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Review Article

Prosthetic reconstruction following resection of lower extremity bone neoplasms: A systematic review and *meta*-analysis

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HIGHLIGHTS

- Prosthetics are the mainstay in surgery after resection of extremity bone tumors.
- For these patients gait parameters deteriorated compared to healthy individuals.
- Further refinement of surgical techniques is required.
- New rehabilitation strategies and follow-up programming are needed.

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ABSTRACT

Prosthetic reconstructive procedures have become the mainstay in contemporary surgical treatment following resection of extremity bone neoplasms. Given that these patients are of young age most of the time, achievement of robust functional outcomes is of paramount importance. The aim of this study is to assess the impact of this procedure on the gait parameters of cancer patients compared to healthy individuals. The Medline, Scopus and Cochrane databases were systematically searched until January 2022 for eligible studies. Gait parameters measured by gait analysis after prosthetic reconstruction were the outcomes of interest. Eight cohort studies were included in our analysis. From these, seven studied prosthetic reconstruction of the knee (distal femur or proximal tibia) and only one exclusively studied prostetic reconstructions of the proximal femur. Compared to healthy individuals a significant decrease was evident in gait velocity (-0.16 m/*sec*, 95 %CI: −0.23 to −0.09, p-value < 0.001), in stride length (-6.07 %height, 95 %CI: −9,36 to −2.78, p-value < 0.001), in cadence (-3.96 stride/min, 95 %CI: −5.41 to −2.51, p-value < 0.001) and significant increase in cycle time (0.10 s, 95 %CI: 0.03 to 0.17, p-value = 0.005). Prosthetic reconstruction following lower limb tumor resection significantly affects the gait of patients. This knowledge can be utilized for further refinement of surgical techniques, rehabilitation strategies and follow-up programming.

1. Introduction

The standard of surgical treatment for lower limb neoplasms had been characterized by mutilating techniques, leading to severe kinetic impairment of the patients [1]. The advent of neoadjuvant and adjuvant chemotherapy, as well as radiotherapy transformed the extremity tumor management, promoting limb salvage procedures as efficient treatment modalities regarding oncological control and survival benefit [2]. These scientific realizations, combined with constant dynamic evolution of imaging and surgical techniques, resulted in replacement of more than 80 % of amputations by limb sparing treatments, paving the way for more anthropocentric tumor management practices [3].

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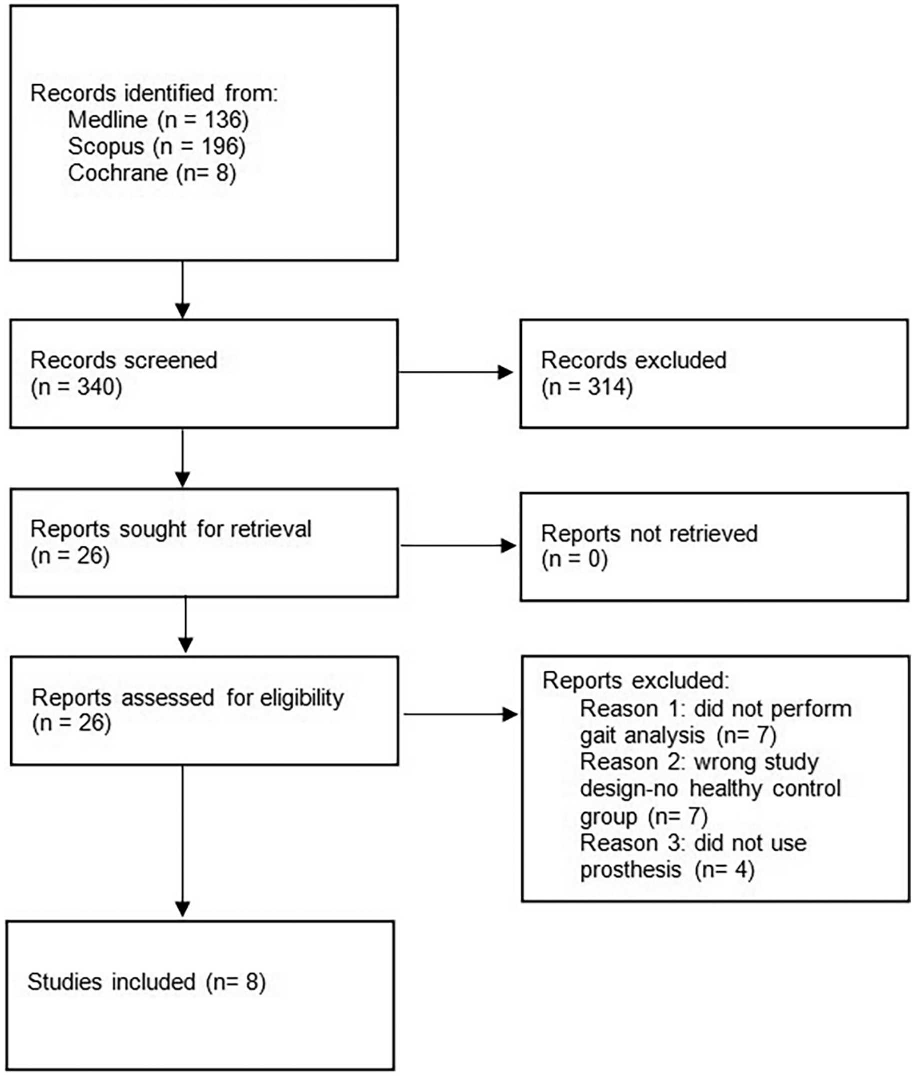


Fig. 1. Review flow chart.

It should be highlighted that the vast majority of patients with lower extremity neoplasms are diagnosed at a young age. This should be evident by the fact that bone sarcomas are the fourth most common tumor in individuals under the age of 25 [4]. Thus, it is essential to achieve durable long-term kinetic and kinematic outcomes, reassuring satisfactory quality-of-life for the patients, a term which entails both functional and psychological results. For this purpose, a plethora of reconstruction options have been invented and continuously being updated, such as: modular endoprosthetic reconstruction; bone graft reconstruction; bone transport; arthrodesis; and rotationplasty.

Prosthetic reconstructive procedures have become the mainstay in contemporary surgical treatment of extremity bone neoplasms [5]. The aim of this systematic review and *meta*-analysis is to assess the current standpoint of the prosthetic reconstructions following lower limb tumor resection in the research literature, to evaluate the effectiveness in terms of gait analysis of the procedure when compared to healthy individuals, as well as to attempt to provide approximate measures of the gait parameter changes after receiving the surgery, which will greatly benefit the pre-surgical clinician-patient interaction.

2. Materials and methods

2.1. Search strategy and study selection

We systematically searched Medline, Scopus and Cochrane databases until January 2022 without time restriction for studies of any duration and design that performed gait analysis in patients who received lower limb prosthetic reconstruction after tumor resection and compared their gait parameters with those of healthy individuals. The search algorithm contained: “gait”, “gait analysis”, “neoplasm*”, “tumor*”, “prosthesis”, “megaprosthesis”, “endoprosthesis”, “prosthetic reconstruction”, “prosth*”. This systematic review and *meta*-analysis was reported in accordance to the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) reporting guideline [6]. Details of the protocol for this systematic review were registered on PROSPERO (CRD42022314791).

Two independent invsestigators (PF, NF) screened the articles by title and abstract. Any study identified as having the potential to fulfill our inclusion criteria underwent full-text evaluation. If concurrence on eligibility was not reached between the two investigators, a third investigator (DV) was involved to evaluate the article. Database searches were supplemented by screening of the reference lists. The eligibility was defined by the PICO framework: Population (P): patients undergoing gait analysis; Intervention (I): patients with lower limb prosthetic

Table 1
Characteristics of the included studies.

Author	Year of publication	Study design	Intervention (n)	Healthy controls (n)	Age (mean)	Evaluation months after surgery (mean)	Tumor type	Location of tumor	Type of implant	Gait assessment
Kim	2021	retrospective	7	18	21	67	Osteosarcoma, Ewing's sarcoma	Distal femur, Proximal tibia	Modular endoprostheses	Eight-camera, three-dimensional motion analysis system with two Kristler force plates
Benedetti	2000		16	10	29	44	Osteogenic sarcoma, Malignant Fibrohistiocytoma, Fibrosarcoma	Distal Femur	Modularhinged cementless prosthesis (KMFTR)	Stereophotogrammetric system (Elite) and two Kristler force plates
Pesenti	2018	retrospective	6	15	25	97	Osteosarcoma,Ewing's sarcoma	Distal femur	Megaprosthesis with fixed hinge and cemented stem	Six HiRes infrared cameras registering the position of 15 retroflective markers and two force platforms
Okita	2013	cross-sectional	8	8	30	91	Osteosarcoma, giant cell tumor, chondrosarcoma	Distal femur, Proximal tibia	Kyocera Limb Salvage System, Howmedica Modular Resection System, Japan Medical Materials K-MAX KNEE System K-5	Seven-camera 3-dimensional motion analysis system (Vicon MX) with 2 Kristler force plates
Colangeli	2007		10	10	22	63		Proximal tibia	Howmedica KMFTR noncemented hinged megaprosthesis	Stereophotogrammetric system for kinematic variables (Elite) and two Kistler force plates
Benedetti	2013	retrospective	10	10	41	118	Osteoblastoma, osteogenic sarcoma, Ewing's sarcoma, giant cell tumor, condrosarcoma	Proximal femur	Modular prosthetic replacement Howmedica KMFTR	Stereophotogrammetric system (Elite)
Visser	2000	Case series	19	10	46	18		Knee and proximal femur	Distal femoral kneeprosthesis and proximal femoral or saddle prosthesis	Gait laboratory
Bernthal	2015	retrospective	22	8	37	158	Primary bone sarcoma	Proximal femur, Distal femur, Proximal tibia	Howmedica, Techmedica, or Stryker with rotating hinge knee components and cemented stems	Gait laboratory

Table 2
Risk of bias assessment.

Author,Year	Selection	Comparability	Outcome
Kim,2021	***		***
Benedetti,2000	***		***
Pesenti, 2018	***		***
Okita,2013	***	*	***
Colangeli,2007	***	*	***
Benedetti,2013	***		***
Visser,2000	***	*	***
Bernthal,2015	***		***

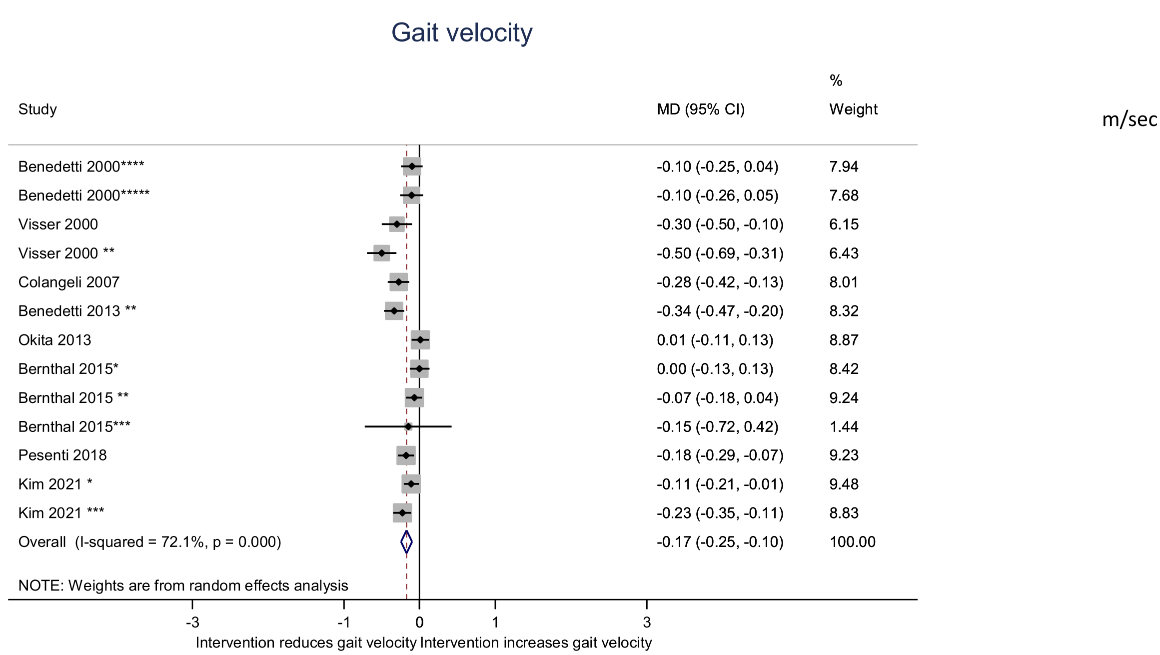
reconstruction after tumor resection; Comparison (C): gait analysis of healthy individuals; Outcomes (O): differences of the gait parameters between the two groups. Studies with patient population receiving prosthetic reconstruction for reasons other than lower limb tumor resectio or not performing gait analysis or not containing a healthy control group or gait parameters were not accessible and studies that were not in English, were excluded. The outcomes of interest for our research were the spatiotemporal gait parameters: gait velocity, stride length, gait cycle duration, swing duration, stance duration and cadence. Gait velocity is the time required for a person to traverse a specific distance in the direction of walking. Stride length is measured as the distance covered between two successive contacts of the same foot with the floor and is normally equal to the distance travelled by performing two consecutive steps. The gait cycle consists of the stance phase, when the foot is in contact with the floor, and the swing phase, when the foot is swinging without touching the floor. Finally, cadence refers to the walking rate and is calculated in steps per minute [7].

2.2. Data extraction

The data extraction was performed by two authors (PF,DD) who filled in a pre-piloted extraction from independently. Any disagreement was resolved by consensus. Records of the same trial reporting at different follow-ups were considered a single trial. In case of double reporting data, data from the most-informative publication and highest level of evidence were used. The data exctraction sheet included: first author, year of publication, study design, number of participants (overall and by group), age, BMI, weight, height, type of lower limb tumor, tumor location (hip, knee, ankle), type of surgery and type of prosthetic implant, gait analysis system used, gait velocity (m/s or cm/s), stride length (2 consecutive steps in cm or percentage of height), cycle duration (seconds), swing duration (seconds), stance duration (seconds) and cadence (steps/minute).

2.3. Quantitative synthesis, analysis and risk of bias

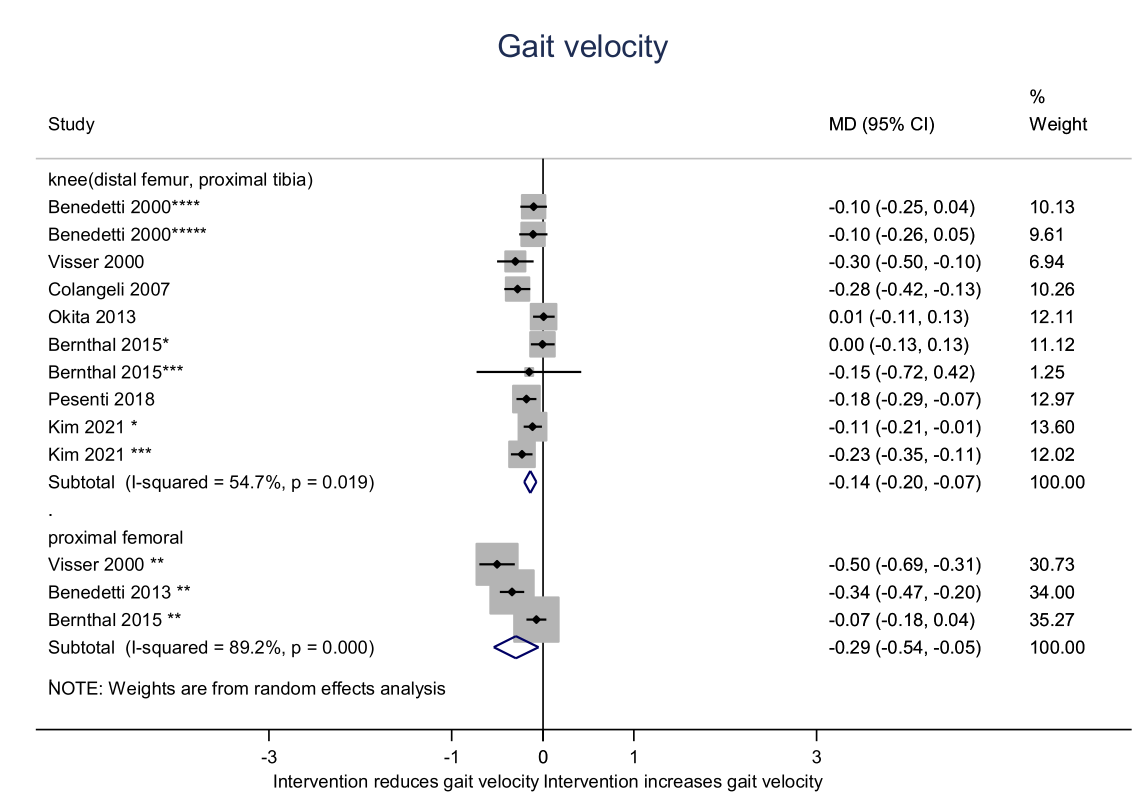
Summary mean differences were calculated, along with the corresponding 95 % CI, by pooling the study specific estimates using random-effects models [8]. The presence of heterogeneity was estimated with the Cochran's Q statistic and it was quantified with I^2 [9]. We further assessed the possible small study effects (an indication of publication bias) by visual inspection of funnel plots and Egger's test [10]. All analyses were performed using Stata (version 14; StataCorp, College Station, TX, USA). Risk of bias was assessed using the Newcastle- Ottawa quality assessment scale [11].



*distal femoral replacements
**proximal femoral replacements
***proximal tibia replacements

Benedetti 2000
****Group 1 consisted of patients who had removal of the vastus medialis and the vastus intermedius and who had removal of the vastus medialis only (medial approach)
*****Group 2 consisted of patients who had removal of the vastus lateralis and the vastus intermedius (lateral approach)

Fig. 2. Forest plot of gait velocity (meter/second) for knee (distal femur/proximal tibia) and proximal femoral reconstructions overall. Benedetti 2000 is marked and used twice due to two different surgical approaches. Kim 2021 is marked and used twice because distal femoral and proximal tibia were studies seperately. Visser 2000, Benedetti 2013 and Bertnthal 2015 are marked to indicate that they studied the proximal femoral reconstructions.



*distal femoral replacements
**proximal femoral replacements
***proximal tibia replacements

Benedetti 2000
****Group 1 consisted of patients who had removal of the vastus medialis and the vastus intermedius and who had removal of the vastus medialis only (medial approach)
*****Group 2 consisted of patients who had removal of the vastus lateralis and the vastus intermedius (lateral approach)

Fig. 3. Forest plot of gait velocity (meter/second) for knee (distal femur/proximal tibia) and proximal femoral reconstructions with subgroup analysis. Benedetti 2000 is marked and used twice due to two different surgical approaches. Kim 2021 is marked and used twice because distal femoral and proximal tibia were studies seperately. Visser 2000, Benedetti 2013 and Bertnthal 2015 are marked to indicate that they studied the proximal femoral reconstructions.

3. Results

3.1. Study selection and population characteristics

The systematic search of the electronic databases (Medline, Scopus and Cochrane) identified a total of 340 studies, 26 of which were selected for full text screening. Eight studies were considered eligible for data extraction and *meta*-analysis according to our criteria of eligibility [12–19]. Fig. 1 shows the flow chart of the study selection process. Table 1 presents the charachteristics of the included studies. The majority of the studies were published at the last decade and were retrospective. Seven of the studies consisted of knee prosthetic reconstructions (distal femur and/or proximal tibia), while three of the 8 studies included proximal femoral reconstructions. The overall population of the studies was 187, 98 cancer patients which were of young age as expected and 89 healthy controls. The gait evaluation took place several years after the surgery (range 18–158 months). The study of Kim et al. [12] consisted of two group comparisons, one for distal femoral and one for proximal tibia reconstruction, and both of these comparisons are taken into consideration for the analysis. Similarly, the study of Benedetti et al. (2000) [18] also consisted of two comparisons, one for lateral and one for medial approach, which are both included seperately in the analysis. Risk of bias assesment is presented in Table 2.

3.2. Study outcomes

All included studies provided information for a variety of outcomes. We were able to obtain adequate data to proceed with a quantitative synthesis for Gait velocity, stride length, cycle time, stance time and candence. 8 studies with a total of 249 participants reported results on Gait velocity. Overall, prosthetic reconstructions statistically significantly reduced the Gait velocity by a summary mean difference of -0.17 m/*sec* (95 % CI: -0.25, -0.10; $p < 0.001$; $I^2 = 72.1$ %) (Fig. 2). Subgroup analysis, regarding knee and proximal femoral, reveals that prosthetic reconstructions statistically significant reduces gait velocity by -0.12 m/*sec* (95 % CI: -0.19, -0.05; $p < 0.001$; $I^2 = 52.7$ %, N = 7 studies) in case of knee. No statitically significant differences observed in case of proximal femoral (Fig. 3). No evidence of small study effects was observed, as Egger's test was not statistically significant ($p = 0.249$) (Fig. 4). 4 studies with a total of 96 participants reported results on stride length. Overall, prosthetic reconstructions statistically significantly reduced stride length, measured as % of height, by a summary mean difference of -6.95 % (95 % CI: -9.84, -4.06; $p < 0.001$; $I^2 = 0$ %) (Fig. 5a). When study of Benedetti et al., 2013 [16] that included patients with proximal femoral replacements, removed from the analysis the results did not differentiate significantly (summary mean difference of -6.07 %; 95 % CI: -9.36, -2.78; $p < 0.001$; $I^2 = 0$ %) (Fig. 5b). Three studies with a total of 95 participants reported results on cycle time. Overall, prosthetic reconstructions statistically significantly increased

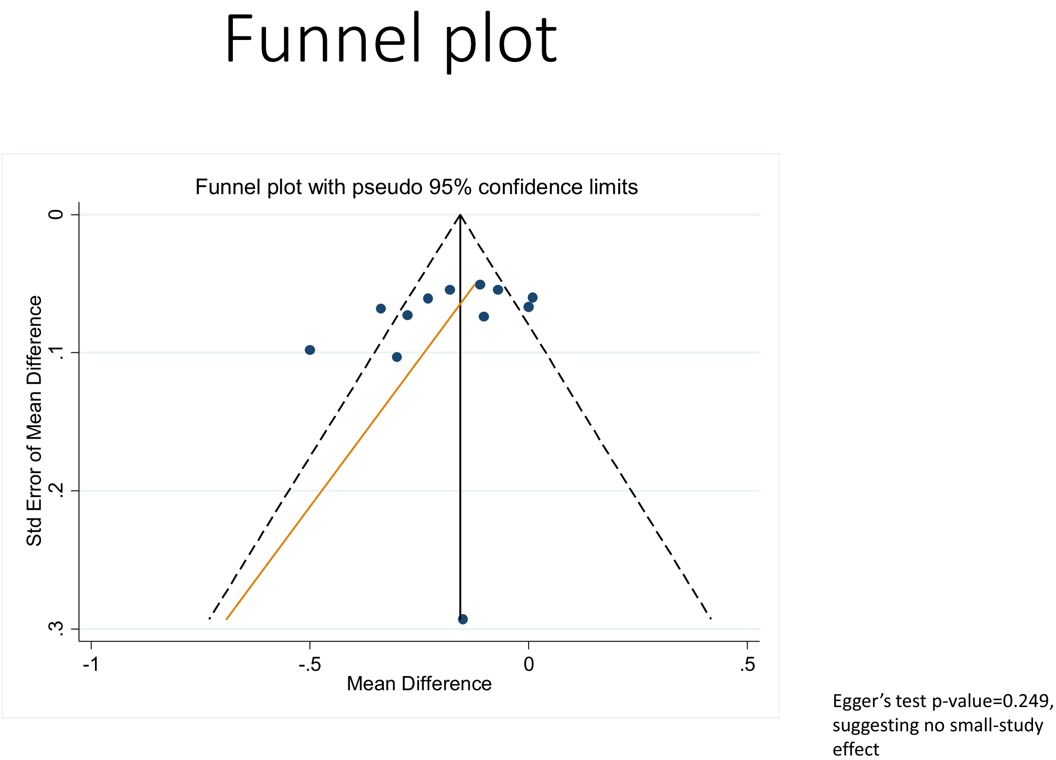


Fig. 4. Funnel plot (Egger's test).

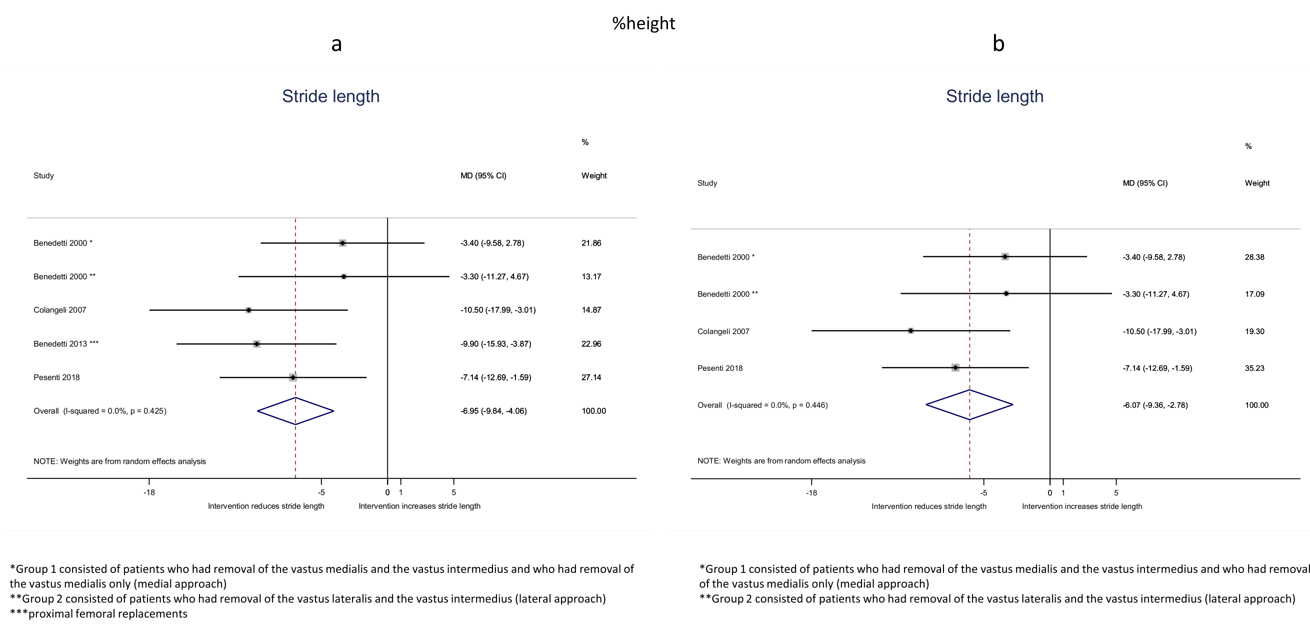


Fig. 5. Forest plot of stride length (%height) overall (5a) and for knee prosthetic reconstruction (5b). Benedetti 2000 is marked and used twice due to two different surgical approaches. Benedetti 2013 is marked to indicate that they studied the proximal femoral reconstructions.

cycle time, by a summary mean difference of 0.11 *sec* (95 % CI: 0.03, 0.19; $p = 0.005$; $I^2 = 54.5$ %) (Fig. 6a). When we excluded from the analysis the group of participants with proximal femoral replacements from Visser et. al, 2000 study [19] the results did not differentiate; prosthetic reconstructions statistically significant increased cycle time, by a summary mean difference of 0.10 *sec* (95 % CI: 0.03, 0.17; $p = 0.005$; $I^2 = 53.6$ %) (Fig. 6b).

5 studies with a total of 167 participants reported results on stance time. Overall, prosthetic reconstructions had a non-signifcant effect on stance time, measured as % of cycle (Fig. 7a). When we excluded from the analysis the group of participants with proximal femoral replacements from Visser et. al, 2000 study [19] and the study of Benedetti et al., 2013 [16] the results did not differentiate significantly (Fig. 7b). Four studies with a total of 110 participants reported results on cadence. Overall, prosthetic reconstructions statistically significantly reduced cadence, measured as stride/min, by a summary mean difference of −4.65 stride/min (95 % CI: −6.42, −2.87; $p < 0.001$; $I^2 = 40.4$ %) (Fig. 8a). When we excluded from the analysis the group of participants with proximal femoral replacements from the study of Benedetti et al., 2013 [16] prosthetic reconstructions statistically significantly reduced

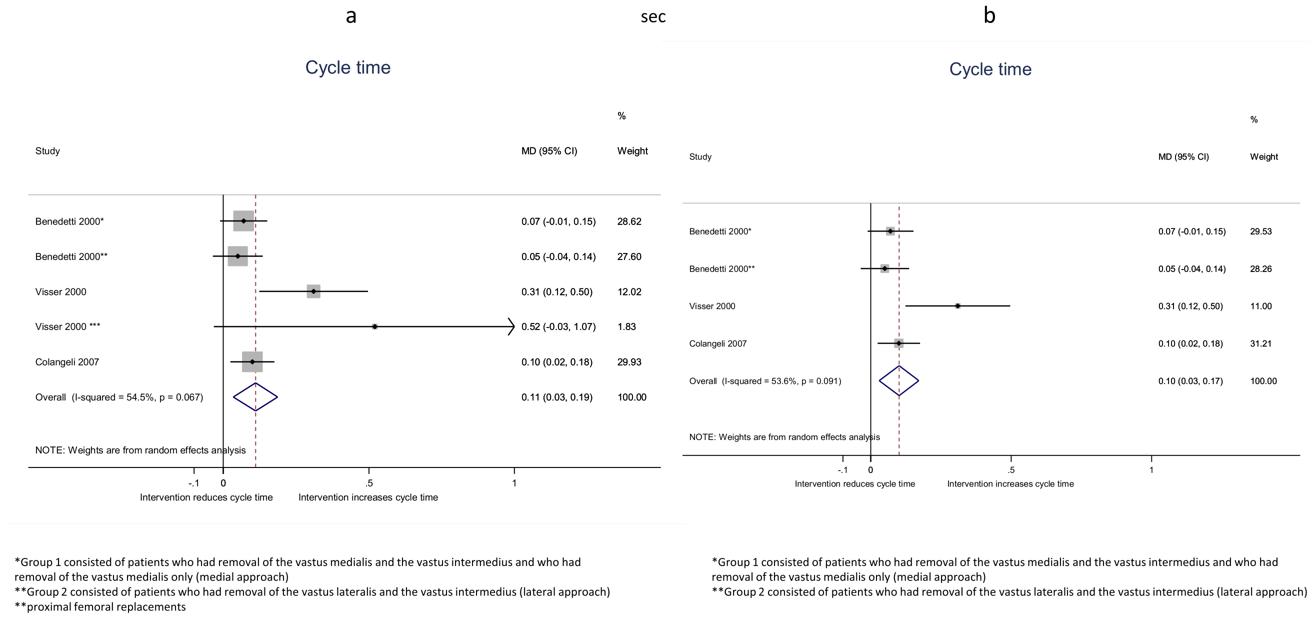


Fig. 6. Forest plot of cycle time (seconds) overall (6a) and for knee prosthetic reconstruction (6b). Benedetti 2000 is marked and used twice due to two different surgical approaches. Visser 2000 is marked to indicate that they studied the proximal femoral reconstructions.

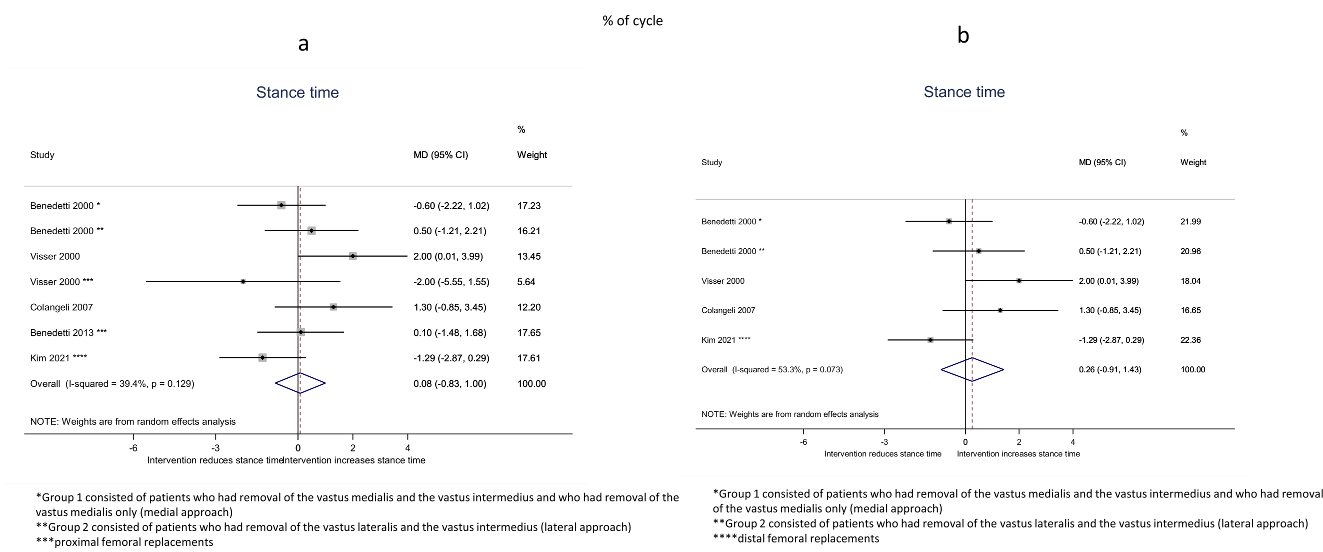


Fig. 7. Forest plost of stance time (% of cycle) overall (7a) and for knee prosthetic reconstruction (7b). Benedetti 2000 is marked and used twice due to two different surgical approaches. Kim 2021 is marked because it consists of the distal femoral group of the study. Visser 2000 and Benedetti 2013 are marked to indicate that they studied the proximal femoral reconstructions.

cadence, measured as stride/min, by a summary mean difference of −3.29 stride/min (95 % CI: −4.93, −1.64; $p < 0.001$; $I^2 = 0$ %) (Fig. 8b).

4. Discussion

To our knowledge, this is the first study that aimed to present the effects of lower limb prosthetic reconstruction on the gait of cancer patients, driven from comprehensive analysis of the current published data. Our results indicate that prosthetic reconstruction following lower limb tumor resection significantly reduces all the gait parameters measured by gait analysis of the patients. However, while critically appraising these results it is essential to always note the dinstinction of the terms statistically significant and clinically significant. The interpretention of the data from a clinical standpoint does not reveal a major clinically important difference and a comfortable gait speed (above 0.6 m/s) was achieved post reconstruction in every study [20].

The fact that only the percentage of stance time, and therefore of swing time, of the gait cycle was the only analyzed gait parameter that did not significantly differ with the control group shows that in patients with prosthetic reconstructions both stance and swing time were affected uniformly. As for double support time, most of the authors did not give any results, except the study of De Visser et al.[19] According to the authors all the patients presented a shortening of the stance phase of the affected leg compared to the non-affected leg, as well as a longer stance phase of the non-affected leg in patients when compared to the controls. For the double-limb support time, they found slightly elevated values for the patient groups (mean 14 %, SD: 3), but no significant difference with the controls (mean 11 %, SD 1). However, Colangeli et al.[17] reported that a significantly prolonged stance time was observed on the contralateral side. This presumably could be explained

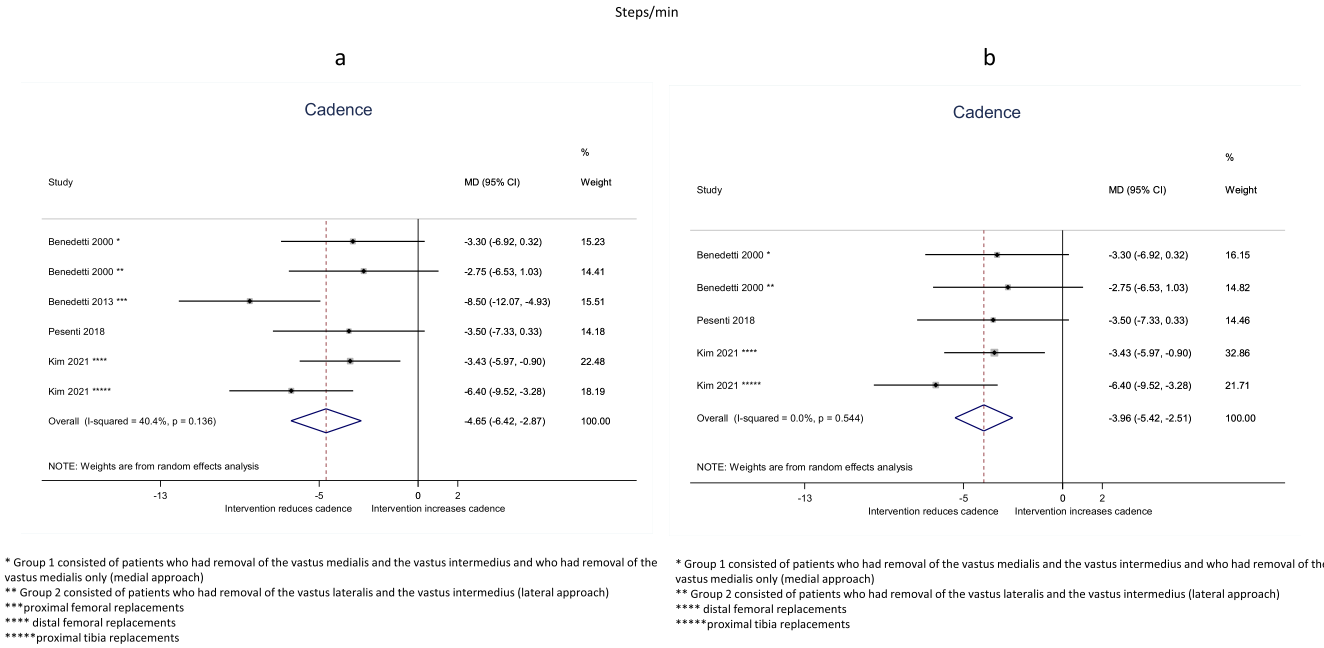


Fig. 8. Forest plot of cadence (steps/min) overall (8a) and for knee prosthetic reconstruction (8b). Benedetti 2000 is marked and used twice due to two different surgical approaches. Kim 2021 is marked and used twice because distal femoral and proximal tibia were studies seperately. Benedetti 2013 is marked to indicate that they studied the proximal femoral reconstructions.

as taking over part of the loading function of the affected leg. The non-affected leg had to provide support, which lasted long enough to allow the swing to be made by the fast leg. In agreement with the present study, the data of Dietz et al. showed that in limping, the duration of the swing phase was quite flexible [21].

The included studies of this *meta*-analysis were divided in two subgroups, the proximal femoral reconstruction group and the knee reconstruction group. The results between the two groups were similar and when the overall estimate was calculated, it was not different compared to the two groups in a statistically significant manner. The knee subgroup consisted of reconstruction in the distal femur or the proximal tibia or both. Interestingly, only the Kim et al study attempted to compare kinematic outcomes according to tumor location [12]. The authors showed that there are differences in gait between the distal femur and proximal tibia groups, one of them being that the proximal tibia group maintained a flexed hip during the entire gait cycle compared with the distal femur group. The better functional outcome of the distal femur has been reported in another study, and could be explained by the need for reconstruction of the extensor mechanism that accompanies the proximal tibial resection [22]. As far as proximal femur reconstructions are concerned, it is essential to highlight that the procedure should be complemented by abductor mechanism reconstruction, when feasible, in order to avoid limbing, instability and pain [23].

The continuous research progress has led to the evolution of not only surgical procedures, but also of measuring and monitoring techniques. The increasing use of modern measurement methods, such as gait analysis, has enabled the more accurate depiction of results [24]. The affected muscles and the extent of the tumor can vary, depending on tumor location, which can affect gait function [25]. Also, any imbalance observed between the pathological and the non-affected lower extremity can lead to differences in gait parameters [15]. Finally, in cases where a comparison is made between a pathological and the opposite lower extremity, it should be considered that both of them have been affected in gait parameters, as the non affected extremity compensates the impairment of the affected one. However, the above does not apply to healthy people participating in a control group.

The kinematic potency of the patients should not be the only long-term outcome of interest. As in every surgical procedure, possible complications could seriously affect the quality of life of the patients, as well as endanger their well-being. Thus, a long postoperative follow-up is crucial. Some of the most common complications following prosthetic reconstruction are aseptic loosening (3 %), deep infection (10 %), soft tissue failure (6 %), structural failure (7 %), periprosthetic fracture (2 %), wound healing disorders (8 %), joint instability (1 %), local recurrences (4.5 %), peroneal nerve palsy (3 %) and mechanical dysfunctions (17 %) [26–28].

Limitations of our study were the small patient sample which was accompanied by high heterogeneity between the studies. However, this is inevitable due to the number of patients who undergo these operations and at the same time are evaluated with modern techniques. Moreover, borderline insufficient follow-up durations, like the one noticed in the De Visser et al. study (12 to 24 months) [19], may produce misleading results, since in this type of surgery functional improvement of the patients can be observed one year postoperatively or more. In the same study of De Visser [19], a subpopulation of the patients that underwent hip surgery received saddle prosthesis, indicating pelvic reconstruction and thus making the patient sample more heterogeneous. The limited amount of available gait analysis data has been another bottleneck of our study. Our analysis consisted only from gait velocity, stride length, cycle time, stance time and cadence. Analyses regarding a plethora of other kinematic parameters, such as knee range of motion, knee moment, knee flexion and knee power could and should be feasible in the future, in order to achieve a more robust overview on this research topic. Furthermore, as more studies on this subject are published, separate analyses for proximal femur, distal femur, proximal tibia and the ankle could reveal interesting information. An important advantage of our study was the detailed statistical analysis with outlier study exclusion to investigate possible change of results.

5. Conclusion

In conclusion, prosthetic reconstruction after surgical removal of lower limb tumours affects the gait parameters of the patients as it was expected. These results do not intend to demote the clear transformative benefits that prosthetic reconstruction has brought in the scenery of orthopaedic oncology, but are indicative of the potential room for improvement regarding the surgical techniques, as well as the rehabilitation strategies following the surgery. Nonetheless, our study provides essential clinical information which would be able to accommodate more substantial pre-surgical patient briefing, meliorating the patient-clinician interaction. Multicenter, well-designed trials, with high patient accrual are needed to provide conclusive and adequate statistically powerful evidence.

6. The role of the funder

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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