Bone mineral density in osseointegration implant surgery: A review of current studies (Review)

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Abstract. Osseointegration implant (OI) surgery is the latest rehabilitation technology for amputees, where a bone-anchored implant obviates the limitations of traditional socket prostheses. The bone mineral density (BMD) in the periprosthetic and other anatomical regions can be used to assess bone remodelling following OI surgery. Currently, limited studies have used BMD measurements in reporting post-operative OI outcomes and the association between the maintenance of BMD and implant efficacy has remained elusive. This review captured and analysed all studies that have reported the BMD as an objective outcome measure in patients with trans-femoral or trans-tibial OI. The PubMed, Medline, Scopus and Web of Science databases were searched using the terms 'amputation', 'osseointegration' and 'bone mineral density'. A total of 6 studies involving human participants were included for analysis. All studies used dual X-ray absorptiometry and/or X-rays for measuring BMD. Rehabilitation of trans-femoral or trans-tibial amputation using OI may help restore healthy BMD by enabling physiological bone loading. However, there is a low correlation between the BMD around the OI and the success of OI surgery or the risk of periprosthetic fractures. This review summarises the current evidence on BMD assessment in OI for lower limb amputee rehabilitation. Despite the great variability in the results, the available evidence suggests that OI may help restore BMD following surgery. The limited evidence calls for further investigation, as well as the development of a standard BMD measurement protocol.

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1. Introduction

Osseointegration implant (OI) technology is based on the attachment and integration of bone to an artificial implant, used in different orthopaedic applications to enable musculoskeletal repair. The term 'osseointegration' was first introduced in dentistry by Dr R. Branemark, who used titanium for dental implants in a clinical study in 1965 (1). Over the last two decades, OI has evolved to provide a new method of rehabilitation following limb amputation, which has been reported to increase patient satisfaction and quality of life (QOL) compared to traditional socket prostheses (2-4). Since its initial application in dentistry, osseointegration surgery has revolutionised orthopaedics and rehabilitation, and led to improved quality of life and functional restoration for amputees (5). In the context of this paper, OI refers specifically

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to those implants that have been used for limb rehabilitation in amputees.

Amputations significantly affect mobility and QOL, occurring as a result of non-communicable diseases such as diabetes, or due to trauma, tumours and congenital diseases (6). In Australia, ~8,000 amputations occur annually, largely as a result of complications of diabetes (7). In 2017, there were 57.7 million individuals worldwide with an amputation from traumatic causes, such as falls and road injuries (6). Conventional amputation rehabilitation methods utilise socket prostheses attached to the residual limb in the form of a cup, but users experience functional and aesthetic limitations that impact their QOL. Common issues with socket prostheses include discomfort, sweating in the socket, phantom limb pain and ill-fit of the socket due to the dynamic nature of the residual limb (8-10). These issues have prompted the development of new OI technology to directly attach the prosthetic device to the bone of the residual limb (Fig. 1). A range of implant types have evolved, such as integral leg prosthesis (ILP), osseointegration prosthetic limb (OPL), osseointegrated prostheses for the rehabilitation of amputees (OPRA) and percutaneous osseointegrated prosthesis (POP), most of which involve a titanium implant for interfacing with bone together with certain design variations, except for the ILP made from cobalt-chromium-molybdenum (5,6).

Since its recent application in the last two decades, OI has demonstrated significant promise as an alternative treatment for amputees who have failed to mobilise with traditional socket prostheses. Lower limb OI allows for direct skeletal attachment, which has been shown to improve range of motion (2) and mobility (3), and reduce the amount of energy used when mobilising (11). The mechanisms by which OI integrates with bone and induces regenerative bone growth has been described in a number of studies (12). As OI has only recently been introduced into clinical practice, the understanding of their efficacy and associated analysis techniques are limited to patient questionnaires and functional outcome measurements. While these are effective indicators of patient satisfaction and indirect predictors of implant integration, an objective measurement of periprosthetic bone health as a direct indication of implant integration is rarely used.

Bone mineral density (BMD) is the gold standard for measuring bone health, and is clinically used to diagnose bone-related diseases or determine the risk of developing fractures (13). The BMD can be measured by dual-energy X-ray absorptiometry (DEXA), quantitative computed tomography and quantitative magnetic resonance imaging (14). Most well-known for its use in the diagnosis of osteoporosis and identifying high fracture risk populations, the BMD is also used to assess the effectiveness of treatment (15) and rehabilitation (16). The BMD can be measured at multiple anatomical locations; however, femoral neck measurements are the best predictor of a future fracture near the hip (17). BMD measurements compare the density of the patient's bone to that of healthy, young individuals, referred to as the T-score (18). A previous study described the effects of lower limb OI on BMD and potential benefits in restoring more natural biomechanical loading of the femoral neck (19). While this is important in ensuring a return to baseline function in lower limb amputees, the local periprosthetic effects of OI for assessing risk of failure or fracture at the implant site have remained to be properly characterised. Objective measurements obtained through bone imaging may serve as a window for understanding how OI integrates biologically with the skeleton or whether the patient is at risk of developing future complications, and guide amputees in their rehabilitation or direct engineers to develop implants with greater efficacy. For numerous years, it has been understood that bone loading through resistance exercises and low-impact activities supports positive BMD changes in older adults (20). It has also been shown that OI leads to non-uniform load distribution that influences the outcome of bone regeneration, with higher load areas having more favourable outcomes (21).

The efficacy of OI technology for treating amputations is currently measured by QOL and functional testing. BMD as an objective measure to reflect post-implantation bone quality has significant applicability in clinical practice for assessing implant integration and hence predicting the risk of periprosthetic fracture or implant failure. While previous reviews have evaluated the efficacy of OI on amputee rehabilitation (6,22-24), none had a focused approach to analysing BMD measurements as an objective indicator of bone quality post-implantation. The present review captures all existing studies that reported BMD measurements following OI surgery in amputees and reflects on the usefulness of the BMD as a predictor of bone regeneration, implant failure and post-operative complications, as well as its role in guiding patients through rehabilitation and engineers in implant development. The findings of relevant studies were summarised and discussed in the form of a narrative review due to the limited evidence currently available. Systematic reviews or meta-analyses may be possible in the future following further build-up of high-quality clinical evidence on this emerging topic area.

2. Selection of studies for analysis

PubMed, Medline, Scopus and Web of Science were searched using combinations of the key words 'amputation', 'osseointegration' and 'bone mineral density' from inception to March 1st, 2024. The reference lists of included studies were also manually scanned for any additional studies missed by the electronic search. Details of the search strategy are provided in Table SI.

The eligibility criteria for selecting studies for subsequent analysis were as follows: i) All types of clinical studies involving human participants; ii) the study involved trans-femoral or trans-tibial amputees rehabilitated using OI, through either a single-stage or two-stage surgical procedure; and iii) the study involved quantitative BMD measurement using one or more bone imaging techniques. Studies were not used for analysis if they were: i) Non-human studies or experimental studies performed in a laboratory; ii) reviews or other non-original research studies; iii) studies of which the full text was unavailable; and iv) studies not written in English.

Due to limited research on OI retrieved using the above criteria, additional studies involving BMD measurements following total hip arthroplasty (THA) and total knee arthroplasty (TKA) were included as supporting information (Table SII) for comparison and discussion.

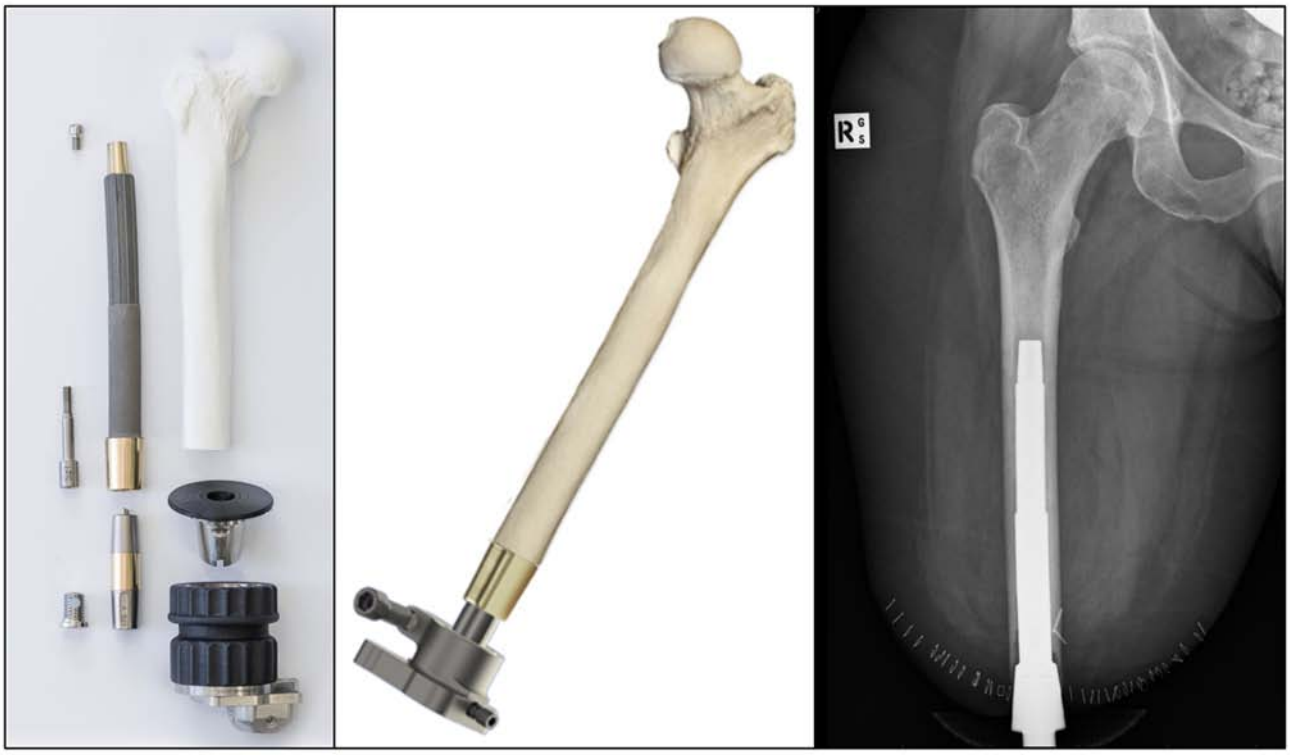

Figure 1. Illustrations of a trans-femoral osseointegrated implant.

Relevant data from each selected study on OI were extracted and summarised in Table I, including: i) Basic study characteristics (first author, country, year of publication); ii) study design (type, sample size, implant type, follow-up duration); iii) analyses performed (BMD measurements, other measurements); and iv) main BMD-related findings and limitations stated. The quality of included studies was evaluated based on the tool for assessing risk of bias in non-randomised studies of interventions (25). The risk of bias was assessed according to 9 domains, in which each study was assigned a high, low or unclear risk. An overall risk of bias judgement was then made based on the results in the 9 domains, as presented in the last column of Table SIII, as low, moderate, serious or critical risk of bias.

3. Characteristics of selected studies

A total of 1,634 articles were retrieved from database searches, of which 576 were considered potentially eligible based on title and abstract. Following in-depth screening and selection of articles based on eligibility criteria, 6 articles (19,21,26-29) were used for analysis in the present study (Table I).

The selected studies were from Europe, Australia and the USA. Study types included observational cohort studies (prospective or retrospective), consecutive case control studies and a precision study. All studies had a sample size of <50 patients and used a variety of OI types, including ILP, OPL, OPRA and POP. All studies assessed OI for trans-femoral amputations, while only one study by Thomson *et al* (19) included both trans-femoral and trans-tibial amputees. Follow-up durations varied, ranging between 12 and 36 months in most studies. BMD measurements had been performed using DEXA in 3 studies, DEXA and X-rays in 2 studies and X-rays only in 1 study.

4. Quality of selected studies

Assessment of risk of bias for each study selected for analysis is shown in Table SIII. Although there was variation among studies, the majority of selected studies had a low risk of bias across the assessed domains. In the 'conflict of interest' and 'incomplete outcome data' domains, all studies showed unclear risk of bias. In the other 7 domains, high risk of bias was seen in 7/7 domains in one study (26), 6/7 domains in another study (21) and 2/7 domains in a third study (27), while the remaining studies showed low risk of bias in all 7 domains. Of the two studies rated to have overall serious risk of bias, one included 27 patients who underwent OI at a single institution and were followed up for various time periods that were grouped into averages of 12 and 24 months. DEXA measurements were used to determine the BMD at the hip neck of healthy and amputated sides using a software and values of changes in BMD were reported (21). However, specific methods for DEXA measurements as well as the initial and final BMD values were not stated. The other study used 2 cadaveric femoral bones from patients who received OI and reported BMD changes measured by DEXA as a result of altering leg position during scanning (26). The study focused on investigating the precision of BMD measurements and did not report the absolute or change in BMD values before and after OI surgery, or the time after OI when the BMD measurements were made. There was no control limb and statistical methods were not described. Significant variations in study design can potentially introduce risk of bias in the studies

Table I. Summary of included studies.

First author, year	Study type	Country	Study size/ type	Analyses	BMD measure-ment technique	Other measure-ments	Initial BMD measurement	Final BMD measurement	Follow-up duration	Change in BMD	Main BMD-related outcomes	Limitations stated	(Refs.)
Haket *et al*, 2017	Consecutive case-control, level 3 prognostic study	The Netherlands	27 patients/ ILP	Femoral hip BMD, peripros-thetic cortical thickness	DEXA and X-rays	Nil	Pre-operatively, significant difference in BMD of hip neck between healthy and amputated legs, with mean difference of 0.24 g/cm^2	On the amputated side, BMD was 0.68, 0.67 and 0.69 g/cm^2 pre-operatively and 12 and 24 months post-operatively, respectively	12 and 24 months	Insignificant change in BMD, but initial and final values not reported	Bilateral hip BMD and periprosthetic cortical thickness were improved with OI. BMD of hip neck on amputated side was substantially lower than that of the contralateral side, but did not show significant change at 24-month follow-up	Limited control of rotation during X-rays affecting accuracy of cortical thickness measurements. Follow-up period was relatively short	(21)
Hansen *et al*, 2018	Precision study and validation	Denmark	2 cadaveric femoral bones/ OPRA	BMD	DEXA	Nil	Not reported	Not reported	Not reported	Neutral (0°) ROI: 1, 1.95 g/cm^2; 2, 1.72 g/cm^2; 3, 1.74 g/cm^2; 4, 1.74 g/cm^2; 5, 1.58 g/cm^2; 6, 1.57 g/cm^2; 7, 1.65 g/cm^2. 0-10° flexion ROI: 1, 0.4 g/cm^2; 2, 1.2 g/cm^2; 3, 5.9 g/cm^2; 4, 3.1 g/cm^2; 5, 0.3 g/cm^2; 6, 2.1 g/cm^2; 7, 1.7 g/cm^2. 0-20° flexion	In most positions, the mean BMD showed a significant change compared to the neutral position. 5% flexion or rotation had the most impact on average BMD in the majority of ROIs	The femur was only examined in the anterior-posterior position. Edge-detection errors were present due to the software being designed for different anatomical structures. Population represented a heterogeneous group with a large variation in BMD values	(26)

Table I. Continued.

First author, year	Study type	Country	Study size/ type	Analyses	BMD measure-ment technique	Other measure-ments	Initial BMD measurement	Final BMD measurement	Follow-up duration	Change in BMD	Main BMD-related outcomes	Limitations stated	(Refs.)
										ROI: 1, 3.8 g/cm^2; 2, 3.9 g/cm^2; 3, 9.1 g/cm^2; 4, 9.9 g/cm^2; 5, 6.3 g/cm^2; 6, 2.3 g/cm^2; 7, 0.0 g/cm^2. 0-10° external rotation ROI: 1, 1.0 g/cm^2; 2, 3.7 g/cm^2; 3, 2.7 g/cm^2; 4, 1.9 g/cm^2; 5, 0.6 g/cm^2; 6, 0.6 g/cm^2; 7, 2.2 g/cm^2. 0-20° external rotation ROI: 1, 0.7 g/cm^2; 2, 6.6 g/cm^2; 3, 0.7 g/cm^2; 4, 0.8 g/cm^2; 5, 0.5 g/cm^2; 6, 1.1 g/cm^2; 7, 2.7 g/cm^2		among patients	
Hansen *et al*, 2019	Prospective cohort study	Denmark	19 patients-NRI vs. later RI/ integrum AB	Peripros-thetic BMD and bone marker turnover	DEXA	Blood samples: Parathyroid hormone, vitamin D, calcium ion, N-terminal propeptide of type-I procollagen, C-terminal	Proximal femur: - Intact side: 1.03 g/cm^2; Amputated side: 0.66 g/cm^2; Spine: L1-L4: 1.13 g/cm^2	RI group (n=8): Proximal femur: - Intact side, 0.97 g/cm^2; Amputated side, 0.55 g/cm^2; Spine L1-L4, 1.09 g/cm^2.	30 months	Mean BMD in RI group reduced between 27 and 38% at 30-month follow-up. Mean BMD in NRI group returned to baseline	Mean proximal femur BMD on amputated side decreased by 9% at 6 months after S1 surgery. Mean proximal femur BMD on intact side did not change at all time-points	Matching criteria were required to be extended for 27 control patients; control group consisted of patients with hip or knee osteoarthritis.	(28)

Table I. Continued.

First author, year	Study type	Country	Study size/ type	Analyses	BMD measure-ment technique	Other measure-ments	Initial BMD measurement	Final BMD measurement	Follow-up duration	Change in BMD	Main BMD-related outcomes	Limitations stated	(Refs.)
						telopeptide of type-I collagen, osteocalcin and bone-specific alkaline phosphatase		NRI group (n = 11): Proximal femur: - Intact side, 1.03 g/cm^2; Amputated side, 0.68 g/cm^2; Spine L1-L4, 1.15 g/cm^2		values after 30 months	No difference in mean proximal femur BMD between RI and NRI groups at any follow-up. Precision measurement of BMD was 1.2% for spine (L1-L$), 2.1% for proximal femur (amputated), and 1.1% for proximal femur (intact).	Lower activity level compared to normal populations, hence control group could have lower BMD compared to average population. Small sample size and patient group heterogeneity could have resulted in errors.	
Thomson *et al*, 2019a	Retrospective cohort study	Australia	28 patients-15 in ILP group and 13 in OPL group	Peripros-thetic BMD and femoral BMD	X-rays	Nil	Not reported	Not reported	36 months	Not reported	ILP group had greater decrease in BMD than OPL group in most zones Periprosthetic BMD decreased in all zones along the length of both implant types	Femoral soft-tissue distribution was assumed to be equal to the baseline measurement of each patient, as their BMI had not changed significantly. There were differences in contours in ROI during measurements	(29)
Thomson *et al*, 2019b	Prospective cohort study	Australia	48 patients-15 TTA, 22 TFAL and 11 TFAS/ ILP or OPL	Spine and femoral BMD	DEXA	6MWT, TUG	Spine (L2-L4):TTA, 1.3164 g/cm^2; TFAL, 1.268 g/cm^2; TFAS,	Femur neck operative: TFAL, 1.078 g/cm^2 after 1 year and	12 and 36 months	Operative femoral neck Z-score of 0.719 average increase across all.	BMD was restored in patients with OI. Statistically significant	Mean femoral neck Z-scores were lower than expected, which could be due to the	(19)

Table I. Continued.

First author, year	Study type	Country	Study size/ type	Analyses	BMD measure-ment technique	Other measure-ments	Initial BMD measurement	Final BMD measurement	Follow-up duration	Change in BMD	Main BMD-related outcomes	Limitations stated	(Refs.)
							1.173 g/cm^2. Femur neck operative: TTA, 0.9747 g/cm^2; TFAL, 0.709 g/cm^2; TFAS, 0.6725 g/cm^2. Femur neck contralateral: TTA, 1.072 g/cm^2; TFAL, 1.016 g/cm^2; TFAS, 1.01 g/cm^2	0.364 g/cm^2 after 3 years		groups No significant change in spine BMD for any group	increase in Z-scores on operative side for TFAL and TFAS groups from pre-operative to follow-up. No significant change in TTA group on operative side	lower mobility of patients within this study compared to the literature. In the TFAS group, a lag screw was passing through the cancellous bone in the operative femoral neck, as this region was excluded from the study; the results showed a higher BMD and Z-score on the operative femur neck	
Sinclair *et al*, 2022	Prospective cohort study	USA	10 patients/ POP	Adverse events, peripros-thetic BMD and radiographs	DEXA and X-rays	Prosthetic put on and take off time, 6MWT and Q-TFA	Not reported	Pre-loading: Medial, 1.44 g/cm^2; Proximal, 1.66 g/cm^2; Lateral, 1.39 g/cm^2; Ipsilateral, hip, 0.84 g/cm^2; Lumbar spine, 1.31 g/cm^2. Post-loading at 26 months: Medial, 1.97 g/cm^2; Proximal, 1.62 g/cm^2;	3, 6, 13 and 26 months	Significant increase in average BMD in lumbar spine, medial and lateral areas. Ipsilateral hip and proximal regions also showed an increase in BMD, but were not significant	OI showed improvements in BMD	Small sample size, single-centre study, no female participants, and small number of surgeons conducted the OI surgery	(27)

Table I. Continued.

First author, year	Study type	Country	Study size/ type	Analyses	BMD measurement technique	Other measurements	Initial BMD measurement	Final BMD measurement	Follow-up duration	Change in BMD	Main BMD-related outcomes	Limitations stated	(Refs.)
								Lateral, 2.19 g/cm^2; Ipsilateral hip, 0.88 g/cm^2; Lumbar spine, 1.35 g/cm^2					

6MWT, 6-minute walk test; ILP, integral leg prosthesis; OI, osseointegration implant; OPL, osseointegration prosthetic limb; OPRA, osseointegrated prostheses for the rehabilitation of amputees; POP, percutaneous osseointegrated prosthesis; Q-TFA, questionnaire for persons with a transfemoral amputation; TUG, timed up and go; NRI, non-removed OI; RI, removed OI; BMD, bone mineral density; TTA, trans-tibial amputees; TFAL, trans-femoral amputees with long residual femurs; TFAS, trans-femoral amputees with short femurs; DEXA, dual X-ray absorptiometry; ROI, region of interest.

selected for analysis in this review and the quality of studies should be considered when drawing conclusions from the findings.

5. BMD measurements for OI in amputees

Of the six selected studies, two reported insignificant changes in BMD following OI surgery in amputees, while the remaining studies showed varying results. Haket *et al* (21) found an insignificant change in BMD from baseline to 24 months, which was similarly reflected in the study by Hansen *et al* (28), indicating that the BMD returned to baseline values at 30 months following a reduction. Thomson *et al* (29) found a reduction in the BMD at >24 months follow-up compared to baseline measurements, which was speculated to be caused by stress shielding of the implant. In a different study, Thomson *et al* (19) reported Z-score results implying that OI could effectively support bone remodelling and increase BMD in the femoral neck of the amputated limb. This was supported by the study by Sinclair *et al* (27), which noted an increase in BMD at the ipsilateral hip and proximal to the implant stem, although the change was not significant. One study did not report initial and final BMD measurements, as this was a validation study performed using cadaver limbs (26).

Due to the limited evidence retrieved on BMD measurements in lower limb amputees rehabilitated using OI, a supplementary table was generated to summarise studies reporting BMD measurements in patients who received an osseointegrated prosthesis for hip or knee joint replacement procedures (THA and TKA; Table SII). Many of these supplementary studies on both THA and TKA reported an overall decrease in BMD for all measured regions of interest (ROIs) (30-35). In addition, others found variations in BMD changes from no change to decreased BMD post-surgery in different ROIs (36,37). Certain studies noted that the BMD tended to decrease at proximal ROIs (38,39), with an eventual approach back to baseline levels at the 6-month follow-up (38).

A number of studies on THA and TKA found an increase in BMD at the tip of the implant but a notable decrease in the middle ROIs (40,41), and one found insignificant changes in BMD post-implantation (42). Interestingly, one study also found that a short stem implant resulted in significantly less BMD loss compared to a standard straight stem (43).

To combat the apparent reduction in BMD post-implantation, studies have investigated factors that may help maintain BMD. One study found that the use of zoledronic acid led to a minor increase in BMD by 2.2% at 12 months, while no change was noted in the placebo group (44). Another study found that cementless implants led to an increase in average BMD at the 3- and 6-month follow-ups, while cemented implants led to decreased BMD (45).

6. Discussion of current findings from BMD measurements following OI surgery

Of the >500 articles considered potentially eligible for inclusion in the present study, only 6 met the inclusion and exclusion criteria, emphasising the limited evidence on the use of BMD measurements for evaluating the outcomes of OI surgery in rehabilitating trans-femoral and trans-tibial amputees. Many

of the excluded articles focused on osseointegration in dental implants, or animal or computer models of osseointegration in amputated limbs (46,47). Other articles focused on BMD measurements in amputees without implants (48), or only reported subjective measurements such as quality of life surveys following OI surgery (4,49). Although excluded from this review, these studies can be used to gain a better understanding of the research space.

BMD can be measured by different methods, including DEXA, X-rays and radiostereometric analysis. The included studies used DEXA and/or X-rays to gather BMD data, while the supplementary studies on THA or TKA used all three methods individually or in combination. The BMD of the implant group can be compared to the average BMD of a young, healthy adult to give a T-score. The included studies generally pointed to the eventual restoration of baseline BMD in lower limb amputees rehabilitated with OI.

In a study by Haket *et al* (21) in 2017, changes in bone remodelling were observed at 12 and 24 months following femoral OI surgery using the ILP implant, which were measured through DEXA and anteroposterior (AP) radiographs. While AP radiographs showed an increase in cortical thickness, reflecting bone regeneration and restoration of natural biomechanics, there was no significant change in BMD values after 2 years. The authors speculated that the lack of change in BMD could be because the newly formed bone around the implant had not reached a normal density, yet. All participants continued to use their OI after this study, with 0 of 27 patients listed as a failed case. However, in this study, the lack of correlation between change in BMD and success of the OI surgery raised doubts about the ability of the BMD to be used as an objective measure of OI outcome. It should be noted that this study presented a high risk of bias across numerous items; hence, further investigation with longer follow-up and a larger sample size is warranted.

There were certain similarities in the observations made by Thomson *et al* (29) in 2019. This study monitored 28 patients with trans-femoral OI for 2 years, of which 15 received ILP and 13 received OPL. X-rays were used to measure changes in BMD, indicating that the OPL implant led to increased bone thickness, while in contrast to Haket *et al* (21), the ILP implant led to bone resorption at the distal end, which was suspected to be caused by stress shielding. The study also showed statistically significant decreases in BMD for both implant types at 2 years after surgery. Lower BMD values are typically associated with a higher risk of fracture, although none of the participants sustained a fracture or had implant failure during the study period. The findings of the present study again suggest that BMD may not be an accurate indicator of OI success.

Another study by Thomson *et al* (19) from 2019 observed changes in BMD of the femoral neck and spine for 3 years after OI implantation using ILP or OPL. The focus of this study is noteworthy, since the other included studies all assessed BMD around the implant site. The femoral neck and spine are both sites frequently employed when evaluating osteoporosis and fracture risk in patients without amputation, and their relevance in this study arises from the understanding that OI may help to restore native biomechanics through the femur and hence potentially stimulate bone regeneration. The results showed a statistically significant increase in BMD at 1 year compared to baseline for all trans-femoral participants receiving OI, while the increased BMD observed in trans-tibial participants was not significant. This was thought to be due to the retention of the full femur and knee joint in trans-tibial amputees, allowing the femoral neck and spine to maintain a more natural biomechanical state. In this study, BMD measurements at relevant anatomical sites other than those around the implant had a good correlation with the performance of OI in the rehabilitation of lower limb amputation.

Hansen *et al* (26) published a validation study in 2018 with the aim of evaluating the precision and feasibility of a scan protocol for conducting BMD measurements. This study used the proximal part of two cadaveric human femoral bones with the OPRA implant, mounted on a positioning jig to position them from neutral (0°) to 20° flexion and rotation. DEXA scans were used to evaluate variations in BMD as a result of changes in femur position angle. Furthermore, 20 patient examinations were conducted to evaluate the precision error for each of the elected ROIs. Importantly, this study found significant changes in average BMD values depending on the degree of flexion and rotation. The authors stressed the importance of creating a reproducible scan protocol for conducting BMD measurements in clinical studies to facilitate valid cross-comparisons of study group results following OI surgery.

Hansen *et al* (28) published another study in 2019 using the same scanning protocol established in the 2018 study to observe changes in BMD and bone turnover markers over 30 months in 20 patients with OI. They noted a decrease in the average periprosthetic BMD between the initial measurement and the 6-month follow-up. During the study, 8 of the 19 participants required their implant to be removed due to infection, pain or inability to use the implant. These participants were moved into a separate group (RI group) with their BMD measurements taken alongside participants who did not require implant removal (NRI group). The NRI group showed an increase in BMD that realigned to pre-operative readings at 30 months, while the RI group showed a significant reduction in BMD. In contrast to the studies discussed above, this study indicated the possibility of using the BMD as a predictor for OI failure in trans-femoral amputees.

Sinclair *et al* (27) published a prospective cohort study in 2022 involving 10 patients implanted with POP to evaluate the safety and efficacy of this press-fit OI. All participants were male and underwent unilateral trans-femoral amputation at least 6 months prior to study commencement. BMD measurements were made using DEXA scans taken at 2 years following OI surgery and qualitative radiograph assessment. The study noted significant increases in BMD of the lumbar spine, as well as in ROIs medial and lateral to the distal porous coated region of the implant compared to baseline. Furthermore, the BMD in the ipsilateral hip and region proximal to the implant stem increased from baseline, although the changes were not significant. Qualitative radiograph assessment indicated an increase in bone density of the distal femur throughout the length of the bone from baseline to 1 year post-implantation. The perceived increase in BMD following OI surgery may have a role in preventing degenerative musculoskeletal changes after lower limb amputation.

Among the studies analysed in the present review, it is clear that varied conclusions can be drawn when examining the

usefulness of the BMD as an objective tool for measuring the success of OI surgery. Certain studies have shown an increase in periprosthetic bone thickness following OI implantation but no significant increase in periprosthetic BMD (21,29). Other studies have observed no implant failure accompanied by a trend of increasing BMD values post-implantation (19,27,28), suggesting a potential association between BMD measurements and the success of rehabilitation using OI. Regardless, the lack of a standardised approach to the scanning and measurement procedure for BMD readings in amputee patients receiving OI makes it difficult to compare studies conducted by different research groups, as identified by Hansen *et al* (26).

Although not directly comparable to the included studies, the supplementary studies reporting BMD measurements for OI surgery in THA and TKA patients provide valuable insight into related clinical results over larger sample sizes and more varied patient demographics. The experimental procedures and outcomes of these studies may be beneficial in guiding the future standardisation of BMD measurement protocols for patients receiving OI for various indications. Overall, the findings of the supplementary studies on THA and TKA were highly varied, reflecting a lack of standardised methods for conducting BMD measurements as well as heterogeneous study outcomes. The range of follow-up periods was similar to the included studies, which was mostly within 36 months, while patient demographics were mostly limited to Western countries with the vast majority of studies being conducted in Europe. The available evidence on BMD measurements in patients with OI, both for amputation rehabilitation and other indications, calls for higher-quality studies with larger sample sizes, longer follow-up and wider demographics of populations in various different continents.

7. Towards the standardisation of BMD measurement protocols

The studies analysed in the present review utilised DEXA and X-ray analysis as the primary techniques for measuring BMD. DEXA scans can be taken in various positions with different ROI placement. This introduces potential variations in BMD measurements and resulting measurement values, driving the need to develop a standardized measurement protocol that can be applied to all OI types to evaluate implant survival. Hansen *et al* (26) highlighted the importance of having a reproducible set-up for DEXA scans to reduce BMD measurement errors. The Lunar Prodigy Scanner (GE Healthcare) was used in this study as an acceptable device for precise BMD measurement in proximity to the OI. With a common protocol in place that introduces minimal variations in limb positioning when measuring BMD, scans from different research groups and clinical settings will be comparable. Given that the majority of included studies used DEXA scans to assess BMD and presented useful data from their investigations, it is proposed that DEXA should be used as the universal technique for measuring BMD considering its accessibility.

All of the selected studies reported BMD measurements after OI surgery in trans-femoral amputees, with all but one study investigating periprosthetic bone remodelling. There was considerable variation in the observed changes in BMD across different ROIs and across different time-points, both among the included studies and at times within the same study. In a standard protocol, it is advisable to conduct BMD measurements both in the periprosthetic region and at other relevant anatomical locations, such as the femoral neck and spine. At least 7 ROIs should be used in each region and follow-up should be conducted for at least 36 months.

8. Limitations

The current review provides the first summary of the current evidence on the quantitative assessment of BMD in trans-femoral and trans-tibial amputees rehabilitated using OI, to the best of our knowledge. A number of limitations should be considered when drawing conclusions from the findings given the small number of studies available in this topic area. First and foremost, amputee rehabilitation using OI surgery is a small but evolving field, with a limited amount of clinical evidence that has only built up in the last two decades. The lack of standardisation in this field regarding patient characteristics, surgical protocols, implant selection, outcome measures, follow-up period and other study characteristics introduces significant heterogeneity among available studies, making it difficult to perform meaningful comprehensive and comparative analyses or draw conclusions on current outcomes without overinterpreting the data. In the present review, the very restricted number of six studies that fit the selection criteria meant that it was not possible to perform a comprehensive analysis in the form of a systematic review or meta-analysis, or to further categorise study characteristics or outcomes, e.g. by anatomical location of the implant surgery, type of surgical protocol or implant type used. However, this first review on assessing BMD in OI surgery may serve as a starting point and a call for future in-depth studies, e.g. using a retrospective case-control design, larger sample sizes, longer follow-up and incorporation of standardised BMD measurements. Furthermore, the present study did not analyse the supplementary results presented on BMD measurements for implant surgery in patients with THA and TKA in detail. It was outside the intention of this review to discuss findings from THA and TKA studies, as the implants used were to replace joints rather than to reconstruct lower limb amputations. The implant materials, design, surgical placement and outcome measures were completely different from OI in amputees and hence not directly comparable to the six studies selected for the present review. In addition, the vast majority of patients with THA and TKA received the indication for osteoarthritis or other degenerative joint disorders, while amputations are mostly indicated due to traumatic injuries. These diverging patient characteristics also make meaningful comparisons challenging. Hence, only the THA and TKA studies were used to supplement our discussion on measuring BMD for amputees rehabilitated with OI and to strengthen the call for a more standardised BMD measurement protocol. Secondly, the majority of the included studies were conducted in Europe involving a predominantly Caucasian population, which may not reflect the outcomes in other demographic populations and ethnic groups. Furthermore, the studies mostly reported outcomes in trans-femoral amputees despite the increasing prevalence of OI in trans-tibial amputees. From the results of

a single available study (19), the BMD-related outcomes are not generalisable across these two types of patients. Finally, the present review did not separately analyse patients who underwent OI surgery through the single or two-stage surgical procedure, since the majority of existing studies used the conventional two-stage procedure. Among various two-stage protocols for limb reconstruction and rehabilitation using OI, a period of 4-18 months is required from the time of the initial surgery (50). A surgery is first performed to insert the implant, and a second surgery is then performed several months later to create a percutaneous skin opening, which then allows prosthesis fitting. The single-stage OI procedure has evolved since 2014, predominantly being performed in Australia and combining the two-stage procedure into a single surgery, thereby shortening the recovery time to 3-6 weeks (50). Due to the greatly reduced recovery time, as well as savings on cost and healthcare resources by removing multiple surgeries, single-stage OI has the potential to gain greater popularity in the coming years. It should be noted, however, that although the single-stage study protocol (50) produced pilot study data in 10 patients indicating improvements in quality of life and functional outcomes compared to pre-operative values, the study findings for single-stage OI have not yet been published and outcome comparisons with two-stage surgery are not available. Whether the difference in OI surgical protocol may impact post-operative changes in BMD remains to be investigated in future studies.

9. Conclusion

The development of OI technology has demonstrated great potential in improving patient quality of life and functional outcomes, which is becoming a more preferred choice in the rehabilitation of lower limb amputees for returning to normal activities. BMD changes are currently not commonly measured in this population, but have potential to provide additional information on the progress of bone remodelling following OI placement. The limited available evidence suggests that OI may help restore a healthy BMD in lower limb amputees, although post-operative BMD changes were not strongly correlated with the success of OI surgery or periprosthetic fracture risk. Significant variability was observed among the results of studies analysed in this review, calling for future investigations with larger sample sizes and longer follow-up times, as well as the development of a standardised protocol for measuring BMD in patients with OI.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author

Authors' contributions

Study design: JJL and DX; acquisition, analysis and interpretation of data: JCC, SPP, AG, CS, AMK, EMC, DX and JJL; manuscript drafting/critical revision: JCC, SPP, AG, CS, AMK, EMC, XL, AO, WL, MAM, JJL and DX. All authors have read and approved the final manuscript for submission. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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