Safety and Performance of Bone-Anchored Prostheses in Persons with a Transfemoral Amputation

A 5-Year Follow-up Study

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Background: For almost 30 years, bone-anchored prostheses have offered an alternative solution to prosthetic sockets by attaching the artificial limb directly to the femoral residuum by means of an osseointegration implant. Osseointegration implant surgery was introduced in our center in 2009. The aim of the present study is to report on safety, prosthesis-wearing time, and health-related quality-of-life (HRQoL) for patients with femoral bone-anchored prostheses during a 5-year follow-up period.

Methods: All patients who underwent implantation of a press-fit osseointegration implant between May 2009 and November 2013 were eligible for the present study. Implantation was performed in 2 stages. Adverse events included infectious complications (grade 1 to 4), aseptic loosening, breakage, stoma-redundant tissue, and stoma hypergranulation. Prosthesis-wearing time and HRQoL were measured with the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) prosthetic use score and global score, respectively.

Results: Thirty-nine of 42 eligible patients were included. Thirty patients (77%) presented with some kind of infection (156 events in total), with 148 (95%) events being classified as grade 1 or 2 and 8 events (5%) being classified as grade 3; the latter 8 events occurred in 4 patients. There were no instances of septic loosening. The intramedullary stem of the osseointegration implant broke in 2 patients. In total, soft-tissue refashioning had to be done 30 times in 14 patients. The Q-TFA median prosthetic use and global scores improved significantly from 71 to 100 and from 33 to 75, respectively ($p < 0.001$).

Conclusions: Despite the adverse events, patient prosthetic use and HRQoL improved significantly. Grade-1 and 2 infections were frequent but could mostly be treated with nonoperative measures. Most infections seemed to occur in the first 2 years and did not lead to deep infections. Two broken intramedullary stems were revised successfully. Current developments focus on reduction of infectious complications and prevention of osseointegration implant breakage.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Performance of the prosthetic socket is often reported as unsatisfactory in patients with a lower-extremity amputation despite various developments in prosthetic socket technology[1]. Common socket-related problems include pain, blisters, skin infections, eczema, unpleasant smell, instability, back problems, pain in the sacroiliac joint, loss of the prosthesis, and time-consuming donning and doffing of the prosthesis[2-4].

Since 1990, an alternative solution has been available, offering direct attachment of the prosthetic parts to the femur (bone-anchored prosthesis) and connection to an osseointegration implant[5]. The advantage of an osseointegration implant is that it provides a direct skeletal attachment for the artificial leg[5]. This solution results in more physiological and stable prosthetic control, osseoperception, improved walking and sitting conditions, and elimination of the socket-stump interface with all of its related problems[6-9]. Four CE (Conformitè Europëenne)-certified osseointegration implants are commercially available: the Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA; Integrum), the Integral Leg Prosthesis (ILP; Orthodynamics), the Osseointegrated Prosthetic Limb (OPL; Permedica), and the Osseointegrated

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Femur Prosthesis (OFP; OTN Implant BV). All of these osseointegration implants are press-fit implants, except for the OPRA, which is a screw-type implant.

Multiple studies investigating safety and quality of life (QoL) in individuals with transfemoral amputation have indicated a low frequency of osteitis (inflammation of bone) and/or septic loosening[7-21]. Soft-tissue infections have been seen frequently, although with significant increases in QoL and functional outcomes. Those studies presented either a short follow-up period of ≤2 years[8,9,11], had no fixed follow-up period[12,13,18,20], and/or involved the use of a screw osseointegration implant[17,19,21]. We believe that we are the first to report on the safety, prosthesis-wearing time, and health-related QoL (HRQoL) of a cohort of patients who were followed for 5 years after implantation of a press-fit osseointegration implant.

Materials and Methods

The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational cohort studies were used for the present study.

Study Design

The present study was a single-center retrospective cohort study with 5-year follow-up. One-year and minimum 2-year follow-up results for this sub-cohort were published earlier[9,12].

Participants

All individuals who underwent osseointegration implant surgery at the Radboud University Medical Center between May 2009 and November 2013 were included, and informed consent was obtained. All individuals were registered in a web-based database (Castor EDC). The present study was approved by the institutional Ethics Committee (2017-3769). Patients were eligible for a bone-anchored prosthesis if they were experiencing irreversible socket-related problems and/or had difficulties using their socket-suspended prosthesis according to the patient-reported Questionnaire for Persons with a Transfemoral Amputation (Q-TFA)[22] and as assessed by our multidisciplinary outpatient team consisting of a surgeon, rehabilitation physician, physiotherapist, and prosthetist. The exclusion criteria for the use of a bone-anchored prosthesis were diabetes, peripheral vascular disease, exposure of the amputated limb to radiation, ongoing chemotherapy, an immature skeleton, mental illness, and the inability to comply with the rehabilitation protocol[12].

Surgical Technique

A press-fit cobalt-chromium-molybdenum osseointegration implant (ILP) with an approximately 1.5-mm microporous tripod coating was used, with a 2-stage surgical approach (Fig. 1). Stage 1 included any shortening of the femoral residuum at the calculated level, if applicable, combined with soft-tissue preparation; identification of the sciatic nerve stump and excision of neuroma, if applicable; release of any tethering tissue; reaming of the medullary canal; press-fit implantation of the intramedullary stem; and mounting of a temporary cannulated endcap with final closure of the stump.

Stage 2 was performed about 6 to 8 weeks later. A guidewire was used to localize the center of the cannulated endcap. A coring device was then passed over the guidewire, perforating the skin and subcutaneous tissue to create the so-called stoma. After removal of the endcap, a dual-cone adaptor of appropriate length was inserted into the intramedullary stem and was secured with an internal locking screw. This dual-cone adapter has a weak point, which acts as a safety system (Fig. 1). Specifically, the weak point breaks when high rotational forces are at work so that these forces will not be transmitted into the osseointegration implant.

Rehabilitation Protocol

Rehabilitation[23] started 2 weeks after the stage-2 procedure with loading on a short prosthesis. After 2 weeks, loading was continued with a full-length prosthesis. Weight-bearing was gradually increased, depending on pain. The use of walking aids was phased out on the basis of gait analysis for the evaluation of gait asymmetry. If gait asymmetry permanently increased after the use of walking aids had been phased out, we advised the patients to continue the use of walking aids. Furthermore, walking with different speeds, on uneven surfaces, and on slopes was practiced. Patients attended group rehabilitation sessions twice a week; each session was 2 hours. In total, the duration of the predefined rehabilitation program was 13 weeks.

Study Procedure

All radiographs that were made during follow-up and all clinical data were retrospectively retrieved by 3 researchers (D.R., R.A., J.M.) from the patient records at our center and were registered in a certified cloud-based Electronic Data Capture platform (Castor EDC). In addition, the patients' general practitioners were approached to review the medical records for bone-anchored prosthesis-related problems in order to gain as full insight as possible into all adverse events within the 5-year follow-up. The descriptive notes of the patients' general practitioners were used to rank the adverse events.

Patients filled in the Q-TFA preoperatively and postoperatively. As mailing of postoperative questionnaires was not automated at the beginning of the study period, some postoperative Q-TFA scores were not obtained at exactly 5 years postoperatively. All available preoperative Q-TFAs and all

Fig. 1

Illustration of the osseointegration implant, including the intramedullary stem (1), the dual-cone adaptor (3), and the weak point as indicated by the arrow (2).

postoperative Q-TFAs completed 4 to 7 years after the procedure were eligible for inclusion.

Study Outcomes

We focused on safety-related outcomes, including infections, aseptic loosening, osseointegration implant breakage, and stoma-redundant tissue (soft-tissue surplus around transcutaneous connection). Additionally, stoma hypergranulation (hypergranulation tissue at the transcutaneous opening) was registered (Fig. 2). Infections were classified with use of the system of Al Muderis et al.[12] (Table I) and were graded on the basis of clinical findings, conventional radiographic findings (on radiographs made during follow-up or as indicated), and treatments given as described in the electronic patient records. If an infectious event was not treated with antibiotics or surgery (e.g., syringing the stoma), it was classified as grade 1 to 3 without subdivision. Every new contact with a new kind of adverse event was counted as a new event. Prosthesis-wearing time was determined with use of the Q-TFA prosthetic use score (0 to 100 points; calculated as the product of hours per day and days worn divided by a given factor) and HRQoL was determined with use of the Q-TFA global score (0 to 100 points; calculated as the sum of scores divided by given factor)[22]. Higher Q-TFA prosthetic use and global scores represent a longer prosthesis-wearing time and a higher HRQoL, respectively.

Data Analysis

Descriptive statistics were used for participant demographic characteristics and safety-related outcomes. Changes over time in terms of prosthesis-wearing time and HRQoL were analyzed in a complete-case analysis with the Wilcoxon signed-rank test. The level of significance was set at $p < 0.05$. Categorical data were presented as exact numbers, and percentages were calculated for the various levels within a categorical variable. For continuous data, normally distributed data were presented as means and standard deviations and non-normally distributed data were presented as medians with 25th and 75th percentiles.

Results

Participant Characteristics

Thirty-nine of 42 eligible patients were included (Table II). Three patients were lost to follow-up; 2 patients did not provide written informed consent, and 1 patient died (Fig. 3).

Two of the 39 patients requested removal of the osseointegration implant because of persistent pain. The outer part of the intramedullary stem was removed and the stoma was closed, 24 and 26 months after the initial osseointegration implant surgery, in order to allow for the use of a socket prosthesis again. All safety outcomes for these 2 patients were included in the analysis. During the 5-year follow-up, no infectious events occurred after closure of the stump, despite the fact that the proximal part of the osseointegration implant was still in situ. At the 5-year follow-up, 1 of these patients was wheelchair-bound and the other was mobile with a socket prosthesis again. For both patients, this level of functioning conformed to that prior to the osseointegration implant surgery.

Safety-Related Outcomes

Nine (23%) of the 39 patients had an uneventful follow-up period, resulting in a complication rate of 77%. All safety-related outcomes are summarized in Table III.

Infection

During the follow-up period, 30 patients (77%) presented with a total of 156 infection-related events. Of these, 148 events (95%) were classified as grade 1 or 2 and 8 events (5%) were classified as grade 3; the latter 8 events occurred in in 4 patients. No grade-4 infections occurred during the follow-up period. If an infectious complication had to be treated surgically, infected tissue was removed and possible abscesses were drained.

Seventy-nine (53%) of the 148 grade-1 and 2 infections occurred in the first 2 years of follow-up, and 33 (22%) occurred in the first year of follow-up. Six (75%) of the 8 grade-

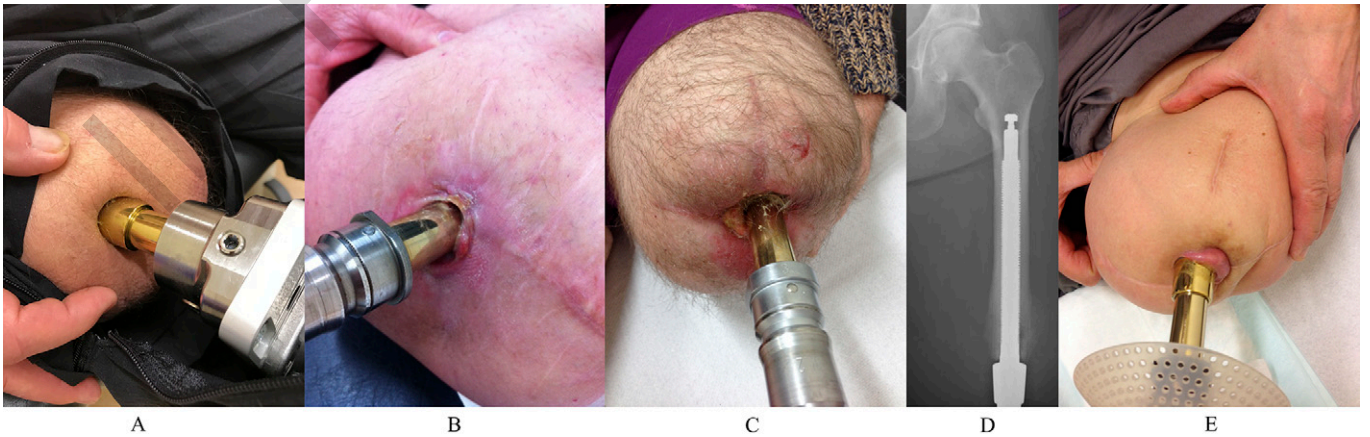

Fig. 2

Fig. 2-A Normal stoma. **Fig. 2-B** Grade-1 infection. **Fig. 2-C** Grade-2 infection with some purulent discharge. **Fig. 2-D** Radiograph showing a grade-3 infection, with distal osteitis. **Fig. 2-E** Stoma hypergranulation.

TABLE I Classification of Infections[12]*

Level of Severity	Symptoms and Signs, Treatment
Low-grade soft-tissue infection	Cellulitis with signs of inflammation (redness, swelling, warmth, stinging pain, pain that increases on loading, tense)
Grade 1	No antibiotic or surgical treatment
Grade 1A	Oral antibiotics
Grade 1B	Parenteral antibiotics
Grade 1C	Surgical intervention
High-grade soft-tissue infection	Pus collection, purulent discharge, raised level of C-reactive protein
Grade 2	No antibiotic or surgical treatment
Grade 2A	Oral antibiotics
Grade 2B	Parenteral antibiotics
Grade 2C	Surgical intervention
Bone infection	Radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum)
Grade 3	No antibiotic or surgical treatment
Grade 3A	Oral antibiotics
Grade 3B	Parenteral antibiotics
Grade 3C	Surgical intervention
Implant failure	Radiographic evidence of loosening
Grade 4	Parenteral antibiotics, explantation

*Patients showing signs of grade-1 to 3 infections who did not receive antibiotic or surgical treatment (e.g., those who received other treatment such as better stoma hygiene) were classified as grade 1 to 3 without subdivision into A to C. (Reproduced, with modification, from: Al Muderis M, Khemka A, Lord SJ, Van de Meent H, Frölke JP. Safety of osseointegrated implants for transfemoral amputees: a two-center prospective cohort study. J Bone Joint Surg Am. 2016 Jun 1;98[11]:900-9.)

3 events occurred in the first 2 years, and 2 (25%) occurred in the first year of follow-up.

Zero to 1 infectious event occurred in 13 individuals, 2 to 3 events occurred in 10 individuals, and >3 events (range, 4 to 20 events) occurred in 16 individuals. Fifty-seven infectious complications occurred in 4 individuals (representing 37% of all infectious events and 10% of all individuals).

Aseptic Loosening

One patient had radiographic evidence of aseptic loosening of the osseointegration implant (i.e., a radiolucent line) at the 1-year follow-up. The patient was asymptomatic and therefore was managed with observation. No signs of septic loosening or progression were seen on later follow-up.

Osseointegration Implant Breakage

The intramedullary stem broke in 2 patients 57 and 48 months after implantation. In both cases, breakage occurred at the level of the junction between the end of the tripod coating and the head of the stem. Both patients underwent successful implant revision with a larger-diameter titanium implant (OPL; Permedica). Twenty-one dual-cone adaptors broke in 19 patients; 18 breakages occurred at the weak point, and 3 breakages occurred at the distal part of the taper. One dual-cone adaptor with distal taper breakage was replaced during a 1-day admission, and the rest of the dual-cone adaptor revisions were done in an outpatient clinic.

Stoma-Redundant Tissue

Soft-tissue refashioning had to be done 30 times in 14 patients because of soft-tissue irritation. One patient underwent 9 of the 30 refashioning procedures.

Stoma Hypergranulation

Eight patients showed hypergranulation tissue at the level of the stoma, with 13 events requiring local excision or treatment with silver nitrate.

Prosthesis-Wearing Time and HRQoL

The prosthesis-wearing time (Q-TFA prosthetic use score) and HRQoL (Q-TFA global score) were analyzed for 34 and 33 patients, respectively. The remaining patients had incomplete data because the patient had forgotten to fill in the preoperative global score (1 patient), the full preoperative Q-TFA score was missing (2 patients), or the full postoperative Q-TFA score was missing (3 patients, including the 2 previously mentioned patients who had had implant removal because of persistent pain) (Fig. 3). Follow-up data were derived at a median of 62 months (25th percentile, 58 months; 75th percentile, 64 months) (range, 52 to 77 months) postoperatively.

The median prosthetic use score increased significantly from 71 (25th percentile, 20; 75th percentile, 90) at baseline to 100 (25th percentile, 90; 75th percentile, 100) at the time of follow-up ($p < 0.001$).

TABLE II Participant Characteristics

No. of participants	39
Male sex *(no. of patients)*	30 (77%)
Age at inclusion* *(yr)*	48.7 ± 13.9 (22-80)
Age at primary amputation† *(yr)*	26 (21, 41) (13-69)
Time between primary amputation and inclusion† *(yr)*	12 (5, 33) (1-52)
Smoking *(no. of patients)*	
Yes	6 (15%)
No	32 (82%)
Missing	1 (3%)
BMI* *(kg/m²)*	26.2 ± 4.0 (19.4-40.2)
Amputation side *(no. of patients)*	
Unilateral	38 (97%)
Bilateral	1 (3%)
Cause of primary amputation *(no. of patients)*	
Trauma	29 (74%)
Tumor	6 (15%)
Infection	3 (8%)
Other (compartment syndrome)	1 (3%)

*The values are given as the mean and the standard deviation, with the range in parentheses. BMI = body mass index. †The values are given as the median and the 25th to 75th percentiles, with the range in parentheses.

The median global score improved significantly from 33 (25th percentile, 21; 75th percentile, 50) to 75 (25th percentile, 58; 75th percentile, 83) ($p < 0.001$). Changes over time are shown in Figure 4.

Discussion

The present study demonstrated that prosthesis-wearing time and HRQoL improved significantly in association with the use of a bone-anchored prosthesis. Soft-tissue infections were common complications in this cohort of patients. Most infections could be treated with nonoperative measures. Deep infections did not occur during the 5 years of follow-up, although 2 implants were removed because of pain without signs of infection during the follow-up period. Two patients with osseointegration implant breakage were revised successfully.

During the 5-year follow-up, low-grade and high-grade soft-tissue infections were the most common adverse events in individuals with a transfemoral osseointegration implant; this finding is consistent with those in the short-term follow-up studies of this cohort[9,12]. It seems that there was no progression from grade-1/2 to grade-3/4 infections, which is promising for the long-term use of bone-anchored prostheses.

Since introduction of osseointegration implant surgery, the technique of creating the so-called stoma (transcutaneous connection) was further developed[18,24]. Initially, the muscular fasciae were closed to cover the osseointegration implant during stage 1 in order to create a barrier between the outer surface and the osseointegration implant. However, this practice led to mechanical friction at the site of the dual-cone adaptor with subsequent discharge ("wet stoma"), necessitating revision procedures for the treatment of stoma-redundant tissue. Therefore, the surgical technique was adapted, in 2012[24], by attaching the muscular fasciae to the distal part of the femur, close to the cutting edge, with removal of almost all of the subcutaneous tissue ("dry stoma"). In the first 27 patients in the present cohort, the initial technique was used at time of the primary procedure. Future studies, in a larger cohort, are in progress to compare the impact of both surgical techniques.

A learning curve also might have an influence on outcomes (e.g., infections, stoma-redundant tissue), as has been described in other studies on the implementation of new surgical techniques[25,26].

Brånemark et al.[17], in a recent 5-year follow-up study of 51 patients (55 implants), showed similar results in terms of soft-tissue infections in association with the use of a screw osseointegration implant (OPRA); in that study, 34 patients (67%) had a total of 70 such events. However, they reported a higher percentage of deep infections, with 11 patients (22%) having a total of 14 such events. Matthews et al.[21], in a study of 18 patients who were managed with a custom-made screw osseointegration implant between 1997 and 2008, reported a higher rate of deep

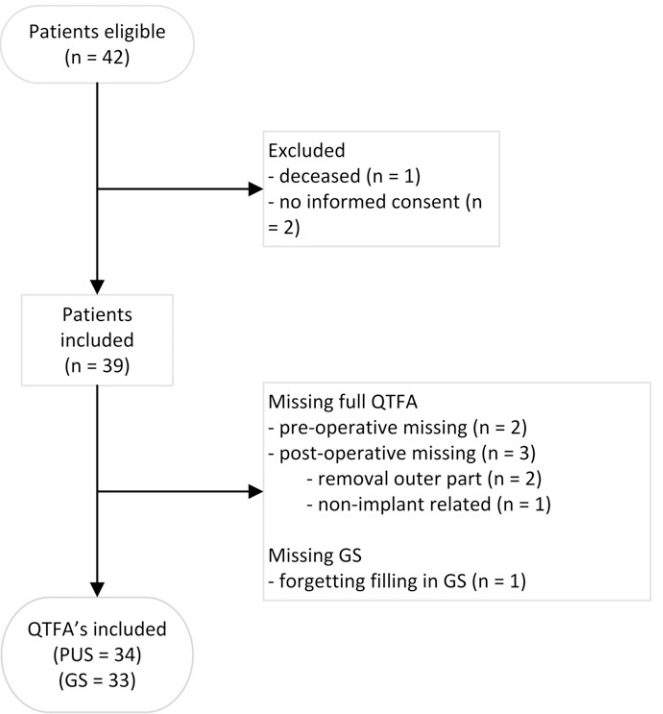

Fig. 3

STROBE diagram showing the numbers of patients who were included and the number of Q-TFA scores that were used for the analysis. PUS = prosthetic use score, and GS = global score.

TABLE III Complications

Type of Complication	No. of Patients (N = 39)	No. of Events
Infection*		
Low-grade soft-tissue infection		
Grade 1	9 (23%)	9
Grade 1A	21 (54%)	37
Grade 1B	2 (5%)	2
Grade 1C	2 (5%)	2
High-grade soft-tissue infection		
Grade 2	25 (64%)	37
Grade 2A	29 (74%)	48
Grade 2B	4 (10%)	5
Grade 2C	6 (15%)	8
Bone infection		
Grade 3	1 (3%)	1
Grade 3A	4 (10%)	5
Grade 3B	0	0
Grade 3C	2 (5%)	2
Implant failure		
Grade 4	0	0
Aseptic loosening	1	1
Intramedullary stem breakage	2	2
Dual-cone adaptor breakage		
Weak point	16	18
Distal taper	3	3
Stoma-redundant tissue	14	30
Stoma hypergranulation	8	13

*In all, a total of 30 patients had a total of 156 infections.

infections (5 patients [28%]) but a comparable rate of soft-tissue infections (11 patients [61%]) over a follow-up period up to 19 years (range, 2-19 years). Aschoff and Juhnke, in a study of 86 patients (94 implants) who were managed with a press-fit osseointegration implant (ILP) between 2003 and 2014, explanted 3 intramedullary components (3%) because of deep infection[27]. The limitation of that study was that the duration of follow-up was unclear for the included individuals.

No septic loosening occurred in our cohort within 5 years of follow-up, resulting in a prevalence of 0%; this rate is lower than the widely accepted rates of periprosthetic joint infection following total hip arthroplasty[28,29].

Similar to the findings in studies with a follow-up period of up to 2 years[7-9,11,19,20,30], HRQoL and prosthetic use increased significantly. Most studies have represented Q-TFA scores as means[7,19,20,30]. In those studies, the mean prosthetic use score increased significantly by 32 points (baseline scores ranged from 47 to 52 points; follow-up scores ranged from 79 to 84 points)[7,19] and the mean global score increased significantly by 26 to 39 points (baseline scores ranged from 38 to 48 points; follow-up scores ranged from 71 to 84 points)[7,19,20,30]. The results for our earlier sub-cohort[9] even showed these significant improvements 1 year after osseointegration implant surgery; the prosthetic use score improved from 56 hours per week at baseline to 101 hours per week at follow-up and the global score improved from 39 points at baseline to 63 points at follow-up. As we used medians, it is difficult to compare our results with those of previous studies in a mathematical manner. On the basis of the results of the previously mentioned studies with follow-up periods of 1 to 2 years, it seems that the improvements in functional outcomes are maintained over 5 years.

The most important limitation of the present study was its retrospective design. The grading system for infections was implemented later in the treatment process. Thus, infections could not be graded in a prospective manner and had to be reproduced on the basis of data in the patient record. However, we believe that this factor might only have led to an overestimation of the frequency of infections. Second, because of the undefined follow-up moments, some of the Q-TFAs were missing and some Q-TFAs were not completed at exactly 5 years postoperatively. However, we assume that there is no substantial difference between the Q-TFA scores that were collected at exactly 5 years and the Q-TFA scores that were derived after a median of 62 months as these scores were comparable with those in a previous 5-year follow-up study[17].

The present study also had strengths. First, to our knowledge, ours is the first study of patients managed with a transfemoral bone-anchored prosthesis using a press-fit osseointegration implant with a fixed 5-year follow-up. Second, we included the data of the general practitioners in our analysis to present a complete overview of all adverse events.

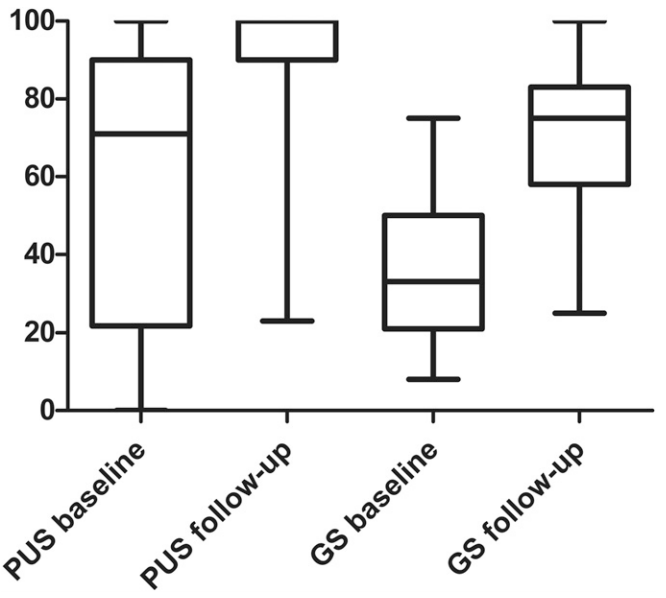

Fig. 4

Box plots showing the Q-TFA prosthetic use score (PUS) and global score (GS) at baseline and follow-up. The top and bottom of each box represents the 25th and 75th percentile, and the line within the box represents the median.

For future studies, structural use of the infection classification system and prospective registration are mandatory to avoid misinterpretation.

In conclusion, this 5-year follow-up study on patients who were managed with an osseointegration implant after transfemoral amputation showed that prosthesis-wearing time and HRQoL improved significantly in spite of adverse events. Grade-1 and 2 infections were frequent, without a trend of increasing severity over time. The majority of the adverse events were treated with simple measures. ■

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