months postoperatively (change from pre-operative to 6 months after: 95% confidence interval [CI] −43 to −28, $p < 0.001$).

TABLE 1 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)
White	30 of 30

Abbreviation: BMI, body mass index.

Activity and recovery

On a cumulative period of 5558 days of step count data, there were 79 days with no data collected (1.42%). Most patients used their own phone (26 out of 30). Activity before surgery showed a group median of 4431 (range 1632–10,340) 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 2, change from pre-operative to 6 months after: 95% CI −669 to 912, $p = 0.76$). Graphs with individual activity data and a linear fit reflecting the recovery are depicted in Figure S1. 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 s (range 8.0–28.1 s). During the postoperative period, it decreased to 10.8 s (range 8.0–28.7) at 6 weeks and eventually to 8.3 s (range 6.1–26.3) at 6 months (change from pre-operative to 6 months after: 95% CI 2.7–4.8, $p < 0.001$).

Quadriceps strength

Quadriceps strength decreased after surgery and increased again over the follow-up period. Before surgery the median strength was 149 N (range 48–265), deceased at 6 weeks to 119 N (range 51–245) and increased to 153 N (range 87–244) at 6 months (change from pre-operative to 6 months after: 95% CI −23 to 9, $p = 0.39$).

Grip strength

Grip strength before surgery (median 31.2, range 14.7–60.1) did not significantly change at 6 weeks (median 31.3, range 15.0–59.3) and 6 months after (median 32.3, range 14.8–57.5, change from pre-operative to 6 months after: 95% CI −1.8–1.2, $p = 0.65$).

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 2).

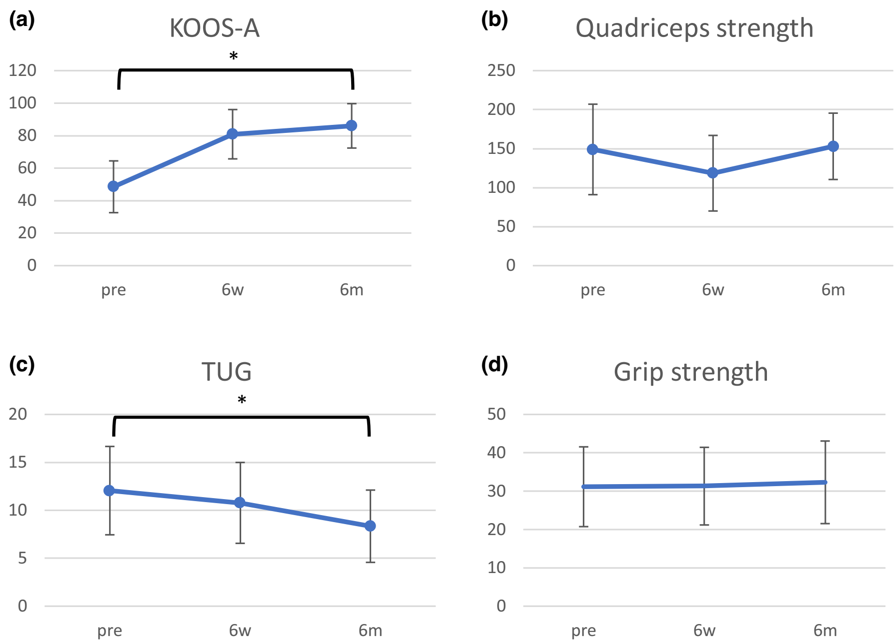

FIGURE 1 Clinical measurements over time (median values with SD). (a) KOOS-ADL, (b) quadriceps strength, (c) timed up-and-go completion time, and (d) grip strength. *=$p<0.05$. KOOS-ADL, Knee Injury and Osteoarthritis Outcome Score – activities of daily living; preop, pre-operative

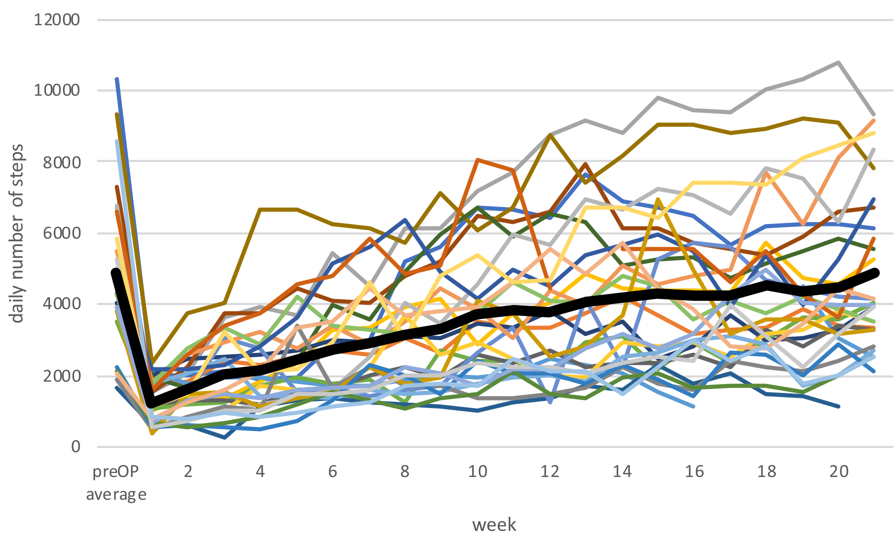

FIGURE 2 Activity before surgery until 6 months after (separate line per patient). Activity before TKA was measured over a 2-week period. Activity dropped to a minimum after TKA for all patients. The thick black line represents the group average. KOOS-ADL, Knee Injury and Osteoarthritis Outcome Score – activities of daily living; TKA, total knee arthroplasty; TUG, timed up-and-go

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 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 one unit of CP5 abundancy, recovery increases with 0.13 steps/week ($p = 0.04$). For every one 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 and is depicted in Figure 4a-c (per predictor, the other 2 predictors are fixed to the median value).

TABLE 2 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

Abbreviations: KOOS, Knee Injury and Osteoarthritis Outcome Score; TUG, timed up-and-go.

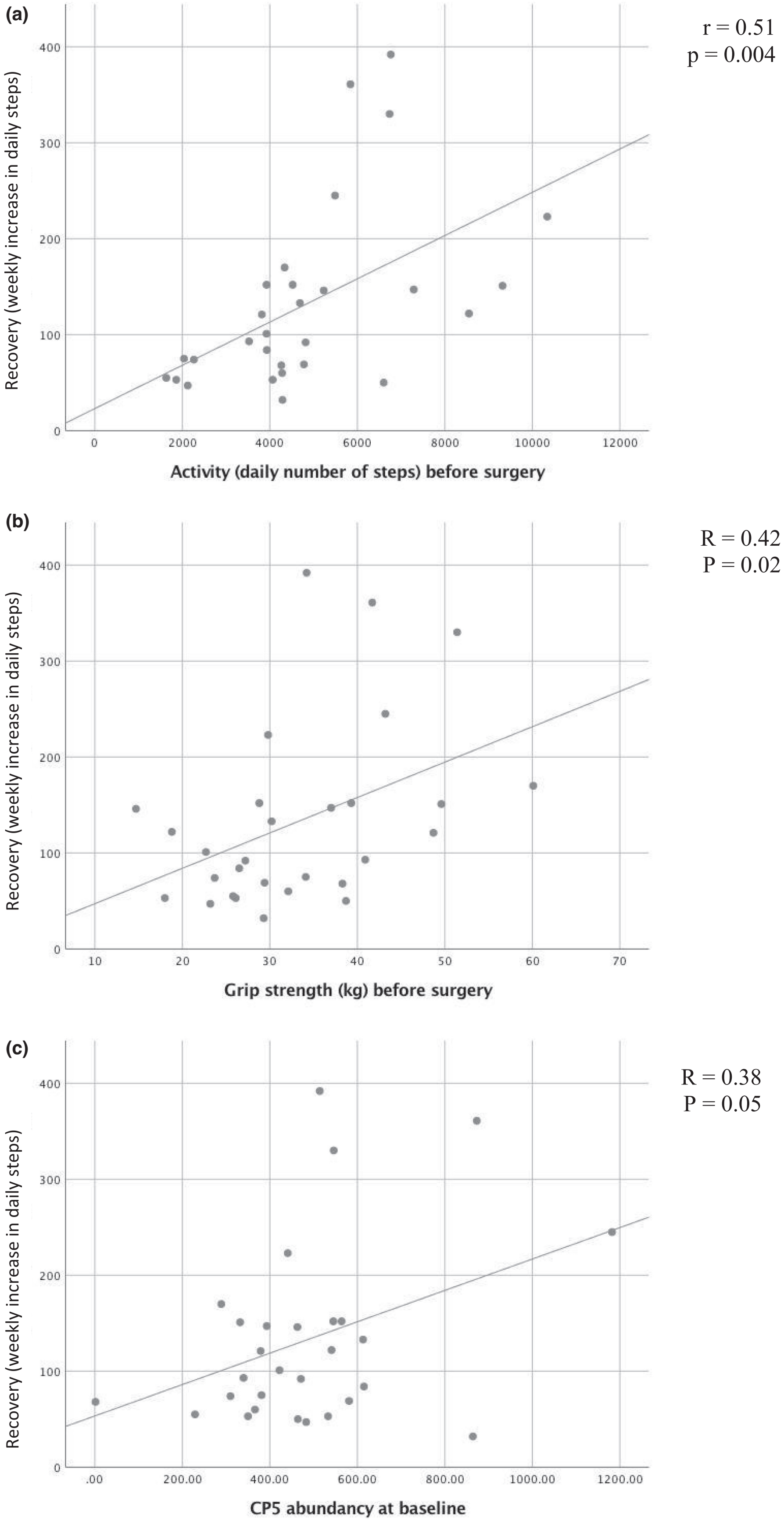

FIGURE 3 (a–c) Pearson correlations between recovery (weekly change in activity) and predictors before surgery. CP5, complex 5

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 the 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.

TABLE 3 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

Abbreviation: CP5, complex 5.

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.

In a recent article, Toth et al.[41] showed that muscle quality and mitochondrial content decreased after a TKA procedure. Although the postoperative muscle biopsy was taken only 5 weeks after the procedure, there were marked reductions in whole muscle size and strength, contractility, and deficits in myosin heavy-chain fibers and myosin-actin cross bridges. The proposed mechanism was muscular atrophy due to relative disuse, which is inevitable after TKA and it is unknown whether the effects can be reversed by rehabilitation. Enhancing mitochondrial function before surgical procedures is a new concept, but might in fact improve postoperative recovery. Increasing physical activity before surgery has proven to be efficient,[42] however, this is not always possible in patients with physical restrictions, such as severe OA. In these cases, pharmacologically enhancing mitochondrial function would be an interesting option. 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.[43–46] Even more interesting, urolithin A, a novel compound that increases mitophagy, has shown promising results in clinical trials by enhancing physical performance through improved mitochondrial health. In one study, urolithin A improved the 6-min walk distance, muscle endurance in hand and leg muscles, and biomarkers associated with mitochondrial and cellular health in a group of older adults.[47] In another study, urolithin A improved aerobic endurance (peak oxygen consumption), physical performance (6-min walk test), an increase in mitochondrial metabolism, and a reduction in C-reactive protein.[48] Improving muscular performance by mitochondrial function might be very useful in not only postoperative rehabilitation, but a variety of conditions and even aging itself.

Despite the many rehabilitation modalities available, the optimal rehabilitation strategy after TKA has yet to be determined. In a systematic review, Davilla Castrodad et al.[49] analyzed study designs, rehabilitation methods, and outcome measures of postoperative rehabilitation

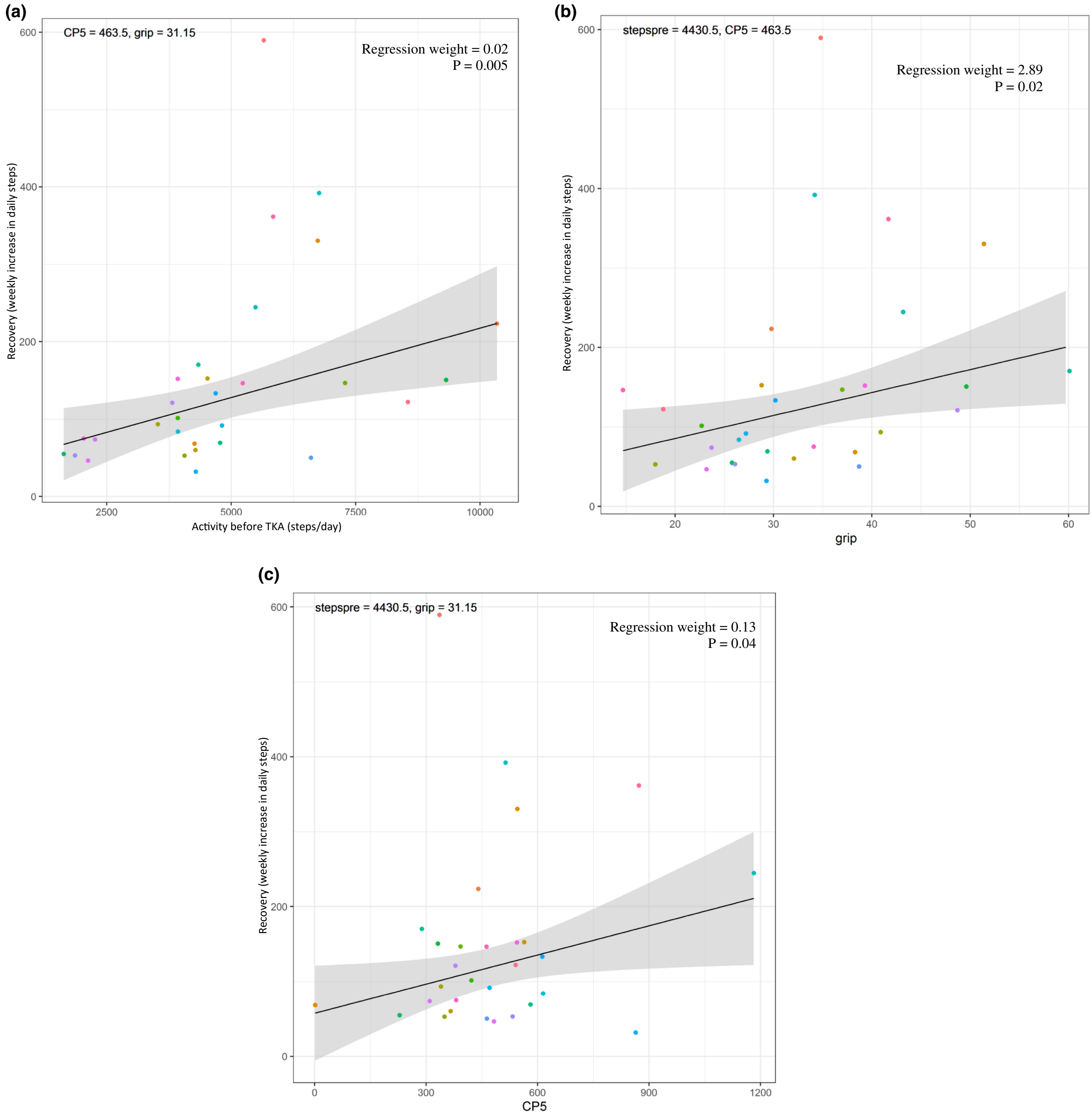

FIGURE 4 Predicted recovery plots with regression weights for different values of correlating predictors. (a) Activity, (b) grip strength, and (c) CP5 abundancy. 95% confidence intervals depicted as shaded area. Regression weights and *p* values in legend per graph. CP5, complex 5; TKA, total knee arthroplasty

protocols from 2014 to 2019. They concluded that due to their increased deficits, TKA recipients had best outcomes with more aggressive rehabilitation, with emphasis on high intensity, and high velocity exercises. Furthermore, monitored home-based therapy and group therapy were found to be just as efficient in improving postoperative TKA outcomes as the much costlier one-on-one inpatient physical therapy. The use of telerehabilitation was found to be of great value as physical therapists could monitor progress through patient videos and provide feedback as necessary.[50] Wearable technology to track activity could play an important role in this.

Measuring mitochondrial function prior to surgery could be a way to select candidates for presurgery rehabilitation, but this is not possible in the routine clinical setting due to lack of reliable noninvasive 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.[51] 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.

There is an increasing amount of literature discussing the advantages and difficulties in integration of wearable technology into the electronic health record. Although wearables have the potential to transform patient care, issues such as concerns with patient privacy, system interoperability, and patient data overload pose a challenge to the adoption of wearables by providers. To protect against potential cybersecurity attacks and missing or stolen patient records through the implementation of wearable health technologies, hospitals must ensure that devices are connected to a secure network and monitor the hospital data network continuously. To prioritize data privacy, health systems are likely to be required to set up another secure network for wearable devices, separate from the main network.

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.[52] It is known that patient satisfaction after a surgical intervention can be negatively influenced by unmet patient expectations,[53] 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. In addition, the patient would be able to monitor his/her own recovery, which could work motivationally.

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 provide 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.

AUTHOR CONTRIBUTIONS

M.P.J.vD., D.Z., M.D.K., M.R.B., P.L., J.A.J.J., B.A.M.S., M.G.J.G., A.F.C., R.G.H.H.N., and G.J.G. wrote the manuscript. M.P.J.vD., M.R.B., J.A.J.J., B.A.M.S., M.G.J.G., A.F.C., R.G.H.H.N., and G.J.G. designed the research. M.P.J.vD., M.D.K., P.L., and J.A.J.J. performed the research. M.P.J.vD., D.Z., A.F.C., and G.J.G analyzed the data.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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REFERENCES

1. Register D.A. LROI annual report 2019; 2019.
2. Argenson JN, Boisgard S, Parratte S, et al. Survival analysis of total knee arthroplasty at a minimum 10 years' follow-up: a multicenter French nationwide study including 846 cases. *Orthop Traumatol Surg Res*. 2013;99(4):385-390.
3. Mizner RL, Petterson SC, Snyder-Mackler L. Quadriceps strength and the time course of functional recovery after total knee arthroplasty. *J Orthop Sports Phys Ther*. 2005;35(7):424-436.
4. Keurentjes JC, Fiocco M, So-Osman C, et al. Patients with severe radiographic osteoarthritis have a better prognosis in physical functioning after hip and knee replacement: a cohort-study. *PLoS One*. 2013;8(4):e59500.
5. Dunbar MJ, Richardson G, Robertsson O. I can't get no satisfaction after my total knee replacement: rhymes and reasons. *Bone Joint J*. 2013;95-b(11 Suppl A):148-152.
6. van de Water RB, Leichtenberg CS, Nelissen RGHH, et al. Preoperative radiographic osteoarthritis severity modifies the effect of preoperative pain on pain/function after total knee arthroplasty: results at 1 and 2 years postoperatively. *J Bone Joint Surg Am*. 2019;101(10):879-887.
7. Mizner RL, Petterson SC, Stevens JE, Axe MJ, Snyder-Mackler L. Preoperative quadriceps strength predicts functional ability one year after total knee arthroplasty. *J Rheumatol*. 2005;32(8):1533-1539.
8. Bokshan SL, DePasse JM, Daniels AH. Sarcopenia in orthopedic surgery. *Orthopedics*. 2016;39(2):e295-e300.
9. Marzetti E, Calvani R, Cesari M, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. *Int J Biochem Cell Biol*. 2013;45(10):2288-2301.
10. Safdar A, Hamadeh MJ, Kaczor JJ, Raha S, deBeer J, Tarnopolsky MA. Aberrant mitochondrial homeostasis in the skeletal muscle of sedentary older adults. *PLoS One*. 2010;5(5):e10778.
11. Waters DL, Mullins PG, Qualls CR, Raj DSC, Gasparovic C, Baumgartner RN. Mitochondrial function in physically active elders with sarcopenia. *Mech Ageing Dev*. 2009;130(5):315-319.
12. Lanza IR, Nair KS. Muscle mitochondrial changes with aging and exercise. *Am J Clin Nutr*. 2009;89(1):467 s-71 s.
13. Fernandez-Vizarra E, Enríquez JA, Pérez-Martos A, Montoya J, Fernández-Silva P. Tissue-specific differences in mitochondrial activity and biogenesis. *Mitochondrion*. 2011;11(1):207-213.
14. Stevens-Lapsley JE, Schenkman ML, Dayton MR. Comparison of self-reported knee injury and osteoarthritis outcome score to performance measures in patients after total knee arthroplasty. *PM R*. 2011;3(6):541-549. quiz 549.
15. Omura JD, Carlson SA, Paul P, Watson KB, Fulton JE. National physical activity surveillance: users of wearable activity monitors as a potential data source. *Prev Med Rep*. 2017;5:124-126.
16. Hammer HB, Uhlig T, Kvien TK, Lampa J. Pain catastrophizing, subjective outcomes, and inflammatory assessments including ultrasound: results from a longitudinal study of rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)*. 2018;70(5):703-712.
17. Andersen LO, Husted H, Otte KS, Kristensen BB, Kehlet H. High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. *Acta Anaesthesiol Scand*. 2008;52(10):1331-1335.
18. Kramer KA, Oglesbee D, Hartman SJ, et al. Automated spectrophotometric analysis of mitochondrial respiratory chain complex enzyme activities in cultured skin fibroblasts. *Clin Chem*. 2005;51(11):2110-2116.
19. Krahenbuhl S, Talos C, Wiesmann U, Hoppel CL. Development and evaluation of a spectrophotometric assay for complex III in isolated mitochondria, tissues and fibroblasts from rats and humans. *Clin Chim Acta*. 1994;230(2):177-187.
20. Guerrieri F, Capozza G, Kalous M, Papa S. Age-related changes of mitochondrial F0F1 ATP synthase. *Ann N Y Acad Sci*. 1992;671:395-402.
21. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes*. 2003;1:17.
22. de Groot IB, Favejee MM, Reijman M, Verhaar JAN, Terwee CB. The Dutch version of the knee injury and osteoarthritis outcome score: a validation study. *Health Qual Life Outcomes*. 2008;6:16.
23. Collins NJ, Prinsen CAC, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthr Cartil*. 2016;24(8):1317-1329.
24. Yuksel E, Kalkan S, Cekmece S, Unver B, Karatosun V. Assessing minimal detectable changes and test-retest reliability of the timed up and go test and the 2-minute walk test in patients with total knee arthroplasty. *J Arthroplasty*. 2017;32(2):426-430.
25. Koblbauer IF, Lambrecht Y, van der Hulst MLM, et al. Reliability of maximal isometric knee strength testing with modified hand-held dynamometry in patients awaiting total knee arthroplasty: useful in research and individual patient settings? A reliability study. *BMC Musculoskelet Disord*. 2011;12:249.
26. Sultan P, Hamilton MA, Ackland GL. Preoperative muscle weakness as defined by handgrip strength and postoperative outcomes: a systematic review. *BMC Anesthesiol*. 2012;12:1.
27. Kooiman TJM, Dontje ML, Sprenger SR, Krijnen WP, van der Schans CP, de Groot M. Reliability and validity of ten consumer activity trackers. *BMC Sports Sci Med Rehabil*. 2015;7:24.
28. Andreux PA, van Diemen MPJ, Heezen MR, et al. Mitochondrial function is impaired in the skeletal muscle of pre-frail elderly. *Sci Rep*. 2018;8(1):8548.
29. Joseph AM, Adhihetty PJ, Buford TW, et al. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. *Aging Cell*. 2012;11(5):801-809.
30. Coen PM, Jubrias SA, Distefano G, et al. Skeletal muscle mitochondrial energetics are associated with maximal aerobic capacity and walking speed in older adults. *J Gerontol A Biol Sci Med Sci*. 2013;68(4):447-455.
31. Kucharczyk R, Zick M, Bietenhader M, et al. Mitochondrial ATP synthase disorders: molecular mechanisms and the quest for curative therapeutic approaches. *Biochim Biophys Acta*. 2009;1793(1):186-199.
32. Wang L, Lee M, Zhang Z, Moodie J, Cheng D, Martin J. Does preoperative rehabilitation for patients planning to undergo joint replacement surgery improve outcomes? A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2016;6(2):e009857.

33. Yakkanti RR, Miller AJ, Smith LS, Feher AW, Mont MA, Malkani AL. Impact of early mobilization on length of stay after primary total knee arthroplasty. *Ann Transl Med*. 2019;7(4):69.
34. Tudor-Locke C, Craig CL, Thyfault JP, Spence JC. A step-defined sedentary lifestyle index: <5000 steps/day. *Appl Physiol Nutr Metab*. 2013;38(2):100-114.
35. Allard JP, Keller H, Teterina A, et al. Lower handgrip strength at discharge from acute care hospitals is associated with 30-day readmission: a prospective cohort study. *Clin Nutr*. 2016;35:1535-1542.
36. Davies CW, Jones DM, Shearer JR. Hand grip--a simple test for morbidity after fracture of the neck of femur. *J R Soc Med*. 1984;77(10):833-836.
37. Shyam Kumar AJ, Beresford-Cleary N, Kumar P, et al. Preoperative grip strength measurement and duration of hospital stay in patients undergoing total hip and knee arthroplasty. *Eur J Orthop Surg Traumatol*. 2013;23(5):553-556.
38. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39(4):412-423.
39. Cooper R, Kuh D, Hardy R. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ*. 2010;341:c4467.
40. Savino E, Martini E, Lauretani F, et al. Handgrip strength predicts persistent walking recovery after hip fracture surgery. *Am J Med*. 2013;126(12):1068-75.e1.
41. Toth MJ, Savage PD, Voigt TB, et al. Effects of total knee arthroplasty on skeletal muscle structure and function at the cellular, organellar, and molecular levels. *J Appl Physiol (1985)*. 2022;133(3):647-660.
42. Menshikova EV, Ritov VB, Fairfull L, Ferrell RE, Kelley DE, Goodpaster BH. Effects of exercise on mitochondrial content and function in aging human skeletal muscle. *J Gerontol A Biol Sci Med Sci*. 2006;61(6):534-540.
43. Ryu D, Mouchiroud L, Andreux PA, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat Med*. 2016;22(8):879-888.
44. Andreux PA, Houtkooper RH, Auwerx J. Pharmacological approaches to restore mitochondrial function. *Nat Rev Drug Discov*. 2013;12(6):465-483.
45. Karaa A, Haas R, Goldstein A, Vockley J, Weaver WD, Cohen BH. Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy. *Neurology*. 2018;90(14):e1212-e1221.
46. Daubert MA, Yow E, Dunn G, et al. Novel mitochondria-targeting peptide in heart failure treatment: a randomized, placebo-controlled trial of elamipretide. *Circ Heart Fail*. 2017;10(12):e004389.
47. Liu S, D'Amico D, Shankland E, et al. Effect of urolithin A supplementation on muscle endurance and mitochondrial health in older adults: a randomized clinical trial. *JAMA Netw Open*. 2022;5(1):e2144279.
48. Singh A, D'Amico D, Andreux PA, et al. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. *Cell Rep Med*. 2022;3(5):100633.
49. Dávila Castrodad IM, Recai TM, Abraham MM, et al. Rehabilitation protocols following total knee arthroplasty: a review of study designs and outcome measures. *Ann Transl Med*. 2019;7(Suppl 7):S255.
50. Klement MR, Rondon AJ, McEntee RM, Greenky MR, Austin MS. Web-based, self-directed physical therapy after total knee arthroplasty is safe and effective for most, but not all, patients. *J Arthroplasty*. 2019;34(7 s):S178-s182.
51. Lebleu J, Poilvache H, Mahaudens P, De Ridder R, Detrembleur C. Predicting physical activity recovery after hip and knee arthroplasty? A longitudinal cohort study. *Braz J Phys Ther*. 2021;25(1):30-39.
52. Konan S, Hossain F, Patel S, Haddad FS. Measuring function after hip and knee surgery: the evidence to support performance-based functional outcome tasks. *Bone Joint J*. 2014;96-b(11):1431-1435.
53. Harris IA, Harris AM, Naylor JM, Adie S, Mittal R, Dao AT. Discordance between patient and surgeon satisfaction after total joint arthroplasty. *J Arthroplasty*. 2013;28(5):722-727.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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