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Muscle strength characteristics following megaprosthetic knee reconstruction for bone sarcoma

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ABSTRACT

Objective: To assess muscle strength characteristics in patients with resection and megaprosthetic reconstruction of the knee for bone sarcoma compared to age- and sex-matched controls.

Methods: This was a cross-sectional, case-control study. Muscle strength characteristics for knee extension and -flexion were assessed isokinetically at three different joint velocities: 60, 120 and 180°/s, and by the rate of force development (RDFmax) in knee extension. The Toronto Extremity Salvage Score (TESS) was used in patients.

Results: Eighteen patients (91.6 months postop.) and 18 controls were included. Relative to controls, patients generated maximal torques of 19%, 23% and 23% in knee extension at 60, 120 and 180°/s, respectively. For knee flexion, patients generated maximal torques of 58%, 53% and 60% at 60, 120, and 180°/s, relative to the controls. RDFmax of the operated leg was 2.75 ± 2.13 N/ms, 7.16 ± 4.78 N/ms for the non-operated leg, and 7.95 ± 4.29 N/ms for the controls. The mean TESS score was 84.0.

Conclusion: Patients reached approximately 20% of the maximal knee extension torque. In isometric assessments, they used double the amount of time to generate one-third of the maximal force compared to the controls despite good TESS scores.

1. Introduction

Advances in chemoradiotherapy and improved knowledge of surgical techniques and margins have led to limb-saving surgery being the preferred treatment option for >90% of extremity localised bone sarcomas [1–3]. However, despite these advances, resection of tumours around the knee is still associated with considerable morbidity and functional deficits [4,5].

The scientific level of evidence that guides surgical management of malignant primary bone tumours is low and primarily based on observational studies [6]. In addition to patient- or reconstruction survivorship, surgical success is often evaluated by patient satisfaction as gauged by patient-reported outcome measures (PROMS) [7,8]. These are reports of self-assessed functioning in physical or social circumstances. They are complex and multifaceted and limited by bias (recall- and social desirability bias) [9].

Rehabilitation following bone sarcoma surgery is challenging since it is followed by immobilisation and chemotherapy, with few randomised controlled trials to guide evidence-based practice. In fact, rehabilitation is left out of bone sarcoma care guidelines [10,11]. To better understand and guide rehabilitation, we need to look beyond PROMS and measure core changes in objective physical function, such as muscle strength or similar outcome variables closer to the intervention.

To date, studies evaluating gait- and muscle function following knee reconstruction for bone sarcoma have shown slower walking speeds, characterized by a stiff-legged gait pattern [12–15] and lower muscle strength in the operated leg. Reported asymmetries range from 50 to 70% [16,17]. Tanaka et al. reported decreasing muscle strength as a function of the number of resected quadriceps muscles in patients with soft tissue sarcoma [18,19], but such relationships have not been

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reported in patients with bone sarcoma. He et al. reported that post-surgery patellar height (i.e., the Insall-Salvati ratio (ISR) and the Blackburne-Peel index (BPI)) were negatively associated with a physical function score [20], but did not include muscle strength analysis, leaving the relationship between BPI and muscle function in this population unknown. Although muscle strength deficits have been addressed briefly by other authors, additional information on muscle length/-strength relationships (i.e., muscle strength generating ability across the joint range of motion), rate of force development and total work capacity are needed since they have been linked directly to the ability to perform ADL in the primary knee arthroplasty setting [21,22]. Identifying associations between muscle strength characteristics and patient- and treatment-related variables can also help identify strategies for rehabilitation following knee megaprosthetic reconstruction in patients with bone sarcoma.

The primary aim of this study was to evaluate isokinetic knee extension muscle strength (torque) in patients with a history of knee resection and megaprosthesis reconstruction for bone sarcoma, compared to the non-operated knee and age- and sex-matched controls. Secondary aims were to evaluate additional knee extension and -flexion muscle strength characteristics and explore relations between the primary endpoint and other patient- and treatment-related outcomes.

2. Materials and methods

This observational case-control study assessed muscle strength- and gait characteristics in patients with previous knee resection and megaprosthesis reconstruction for bone sarcomas. The study was approved by the Regional Committee for medical and Health Research Ethics (reference number: 2017/1058). Participants or guardians provided written informed consent before any study-related assessment, and all data were handled according to local regulations. The results are reported in accordance with the STROBE checklist.

2.1. Patients and eligibility

Patients diagnosed between 1997 and 2017 were identified from the prospective hospital tumour database. Inclusion criteria were: 1) 12 years of age or older, 2) bone sarcoma surgery with insertion of a megaprosthesis in the distal femur or proximal tibia, 3) minimum 12 months follow-up at inclusion, 4) no major walking limitations (use of walking aid or disabling motor neuropathy since these represents only a small proportion of the available patient population), 5) no metastatic disease or local relapse, and 6) not suffering from severe anxiety or depression.

The control cohort was recruited through advertisements with the following inclusion criteria: 1) matched for age (i.e., born within the same year as their matched patient) and sex to participants in the patient cohort, 2) no history of any cancer, and 3) no walking limitations.

2.2. Surgical procedures

Surgical resection of bone sarcoma around the knee uniformly entails the resection of a given length of bone determined by the size and location of the tumour, as well as the required surgical margin. Surgeries were individualised, based on tumour size and location, and performed at Oslo University Hospital, Division of Orthopaedic Oncology. All patients underwent intra-articular resections. In patients with tumours of the distal femur, the patellar tendon remained attached, but to achieve a safe surgical margin, the *m. Vastus intermedius* and other involved musculature of the *m. Quadriceps femoris* were removed. The hamstrings insertions and gastrocnemius origins were also released. In patients with tumours of the proximal tibia, the resection involved detachment and later reattachment of the patellar tendon and muscle resection was guided by placement of the soft tissue extension. They are not specified since these do not exert force across the knee joint. A medial gastrocnemius flap and a split skin graft were routinely performed to secure patellar tendon reattachment and for soft tissue coverage. In patients with tibial resections, post-operative immobilisation in a brace was applied, initially locked in extension, with a gradual increase of range in motion (ROM) eight to 12 weeks after surgery.

2.3. Participant characteristics

Demographic and treatment variables (i.e., age, time since surgery, chemotherapy, tumour location, resected muscles, surgical access, and prosthetic length) were obtained from the hospital medical records. In addition, pre- and post-surgery patellar positions were assessed by the Blackburne-Peel Index (BPI) as described by Chiang and Jiang (2010) [23].

2.4. Patient-reported outcome measures

The lower extremity version of the Toronto Extremity Salvage Score (TESS) was used to assess self-reported physical disability. Specifically, the questionnaire consists of 30 questions covering activities of daily living, yielding a total score that ranges from 0 to 100 (higher scores indicating greater autonomy).

2.5. Muscle strength assessments

After a 5-min warm-up on a stationary bike or brisk walking if limited knee-joint ROM, the participant was seated in a dynamometer (HUMAC NORM, CSMi, Stoughton, MA, USA), which was individually adjusted to ensure that the external axis of rotation was aligned with the knee joint axis of rotation. Each participant performed three warm-up sets of three repetitions with increasing effort. Both maximal knee extension and -flexion torques were assessed and recorded over a knee angle range of 80°, or within the ROM the patient could perform, at three different angular velocities: 60° per second (°/s), 120°/s, and 180°/s. The non-operated leg was tested first in the patient population, and the corresponding leg was assessed first for their matched control. To explore muscle force-muscle length relationships, or total work across joint ROM, for knee extension and flexion, raw data for torque and joint angles across participants' ROM for all participants were exported from the Humac Norm. The total work (torque/joint angle) curves were then created for all participants and presented as average values (joule) for all groups.

Next, participants were seated in a custom-made knee extension apparatus (Gym2000, Geithus, Norway), where the level arm was connected to a fixed strain gauge (HBM U2AC2, Darmstadt, Germany). The knee angle was fixed at approximately 50°, which was the most acute angle that allowed for isometric maximal voluntary contraction (MVC) assessments of knee extensors in the patients (one patient could not complete this assessment due to pain). Following familiarisation with the test protocol, participants were given five warm-up trials with increasing effort before attempting maximal contractions. Participants were instructed to generate force as rapidly as possible, and maximal rate of force development (RFD_{max}) was calculated as the largest increase in force in Newton per millisecond, from ten to 70% of maximal force. Each subject was given several trials (range four to seven) to achieve MVC. The average of the two best trials, characterized by a rapid increase in force and a visible plateau in force, was used for RFD_{max} calculations. Force signals were sampled at 2000 Hz and low-pass filtered at 50 Hz, based on visual inspection of force curves of trials in the operated legs.

2.6. Statistical analysis

Descriptive statistics (mean and standard deviation (SD)) were calculated in Excel (Microsoft Corp., Redmond, WA, USA). Knee extension and knee flexion total work were analysed as the area under the curve (AUC) (group mean joule, standard error of the mean (SEM) and 95% confidence intervals (95% CI)) using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). Descriptive statistics for RFD_{max} were also calculated using GraphPad Prism. An unpaired T-test with Welch's correction was used to explore any differences between the operated leg and the non-operated leg, and the matched controls, as we expected larger SDs in the operated leg. Univariate linear regressions were performed to explore relations to peak torque in knee extension at 60°/s. Analyses were performed in Rstudio version February 1, 5042 with R version 4.0.0 for Windows.

3. Results

From January 2018 to October 2019, a total of 36 participants (18 patients and 18 matched controls) were included in the study. Of the 18 patients included (average time since surgery: 91.6 ± 74.9 months; range: 12–246 months), nine had a tumour in the distal femur and nine in the proximal tibia. The average TESS score in patients was 84.0, and the remaining demographic data are presented in Table 1. All features were similar between the groups, except for sex distribution. Also, individual participant demograpics and all individual results are presented in the supplementary file.

4. Muscle strength characteristics

4.1. Knee extension torque

The mean peak torque in knee extension at 60°/s was 36.3 ± 25.1 Nm for the operated leg, 168.4 ± 51.9 Nm for the non-operated leg, and 186.2 ± 56.0 Nm for the controls (Table 2). At 120°/s the knee extension peak torque was 34.0 ± 20.9 Nm for the operated leg, 128.2 ± 40.4 Nm for the non-operated leg, and 148.7 ± 43.9 Nm for the reference group, while at 180°/s the knee extension peak torque was 29.5 ± 19.7 Nm for the operated leg, 110.3 ± 38.6 Nm for non-operated leg, and 129.2 ± 38.6 Nm for the controls (Table 2). Patients generated a lower peak torque with the operated leg compared to the non-operated leg ($p < 0.001$) and achieved 19–23% of the peak torque across the angular velocities compared to the controls (Table 2) ($p < 0.001$).

4.2. Knee flexion torque

Mean peak torque in knee flexion at 60°/s was 66.6 ± 27.1 Nm for the operated leg, 105.6 ± 29.9 Nm for the non-operated leg, and 114.1 ± 27.7 Nm for the controls (Table 2). At 120°/s the knee flexion peak torque was 57.3 ± 23.8 Nm for the operated leg, 89.5 ± 24.5 Nm for the non-operated leg, and 96.1 ± 22.3 Nm for the controls, while at 180°/s the knee flexion peak torque was 50.5 ± 23.0 Nm for the operated leg, 78.7 ± 22.1 Nm for non-operated leg, and 85.6 ± 19.4 Nm for the controls, (Table 2). Patients generated a lower peak torque with the operated leg when compared to the non-operated leg ($p < 0.001$) and achieved 25–60% of the peak torque across the angular velocities compared to the controls ($p < 0.001$) across all joint velocities.

Table 1
Patient characteristics. Values are presented as numbers, relative numbers and mean (standard deviation).

	All patients	Distal femur	Proximal tibia	Controls
Female/male	10/8	8/1	2/7	10/8
Age	31.0 (11.7)	34.3 (9.7)	27.7 (13.0)	31.0 (11.7)
Body weight (kg)	72.9 (14.2)	72.2 (15.0)	73.5 (14.2)	72.9 (10.9)
Height (cm)	172.9 (9.5)	166.8 (5.4)	179.0 (8.8)	174.5 (7.3)
Time since surgery (months)	91.6 (74.9)	106.7 (75.3)	76.5 (75.8)	
Age at resection	23.4	25.6	21.2	
Operated side left/right	7/11	5/4	6/3	
Prosthetic length	14.5 (5.4)	16.6 (5.9)	12.4 (4.2)	
Surgical access medial/lateral	11/7	3/6	8/1	
Chemotherapy yes/no	14/4	7/2	7/2	
BPI Pre (1 distal missing)	1 (0.2)	0.9 (0.2)	1 (0.2)	
BPI last	0.6 (0.2)	0.6 (0.2)	0.7 (0.3)	
TESS	84.0 (7.9)	84.0 (8.3)	82.7 (7.9)	

BPI, Blackburne-Peel index; TESS, Toronto Extremity Salvage Score.

Table 2
Muscle strength characteristics. Values are presented as mean (standard deviations).

Variables	All patients	Distal femur	Proximal tibia	Controls	Patients *Vs.* Controls (%)
Operated leg or matched leg in controls					
Isokinetic knee extension peak torque (Nm)					
60°/s	36.3 (25.1)	31.2 (22.6)	41.4 (27.6)	186.2 (56.0)	19.4
120°/s	34.0 (20.9)	27.5 (16.8)	40.5 (23.5)	148.7 (43.9)	22.9
180°/s	29.5 (19.7)	23.7 (15.0)	35.2 (23.0)	129.2 (38.6)	22.8
Isokinetic knee flexion peak torque (Nm)					
60°/s	66.6 (27.1)	66.2 (22.1)	67.0 (32.7)	114.1 (27.7)	58.3
120°/s	57.3 (23.8)	55.6 (18.6)	59.1 (29.1)	96.1 (22.3)	53.4
180°/s	50.5 (23.0)	49.3 (17.0)	51.8 (28.8)	85.6 (19.4)	60.0
Knee extension MVC (N)					
Knee ext.	184.3 (83.7)	195.1 (58.0)	172.1 (108.8)	584.4 (203.0)	31.5
Non-operated leg or matched leg in controls					
Isokinetic knee extension peak torque (Nm)					
60°/s	168.4 (51.9)	148.4 (47.1)	188.4 (51.0)	177.4 (52.3)	94.9
120°/s	128.2 (40.4)	114.2 (41.2)	142.2 (36.6)	140.5 (53.3)	91.3
180°/s	110.3 (38.6)	93.6 (35.1)	127.1 (36.1)	123.0 (34.2)	89.7
Isokinetic knee flexion peak torque (Nm)					
60°/s	105.6 (29.9)	97.9 (23.4)	113.4 (34.9)	109.9 (27.6)	96.1
120°/s	89.5 (24.5)	82.2 (20.6)	96.9 (27.0)	94.8 (24.2)	94.4
180°/s	78.7 (22.1)	72.1 (17.6)	85.2 (25.1)	84.9 (21.4)	92.7
Knee extension MVC (N)					
Knee ext.	496.5 (150.4)	451.0 (118.9)	547.8 (172.7)	555.6 (220.2)	89.4

Nm, Newton meter; °/s, degrees per second; MVC, Maximal Voluntary Contraction.
N, Newton; Knee ext., Knee extension.

4.3. Knee joint work capacity

The AUC for knee extension in the operated leg was 2554 J (SEM: 336; 95% CI: 1897 to 3212), 12,228 J (SEM: 783; 95%CI: 10,694 to 13,762) for the non-operated leg, and 14,695 J (SEM: 759; 95% CI: 13,208 to 16,182) for the controls (Fig. 1a). AUC for flexion in the operated leg was 4428 J (SEM: 431; 95% CI: 3583 to 5274), 7587 J (SEM: 465; 95% CI: 6676 to 8497) for the non-operated leg, and 8830 J (SEM: 464; 95% CI: 7922 to 9739) for the controls (Fig. 1b). The lower SDs observed at both ends of the graphs in the operated leg represent fewer patients capable of generating force at either end of the defined ROM.

4.4. Maximal voluntary contraction and rate of force development

Peak knee extension MVC of the operated leg (184.3 ± 83.7 N) was

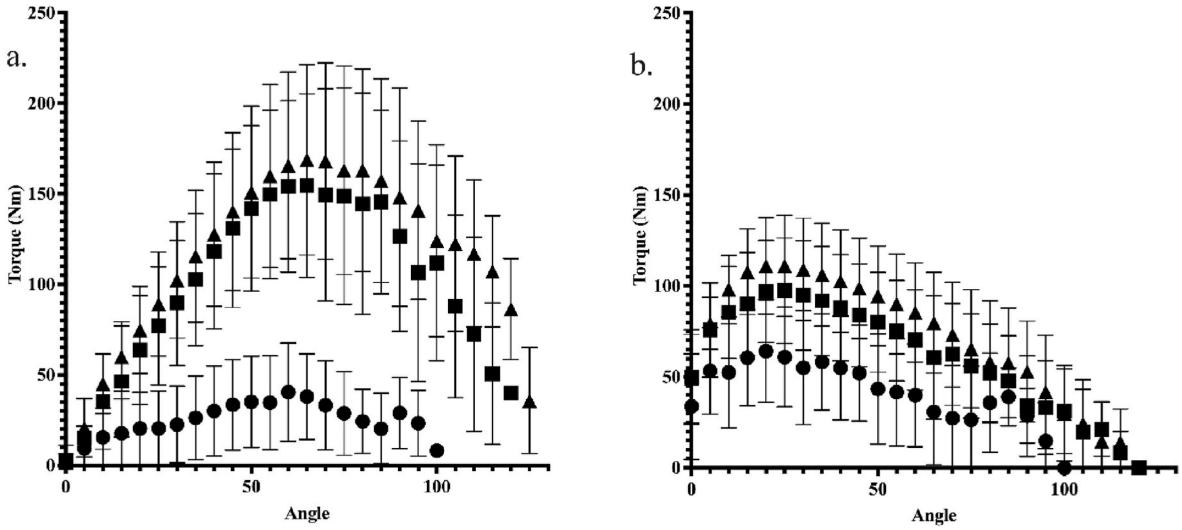

Fig. 1. Muscle force/muscle length-relationship in patient's operated leg (circles), non-operated leg (squares), and controls (matched leg to the operated leg in patients) (triangles), in knee extension (a.) and knee flexion (b.).

significantly lower than both the non-operated leg (496.5 ± 150.4 N) ($p < 0.001$) and the controls (584.4 ± 203.0 N) ($p < 0.001$) (Table 2, Fig. 2a). In addition, RDF_{max} of the operated leg (2.75 ± 2.13 N/ms) was significantly lower than both the non-operated leg (7.16 ± 4.78 N/ms) ($p = 0.018$) and the controls (7.95 ± 4.29 N/ms) ($p < 0.001$) (Fig. 2b).

4.5. *Relations to operated knee extensor torque*

Greater body mass was associated with increased muscle strength. Specifically, each additional kilogram of body mass was associated with a 0.9 Nm greater isokinetic knee extensor torque at 60°/s ($p = 0.04$, Table 3). Furthermore, males generated a 17.7 Nm greater torque on average than females ($p = 0.15$) (Table 3). No treatment-related outcome variable showed any associations with muscle strength (Table 3).

5. Discussion

Our main finding was the large muscle strength deficits in knee extension and -flexion in patients following knee resection and

Table 3
Associations between Peak torque at 60° per second and patient- and treatment related outcome (univariate linear regression).

Variables	Peak torque 60° per second		
	Estimate[a]	SEM	p-value
Sex (female/male)	−17.73	11.72	0.15
Age	0.24	0.54	0.66
Body weight	0.85	0.39	0.04
Tumour location (distal femur/proximal tibia)	8.00	12.29	0.52
Time since surgery (months)	0.05	0.08	0.57
Operated side (left/right)	−7.61	12.63	0.56
Prosthesis length	0.00	1.18	1.00
Surgical access (medial/lateral)	−0.57	12.77	0.96
Resected muscles	1.79	7.15	0.81
Chemotherapy (yes/no)	17.00	14.36	0.25
BPI last	32.60	25.06	0.21
BPI last	30.97	27.28	0.28
BPI change	21.55	18.27	0.26

SEM, Standard error of the mean; BPI, Blackburne-Peel Index (BPI).
[a] Estimate, indicates influence of each variable on peak torque.

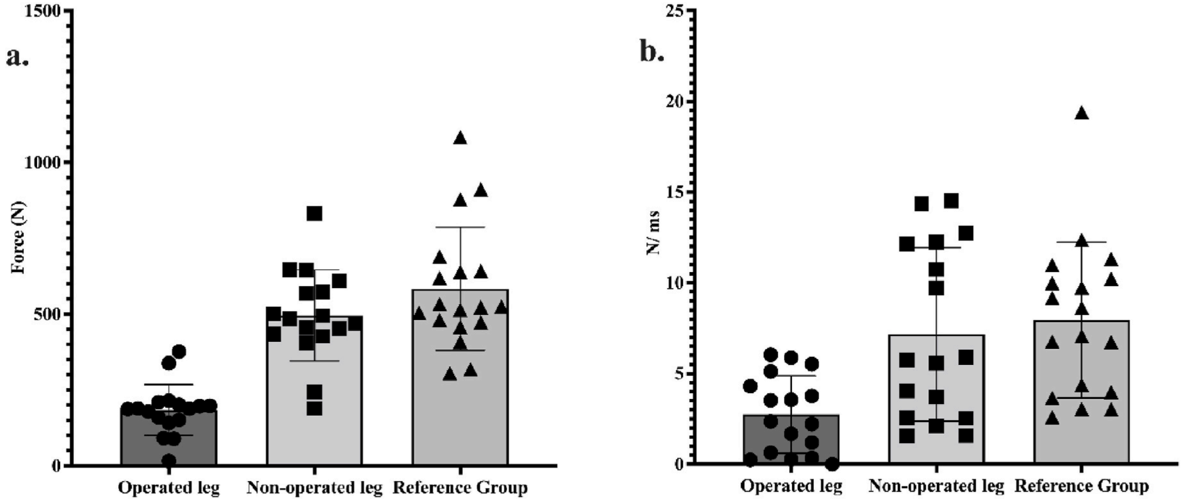

Fig. 2. Maximal voluntary knee extension contraction force in patients' operated leg (circles), non-operated leg (squares), and controls (matched leg to the operated leg in patients) (triangles) (a.), and rate for force development, defined as an increase in force (N, Newton) per time unit (ms, millisecond), recorded between 10% and 70% of maximal voluntary contraction force (b.).

megaprosthetic reconstruction for bone sarcoma compared to the non-operated leg and age- and sex-matched controls. Specifically, patients were only able to produce 17% of the work as compared to the control group. In addition, the MVC analysis showed that patients used twice the time to achieve one-third of the maximal force in knee extension. However, we did not observe any relationships between patients' force-generating ability and treatment-related factors such as tumour location distal or proximal to the knee, number of resected muscles, and reconstruction length. Regardless of such strength impairments, patients included in the present study still reported an average TESS score of 84, which is considered a good functional result.

Compared to controls, patients in the current study generated knee extension and -flexion maximum torques of 20% and 58%, respectively, which is similar to earlier reports [24]. Although we found somewhat larger strength deficits in patients with a distal femoral tumour location compared to the study by Bernthal et al. (2015) [17], our results are in line with patients with proximal tibia tumour location from this study, and to the patients included in the study by Tsau et al. (2006) [16]. In contrast to Bernthal et al. (2015) [17], we found no observed differences between patients with distal femur and proximal tibia tumours. Our cohort has a skewed sex distribution between the group of the tibia (7 men, 2 women) and femoral cases (1 man, 8 women). In addition, our results indicate that males had a greater torque-generating capacity than females. Consequently, this might have influenced the differences between tumour location and strength deficit.

We did not find any relationship between knee extension torque and the extent of quadriceps muscle resection in our study, which was reported earlier in patients with soft tissue sarcoma [18,19]. It is important to note that patients treated for soft tissue sarcoma do not undergo joint resection and megaprosthesis reconstruction. Thus, it is plausible that the prosthesis design impedes the force transfer across the knee joint. Future studies should consider internal joint leveller arms when evaluating muscle strength in patients with megaprosthesis.

Alternatively, our findings might have a more "global" explanation. Knee surgery for bone sarcoma involves resectioning a large proprioceptive joint, followed by severe pain and immobilisation. A consequence of the procedure might be a pronounced loss of neuromuscular function. The fact that short resections without detachment of the patellar tendon resulted in similar torque deficits as more extensive resections and similar knee extensor torque output in the distal femur and proximal tibia cases support this notion. However, we cannot rule out that the lack of association between the extent of muscle resection and knee extension peak torque observed in the present dataset is caused by high heterogeneity and low sample size.

Our measurement of the rate of force development revealed that patients in the present study used twice the time to reach peak force compared to age- and sex-matched controls. This is particularly concerning, considering patients could only generate one-third of the maximal force as their healthy counterparts. Moreover, this is a clinically important finding since a reduced rate of force development is an impairment likely to impact the ability to perform activities of daily living [21,22].

As a point of consideration for future studies, we found no differences between the non-operated leg and the matched controls. This validates using the non-operated leg as a control group and might mitigate the need for untreated controls. Hence, similar studies can be performed with simpler designs [25].

We excluded patients with walking aids or motor neuropathies to ensure good adherence to our assessments and to limit heterogeneous results without the statistical power to perform subgroup analysis. As a result, we might have selected a cohort at the upper end of the "functional spectrum", as walking aids or motor neuropathies are related to muscle strength deficiencies. Consequently, our study sample may not represent an unselected population of patients. Given the large deficits in muscle strength characteristics we observed within our study cohort, this is a critical perspective and raises questions about the external validity of our findings. Furthermore, although all patients received individualised rehabilitation programs and follow-ups by both physiotherapists at the clinic and in the municipalities, we have no data on the specific content or on patient adherence to their rehabilitation. Therefore, we cannot rule out that differences in rehabilitation content and patient adherence can explain some of the variations in our results. Finally, the patients were included in the study at different time points in relation to their diagnosis, which may also have contributed to the variation.

In summary, major muscle strength deficits were observed in our study cohort, having undergone megaprosthetic knee reconstruction for bone sarcoma. Specifically, patients achieved only 17% of the total work in knee extension and used twice the amount of time to achieve only one-third of the maximal force compared to age- and sex-matched controls.

Author contributions

All authors contributed to the study conception and design. MLJ and TSN obtained funding. Data collection and analysis were performed by MLJ, TSN, OE and TW. The first draft of the manuscript was written by MLJ, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2023.101944.

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