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# Impact of anti-gravity treadmill rehabilitation therapy on the clinical outcomes after fixation of lower limb fractures: A randomized clinical trial

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**Abstract**

**Objective:** To compare the effects of anti-gravity treadmill rehabilitation with those of standard rehabilitation on surgically treated ankle and tibial plateau fractures.

**Design:** Open-label prospective randomized multicenter study.

**Setting:** Three level 1 trauma centers.

**Subjects:** Patients with tibial plateau or ankle fractures who underwent postoperative partial weight-bearing were randomized into the intervention (anti-gravity treadmill use) or control (standard rehabilitation protocol) groups.

**Main measures:** The primary endpoint was the change in the Foot and Ankle Outcome Score for ankle fractures and total Knee injury and Osteoarthritis Outcome Score for tibial plateau fractures (0–100 points) from baseline (T1) to six weeks after operation (T4) in both groups. Leg circumference of both legs was measured to assess thigh muscle atrophy in the operated leg.

**Results:** Thirty-seven patients constituted the intervention and 36 the control group, respectively; 14 patients dropped out during the follow-up period. Among the 59 remaining patients (mean age 42 [range, 19–65] years), no difference was noted in the Foot and Ankle Outcome Score (54.2 ± 16.1 vs. 56.0 ± 16.6) or Knee injury and Osteoarthritis Outcome Score (52.8 ± 18.3 vs 47.6 ± 17.7) between the intervention and control groups 6 weeks after operation. The change in the leg circumference from T1 to T4 was greater by 4.6 cm in the intervention group (95% confidence interval: 1.2–8.0, $P = 0.005$). No adverse event associated with anti-gravity treadmill rehabilitation was observed.

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**Conclusion:** No significant difference was noted in patient-reported outcomes between the two groups. Significant differences in muscular atrophy of the thigh were observed six weeks after operation.

**Keywords**
Anti-gravity treadmill rehabilitation, standard rehabilitation, ankle fractures, muscular atrophy, tibial plateau fractures

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## Introduction

Partial or non-weight-bearing rehabilitation programs are commonly implemented after surgery for intra-articular fractures.[1–3] Most protocols include partial weight-bearing with the use of crutches for several weeks after surgical intervention to protect the affected musculoskeletal structures and implants (osteosyntheses, prostheses, or sutures). However, the optimal postoperative rehabilitation protocol after surgical treatment of tibial plateau and ankle fractures has not been determined to date.[4,5]

Partial weight-bearing on crutches is associated with different adaptation processes. In addition to a decrease in the muscular strength owing to muscular atrophy, degeneration of the immobilized tissue and joint stiffness are essential factors that lead to prolonged healing. The skeletal musculature is crucial for maintaining the functional capacity and health status.[6–9]

Studies that have attempted to prevent muscular atrophy with electrical stimulation have reported either no positive effects or unsatisfactory results.[10] However, it is well-understood that the time required for physiotherapeutic rehabilitation and muscle gain must be at least twice the immobilization period to fully compensate for muscular atrophy.[11]

This prospective randomized open-label multicenter study aimed to investigate whether an anti-gravity treadmill rehabilitation has benefits for postoperative partial weight-bearing patients and to compare the effects of this protocol with those of a standard rehabilitation protocol.[12] We hypothesized that patients would benefit more from anti-gravity treadmill rehabilitation based on the patient-reported outcomes and muscular atrophy measurements. We assumed that patients receiving anti-gravity treadmill treatment have better reported outcomes and reduced muscular atrophy.

## Materials and methods

This multicenter prospective randomized controlled open-label study was performed in three level 1 trauma centers between August 2016 and June 2018. The study protocol was approved by the ethical review committee of the University of Leipzig (reference number: 176/14-ff) and the ethics review committee of the State Chamber of Physicians of Saxony (reference number: EK-allg-7/16–1). This study was conducted in accordance with the guidelines of the Declaration of Helsinki and International Conference on Harmonization (Good Clinical Practice guidelines). The trial was registered at clinicaltrials.gov (NCT02790229). The study protocol was amended during the course of the study; this amendment was also evaluated and approved by the relevant ethics committee. Furthermore, the study protocol was previously published.[12] Intensive explanations were provided to the patients, who then provided written informed consent for their participation in the study. An independent study monitor guaranteed the accuracy of the analyses, completeness of the data obtained, and authenticity of the clinical trial protocol. A statistical analysis plan was developed and is available on request.

Patients were included if they were aged between 18 and 65 years and had undergone surgery because of an isolated closed tibial plateau or ankle fractures and received postoperative rehabilitation with partial weight-bearing of 20 kg for six weeks after surgical fixation. The exclusion criteria included body weight $>100$ kg (a limitation associated with device

configuration), serious illness or poor general health that may influence rehabilitation, as judged by a physician, open fractures (>1° according to Gustilo and Anderson),[13] severe injury, alcohol or drug addiction, pregnancy, neuromuscular disorder, or preexisting muscle atrophy.

After applying the inclusion and exclusion criteria, the eligible patients were randomized, and the primary data, including the patient-reported outcomes, were recorded (baseline, T1). Before discharge from the hospital, a second evaluation was performed (T2; 5.9 ± 3.5 days [range 2–17]). The patients were followed-up and interviewed in the outpatient clinic at three (T3) and six (T4) weeks after the operation.

The patients were randomized in a 1:1 ratio to either the intervention group or the control group stratified by the type of injury using computer-aided block randomization with a random block length. The patients were assigned to the respective group by the Centre for Clinical Trials through blinded faxes sent to each participating institution.

During the hospital stay, all patients received the same therapy, including manual lymphatic drainage, cryotherapy, and physiotherapy with mobilization under partial weight-bearing using crutches. The patients were allowed to move their affected joint freely while maintaining partial weight-bearing. The number of therapy sessions attended and interruptions (e.g. disruption of therapy owing to illness) were documented by the rehabilitation center. The patients in the control group received standard physiotherapy, including manual lymphatic drainage, cryotherapy, and 20-minutes physiotherapy sessions two to three times per week for six weeks. Physiotherapy included passive movement and mobilization of the operated joint and adjacent joints and gait training on crutches. Cryotherapy and lymphatic drainage were provided for 20 minutes until the swelling of the soft tissue in the affected area had subsided. The patients in the intervention group received manual lymphatic drainage and cryotherapy and exercised for 20 minutes on an anti-gravity treadmill two to three times per week, according to a predefined schedule, for six weeks (Supplemental Figure 1). In this schedule, the speed on the treadmill was gradually increased during the six weeks of treatment.[12] Moreover, anti-gravity treadmill rehabilitation therapy involved exercising on a treadmill with a surrounding chamber. The patient's lower body was sealed inside the chamber using a neoprene skirt. The pressure inside the chamber was increased using an air compressor; thus, the gravitational load decreased, thereby, allowing patients to walk or run on the treadmill under simulated fractional gravity conditions with a predefined load of 20 kg.

The primary endpoint of the short-term follow-up was change in the total Foot and Ankle Outcome Score for ankle fractures and total Knee injury and Osteoarthritis Outcome Score for tibial plateau fractures from baseline (T1) to the day of discharge (T2) and six weeks postoperatively (T4) in each group. The total Knee injury and Osteoarthritis Outcome Score or Foot and Ankle Outcome Score was calculated by the summation of the subscores. A detailed manual delineating the calculations is available at www.koos.nu.[14–18] The baseline was defined as the day on which the patient was enrolled in the study. Due to the design of this patient reported outcome evaluation of the condition of the affected joint for up to a maximum of four weeks before the injury.

The secondary endpoints were changes in the Foot and Ankle Outcome Score subscores (Symptoms, Pain, Function in daily living, Function/sports and recreational activities, Quality of Life) for ankle fractures and in the Knee injury and Osteoarthritis Outcome Score subscores (exactly the same subscores as those for the Foot and Ankle Outcome Score) for tibial plateau fractures from T1 to T2 and T4 for each group, and the values were compared between the two groups. The total Foot and Ankle Outcome Score and total Knee injury and Osteoarthritis Outcome Score and the subscores were determined (maximum 100); a lower score represented more symptoms or pain, greater difficulty in performing the Function in daily living and Function/sports and recreational activities, and poorer Quality of Life. A high degree of variation in the standard deviation for the subscores of the Foot and Ankle Outcome Score and Knee injury and Osteoarthritis Outcome Score has been described in different studies, with the reported standard deviation varying

from 7 (e.g. for the score Function in daily living) to 32 (e.g. for the score Function/sports and recreational activities).[14–17] Thus, we presumed a normal standard deviation of 20 and assumed an effect size of $\Delta = 15$, which are in line with the values in the study by Harris et al.,[19] who reported a minimal clinically relevant difference for the five subscales of between 10.7 (symptoms) and 18.3 (Function in daily living). Assuming a standard deviation of 20, $2 \times 25$ patients were required to detect an effect of $\Delta = 15$ with a t-test for independent samples with >80% power. Considering a dropout rate of 20%, 60 patients were required for each type of injury; thus, a total of 120 patients were needed.

To assess muscular atrophy of the thigh and lower leg, the leg circumference was measured at 10 and 20 cm above the knee joint line and 10 cm below the knee joint line, with the knee in a neutral position at T1, T2, T3, and T4 for each group, and the values were compared.[20] The data were obtained in the respective clinics or outpatient clinics by the investigators or study assistants.

Adverse events were defined as all adverse medical events, unintended diseases or injuries, or unwanted clinical diagnoses (including laboratory anomalies), regardless of any association with the study protocol. Events resulting in mortality or impairment of health (e.g. life-threatening disease or injury, permanent impairment of body structure or function, hospitalization or prolongation of hospitalization, or medical or surgical intervention to prevent life-threatening disease/injury) were defined as serious adverse events. Adverse events/serious adverse events that occurred between discharge from the hospital and the six-week follow-up were determined by assessing the patients during the follow-up examinations and by conducting telephone interview between the follow-up appointments, if required.

All patients who received at least one therapy session were included in the full analysis set (FAS). Analyses were performed primarily in line with the intention-to-treat principle based on the ICH E9 statistical principles for clinical trials. For sensitivity analysis, a per-protocol set was analyzed. The patients who completed the trial treatment prematurely or received more than the treatment scheduled in the protocol were excluded from the per-protocol set.

The measurements were presented as mean ± standard deviation, minimum and maximum values for continuous and questionnaire data and absolute and relative frequencies for count data. The primary and secondary endpoints were analyzed using linear mixed models with random intercepts. This method is also suitable in case of missing data. The differences between the study arms inclusive 95% confidence interval were estimated by contrast analysis using the Westfall method to correct for multiple testing. The mean estimates including the 95% confidence interval provided the basis for the error bar plots showing the change in the Foot and Ankle Outcome Score and Knee injury and Osteoarthritis Outcome Score and their subscores.

The proportions were compared using the chi-square test and Fisher's exact test, if necessary. The data were prepared and descriptive statistics were computed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY) and linear models using R, version 3.4 (R Core Team. R: A Language and Environment for Statistical Computing; Vienna, Austria, 2019). The level of significance was set at $P < 0.05$ for two-tailed testing.

## Results

In total, 570 patients with a tibial plateau or ankle fracture were assessed for eligibility; 497 were excluded for different reasons, as outlined in Figure 1. Seventy-three patients were randomly assigned to either the intervention group ($n = 37$) or control group ($n = 36$).

The intervention and control groups were balanced for sex, age, body mass index, type of fracture (AO B or C), and cause of accident (Table 1). In the study cohort, no statistically significant difference was noted in the mean Foot and Ankle Outcome Score or Knee injury and Osteoarthritis Outcome Score at baseline between the intervention and control groups. Similarly, no statistically significant difference was noted in the subgroup analysis of patients with tibial plateau fractures and those with ankle fractures. All data are shown in Tables 2 and 3, and Supplemental Figures 2-4.

Overall, 11 adverse events/serious adverse events occurred in both groups (control group

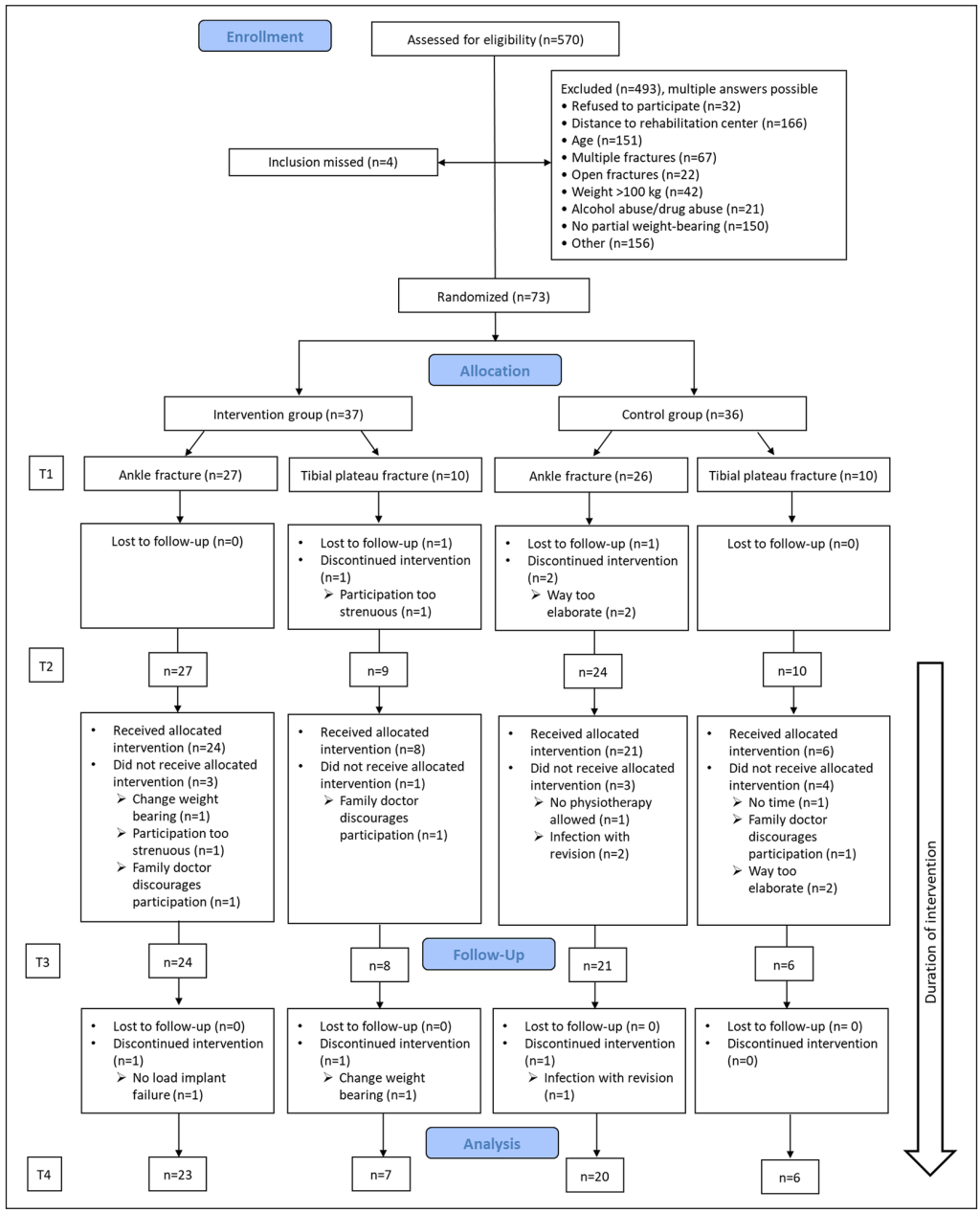


**Figure 1.** CONSORT flow diagram from surgery to six weeks postoperatively.
CONSORT: Consolidated Standards of Reporting Trials; T1: baseline; T2: day of discharge; T3: after three weeks; T4: six weeks after the operation.

[$n=5$] and intervention group [$n=6$]). Serious adverse events did not occur in the intervention group. Furthermore, no adverse events or serious adverse events were associated with tibial plateau fractures. In the intervention group, the adverse events included implant failure without revision ($n=1$), delayed wound healing ($n=1$), common cold ($n=2$), cystitis ($n=1$), and postoperative

**Table 1.** Characteristics of the patients at baseline.

| Characteristics | Intervention ($n=32$) | | Control ($n=27$) | | Full analysis set ($n=59$) | All participants ($n=73$) |
|---|---|---|---|---|---|---|
| | Tibial plateau fracture ($n=8$) | Ankle fracture ($n=24$) | Tibial plateau fracture ($n=6$) | Ankle fracture ($n=21$) | | |
| Sex, male/female | 4/4 | 12/12 | 2/4 | 10/11 | 28/31 | 34/39 |
| Age, mean ± SD (range), years | 42 ± 9 (33–55) | 43 ± 12 (19–65) | 44 ± 9 (32–56) | 40 ± 13 (21–62) | 42 ± 11 (19–65) | 43 ± 12 (19–65) |
| Body mass index, mean ± SD (range), kg/m$^2$ | 27 ± 6.7 (19.9–34.7) | 25.7 ± 3.8 (18.8–34.7) | 26.2 ± 5.6 (17.3–31.6) | 25.1 ± 4.0 (20.5–33.9) | 25.7 ± 4.5 (17.3–38.1) | 25.5 ± 4.1 (17.3–38.1) |
| Type of fracture (%) | | | | | | |
| AO type B | 5 (62.5) | 11 (45.8) | 5 (83.3) | 12 (57.1) | 33 (55.9) | 34 (46.6) |
| AO type C | 3 (37.5) | 13 (54.2) | 1 (16.7) | 9 (42.9) | 26 (44.1) | 39 (53.4) |
| Cause of accident (%) | | | | | | |
| Accident while walking | 1 (12.5) | 3 (12.5) | 1 (16.7) | 1 (4.8) | 6 (10.2) | 11 (15.1) |
| Bicycle accident | 3 (37.5) | 4 (16.7) | 3 (50.0) | 4 (19.0) | 14 (23.7) | 19 (26.0) |
| Motorbike accident | 1 (12.5) | 1 (4.2) | 0 (0.0) | 2 (9.5) | 4 (6.8) | 4 (5.5) |
| Falls from stairs | 0 (0.0) | 2 (8.3) | 0 (0.0) | 3 (14.3) | 5 (8.5) | 5 (6.8) |
| Sports | 2 (25.0) | 5 (20.8) | 1 (16.7) | 5 (23.8) | 13 (22.0) | 16 (21.9) |
| Falls from a height $<3$ m | 1 (12.5) | 2 (8.3) | 0 (0.0) | 1 (4.8) | 4 (6.8) | 4 (5.5) |
| Slipped on a smooth ground | 0 (0.0) | 7 (29.2) | 1 (16.7) | 5 (23.8) | 13 (22.0) | 14 (19.2) |

SD: standard deviation.

**Table 2.** KOOS5, FAOS5, and the corresponding subscores and circumference measurements from T1 to T4.

| Visit | FAOS5/KOOS5 | Tibial plateau fractures | | | | | | | | Ankle fractures | | | | | | | | Total | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Intervention group | | | | Control group | | | | Intervention group | | | | Control group | | | | Intervention group | | | | Control group | | | |
| | | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max |
| T1 | Symptoms | 95.5 | 6.3 | 82.1 | 100.0 | 94.0 | 7.0 | 82.1 | 100.0 | 97.8 | 5.2 | 78.6 | 100.0 | 96.8 | 4.1 | 85.7 | 100.0 | 97.2 | 5.5 | 78.6 | 100.0 | 96.2 | 4.8 | 82.1 | 100.0 |
| | Pain | 96.2 | 7.7 | 77.8 | 100.0 | 94.9 | 12.5 | 69.4 | 100.0 | 99.8 | 0.8 | 97.2 | 100.0 | 99.6 | 1.3 | 94.4 | 100.0 | 98.9 | 4.0 | 77.8 | 100.0 | 98.6 | 5.9 | 69.4 | 100.0 |
| | ADLs | 97.1 | 5.0 | 88.2 | 100.0 | 95.8 | 10.2 | 75.0 | 100.0 | 99.6 | 1.1 | 95.6 | 100.0 | 99.9 | 0.3 | 98.5 | 100.0 | 99.0 | 2.8 | 88.2 | 100.0 | 99.0 | 4.8 | 75.0 | 100.0 |
| | Sport/Rec | 88.8 | 18.7 | 45.0 | 100.0 | 95.8 | 10.2 | 75.0 | 100.0 | 98.8 | 3.0 | 90.0 | 100.0 | 98.6 | 3.2 | 90.0 | 100.0 | 96.3 | 10.2 | 45.0 | 100.0 | 98.0 | 5.4 | 75.0 | 100.0 |
| | QoL | 93.0 | 11.3 | 75.0 | 100.0 | 95.8 | 10.2 | 75.0 | 100.0 | 98.7 | 3.2 | 87.5 | 100.0 | 99.1 | 3.0 | 87.5 | 100.0 | 97.3 | 6.5 | 75.0 | 100.0 | 98.4 | 5.4 | 75.0 | 100.0 |
| | FAOS5/KOOS5 | 95.2 | 6.9 | 80.4 | 100.0 | 95.3 | 10.0 | 75.0 | 100.0 | 99.2 | 1.4 | 95.2 | 100.0 | 99.1 | 1.2 | 95.8 | 100.0 | 98.2 | 3.9 | 80.4 | 100.0 | 98.3 | 4.8 | 75.0 | 100.0 |
| T2 | Symptoms | 32.1 | 18.5 | 3.6 | 57.1 | 41.1 | 18.3 | 14.3 | 57.1 | 29.2 | 13.9 | 0.0 | 60.7 | 26.5 | 18.4 | 0.0 | 75.0 | 29.9 | 14.9 | 0.0 | 60.7 | 29.8 | 19.1 | 0.0 | 75.0 |
| | Pain | 32.6 | 25.2 | 5.6 | 69.4 | 39.4 | 27.0 | 8.3 | 80.6 | 32.4 | 19.9 | 0.0 | 69.4 | 30.2 | 20.7 | 0.0 | 91.7 | 32.5 | 20.9 | 0.0 | 69.4 | 32.2 | 22.0 | 0.0 | 91.7 |
| | ADLs | 15.8 | 20.2 | 0.0 | 61.8 | 26.0 | 15.6 | 5.9 | 39.7 | 27.0 | 17.3 | 0.0 | 60.3 | 27.2 | 17.9 | 0.0 | 64.7 | 24.2 | 18.4 | 0.0 | 61.8 | 27.0 | 17.1 | 0.0 | 64.7 |
| | Sport/Rec | 0.6 | 1.8 | 0.0 | 5.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.4 | 1.4 | 0.0 | 5.0 | 2.9 | 10.2 | 0.0 | 45.0 | 0.5 | 1.5 | 0.0 | 5.0 | 2.2 | 9.0 | 0.0 | 45.0 |
| | QoL | 15.6 | 27.8 | 0.0 | 81.3 | 11.5 | 16.0 | 0.0 | 37.5 | 16.7 | 18.0 | 0.0 | 81.3 | 14.6 | 14.4 | 0.0 | 50.0 | 16.4 | 20.4 | 0.0 | 81.3 | 13.9 | 14.5 | 0.0 | 50.0 |
| | FAOS5/KOOS5 | 20.3 | 14.7 | 5.4 | 48.2 | 26.9 | 13.4 | 8.3 | 41.1 | 24.4 | 12.9 | 0.0 | 53.6 | 23.6 | 14.4 | 3.0 | 63.1 | 23.4 | 13.2 | 0.0 | 53.6 | 24.4 | 14.0 | 3.0 | 63.1 |
| T4[†] | Symptoms | 53.6 | 20.7 | 14.3 | 78.6 | 58.9 | 15.1 | 32.1 | 78.6 | 47.4 | 22.3 | 14.3 | 89.3 | 53.6 | 19.8 | 21.4 | 85.7 | 48.8 | 21.7 | 14.3 | 89.3 | 54.8 | 18.7 | 21.4 | 85.7 |
| | Pain | 68.3 | 22.6 | 36.1 | 97.2 | 65.7 | 23.5 | 30.6 | 100.0 | 74.3 | 22.3 | 11.1 | 100.0 | 66.4 | 19.7 | 33.3 | 100.0 | 72.9 | 22.1 | 11.1 | 100.0 | 66.2 | 20.1 | 30.6 | 100.0 |
| | ADLs | 59.5 | 21.0 | 35.3 | 100.0 | 52.7 | 26.0 | 2.9 | 75.0 | 65.4 | 16.9 | 27.9 | 91.2 | 68.6 | 19.8 | 33.8 | 100.0 | 64.0 | 17.7 | 27.9 | 100.0 | 64.9 | 21.9 | 2.9 | 100.0 |
| | Sport/Rec | 17.9 | 12.2 | 0.0 | 40.0 | 10.0 | 10.5 | 0.0 | 25.0 | 16.3 | 18.9 | 0.0 | 60.0 | 20.0 | 29.2 | 0.0 | 95.0 | 16.7 | 17.4 | 0.0 | 60.0 | 17.7 | 26.3 | 0.0 | 95.0 |
| | QoL | 28.6 | 26.0 | 0.0 | 75.0 | 12.5 | 19.4 | 0.0 | 50.0 | 20.7 | 18.3 | 0.0 | 50.0 | 28.4 | 22.1 | 0.0 | 93.8 | 22.5 | 20.1 | 0.0 | 75.0 | 24.8 | 22.2 | 0.0 | 93.8 |
| | FAOS5/KOOS5 | 52.5 | 18.3 | 26.8 | 86.3 | 47.6 | 17.7 | 13.7 | 61.9 | 54.2 | 16.1 | 23.8 | 81.5 | 56.0 | 16.6 | 29.2 | 91.1 | 53.8 | 16.4 | 23.8 | 86.3 | 54.1 | 16.9 | 13.7 | 91.1 |
| | Circumference (cm)[‡] | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max |
| T1 | 20 cm above | 52.9 | 6.6 | 46.5 | 66.5 | 53.8 | 7.0 | 43.0 | 61.0 | 52.4 | 6.3 | 38.0 | 65.0 | 53.9 | 6.0 | 44.0 | 64.0 | 52.5 | 6.3 | 38.0 | 66.5 | 53.9 | 6.1 | 43.0 | 64.0 |
| | 10 cm above | 45.9 | 6.3 | 39.0 | 59.0 | 47.1 | 6.3 | 38.0 | 54.0 | 44.5 | 4.4 | 38.5 | 53.5 | 45.2 | 5.1 | 35.0 | 53.5 | 44.8 | 4.9 | 38.5 | 59.0 | 45.6 | 5.3 | 35.0 | 54.0 |
| | 10 cm below | 38.8 | 3.5 | 35.0 | 45.0 | 40.1 | 4.2 | 34.0 | 45.5 | 38.0 | 3.7 | 33.0 | 46.0 | 37.6 | 3.4 | 32.0 | 43.5 | 38.2 | 3.6 | 33.0 | 46.0 | 38.1 | 3.7 | 32.0 | 45.5 |
| T2 | 20 cm above | 53.6 | 6.7 | 47.0 | 68.0 | 52.7 | 7.2 | 41.0 | 61.0 | 52.4 | 5.7 | 44.0 | 63.0 | 53.2 | 5.7 | 44.0 | 64.0 | 52.7 | 5.9 | 44.0 | 68.0 | 53.1 | 5.9 | 41.0 | 64.0 |
| | 10 cm above | 46.4 | 5.9 | 39.0 | 58.0 | 45.3 | 6.4 | 35.0 | 52.0 | 44.5 | 4.4 | 39.0 | 53.0 | 44.5 | 4.9 | 36.0 | 54.5 | 45.0 | 4.8 | 39.0 | 58.0 | 44.7 | 5.2 | 35.0 | 54.5 |
| | 10 cm below | 39.0 | 4.1 | 35.0 | 46.0 | 38.6 | 3.5 | 32.0 | 41.0 | 37.8 | 3.4 | 33.0 | 44.5 | 37.0 | 3.7 | 32.0 | 44.0 | 38.1 | 3.6 | 33.0 | 46.0 | 37.4 | 3.6 | 32.0 | 44.0 |
| T3 | 20 cm above | 53.8 | 9.7 | 42.5 | 75.0 | 51.8 | 7.4 | 39.0 | 58.0 | 52.0 | 5.1 | 44.0 | 62.0 | 52.4 | 5.2 | 43.0 | 61.5 | 52.5 | 6.4 | 42.5 | 75.0 | 52.3 | 5.6 | 39.0 | 61.5 |
| | 10 cm above | 44.9 | 7.4 | 36.0 | 61.0 | 43.8 | 5.4 | 35.0 | 49.5 | 42.7 | 3.7 | 36.5 | 50.0 | 43.8 | 4.0 | 36.0 | 50.5 | 43.2 | 4.9 | 36.0 | 61.0 | 43.8 | 4.2 | 35.0 | 50.5 |
| | 10 cm below | 36.8 | 4.5 | 32.0 | 45.5 | 36.5 | 3.9 | 30.5 | 42.0 | 37.1 | 3.1 | 32.0 | 44.0 | 37.1 | 3.1 | 32.0 | 44.0 | 37.0 | 3.4 | 32.0 | 45.5 | 37.0 | 3.2 | 30.5 | 44.0 |
| T4 | 20 cm above | 53.8 | 9.9 | 45.0 | 74.0 | 50.0 | 7.8 | 40.0 | 58.0 | 51.8 | 5.4 | 43.5 | 61.0 | 52.2 | 4.8 | 42.0 | 59.5 | 52.3 | 6.6 | 43.5 | 74.0 | 51.7 | 5.5 | 40.0 | 59.5 |
| | 10 cm above | 44.1 | 6.3 | 38.0 | 57.0 | 42.2 | 5.8 | 35.5 | 50.0 | 43.3 | 4.4 | 36.0 | 50.0 | 43.3 | 4.7 | 34.5 | 51.0 | 43.5 | 4.8 | 36.0 | 57.0 | 43.0 | 4.9 | 34.5 | 51.0 |
| | 10 cm below | 36.1 | 4.9 | 32.0 | 46.0 | 36.4 | 3.6 | 32.0 | 40.5 | 35.5 | 3.6 | 31.0 | 43.5 | 35.0 | 3.0 | 29.5 | 41.0 | 35.7 | 3.9 | 31.0 | 46.0 | 35.3 | 3.1 | 29.5 | 41.0 |

KOOS5: Knee injury and Osteoarthritis Outcome Score; FAOS5: Foot and Ankle Outcome Score; ADL: function in daily living; Sport/Rec: function/sports and recreational activities; QoL: Quality of Life; SD: standard deviation; Min: minimum; Max: maximum.

[†]Leg circumferences (cm) measured 20 cm and 10 cm above and 10 cm below the knee joint line.

**Table 3.** Differences in the KOOS5, FAOS5, and corresponding subscores.

| | | Contrast | Difference | 95% confidence interval | | *P* value |
|---|---|---|---|---|---|---|
| Ankle fracture | FAOS5 | T4-T1† | –1.9 | –13.3 | 9.5 | 0.89 |
| | | T4‡ | –1.8 | –10.0 | 6.3 | 0.81 |
| | Symptoms | T4-T1 | –7.2 | –21.6 | 7.2 | 0.41 |
| | | T4 | –6.2 | –16.5 | 4.1 | 0.29 |
| | Pain | T4-T1 | 7.7 | –8.0 | 23.4 | 0.42 |
| | | T4 | 7.9 | –3.3 | 19.1 | 0.20 |
| | ADL | T4-T1 | –2.9 | –16.5 | 10.7 | 0.83 |
| | | T4 | –3.2 | –12.9 | 6.5 | 0.66 |
| | Sport/Rec | T4-T1 | –3.9 | –17.4 | 9.6 | 0.72 |
| | | T4 | –3.7 | –13.3 | 5.9 | 0.57 |
| | QoL | T4-T1 | –7.4 | –21.4 | 6.6 | 0.37 |
| | | T4 | –7.8 | –17.8 | 2.2 | 0.14 |
| Tibial plateau fracture | KOOS5 | T4-T1 | 4.9 | –18.6 | 28.5 | 0.83 |
| | | T4 | 4.8 | –12.1 | 21.8 | 0.72 |
| | Symptoms | T4-T1 | –6.8 | –32.8 | 19.2 | 0.76 |
| | | T4 | –5.4 | –24.0 | 13.3 | 0.72 |
| | Pain | T4-T1 | 1.2 | –33.8 | 36.3 | 0.99 |
| | | T4 | 2.5 | –22.6 | 27.7 | 0.96 |
| | ADL | T4-T1 | 5.5 | –24.1 | 35.2 | 0.86 |
| | | T4 | 6.8 | –14.5 | 28.0 | 0.67 |
| | Sport/Rec | T4-T1 | 14.9 | –4.0 | 33.9 | 0.14 |
| | | T4 | 7.9 | –5.8 | 21.5 | 0.32 |
| | QoL | T4-T1 | 18.9 | –14.8 | 52.7 | 0.33 |
| | | T4 | 16.1 | –8.2 | 40.3 | 0.23 |
| Total | FAOS5/KOOS5 | T4-T1 | –0.2 | –10.4 | 10.0 | 1.00 |
| | | T4 | –0.3 | –7.6 | 7.0 | 0.99 |
| | Symptoms | T4-T1 | –7.1 | –19.7 | 5.5 | 0.33 |
| | | T4 | –6.2 | –15.2 | 2.8 | 0.21 |
| | Pain | T4-T1 | 6.3 | –8.0 | 20.6 | 0.49 |
| | | T4 | 6.6 | –3.6 | 16.9 | 0.25 |
| | ADL | T4-T1 | –0.9 | –13.5 | 11.7 | 0.98 |
| | | T4 | –0.9 | –9.9 | 8.1 | 0.96 |
| | Sport/Rec | T4-T1 | 0.7 | –10.6 | 12.0 | 0.98 |
| | | T4 | –1.0 | –9.1 | 7.1 | 0.93 |
| | QoL | T4-T1 | –1.1 | –14.4 | 12.1 | 0.97 |
| | | T4 | –2.3 | –11.8 | 7.2 | 0.79 |
| Circumference measured 20 cm above the knee joint line (cm) | | | | | | |
| Ankle fracture | | T4-T1 | 1.0 | –0.5 | 2.6 | 0.26 |
| | | T4 | –0.6 | –4.2 | 3.1 | 0.93 |
| Tibial plateau fracture | | T4-T1 | 4.6 | 1.2 | 8.0 | 0.005 |
| | | T4 | 3.7 | –5.7 | 13.2 | 0.61 |
| Total | | T4-T1 | 1.9 | 0.4 | 3.3 | 0.01 |
| | | T4 | 0.3 | –3.2 | 3.8 | 0.97 |

KOOS5: Knee injury and Osteoarthritis Outcome Score; FAOS5: Foot and Ankle Outcome Score; ADL: function in daily living; Sport/Rec: function/sports and recreational activities; QoL: Quality of Life.
†Difference in the mean changes (baseline to T4).
‡Difference in the means at T4 (six weeks postoperative).

numbness in two toes ($n=1$). In the control group, the adverse events included superficial wound infection without hospitalization or revision ($n=1$), ankle joint pain after another fall ($n=1$), and delayed wound healing ($n=1$), and the serious adverse events were wound healing disorder ($n=1$) and deep wound infection ($n=1$), both requiring re-hospitalization and reoperation. All patients with adverse events were able to continue to participate in the study, whereas the patients with serious adverse events ($n=2$) had to be hospitalized again and could not complete the study protocol.

## Discussion

Our hypothesis was only partially confirmed. We did not note any statistically significant differences in the patient-reported outcomes and the respective subscores between the intervention and control groups. Nevertheless, in the overall study cohort and the tibial plateau fracture group, a significant difference was observed in the degree of change in the leg circumference (as a measure of muscular atrophy) six weeks postoperatively.

Bugbee et al.[21] conducted a prospective randomized study involving patients who received either land-based or anti-gravity treadmill training for four weeks after total knee arthroplasty and reported results similar to our findings. The Knee injury and Osteoarthritis Outcome Score improved in both groups; however, no statistically significant differences were found between the groups. Moreover, in the group with tibial plateau fractures, subscore analysis of the Knee injury and Osteoarthritis Outcome Score showed that the greatest improvement was noted in the function/sports and recreational activities and quality of life subscores when anti-gravity treadmill therapy was provided; these findings are consistent with the results of our study.

A previous study assessed muscle atrophy and reported a significant decrease in the leg circumference at approximately 20 cm above the knee joint gap,[20] which is in line with our results. This finding is interesting from the following two viewpoints: (1) the previous study[20] was considered when planning the protocol of our study and (2) we were able to confirm their results after six weeks at the identical measuring point, although the focus of the investigation between the studies was different. Additional studies confirmed that the decrease in the leg circumference is associated with reduced activation of the musculature with a decrease in the muscle cross-sectional area and contractile protein concentration.[14–17,22–25] Moreover, a relationship between anti-gravity treadmill training and an increase in the thigh muscle strength was confirmed in other studies.[8,26,27] This finding may account for the good results observed in patients with tibial plateau fractures in the intervention group with respect to the Function in daily living, Function/sports and recreational activities, and Quality of Life subscores. Nevertheless, significant differences were not noted in these subscores. In addition, these effects were not apparent in patients with ankle fractures possibly because they experience a lower level of pain and/or show lower compliance with partial load bearing, which was previously described by Braun et al.[28] Furthermore, it is plausible that a full load induces muscle atrophy of less severity in patients who show a worse compliance with maintaining the partial load. Isolated measurements of thigh muscle strength at the specified time-points of the study may be necessary to verify these effects.

Adverse events and serious adverse events were balanced in both groups. Common cold and cystitis were not likely to be related to the intervention. Screw failure was possibly associated with anti-gravity treadmill training; however, the patient was more likely exposed to an incorrect load or a material defect possibly occurred, given that a defined load of 20 kg was maintained when exercising on the anti-gravity treadmill.[28] Surgical site infection developed only in the control group.

Currently, the optimal strategy for the postoperative prevention of muscle atrophy in patients on partial weight-bearing involving implementation of a targeted training program has not been established to date. Nonetheless, we reported a strategy involving the use of an anti-gravity treadmill, especially for patients with tibial plateau fractures. The patient-reported scores are comparable between our anti-gravity treadmill protocol and a standard rehabilitation protocol. In addition, patients with other fractures for whom partial weight-bearing is

intended as part of the treatment may also benefit from the administration of anti-gravity treadmill rehabilitation therapy. An ongoing study (i.e. NCT03562364) may confirm these advantages, especially since the study protocol includes targeted force measurement of the thigh and patient-reported outcome scores similar to those reported in our study

The main limitation of this study was the possible bias associated with the open-label nature of the study and the significant proportion of patients who dropped out. Another limitation was the relatively small number of patients in the compared groups. Although the originally planned total number of patients was reasonable, the premature discontinuation of the study resulted in a relatively small number of patients, especially considering the number of dropouts and the two types of fractures.

### Clinical messages

- The results of our anti-gravity treadmill protocol are comparable with those of a standard rehabilitation protocol.
- Patients who received the anti-gravity treadmill therapy had reduced muscle atrophy without detectable functional benefits.
- In clinical practice, anti-gravity treadmill therapy is safe and may be used as a complementary therapeutic option.

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## Author contributions

R.H. and L.P. were responsible for data control, study supervision, and writing of the manuscript. S.S. D.M., and B.K. performed the data acquisition, data control, and monitoring of the intervention to detect possible adverse events. M.M. performed data curation, formal analysis, validation, and visualization of the study data, as well as further review and revision of the manuscript. C.J., J.B., and R.H. were responsible for the development of the study design, study financing, and project coordination. In addition, C.J. and J.B. undertook the manuscript review. All the authors have approved the final manuscript.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval and informed consent

Approval: Ethical approval was given by the ethical review committee of the University of Leipzig (reference number: 176/14-ff) and the ethics review committee of the State Chamber of Physicians of Saxony (reference number: EK-allg-7/16–1). Accordance: The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (Good Clinical Practice guidelines). Informed consent: After intensive clarification, patients provided written consent for their participation in the study.

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## Trial registration

The study was registered on May 29, 2016, at ClinicalTrials.gov (NCT02790229). Furthermore, the protocol has been published (DOI: 10.1186/s12891-017-1461-0).

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