Reconstruction of the resorbed maxilla with iliac crest or calvarial bone grafts

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A comparison

Dagmar Edith Wortmann

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voor papa

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CHAPTER 1

Introduction

Bone graft surgery

Bone grafting and bone repair has been on people's minds for hundreds of years. In the old testament, it was Adam's rib that was grafted to create Eve. In the Greek myths the gods used ivory to reconstruct a young man's shoulder[1,2]. In 1668, a traumatic defect in a soldier's cranium was repaired by a bone graft taken from the scalp of a dog scalp [1,2]. During that century, the first publications on bone structure and bone healing arose. Bone grafting further developed, with a first focus on what we now call xenografts: animal derived tissue. An early report on autologous bone grafting, meaning the source of the graft is the same person, dates from 1821, when an autograft bone implant was used to replace parts of a skull surgically[1,2]. Several years later the German anatomist and surgeon Julius Wolff brought science on bone grafting to a next level and developed a law stating that bone in a healthy person or animal will adapt to the loads under which it is placed. If loading on a particular bone increases, the bone will remodel itself over time to become stronger to resist that sort of loading[3]. In the twentieth century, bone grafting gained popularity and knowledge on bone graft healing increased further. An important precondition for the successful introduction of bone grafting in the maxillofacial region, was the discovery of penicillin and the subsequent development of other types of antibiotic treatments[2]. This development stimulated a number of surgeons in the fifties and sixties to reconstruct the atrophic mandible with autologous bone grafts. With regards to bone grafting in maxillofacial surgery, a publication arose on the osteoplastic substitution in cases of maxillomandibular defects using parts of the rib[4] in 1908. Clementschitsch had succeeded in reconstructing an atrophic maxilla with a bone graft via an transoral approach in 1948[2] and several others followed. In the mid-1950s, Dr. Paul Tessier further improved the surgical correction techniques for craniofacial deformations. Throughout the 1960s and 1970s, he developed the methods among which the use of autogeneous bone grafts instead of silicone or acrylic to modify skull and facial contours[5] Ever since, bone grafting has developed into a unique scientific endeavor that is essential to many surgical disciplines, including maxillofacial surgery.

Several considerations that must be taken into account when planning for a bone grafting procedure from various donor sites[8]. These include donor site morbidity and its effect on the patient's quality of life, inflicting the patient's acceptance and satisfaction about the procedure[6-8]. In the earliest reports on bone grafts, the success of a bone graft was determined by its macroscopic volume and stability with regards to applied stresses, but nowadays the dynamic and biologic structure of a bone graft is considered very important. Thus, a successful bone graft becomes incorporated, revascularizes and assumes the form desired. Also patient' appreciation of the procedure are no longer seen as of secondary importance. Therefore, the success of bone grafting should be assessed in light of its burdens and the final treatment outcome in general.

Bone graft surgery and implant-supported prosthesis

During the last decades, partial or total edentulism correction by means of implant-supported prostheses has become a reliable routine[9-12]. Unfortunately, severe bone defects, arising from long-standing edentulism, periodontal disease or trauma sequelae, may significantly hamper the placement of oral implants. In these cases, difficulties are caused by the proximity of anatomical structures such as the inferior alveolar nerve, the maxillary sinus and the nasal floor and the absence of sufficient bone volume to placed implants with adequate primary stability in a prosthetically driven position. Also, the arisen unfavorable vertical and/or horizontal intermaxillary relationship may compromise the final prosthetic outcomes[13-16]. To create more favorable conditions in these situations, different bone reconstructive techniques have been proposed, including guided bone regeneration[17-19], maxillary sinus floor elevation[20,21], distraction osteogenesis[22,23] and onlay grafting with autogenous bone blocks[6,13,24-28].

Maxillary reconstruction with bone grafts represents a versatile and very well-documented procedure which allows the correction of most defects in different clinical scenarios [7,11,13,14,24,29]. Autogenous bone remains the gold standard for maxillary reconstruction of severe bone defects as it provides copious amounts of bone material and it possesses the three classic qualities of the ideal graft, viz. osteoinduction, osteoconduction and osteogenesis. To harvest autogenous bone grafts, several sites are in use which include the retromolar region, the mandibular symphysis region, the tuberosity region, the anterior and posterior iliac crest, and the calvarium. In case of large defects, where intraoral donor sites may be not sufficient in terms of bone quantity, the anterior and posterior iliac crest and the calvarium are frequently used donor sites[13,24,30-36].

Anterior iliac crest bone graft harvesting has been a highly popular donor type for decades[1,7,37]. In the past, the posterior aspect of the ilium was frequently chosen as it contains twice as much bone as the anterior site. The surgical complexity is similar for the anterior and posterior approach, and for both approaches there exist a risk of damaging adjacent structures such as nerves and muscles. Both sites are associated with donor site related morbidity. For anterior iliac crest harvesting, this includes pain, sensory disturbances and gait problems which are generally temporary[6,38]. Morbidity is less common when the posterior approach is used compared to the anterior approach, and gait problems are uncommon, however the sequela are potentially more severe due to the proximity of the sacroiliac joint and the sciatic nerve[39] . Fractures of the crest are more frequently seen in the anterior approach, however these fractures remain stable and heal spontaneously in most cases without further complication[40]. On the contrary, graft harvesting related fractures of the posterior iliac crest often require further surgical intervention and might cause functional disability[40]. An important drawback from using posterior ilium is that surgery cannot be performed simultaneously with the grafting in the oral cavity. The patient must be turned during the operation. The anterior iliac crest can be harvested using a two-team

surgical approach to simultaneously harvest the bone and perform the augmentation surgery, thereby reducing surgery time. As anterior iliac crest site is easily accessible, associated with less severe morbidity and can provide considerable amounts of cortical and cancellous bone, this site is often preferred.

More recently, the calvarium demonstrated to be an excellent donor site for intra-oral grafting as well. Ever since the first publications arose[36,41], calvarial bone has showed reliable results in terms of bone quantity due to its rich cortical component and the limited resorption rate. Also, favorable results have been reported on implant survival rates over time[12] and morbidity[13,42,43]. However, some limitations were observed, including acceptance by patients, morbidity related to the procedure and potential complications such as meningitis, accidental dural exposure and tear, entry into the sagittal sinus and brain damage caused by the osteotome used for harvesting the graft[14]. A recent adjustment in the harvesting technique has limited the complication risk dramatically, however[42,44,45].

Choosing the ideal bone graft

When choosing the donor site for an individual patient, one aims to choose the ideal bone graft. As described by Zouhary[37], the ideal bone graft material for dental implant reconstruction should demonstrate the following six features.

- The graft material should have the structural integrity to maintain space during bone ingrowth, graft consolidation and maturation, and implant osseointegration;
- The graft material should be able to promote cells at the recipient site to form bone within the graft;
- The graft material should be able to be resorbed, remodeled and replaced as the viable native bone;
- The resultant augmented maxilla or mandible should be stable over time after implant restoration and functional loading;
- The material should have ease of harvest and placement to minimize procedure length and subsequently maximizing potential for graft success while minimizing patient morbidity;
- The graft should have a repeatable and predictable outcome.

Furthermore, there are several additional factors to consider when choosing the right donor site among which the quantity and type (cortical versus cancellous). These factors should guide the choice of graft material. Exclusively after these factors have been carefully considered in light of the patient's comorbidities and expectations, it should be decided which site(s) are appropriate as a donor site for each particular patient and application.

In case of pre-implant maxillary reconstructions needing large grafts due to severe bone loss, the iliac crest and calvarium bone have been demonstrated to fulfill these criteria to a high extend[35-37,46]. When choosing between both grafts, detailed knowledge on both types is required. Despite several clinical studies on both donor types, detailed up-to-date reports on patient appreciation, postoperative pain and morbidity are scarce and comparative studies are lacking[12,47,48]. Several studies reporting a high overall satisfaction exist for both donor types[33,43,48-51] , however, patients' opinions on the donor site contour changes, scar formation, problems in gait and sensibility alterations are assessed in various ways and conflicting results are reported[49,52] .

Apart from the clinical outcomes of the harvesting surgery, knowledge on the material properties and biological behavior of the graft are needed to decide between the two bone types. Evaluation of qualitative and quantitative factors, such as relative volumetric changes, mineral density and maturation of the graft provide insight into the long-term outcomes of the reconstruction. In this respect, the incorporation of calvarial bone has been frequently questioned as revascularization might be low due to its dense cortical structure. However, several clinical studies demonstrated a higher resorption rate of anterior iliac crest bone grafts compared to calvarial bone graft[33]. The three-dimensional volume reduction after reconstructions with iliac crest bone ranges from 24% [33] after 6 months to 60%[14] after one year. When calvarial bone grafts are used, the resorption is reported to be 0-15%, viz., 8.44% after 6 months[33] and 10%[51] to 19.2%[7] after one year. The numbers of resorption reported are in coherence with evaluations by means of imaging technology such as histology/histomorphometry and microCT[8,45], however comparative studies on graft incorporation following augmentation of the severely resorbed edentulous jaw are lacking.

Objectives

This thesis aims to compare anterior iliac crest and calvarial bone grafts for alveolar reconstructions of the severely resorbed maxilla in terms of clinical and patient reported outcomes, and radiological, and histological features. The specific aims were:

- To review the literature regarding the patient reported outcomes associated with anterior iliac crest or calvarial bone graft harvesting (Chapter 2).
- To assess the biomaterial properties and bone remodeling of calvarial bone grafts as a function of time in patients needing augmentation of the severely resorbed edentulous maxilla (Chapter 3).
- To compare patient satisfaction and patient-reported morbidity following anterior iliac crest and calvarial bone graft harvesting in patients needing augmentation of the severely resorbed edentulous maxilla (Chapter 4).

- To compare donor site related morbidity following anterior iliac crest and calvarial bone graft harvesting in patients needing augmentation of the severely resorbed edentulous maxilla (Chapter 5).
- To compare histological and micro-CT changes of anterior iliac crest and calvarial bone grafts used for augmentation of the severely resorbed edentulous maxilla (Chapter 6).

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CHAPTER 2

Harvesting anterior iliac crest or calvarial bone grafts to augment severely resorbed edentulous jaws:

A systematic review and meta-analysis of patient reported outcomes

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This chapter is an edited version of the manuscript: D.E.Wortmann, B. Van Minnen, K. Delli, J. Schortinghuis, G.M.Raghoebar, A. Vissink. Harvesting anterior iliac crest or calvarial bone grafts to augment severely resorbed edentulous jaws: a systematic review and meta-analysis of patient reported outcomes

Submitted on July 24 2021

Purpose This systematic review's aim was to compare patient reported outcomes after harvesting calvarial or anterior iliac crest bone grafts to reconstruct severe jaw defects to enable implant placement.

Methods The MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases searches included patient satisfaction, pain, disturbances in daily functioning, sensory alterations, donor site aesthetics, and complication rates.

Results Of the 1946 flagged articles, forty fulfilled the inclusion criteria (1 RCT, 1 retrospective comparative case series, 29 prospective cohort studies, 9 retrospective cohort studies). A meta-analysis of 2 studies (74 patients) showed no differences in satisfaction (standard mean difference (SMD) -0.13, 95%CI: -1.17;0.92; p=0.813) and postoperative pain (directly postoperatively: SMD, -2.32; 95%CI: -5.20;0.55; p=0.113; late postoperatively: -0.01; 95%CI -0.14;0.11, p=0.825) between donor sites. Postoperative gait disturbances were highly prevalent among the anterior iliac crest patients (28-100% after one week). The incidence of sensory disturbances and other complications were low, and the donor site aesthetic outcomes were favourable for both graft types.

Discussion Harvesting bone grafts from the calvarium or anterior iliac crest to augment severely resorbed edentulous jaws results in similar patient satisfaction. However, the findings on postoperative pain and disturbances in daily living suggest a trend in favour of calvarial bone grafts if harvested by an adjusted technique.

1 INTRODUCTION

Autologous bone is considered the gold standard for compromised bone grafting[1,2] as it combines all the required properties: osteoinduction, osteogenesis and osteoconduction. Autologous bone is histocompatible and nonimmunogenic. It is widely used in several surgical procedures for bony defect augmentation, including the reconstruction of the mandible or maxilla to allow for reliable implant placement. A frequently used and preferred donor site is the anterior part of the iliac crest[1-4] for large defect reconstructions[1,2]. However, the calvarial bone of the skull serves as a common alternative[5-8].

The anterior iliac crest has several practical benefits: it is easily accessible and can provide copious amounts of cortical and cancellous bone[2,5,7]. Moreover, when using a two-team surgical approach, the harvesting can be done simultaneously with the augmentation surgery, thereby reducing surgery time[9]. A common drawback of this procedure is inherent donor site morbidity including pain, sensory alterations, and gait problems[2]. An alternative is the outer cortex of the posterior parietal skull bone. The calvaria provide copious amounts of cortical bone but cancellous bone can also be obtained by using a safe scraper[11]. Although the morbidity reports following calvarial bone graft harvesting are promising,[5,10] the possibility of dura exposure or the dura tearing are among the major arguments against calvarial bone grafting. This risk has been minimized since the harvesting technique was modified[5,11].

Regardless of the donor site, related morbidity is a frequently mentioned drawback[3,4]. Some reports indicate higher rates of minor complications following anterior iliac crest harvesting and lower rates, but rarer, of severe complications after calvarial bone graft harvesting[3,9,12]. Therefore, the aim of this systematic review was to compare the patient reported outcomes of harvesting from the calvarium and/or the anterior iliac crest to augment the maxilla and mandible with bone grafts. The morbidity and complications of the donor sites were also evaluated.

2 METHODS

2.1 Protocol development

This systematic review was conducted following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. The reporting of this study complied with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) 2020 statement[13] and A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) to ensure quality and completeness. The study protocol was registered in the PROSPERO database (registration number 163926).

2.2 Information sources and search strategy

A thorough search of the literature was conducted with the help of a biomedical literature specialist (S.v.d.W.) and was completed on the 1st of May 2020, followed by an update on June 21st, 2021. The primary database used was MEDLINE (via PubMed), followed by EMBASE and The Cochrane Central Register of Controlled Trials. The search was supplemented by hand-searching the references. MesH terms and free text words were combined in the search strategy according to the syntax rules of each database. Table S1 depicts the strategy.

2.2.1 PICO

The researchers based the literature search on the PICO index:

- Population: patients ≥18 years of age undergoing bone augmentation of the maxilla and/or mandible for dental implant placement
- Intervention: bone grafts harvested from the calvarium
- Control: harvesting bone grafts from the anterior iliac crest
- Outcome: Primary outcome: patient reported outcomes (PROMs) in terms of general satisfaction (measured on a scale, such as a VAS-score, or by means of a dichotomous question). Secondary outcomes: severity (measured on a scale such as a VAS-score) and prevalence of postoperative pain assessed after one week, one month, six months or more than six months postoperatively; donor graft harvesting related disturbances in daily functioning (i.e., difficulties when lying in bed, gait disturbances, headaches, difficulties with wearing clothes), sensory alterations (i.e., anaesthesia, hypesthesia, hyperesthesia or paraesthesia alongside the scar or due to injury of the lateral femoral cutaneous nerve), aesthetic outcomes at the donor site (i.e., patient satisfaction with donor site aesthetics), contour alterations, abnormal scar formation, prevalence of major (i.e., bicortical harvesting of the iliac crest, fracture of the iliac crest, trepanation of the skull with or without dura tear, excessive haemorrhage); and minor perioperative complications (i.e. haematoma, infection, seroma, wound dehiscence).

2.2.2 Inclusion criteria

1. Randomized controlled trials (RCTs), non-randomized controlled trials (CCTs) with a minimum sample of 10 patients (five per group or, in case of a split mouth design, at least five sites per group), case series >5 patients
2. Reconstruction of extremely resorbed mandible and/or maxilla with bone grafts from the calvarium or anterior iliac crest to optimise prosthetic function or for the placement of dental implants
3. Detailed information should be available on patient reported outcomes and procedure morbidities
4. No restriction on language or year of publication. When necessary, a native speaker was asked to translate the title, abstract or full text.

2.2.3 Exclusion criteria

1. Patients treated with bone grafts harvested from other donor sites than the calvarium or anterior iliac crest
2. Patients with known bone disorders or medical conditions that could affect the donor site (parietal skull or anterior iliac crest).
3. Systematic reviews, case reports, letters to the editor, expert's opinion, conference abstracts

2.3 Eligibility criteria

Two observers (D.E.W. and B.v.M) independently assessed the titles and abstracts identified in the initial search according to the inclusion and exclusion criteria. If the title and abstract provided limited information, or in case of doubt, the studies were moved to the next round (full text assessment). In case a study compared anterior iliac crest or calvarial bone grafting with a control group not relevant to this review, such as a group treated with bone harvesting from other donor sites or treated with bone substitutes, it was assessed as a single arm study. The results of the study assessments were compared, the Cohen's Kappa and percentage of agreement were calculated, and any disagreement was resolved through consensus. The full texts of the included titles and abstracts were independently assessed according to the criteria by the same observers. The Cohen's Kappa and percentage of agreement were calculated, and any disagreement was resolved through consensus.

2.4 Risk of bias assessment

The RCTs' risk of bias was assessed with the appraisal Risk of Bias 2 (RoB 2) tool from the Cochrane Handbook for Systematic Reviews of Interventions V.5.1.0[14], which assesses

the following study-level aspects: (1) randomization sequence allocation; (2) allocation concealment; (3) blinding; (4) completeness of outcome data and (5) selective outcome reporting. It classifies studies into low, high, or unclear risk of bias.

The Newcastle-Ottawa Scale (NOS)[15] was used to assess the quality of the nonrandomized studies (non-RCTs) with meta-analyses. Each study is judged on eight items with this tool, categorized into three groups: (1) the selection of the study groups, (2) the comparability of the groups and (3) the ascertainment of either the exposure or outcome of interest of the case-control or cohort studies, respectively.

Discrepancies between the two reviewers when assessing the quality of the included studies were resolved in a consensus meeting. A third reviewer (GMR) was consulted to give a final judgment in case a disagreement persisted. The percentage of agreement between the reviewers and the Cohen's kappa coefficient (κ) were calculated per item/domain of the used tool.

2.5 Data extraction

Data extraction was performed (D.E.W.) using a predefined standardized form. A random sample of 30% of the extracted data was checked by the second reviewer (B.v.M.). Data on the study and patient characteristics, and the primary and secondary endpoints, were extracted. The method of assessment, moment of assessment (number of days or months postoperatively), and the outcomes were noted. In case the moment of assessment varied among the studies regarding a certain outcome, the results were grouped per time frame (first week postoperatively, first month postoperatively, six months postoperatively, more than six months postoperatively). If various rating scales were used for a continuous outcome, the scales were recalculated to a 0-10 score with 0 representing the absence of the outcome ('No pain', or 'Not satisfied') and 10 representing full presence of the outcome ('Worst perceivable pain' or 'Highly satisfied').

2.6 Statistical analysis

Interobserver agreement was calculated with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA). Data on the primary outcome (patient satisfaction) and secondary outcomes (intensity and prevalence of pain, problems in daily functioning, sensitivity alterations, patient satisfaction with scar aesthetics and prevalence of perioperative complications) were collected using Microsoft 365 Excel (version 16.50). The pooled standardized mean difference (SMD), with a 95% confidence interval (CI), was calculated for the continuous variables, i.e. patient satisfaction and the postoperative pain VAS-scores, as these were the best comparable variables between the two distinct surgical sites. Statistical heterogeneity was regarded as substantial if I^2 >50%.

The meta-analysis was performed with R package meta23, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austra), using a random-effects model because of clinical heterogeneity.

3 RESULTS

3.1 Study identification and selection

A total of 3123 papers was identified. After excluding duplicates, 1946 papers were retrieved and screened by title and abstract (Figure 1). Subsequently, 1870 titles and abstracts were excluded (a list of all the identified and excluded papers not presented in this paper can be requested from the corresponding author). Disagreements (n=64) were resolved in a consensus meeting. The percentage of agreement between the reviewers and the Cohen's kappa coefficient (κ) for the titles and abstracts were 94% and 0.62, respectively. The full texts of the remaining 76 reports were screened and, subsequently, 43 reports were included. Among these, three articles used data from studies described by other articles as well[16-21] thus the data from both reports were combined. Finally, 40 studies were included for data collection and quality assessment (Figure 1)[16-58]. The percentage of agreement and the Cohen's kappa coefficient were 91.4% and 0.82, respectively.

3.2 Assessment of methodological quality

The randomized comparative trials[18,19] were assessed with the Rob 2 tool. Low risk of bias was seen in the following domains: 'Deviations from intended interventions', 'Measurement of the outcome' and 'Selection of the reported result'. Intermediate risk of bias was seen in these domains: 'Randomization process' and 'Bias due to missing outcome data'. The other studies were analysed with the NOS tool (Table S2)[16,17,20-59]. High risk of bias was observed in 'Selection of the groups' (69.3%). Unclear risk of bias was seen in 'Exposure' (51.3%). The 'Comparability of the groups' domain was only applicable to one retrospective comparative trial (Table S2)[22], as the remaining studies had only one arm of interest for this review, and this was interpreted as a high risk of bias (97.4%). The Cohen's weighted kappa was 1.0, 1.0 and 0.88 for 'Selection of the groups', 'Comparability of the groups' and 'Exposure', respectively.

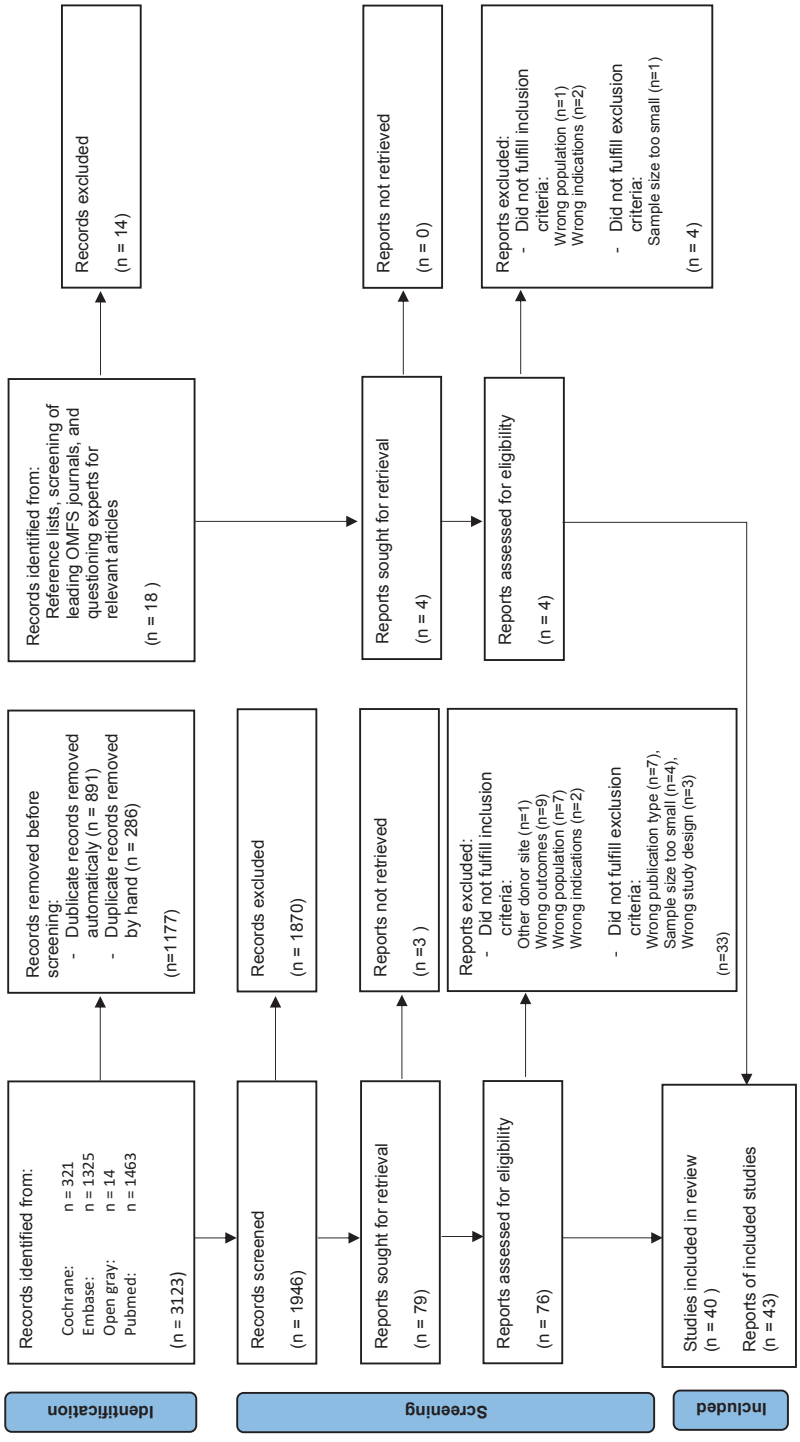

Figure 1. Flowchart presenting the identification of the literature and selection progress.

Table 1 Characteristics of included studies

	Study design			Study population						
				Calvarium			AIC			
Author, year	**Follow-up (Months)**	**Type**	**Setting**	**n**	**Males (%)**	**Age (mean) (Years)**	**n**	**Males (%)**	**Age (mean) (Years)**	**Comorbid.**
Comparative studies										
Kuik et al, 2016[22]	28,8	CCT	MC	27	52%	60 (55-66)	27	44%	61.1 (55-67)	Unk.
Putters et al, 2018[18] (& Wortmann et al, 2019[19])	12	RCT	SC	10	50%	65.9 (SD 8.7)	10	40%	63.5 (SD 7.0)	Exc.
Non-comparative prospective studies										
Raghoebar et al, 1993[38]	16	PCS	SC	0	-	-	22	52%	48 (R: 19-64)	Exc.
Chiapasco et al, 1999[26,1]	12	PCS	SC		-	-	13	22%	42.1(SD 12.5)	Exc.
Raghoebar et al1999[39]	32	PCS	SC	0	-	-	65	52%	42 (SD 11)	Exc.
Stellingsma et al, 2003[40]	12	PCS	SC	0	-	-	19	17%	59 (SD11)	Exc.
Joshi et al, 2004[30]	12	PCS	SC	0	-	-	98	38%	44 (R: 16-75)	Unk.
Nkenke et al, 2004[34]	1	PCS	SC	0	-	-	25	44%	52 (SD 9.6)	Exc.
Weingart et al, 2005[43]	1	PCS	SC	0	-	-	46	44%	55 (R:20-69)	Exc.
Gerressen et al, 2009[29]	5.2	PCS	SC	0	-	-	15	40%	54.9(R: 39-72)	Unk.
Virnik et al, 2009[42]	8	PCS	Unk	0	-	-	20	50%	56.3 (R:43-62)	Exc.
Barone et al, 2011[23]	5	PCS	SC	0	-	-	235	34%	54.3 (SD 10.2)	Exc.
Becker et al, 2011[24]	48	PCS	SC	0	-	-	50	52%	52 (SD 2.0)	Exc.
Felice et al, 2011[20] (& Esposito et al, 2015[21])	12	PCS	MC	0	-	-	13	38%	52 (R:29-65)	Exc.
Marianetti et al, 2013[31]	12	PCS	SC	0	-	-	73	41%	49.3 (14,55)	Exc.
Mertens et al, 2013[95]	15	PCS	SC	12	27%	54 (R: 30-71)	0	-	-	Exc.
Reissmann et al, 2013[95] (& Reissmann et al, 2018[16])	1	PCS	SC	0	-	-	15	40%	46.1 (SD 15.5)	Exc.
Pistilli et al, 2014[35]	8	PCS	MC	0	-	-	14	50%	49.5 (38-62)	Exc.
Sassano et al, 2014[41]	12	PCS	SC	6	33%	63 (60-67)	0	-	-	Exc.
Fretwurst et al, 2015[96]	6	PCS	SC	0			20	25%	54.3 (R: 20-78)	Exc.
Putters et al, 2015[97]	25	PCS	MC	36	39%	59 (SD 8.2)	0	-	-	Exc.
Mertens et al, 2017[32]	54	PCS	SC	17	6%	54.3 (R: 25-71)	0	-	-	Exc.
Cansiz et al, 2019[25]	0.75	PCS	SC	0	-	-	10	50%	43 (SD 10.4)	Exc.
Elhadidi et al, 2019[27]	4	PCS	SC	0	-	-	8	Unk	Unk	Inc.
Putters et al, 2019[36]	4	PCS	SC	13	31%	68 (SD 9)	0	-	-	Exc.
Non-comparative retrospective studies										
Donovan et al, 1994[49]	31	RCS	SC	24	33%	48(R:20-67)	0	-	-	Unk
Lundgren et al, 1997[52]	22	RCS	SC	0	-	-	10	10%	55 (R:43-71)	Exc
Kübler et al, 1999[51]	6	RCS	SC	0	-	-	39	Unk	Unk	Exc
Cricchio et al, 2003[47]	24	RCS	SC	0	-	-	70	39%	56(38-69)	Unk
Yerit et al, 2004[58]	144	RCS	SC	28	29%	58 (SD 10)	0	-	-	Unk
Barone et al, 2005[45]	5	RCS	SC	0	-	-	18	33%	46.7(R: 37-60)	Exc
Szabó et al, 2005[57]	6	RCS	MC	0	-	-	20	45%	52 (R:28-67)	Exc

Table 1 Continued

				Study population						
	Study design			Calvarium			AIC			
Author, year	Follow-up (Months)	Type	Setting	n	Males (%)	Age (mean) (Years)	n	Males (%)	Age (mean) (Years)	Comorbid.
Barone et al, 2007[44]	4.5	RCS	SC	0	-	-	56	32%	Unk(R:27-630	Exc
Pelo et al, 2010[53]	44	RCS	SC	0	-	-	19	37%	58.8 (R:48-68)	Exc
Deppe et al, 2012[48]	6	RCS	SC	0	-	-	54	43%	57.2(Unk)	Exc
Restoy-Lozano et al, 2015[54]	45	RCS	SC	11	20%	44 (R: 18-62)	0	-	-	Exc
Quiles et al, 2015[57]	132	RCS	SC	25	Unk	Unk	0	-	-	Unk
Chiapasco et al, 2018[46]	228	RCS	SC	72	25%	48 (R: 16-72)	0	-	-	Exc
Sakkas et al, 2018[55]	12	RCS	SC	0	-	-	38	Unk	Unk	Exc
Gjerde et al, 2020[50]	94	RCS	SC	0	-	-	44	46%	61.2 (SD13.1)	Exc

Abbreviations: Calvarium: patients treated with calvarium bone grafts; AIC: patients treated with anterior iliac crest bone grafts; RCT: randomized clinical trial; PSC: prospective cohort study; RSC: retrospective cohort study; SC: single centre study; MC: multicentre study; Comorb: patients with comorbidities affecting bone quality or quantity, tissue healing capacities or patients with pathologic conditions at the donor site including previous surgery or irradiation of this area; Exc: excluded; Inc: included; Unk: unknown

[I]This study included 2 patients treated with calvarium bone grafts who did not fit our inclusion criteria, thus only the anterior iliac crest group was included

Table 2 Patient reported satisfaction with the procedure and postoperative pain

	Satisfaction with procedure								Postoperative pain							
									Severity			Prevalence				
	Rating VAS (0-10)		Question 'Yes' (%)		Recommend 'Yes'(%)		Redo 'Yes'(%)		Rating VAS (0-10)		Timing (Mo)	1st week (%)		1 month (%)		6< months (%)	
	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC		Calv	AIC	Calv	AIC	Calv	AIC
Kuik et al, 2016[22]	10(9.4-10)	10(8.3-10)	-	-	96	96	100	89	0.5 (0.0-3.0) 0.0 (0.1-0.0)	4.7 (2.4-8.0) 0.0 (0.0-0.0)	0.25[II] 27	-	-	-	-	0	0
Putters et al, 2018[18] (& Wortmann et al, 2019[19])	8.8(8.1-10)	9.5(9.0-9.5)	-	-	100	100	100	100	3.5 (1.0-5.0 0.3 (0.0-1.0) 0.1 (0.0-0.1)	4.0 (2.0-4.0) 0.6 (0.2-2.1) 0.2 (0.1-0.3)	0.25[III] 0.25[II] 12	20	20	-	-	0	0
Non-comparative prospective studies																	
Stellingsma et al, 2003[40]	-	-	-	-	-	-	-	90	-	-	-	-	85	-	-	-	-
Joshi et al, 2004[30]	-	-	-	-	-	92		85	-	-	-	-	82	-	69	-	-
Nkenke et al, 2004[34]	-	-	-	-	-	-	-	-	-	3.7 (SD 1.4)	0.25	-	-	-	-	-	-
Weingart et al, 2005[43]	-	-	-	-	-	-	-	-	-	1.4 (SD 0.7)	1	-	-	-	-	-	-
Virnik et al, 2009[42]	-	-	-	-	-	-	-	-	-	2.2[IV]	0.25	-	-	-	-	0	
Barone et al, 2011[23]	-	-	-	-	-		-	97	-	5.5 (R:3-8) 3.3 (R:2-6)	0.25 0.5	-	99	-	64		0
Becker et al, 2011[24]	-	-	-	-	-	95	-	80	-	5[V] 2.5[V] 0[V]	0.25 1 12	-	48	-	36	-	0
Felice et al, 2011[20] (& Esposito et al, 2015[21])	-	10	-	-	-	-	-	100	-	-	-	-	100	-	100	-	0
Marianetti et al, 2013[31]	-	-	-	-	-	97		100	-	-	-	-		-	-		-
Mertens et al, 2013[95]	-	-	-	-	-	100		100	0	-	12	0		0	-	0	-
Reissmann et al, 2013[18] (& Reissmann et al, 2018[17])	-	-	-	-	-	-	-	-	-	2.9 (SD 2.5)[VI]	0.25	-	100		100		-
Pistilli et al, 2014[35]	-	-	-	-	-	-	-	-	-	0.6 (SD 0.8)	1	-		-	-	-	-
Sassano et al, 2014[41]	-	-	-	-	-	-	-	-	-	-		-	71	-	-	-	-
Fretwurst et al, 2015[96]	-	-	-	-	-	-	-	-	Unk[VII]	-		-		-	-	-	-

Table 2 Continued

	Satisfaction with procedure								Postoperative pain								
									Severity			Prevalence					
	Rating VAS (0-10)		Question 'Yes' (%)		Recommend 'Yes'(%)		Redo 'Yes'(%)		Rating VAS (0-10)		Timing (Mo)	1st week (%)		1 month (%)		6< months (%)	
	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC		Calv	AIC	Calv	AIC	Calv	AIC
Putters et al, 2015[97]	-	-	-	95	-	-	-	-	-	-	-	-	-	-	25	-	0
Mertens et al, 2017[32]	-	-	-	-	-	-	-	-	0	-	1	36	-	0	-	0	-
Putters et al, 2019[36]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Non-comparative retrospective studies																	
Donovan et al, 1994[49]	-	-	-	-	94		94	-	0[V]	-	12	0	-	0	-	0	-
Lundgren et al, 1997[52]	-	-	-	-	-	95	-	80	-	-	-	-	20	-	20	-	0
Kübler et al, 1999[51]	-	-	-	-	-		-	-	-	-	-	-	5	-	5	-	-
Cricchio et al, 2003[47]	-	-	-	-	-	94	-	-	-	-	-	-	86	-	43	-	0
Yerit et al, 2004[58]	9.5 (R: 8-10)	-	-	-	-	-	100	-	-	-	-	-	-	-	-	-	-
Barone et al, 2005[45]	-	-	-	-	-	-		-	-	-	-	-	22	-	0	-	0
Barone et al, 2007[44]	-	-	-	-	-	-		-	-	-	-	-	11	-	0	-	
Deppe et al, 2012[48]	-	-	-	-	-	-		83	-	-	-	-	54	-	44	-	0
Quiles et al, 2015[57]	-	-	97	-	1	-	1	-	-	-		19	-	-	-	-	-
Chiapasco et al, 2018[46]	-	-	90		-	-	9	-	0.0 (0.0-4.0)	-	0.5	-	-	-	-	-	-
Gjerde et al, 2020[50]	-	-	-	85	-	-	-	-	-	4.4 (SD 2.7)	Unk	-	38		2	-	-

Depiction of the results on patient reported satisfaction with the procedure in general, assessed by means of a VAS-score of a dichotomous question whether they would recommend the treatment to others with a similar problem and whether they would undergo the same treatment again if necessary. Also, patient reported postoperative pain is assessed here. The severity of the pain is presented as a VAS-score and the corresponding timing of the assessment is provided in months, and the prevalence of pain at 1 week, 1 month or 5 months postoperatively is provided.

Abbreviations: Calv: patients treated with calvarium bone grafts; AIC: patients treated with anterior iliac crest bone grafts; SD: standard deviation; IQR: interquartile range; R range.

[I] *The score for pain on a 0-10 scale with 0 representing no pain and 10 representing worst pain thinkable. The scores are presented as mean (SD), median (IQR) or median (r).*

[II] *Postoperative pain was assessed directly after harvesting on recall, and at follow up 2.5 years later.*

[III] *This study's maximum pain scores were seen on days 2 and 3*

[IV] *This study reported that the use of additional pain medication was not necessary in any patient; other reports on pain or the use of medication were not provided*

[V] *This study does not provide details on whether it is mean or median. Additionally, SD, range and IQR are not provided.*

[VI] *This represents the maximum pain felt during the first week*

[VII] *The pain that occurred in the patients was well controlled with nonsteroidal analgesics*

3.3 Study characteristics

The 40 included studies, consisting of one RCT, one CCT, 23 prospective cohort studies and 15 retrospective cohort studies, were published between 1986 and 2020 (Table 1). The follow-up ranged from 3 weeks to 228 months. Two studies declared funding from a research programme[25,42] and 25 studies did not mention funding or conflict of interest[21-24,26-30,32-35,38,39,41,43-45,48,49,51,52,54,56,59]. All the remaining studies declared they did not have any funding or conflict of interest.

3.4 Interventions

All the interventions were performed under general anaesthesia. All 40 included studies provided a description of the graft harvesting procedure, namely monocortical bone blocks and, if necessary, additional cancellous bone or scraped cortical bone fragments.

The techniques used for calvarial harvesting were similar to that described by Tessier[60], Kellman[5,11,61] or Schortinghuis[5,11,18,19,22]. The information on the prevention of intracranial perforations and filling of the contour defect varied. Bone graft harvesting was followed by alveolar ridge reconstructions. In one study, augmentation was combined with direct implant placement[36].

Most of the anterior iliac crest monocortical blocks were harvested from the medial site[19-21,24,25,26,28,31,34,35,39,42,45,52,55,57,58]. In 11 studies, the site of the crest was not mentioned[16,17,22,29,30,38,43,48,51,53,56,59]. Care for the lateral femoral cutaneous nerve, haemostasis and the location of the incision was described in varying detail. Postoperative interventions, such as standard physical therapy and advice to use crutches, was described by 12 studies[18,19,24-28,37,42-44,47,55].

3.5 Primary outcome

3.5.1 Patient reported satisfaction

Regarding the calvarial bone grafts, 6 studies(186 patients in total) reported the satisfaction score for the procedure in general, which ranged from 8.9-10[19,22,58], that 94-100% of the patients [19,22,49,57] would recommend the procedure to others, and 94-100% would undergo the same procedure again if necessary[19,22,46,49,57,58] (Table 2).

Regarding the anterior iliac crest bone grafts, 13 studies (689 patients in total) reported the patients' general satisfaction which, ranged between 9.0-10[19,21,22,58,59], and that 92-100% of the patients[19,22,24,30,31,33,47,52] would recommend the procedure to others and 80%-100%[19,21-24,30,31,33,40,48,52] of the participants were willing to undergo the same treatment again if necessary (Table 2).

3.6 Secondary outcomes

3.6.1 Postoperative pain

3.6.1.1 Postoperative pain severity

The reported median values for the highest pain experienced following calvarial harvesting ranged between 0.0-0.5, measured with a 0-10 VAS-score for all follow-up periods[19,22,33,37,46,49,57,58] (Table 2). The anterior iliac crest's harvesting pain VAS-score during the first week ranged between 2.9-5.5[17,19,22-24,31,34,42] and then between 0.6 and 2.5 after one month [17,24,34]. Both sites' long term median reported pain score was 0.0[22,49] (Table 2).

The RCT compared the direct postoperative course of pain intensity between calvarial and anterior iliac crest harvesting by means of a diary with VAS-scores. The course the pain scores took was statistically significantly higher for the anterior iliac crest patients: the calvarial bone patients' maximum pain score was 3.3 and this deceased to 0 after 14 days, whereas the maximum was 3.5 for the anterior iliac crest patients and this deceased to 0 after 28 days[18]. The comparative case series demonstrated that early postoperative pain, assessed on recall, was significantly higher for the anterior iliac crest patients (calvarial group: 0.5; anterior iliac crest group: 4.7)[22].

The RCT demonstrated higher pain scores for patients with a higher BMI in the anterior iliac crest group (p=0.04), but not in the calvarium group (p=0.93)[19].

3.6.1.2 Postoperative pain prevalence

The two comparative studies mentioned equal outcomes for both sites' postoperative pain prevalences: 20% during the first week[18] and 0%[18,22] after more than 6 months (Table 2).

3.6.2 Disturbances in daily functioning

None of the calvarial bone graft harvesting patients reported disturbances in daily functioning after 6 months[18,22] (Table S3). The anterior iliac crest patients experienced gait disturbances, ranging from 19-100%,[24,26,28,29,31,34,47,52] and the necessity to use a walking aid which ranged between 11-100%[23,28,30,44,47,51] in the first week. This was temporary for most of the patients. However, some studies reported that 4-20% of the patients had difficulties for more than 6 months[18,22,24,47,50] (Table S3).

3.6.3 Postoperative donor site sensory alterations

None of the comparative studies demonstrated statistically significant differences regarding the prevalence of sensory alterations between both donor sites[18,22] (Table S3). Long term objective sensory alterations following calvarial harvesting were seen in 0-15% of the patients[22]. Subjective hypesthesia was reported in 7%[33] of the patients during the first week. Most sensory

alterations following anterior iliac crest harvesting during the first postoperative week were reported as objective (0-52%)[18,23,28,34,51,56] and subjective (0- 26%) hypesthesia[28-30,47,51] (Table S3). Paraesthesia was reported subjectively by 3%-10% of the patients[18,47,48,53,55]. The long term assessments demonstrated objective sensory alterations in some cases (0-10%)[22,50,56].

3.6.4 Aesthetics at donor site

3.6.4.1 Objective donor site aesthetic outcomes

Objective contour alterations were seen in 20-100% of the calvarial bone graft patients[18,22,37,54], with the majority being subtle deficits[18,22,54] (Table S4). Also, 0-85% of the patients mentioned contour alterations[18,22,37]. Scarring alopecia was reported by two studies, in 9 and 20%[22,54] of the cases, respectively. Regarding the anterior iliac crest grafts, objective contour alterations were seen in 3-67%[18,22,47] of the patients even though only 1-19% of the patients reported alterations [18,22,23].

3.6.4.2 Subjective donor site aesthetic outcomes

The satisfaction score for the donor site aesthetics was high for both sites on a 0-10 scale, i.e. 10 for calvarium[22] and 7.3-10[22,24,31] for anterior iliac crest (Table S4). All the calvarium patients confirmed they were satisfied with the donor site appearance[19,22] whereas 60%-100%[19,22,23,30,50] of the anterior iliac crest participants were satisfied with the donor site aesthetics. Joshi et al[30] reported that the younger patients were less satisfied with the aesthetics. Regardless of the donor site, no patients considered the contour changes to be bothersome[22].

3.6.5 Perioperative complications

3.6.5.1 Major complications

Trepanation of the skull was an endpoint in 8 studies. This comorbidity was not seen in 6 of these studies[5,27,32,33,41,46] but the remaining two studies reported an incidence of 11% [18,22](Table S4). After finding an incidence of 11%, one changed the harvesting technique during the study whereupon such complications did not occur anymore[5]. All the defects were closed immediately and healed without consequences in all cases.

The incidence of anterior iliac crest fractures was 0%-5%[18,22-24,28-30,34,47]. All the fractures were treated conservatively and healed without further consequences.

3.6.5.2 Minor complications

The minor complications among the participants treated with calvarial bone grafts or anterior iliac crest are shown in Table S4.

3.7 Meta-analysis

3.7.1 Patient satisfaction with the procedure in general

Data derived from two comparative studies[19,22] showed that the study outcomes varied a lot (I^2 = 79%, p=0.03) but the statistical differences were not significant between the calvarial and anterior iliac crest harvesting VAS scores (SMD -0.13, % CI: -1.17;0.92; z=-0.24, p=0.813; Figure 2). The variations can be explained by differences in assessment timing (12 and 27 months, respectively). No further sub-group or meta-regression analysis could be performed due to the small number of included studies.

3.7.2 Severity of pain

A meta-analysis of the data derived from the two comparative studies[19,22] resulted in great outcome variations (I^2 = 82%, p = 0.02). The VAS score for the direct postoperative pain outcome was slightly lower following calvarial bone harvesting, although the differences were not statistically significant (SMD, -2.32; 95% CI: -5.20; 0.55; z = -1.59; p = 0.113; Figure 3A). Despite the late postoperative pain outcomes varying a lot as well (I^2 = 8%, p = 0.30), the differences in the VAS scores were not statistically significant (SMD, -0.01; 95% CI: -0.14; 0.11; z = -0.22; p = 0.825; Figure 3B). The variations can be explained again by differences in assessment timing (12 and 27 months, respectively). No subgroup or meta-regression analysis could be performed due to the small number of included studies.

3.8 Evidence quality

All the included studies had a high risk of bias due to the nature of the comparison: the surgeons and patients could not be blinded for the donor site used. Furthermore, only 2 studies were comparative.

The quality of the evidence was moderate for patient satisfaction and postoperative pain severity according to GRADE[62-64] . The evidence for the remaining outcomes was of limited quality due to the high variations in outcome measures, the indirectness of the assessments, and due to data imprecision. The data derived from the prospective and retrospective cohort studies were assessed as being very low quality. Endpoints based on very low-quality evidence cannot be used to make recommendations to surgeons and should therefore be interpreted with caution.

Figure 2 Forest plot of pooled patient reported satisfaction after haversting calvarium vs. anterior iliac crest grafts[18,19,22]. Abbreviations: Calv: patients treated with calvarium grafts; AIC: patients treated with anterior iliac crest grafts; MD: mean difference; CI: 95% confidence interval.

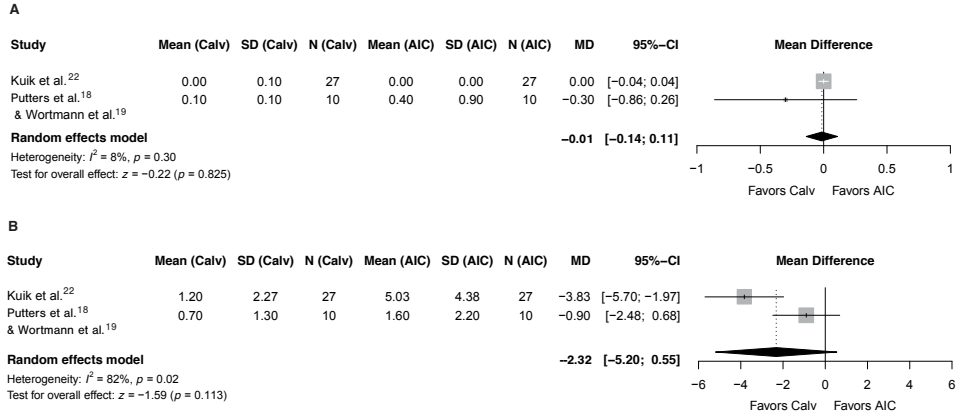

Figure 3 Forest plots of the secondary endpoints: pooled patient reported severity of postoperative pain after harvesting calvarium vs. anterior iliac crest grafts. (A) Direct postoperative pain; (B) late postoperative pain
Abbreviations: Calv: patients treated with calvarium grafts; AIC: patients treated with anterior iliac crest grafts; MD: mean difference; CI: 95% confidence interval.

4 DISCUSSION

This systematic review evaluated patient satisfaction, morbidity and complications associated with anterior iliac crest or calvarial bone graft harvesting for dental implant placement The meta-analysis showed that the patient reported satisfaction after undergoing calvarial bone graft and anterior iliac crest graft harvesting was similar. Furthermore, postoperative pain, sensory disturbances and complications were limited and the donor site aesthetics ratings were generally very positive regardless of the donor site. However, based on both the comparative and non-comparative studies, the prevalence of daily disturbances seemed higher following anterior iliac crest harvesting.

4.1 Patient satisfaction

The comparative studies demonstrated high patient satisfaction regardless of the donor site. Similarly, Falkensammer et al[65] assessed patients' satisfaction with anterior iliac crest harvesting for sinus lifting or onlay bone reconstructions in partially edentulous patients, and reported high acceptance as well; 84% of the patients would agree to undergo the same treatment if they had to choose, and 87% would recommend this treatment to other patients[65]. To the best of our knowledge, no other data on patient satisfaction following calvarial bone grafting exists.

Several possible factors affecting patient satisfaction could be identified from the literature. An important determinant of patient satisfaction is fulfilment of patient expectations, i.e. adequate information provided by health care providers can enhance patient appreciation[66,67]. Additionally, there is evidence that patient sociodemographic factors, e.g. education level, cultural back ground, social network, can affect their satisfaction with the health services[66]. RCTs in the future could limit bias due to health service characteristics and sociodemographic factors. Also, patients who underwent bone grafting surgery as part of a larger treatment procedure and improvements in denture function might override any dissatisfaction with the harvesting surgery. Furthermore, patient reported experiences are important predictors of overall patient satisfaction[65,67]. For example, postoperative pain, disturbances in daily living or unfavourable scar formation may affect patient appreciation of the procedure.

4.2 Secondary outcomes

4.2.1 Pain

In concordance with reports on calvarial or anterior iliac crest harvesting for other indications[7,9,12,65], early postoperative pain was more evident after harvesting anterior iliac crest bone. Several reports on causes of pain following anterior iliac crest harvesting suggested making technical adjustments to limit pain. These include minimizing the manipulation of the abductors from the ilium, avoiding nerve injury as well as using bone wax or other haemostatic materials to treat the cortices, and post-harvest reconstruction of the iliac crest[2,68] . There are also suggestions related to using a bupivacaine pump[2,69]but the evidence of the impact on morbidity is conflicting[2,69]. In the present study, an evaluation of the various harvesting techniques used for anterior iliac crest bone graft harvesting was not feasible as there was lack of documentation of the exact harvesting method in most of the reviewed studies.

When choosing between calvarial and anterior iliac crest, pain should be considered, particularly for patients with a higher a priori risk of elevated postsurgical pain. Specifically, pain severity and duration appears to be higher in patients who are younger, female, have smoking habits, history of depressive symptoms, anxiety symptoms or difficulties, previous preoperative pain and the use of preoperative analgesia[70-73]. However, some of the currently

reviewed studies reported no correlations between age and gender[19,28]. Additionally, in concordance with some of the currently reviewed studies[19,28], higher BMI is associated with pain[70-74] and postoperative adverse events[75,76]. This may be due to compromised wound healing[77] or limited accessibility of the donor site, thereby strengthening the postoperative pain and gait disturbances following a manipulation of the tendo-musculosceletal structures around the donor site.

4.2.2 Gait disturbances

The second most reported morbidity following anterior iliac crest harvesting is acute gait disturbance as well as chronic walking difficulties. This corresponds to a previous review[68]. It is postulated that gluteal stripping and subsequent postoperative pain is a major cause of gait modification following iliac crest bone harvesting[2,65,68]. Thus, the prevalence of pain and gait disturbances is expected to exhibit a similar course.

To the best of our knowledge, disturbances in daily functioning following calvarial harvesting have not been reported. Such complaints are possibly absent because the strain borne by parietal skull and related musculoskeletal structures is neglectable during regular daily activities.

4.2.3 Sensory donor site alterations

Acute sensory disturbances occurred in up to half of the patients whose anterior iliac crest was harvested and these were considered to be mostly objective alterations. Chronic sensory disturbances were not reported, in contrast to other reviews[2,3,68] which included patients undergoing spinal or orthopaedic surgery. Their outcomes may have resulted from technical differences in harvesting surgery or differences in the required volume of grafted bone, since most sensory disturbances are believed to result from direct trauma or stretching injury of the lateral cutaneous nerve during anterior iliac crest harvesting[2,3,68]. Regarding calvarial harvesting, sensory alterations are attributed to a coronal incision or use of electrocautery[7,78,79]. A parasagittal incision and limited use of electrocautery is therefore advised.

4.2.4 Donor site aesthetic outcomes

Irrespective of the harvesting location, the patients were generally satisfied with the donor site aesthetic outcomes. Scalp contour alterations were not reported as causing dissatisfaction, probably because these alterations were covered with hair and most of the deficits were subtle. The appreciation of the aesthetics following iliac crest harvesting was lower in some studies. Patient expectations of the outcomes could play a role here, as patients might be more prepared to scar formation or contour alterations when calvarial bone is harvested. Since only two comparative studies were included, identification of factors affecting satisfaction such as age, gender, and treatment necessity, could not be performed. Still, we assume that the skull is more at risk of significant aesthetic sequelae since it is part of a person's appearance,

particularly since the donor site is located more superficially and hair gets thinner with age. Therefore, contour alterations and alopecia associated with calvarial harvesting should be minimized.

Depression of the skull following calvarial harvesting is common[7,78]. It is explained by the incapacity of the periosteum to reproduce bone tissue of the same magnitude to refill the newly formed defect, in particular for defects greater than 2 cm[2,80-82]. Also, skull deficits are easily detected due to its superficial position. To minimize this, defects should be reconstructed with a biomaterial[83]. Osteoconductive biomaterials which undergo osseointegration are generally preferred[83,84].

Alopecia can be avoided with several technical adjustments[7]. First, it is stated that an incision with an angle of 30 degrees to the follicles preserves the deeper parts of them and decreases the number of hairs that grow back in the scar[85]. Second, tension on the sutures increases the width of the scar[86]. Also, minimal use of electrocoagulation would reduce hair loss together with a reduced scar width[7,79].

4.3.4 Complications

The incidence of major and minor complications was low after both procedures and no long-term sequela of these complications were reported. Additionally, the comparative studies reported no significant differences in complication rates. These outcomes are in line with previous reports[3,9,87,88].

In the literature, calvarial bone graft harvesting has been associated with several perioperative or immediate postoperative complications related to dura exposure. These complications were not reported in the included studies and the incidence in previous reviews was low as well[88-92]. In fact, due to recent adjustment of the technique, the incidence of such complications has drastically decreased[5,88-93]. However, to ensure safe harvesting, a surgeon with experience in the technique and instrumentation is strongly advised[5,88-93].

The most important major complication found in the current review following anterior iliac crest harvesting was, as in previous reviews[2,68], fracture of the crest. A systematic review on morbidity following iliac crest harvesting advised careful patient selection as osteopenia or osteoporosis, female gender and advanced age may increase the incidence of iliac graft site fracture[2].

A recent study comparing anterior iliac crest harvesting and calvarium bone grafts, with respect to various indications, reported higher complication rates for both sites compared to the current review[9]. The discrepancy between those and the current findings could be due to different indications and related patient factors, i.e. bone quality and healing capacity of the donor sites, and technical considerations, i.e. the applied harvesting techniques.

4.5 Implications for future studies

The conclusions drawn in this systematic review need to be interpreted with caution because of the large heterogeneity in study designs and the limited number of eligible studies. The studies demonstrated high patient satisfaction regardless of the donor site, although, the reported outcomes on satisfaction included in the meta-analysis were ambiguous. To enhance the quality of the evidence in the future, we suggest that RCTs comparing calvarial and anterior iliac crest harvesting should be performed using pre-specified and well-defined protocols, with special emphasis on well-defined endpoints, i.e. patient reported outcomes including sources of dissatisfaction to minimize reporting bias and adequate sample sizes to minimize attrition bias. Also, well-defined standardised and validated measures to assess patient reported outcomes, such as validated questionnaires and VAS-scores for satisfaction and postoperative pain, should be used. Additionally, the reporting of patient characteristics, including comorbidities and surgical techniques, i.e. incision, graft harvesting, and donor site reconstructions, should be improved. Future studies should comply with the CONSORT guidelines to ensure high quality reporting of all aspects of the methodology and results[94].

4.6 Conclusions

Harvesting calvarial and/or anterior iliac crest bone grafts results in comparable patient satisfaction. Regardless of the donor site, the morbidity is low and generally temporary, and complications seldom occur. Subsequent adverse sequela in patients were not reported. However, the findings on postoperative pain, disturbances in daily living and complications are more in favour of calvarial harvesting when harvested by the adjusted technique. Thus, current available evidence shows that calvarial bone grafts are a viable alternative to anterior iliac crest bone grafts. To enable a better understanding of the differences between both harvesting sites, randomized controlled trials with validated and structured assessments of patient reported outcomes, are essential.

5 DECLARATIONS

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None.

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SUPPLEMENTAL TABLES

Table S1 Search strategy

PubMed
("Alveolar Ridge Augmentation"[Mesh] OR ((alveolar[tiab] OR maxilla*[tiab] OR mandib*[tiab] OR ridge[tiab]) AND (augment*[tiab] OR elevat*[tiab] OR pre-implant*[tiab] OR preimplant*[tiab] OR preprosthe*[tiab] OR pre-prosthe*[tiab])) OR (alveolar ridge*[tiab] AND reconstruct*[tiab])) AND ("Transplant Donor Site"[Mesh] OR extra-oral*[tiab] OR *(donor[tiab] AND site*[tiab])* OR "Ilium/surgery"[Mesh] OR ilium[tiab] OR iliac crest*[tiab] OR "Parietal Bone"[Mesh] OR "Skull"[Mesh:NoExp] OR parietal[tiab] OR calvar*[tiab] OR (distant[tiab] AND site*[tiab]) OR (harvest*[tiab] AND site*[tiab]) OR ((autologous[tiab] OR autogenous[tiab]) AND (graft*[ti] OR harvest*[ti]))) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])
Embase
('alveolar ridge augmentation'/exp OR 'alveolar bone loss'/exp OR "oral onlay grafting":ab,ti OR ((alveolar OR maxilla* OR mandib* OR ridge) AND (augment* OR elevat* OR "pre-implant*" OR preimplant* OR preprosthe* OR "pre-prosthe*")):ab,ti OR ('alveolar ridge' AND (resorp* OR reconstruct* OR 'bone graft*')):ab,ti) AND ('donor site'/exp OR 'iliac bone'/exp OR 'skull'/de OR 'calvaria'/exp OR 'parietal bone'/exp OR ("extra-oral*" OR *(donor AND site*)* OR ilium OR "iliac crest*" OR parietal OR calvar* OR (distant AND site*) OR (harvest* AND site*)):ab,ti OR ((autologous OR autogenous):ab,ti AND (graft* OR harvest*):ti)) NOT ('animal'/exp NOT 'human'/exp)
Cochrane Trials
(((alveolar OR maxilla* OR mandib* OR ridge) AND (augment* OR elevat* OR "pre-implant*" OR preimplant* OR preprosthe* OR "pre-prosthe*")) OR (alveolar ridge* AND reconstruct*)):ti,ab,kw AND ("extra-oral*" OR ilium OR "iliac crest*" OR parietal OR calvar* OR (distant AND site*) OR (harvest* AND site*) OR (donor AND site*) OR ((autologous OR autogenous) AND (graft* OR harvest*))):ti,ab,kw
Open Grey
(((alveolar OR maxilla* OR mandib* OR ridge) AND (augment* OR elevat* OR "pre-implant*" OR preimplant* OR preprosthe* OR "pre-prosthe*")) OR (alveolar ridge* AND reconstruct*)) AND ("extra-oral*" OR ilium OR "iliac crest*" OR parietal OR calvar* OR (distant AND site*) OR (harvest* AND site*) OR (donor AND site*) OR ((autologous OR autogenous) AND (graft* OR harvest*)))

Table S2 Quality of nonrandomised studies

Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies				
Study name	**I Selection**	**II Comparability**	**III Outcome**	**Total**
Prospective cohort studies and case series				
Raghoebar et al, 1993[38]	*	NA	**	***
Chiapasco et al, 1999[261]	*	NA	*	**
Raghoebar et al1999[39]	*	NA	**	***
Stellingsma et al, 2003[40]	*	NA	**	***
Joshi et al, 2004[30]	**	NA	**	****
Nkenke et al, 2004[34]	***	NA	*	****
Weingart et al, 2005[43]	*	NA	**	***
Gerressen et al, 2009[29]	*	NA	*	**
Virnik et al, 2009[42]	*	NA	**	***
Barone et al, 2011[23]	**	NA	**	****
Becker et al, 2011[24]	***	NA	*	****
Felice et al, 2011[20] (& Esposito et al, 2015[21])	*	NA	**	***
Marianetti et al, 2013[31]	*	NA	*	**
Mertens et al, 2013[95]	**	NA	*	***
Reissmann et al, 2013[95] (& Reissmann et al, 2018[16])	*	NA	*	**
Pistilli et al, 2014[35]	*	NA	**	***
Sassano et al, 2014[41]	*	NA	*	**
Fretwurst et al, 2015[96]	**	NA	**	****
Putters et al, 2015[97]	**	NA	**	****
Mertens et al, 2017[32]	**	NA	*	***
Cansiz et al, 2019[25]	**	NA	***	*****
Elhadidi et al, 2019[27]	*	NA	**	***
Putters et al, 2019[36]	*	NA	**	***
Retrospective cohort studies and case series				
Donovan et al, 1994[49]	*	NA	*	***
Lundgren et al, 1997[52]	*	NA	**	***
Kübler et al, 1999[51]	*	NA	*	***
Cricchio et al, 2003[47]	**	NA	**	****
Yerit et al, 2004[58]	*	NA	*	**
Barone et al, 2005[45]	*	NA	*	**
Szabó et al, 2005[57]	*	NA	*	**
Barone et al, 2007[44]	*	NA	*	**
Pelo et al, 2010[53]	*	NA	**	***
Deppe et al, 2012[48]	***	NA	**	*****
Restoy-Lozano et al, 2015[54]	*	NA	*	**
Quiles et al, 2015[57]	*	NA	*	**
Kuik et al, 2016[22]	**	**	**	******
Chiapasco et al, 2018[46]	*	NA	**	***
Sakkas et al, 2018[55]	*	NA	**	***
Gjerde et al, 2020[50]	*	NA	*	**

Table S3 Difficulties in daily functioning and sensory alterations

	Difficulties in daily functioning Prevalence (%)						**Sensory alterations** Prevalence (objective/subjective) (%)															
							1st week												**6< months**			
	1st week		**1 month**		**6 < months**		**Anesth**		**Hypoesth**		**Hyperesth**		**Paresth**		**Anesth**		**Hypoesth**		**Hyperesth**		**Paresth**	
	Calv	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**	**Calv**	**AIC**
Kuik et al, 2016[22]	-	-	-	-	0 [I]	4 [II]	-	-	-	-	-	-	-	-	-	-	-	-	4/0	4/0	15/0	4/0
Putters et al, 2018[18] (& Wortmann et al, 2019[19])	-	-	-	-	0 [I]	20 [II]	-	-	-	-	0/0	0/0	-	-/10	-	-	-	-	0/0	0/0	-	-
Non-comparative prospective studies																						
Chiapasco et al, 1999[26]. [I]	-	100 [II]	-	69 [II]	-	0 [II]	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-
Joshi et al, 2004[30]	-	87 [III]	-	8 [III] 7	-		-	-	-	0/26	-	-	-	-	-	-	-	-	-	-	-	-
Nkenke et al, 2004[34]	-	28 [II]	-	0 [II]	-	0 [II]	-	-	-	20/0	-	-	-	-	-	-	-	-/0	-	-	-	-
Weingart et al, 2005[43]	-	-	-	0 [II]	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-
Gerressen et al, 2009[29]	-	-	-		-	-	-	-/0		-/0	-	-/0	-	-	-	-/0		-/0		-/0	-	-
Barone et al, 2011[23]	-	100 [III]	-	2 3 [III]	-	-	-	-	-	52/0	-	-	-	-	-	-	-	-	-	-	-	-
Becker et al, 2011[24]	-	34 [II]	-	10 [II]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Marianetti et al, 2013[31]	-	100 [II]	-	58 [II]		0 [II]	-	-/4	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mertens et al, 2013[95]	-		-		-	-	-	-	-		0/7		0/0	-	-	-	-	-	-	-	-	-
Pistilli et al, 2014[35]	-	[IV]	-	[IV]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fretwurst et al, 2015[96, V]	-	65 [II]; 25 [III]	-	Unc	-	0 [II]	-	-	5/5	-	-	-	-	-	-	-	-	-	-	-	-	-
Cansiz et al, 2019[25]	-		-	0 [II]	-		-	-		-	-	-	-	-	-	-	-	-	-	-	-	-
Non-comparative retrospective studies																						
Lundgren et al, 1997[52]	-	100 [II]	-	100 [II]	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-
Kübler et al, 1999[51]	-	100 [III]	-	3 [III]	-	-	-	-	-	3/3	-	-	-	-	-	-	-	-	-	-	-	-
Cricchio et al, 2003[47]	-	44 [II]	-	19 [II]	-	4 [II]	-	-	-	0/13	-	-	-	-/3	-	-	-		-	-	-	-
Szabó et al, 2005[57]	-		-		-	-	-	-	-	-/5	-	-	-	-	-	-	-	-/5	-	-	-	-
Barone et al, 2007[44]	-	11 [II]	-	0 [III]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pelo et al, 2010[53]	-	32 [II,VII]	-	32 [II,VII]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Deppe et al, 2012[48]	-		-		-	-	-	-	-	-	-	-	-	-/2	-	-	-	-	-	-	-	-
Sakkas et al, 2018[55]	-		-		-	-	-	-	-	-	-	-	-	-/0	-	-	-	-	-	-	-	-/0
Gjerde et al, 2020[50]	-	[VI]	-	7 [II, VI]	-	-	-	-	-	-	-	-	-	-	-	-/5	-	-/10	-	-	-	-

Summary of findings on difficulties in daily functioning such as wearing headgear or headaches following calvarial harvesting or difficulties with walking or getting around when anterior iliac crest was harvested. Also, findings with respect to sensory disturbances are provided, both objectively assessed by a physical examination using point blunt discrimination, or subjective assessment by means of questionnaires. The findings are presented as prevalence at one week, one month or six months postoperatively. Abbreviations: Calv: patients treated with calvarium bone grafts; AIC: patients treated with anterior iliac crest bone grafts; Unc: unclear; Anesth: anaesthesia; hypoesth: hypoesthesia; paresth: paraesthesia; [I] Headaches or difficulties wearing headgear; [II] Difficulties with walking; [III] Walking aid necessity; [IV] A mean of 126 (SD 6.3) infirmity days were reported [V] The prevalence of walking aid necessity was higher among patients with higher BMI values (p = 0.018); [VI] Average time of sick leave: 20.2± 18.5 days; [VII] 32% of the patients experienced problems with carrying out normal activities up to 3 months after surgery

Table S4 Esthetics at donor site and complications

	Esthetic outcomes at donor site										Complications											
	Contour alterations						Patient reported satisfaction				Major				Minor							
							VAS (0-10)		Satisfied													
	Objective %		Subjective %		Abnormal scar[I] %		Mean score		'Yes' (%)	AIC	Trepanation[VI]/ Fracture[VI] %		Bleeding[VII] %		Hematoma %		Infection %		Seroma %		Dehiscence %	
	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC
Comparative studies																						
Kuik et al, 2016[22]	51[II] 48[III]	67[II]	85[IV]	19[IV]	20[V]		10	10	100	100	11	4	-	-	0	7	1	-	-	-	-	-
Putters et al, 2018[18] (& Wortmann et al, 2019[19])	50[II] 20[III]	30[II]	10	10	0	-	-	-	100	80	0	0	0	0	0	0	-	-	-	-	0	0
Non-comparative prospective studies																						
Raghoebar et al, 1993[38]	-	-	-	-	-	-	-	-	-	-	-		-	-	-	1	-		-	1	-	-
Joshi et al, 2004[30]	-	-	-	-	-	-	-	-	-	60	-	5	-	-	-	3	-	4	-		-	-
Nkenke et al, 2004[34]	-	-	-	-	-	0	-	-	-	-	-	0	-	-	-	0	-	0	-	0	-	-
Weingart et al, 2005[43]	-	-	-	-	-	-	-	-	-	-	-		-	-	2		2		-		-	-
Gerressen et al, 2009[29]	-	-	-	-	-	-	-	-	-		-	0		0		0	-	0	-		-	0
Barone et al, 2011[23]	-	-	-	1	-	-	-	-	-	94	-	0	-	-	-	1	-		-		-	-
Becker et al, 2011[24]	-	-	-	-	-	-	-	7.4	-	-	-	2	-	-	-	-	-	-	-	-	-	-
Marianetti et al, 2013[31]	-	-	-	-	-	4	-	8.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mertens et al, 2013[95]	-	-	-	-	0[V]	-	-	-	-	-	0	-	-	-	0		0		-		-	-
Sassano et al, 2014[41]	0	-		-	0	-	-	-	-	-	0		0		0		0		-		0	-
Fretwurst et al, 2015[96]	-	-	-	-	-	-	-	-	-	-	-	0		0		5	-	0	-	10	-	0
Putters et al, 2015[97]	100	-	0[VI]	-	0	-	-	-	-	-	11	-	-	-		-	-		-	-	-	-
Mertens et al, 2017[32]		-		-	0[V]	-	-	-	-	-	0	-	-	-	0	-	0		-	-	-	-
Elhadidi et al, 2019[27]	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	-

Table S4 Continued

	Esthetic outcomes at donor site										Complications											
	Contour alterations						Patient reported satisfaction				Major				Minor							
	Objective %		Subjective %		Abnormal scar[I] %		VAS (0-10) Mean score		Satisfied 'Yes' (%)	AIC	Trepanation[VI]/ Fracture[VI] %		Bleeding[VII] %		Hematoma %		Infection %		Seroma %		Dehiscence %	
	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC	Calv	AIC
Non-comparative retrospective studies																						
Kübler et al, 1999[51]	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	3	-	-	-	-
Cricchio et al, 2003[47]	-	3[II]	-	-	-	-	-	-	-	-	-	1	-	-	-	13	-	1	-	-	-	-
Szabó et al, 2005[57]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		-		-	10	-	-
Barone et al, 2007[44]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-		-	-
Restoy-Lozano et al, 2015[54]	55[II]	-	-	-	9[V]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quiles et al, 2015[57]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chiapasco et al, 2018[46]	-	-	-	-	-	-	-	-	-	-	0		0		1		0				0	
Gjerde et al, 2020[50]	-	-	-	-	-	-	-	-	-	90	-	-	-	-	-	-	-	-	-	-	-	-

Findings regarding aesthetic outcomes at the donor site, including objective and subjective assessment of contour alteration, abnormal scar formation and patient reported satisfaction with donor site aesthetics. Also, harvesting surgery complications are depicted. A distinction is made between major complications, i.e. trepanation of the skull or fracture of the iliac crest, and minor complications, i.e. haematoma, infection, seroma and dehiscence at the donor site. Abbreviations: Calvarium: patients treated with calvarium bone grafts; AIC: patients treated with anterior iliac crest bone grafts;

[I]Abnormal scar formation includes, among others, hypertrophic scars, keloid scars and scarring alopecia; [II]Subtle deficits; [III]Evident deficits; [IV]It was not bothersome to the patients; [V]Scarring alopecia; [VI]Bicortical perofration of the skull; [VI]Fracture of the iliac bone; [VII]Major bleeding or excessive blood loss

CHAPTER 3

Morbidity of anterior iliac crest and calvarial bone donor graft sites:

A 1-year randomized controlled trial

This chapter is an edited version of the manuscript: T. F. Putters, D. E. Wortmann, J. Schortinghuis, B. van Minnen, C. Boven, A. Vissink, G. M. Raghoebar. Morbidity of anterior iliac crest and calvarial bone donor graft sites: a 1-year randomized controlled trial

Int J Oral Maxillofac Surg 2018 Nov; 47: 1474-1480

Background Autogenous bone graft harvesting is still commonly considered the gold standard for the reconstruction of a severely resorbed maxillary alveolar ridge; however, the preferred donor site remains a subject of debate.

Purpose This study compared the morbidity of calvarial and iliac crest donor sites after harvesting.

Methods Twenty edentulous patients with an insufficient volume of maxillary bone for reliable implant placement were assigned randomly to either calvarial (n = 10) or anterior iliac crest (n = 10) bone harvesting groups. All patients underwent a maxillary sinus floor elevation procedure combined with widening of the alveolar process using buccal bone blocks. Donor site morbidity was assessed before, during, and at 1 year after the surgery through patient questionnaires, physical examination, and medical records.

Results No perioperative complications occurred. The anterior iliac crest group reported minor postoperative pain after harvesting. The scars after calvaria harvesting were significantly longer (p = 0.003), but this was not bothersome for the group of patients. Long-term pain was negligible, and satisfaction was high in both groups.

Discussion Both the calvaria and anterior iliac crest are associated with low long-term donor site morbidity and high patient satisfaction. Thus, patient-centred decision-making is appropriate when selecting the preferred harvesting method for that patient.

Key words: bone augmentation, iliac crest, calvarial bone, morbidity, patient satisfaction

1 INTRODUCTION

Implant overdentures are widely recognized as the treatment of choice for edentulous patients experiencing problems wearing conventional dentures. Pre-implant augmentation surgery is needed in severe cases of resorption whereby insufficient bone volume is present for adequate implant placement and stability.

Several augmentation techniques have been described[1], either with human bone, animal bone, synthetic materials, or a combination of these. Grafting with autogenous bone is still considered the gold standard[2]. Bone can be grafted from numerous places in the human body, of which the anterior iliac crest is mostly used when a large volume is needed[2]. The anterior iliac crest is easily accessible and can provide considerable amounts of cortical and cancellous bone. Furthermore, when using a two-team surgical approach, the bone harvesting can be done simultaneously with the augmentation surgery, thereby reducing surgery time. However, the common limitation of this procedure is the inherent donor site morbidity including pain, sensory disturbances, and gait problems[3].

The calvaria offers an alternative to the iliac crest as a donor site when large bone grafts are needed. Grafts taken from the outer cortex of the posterior parietal skull bone provide a large volume of cortical bone, while the diploic space contains copious amounts of cancellous bone[4]. The associated donor site morbidity is suggested to be low compared to iliac crest bone grafting. However, the possibility of neurological sequelae represents the major argument against calvarial bone grafting[5]. The recently developed safe harvesting technique, introduced by Kellman[6] and modified by Schortinghuis et al.[4], decreases the risk of intracranial complications to a minimum.

Despite the existing extensive knowledge on donor site morbidity associated with various bone grafting sites[1,3,7–11], the best donor site remains undefined. Accordingly, a prospective comparative trial was designed to assess donor site morbidity and patient satisfaction following anterior iliac crest and calvarial bone harvesting when applied as a pre-implant augmentation procedure to reconstruct a severely resorbed maxilla.

2 MATERIALS AND METHODS

2.1 Patients

Between November 2014 and March 2016, 20 patients fulfilled the inclusion criteria for this study. All patients had been referred to the Department of Oral and Maxillofacial Surgery of the University Medical Centre Groningen (UMCG) because of problems while wearing

an upper denture (pain, mobility, loss of retention, chewing) due to severe resorption of the edentulous maxilla. The patients were eligible to be included in this study when the available bone volume was insufficient for reliable implant placement, i.e., <3 mm bone height in the maxillary sinus area and <2 mm bone width in the anterior maxillary area, as assessed on a cone beam computed tomography (CBCT) scan. Furthermore, the thickness of the parietal bone (>5 mm) in the area between the articular tubercle and the end of the mastoid bone had to be suitable, as assessed on a CBCT scan of the calvaria with frontal reconstructions. Exclusion criteria were the following: presence of contraindications to surgery due to severe health problems, former or current use of intravenous bisphosphonates, currently pregnant or lactating, and a previous operation at the donor site. Informed consent was obtained from all patients. The study was approved by the Medical Ethics Committee of UMCG. The eligible participants were divided randomly into two equal groups. One group was treated using calvarial bone for the augmentation procedure (n = 10) and the other group with bone from the anterior iliac crest (n = 10).

2.2 Surgery

Calvarial bone was harvested after raising a full-thickness flap. Next, the outline of the outer table graft was marked with a burr until the diploë was encountered. A bone scraper (SafeScraper Twist; META, Reggio Emilia, Italy) was used to create a bevelled trough around the calvarial outer table graft to facilitate its removal with a reciprocating saw. Using the scraper, copious amounts (>10 ml) of 'cancellous'-like bone could be collected. Parallel saw-cuts were made in situ so that the graft could be removed piece by piece thus preventing graft breakage[4,12]. The defect in the skull was reconstructed with bone cement (Palacos; Zimmer Biomet, Warsaw, Indiana, USa).

Anterior iliac crest bone was harvested according to the technique of Kalk et al.[13]. The incision was started 1 cm behind the anterior superior iliac spine and continued posteriorly, following the iliac crest. It was carried down sharply to the midcrest, dividing the musculotendinous aponeurosis of the tensor muscle of the fascia lata and the oblique abdominal muscles, without transecting muscle fibres. The bony ilium was exposed directly by reflecting the iliac muscle sub-periosteally and the donor site was exposed with a retractor. The corticocancellous bone blocks were harvested by making two horizontal and five vertical cuts. The superior horizontal cut was made midcrestal with a reciprocating saw. The inferior horizontal cut was made 4 cm inferior in the inner table with a curved osteotome. The horizontal cuts were connected by verticals cuts using a reciprocating saw. After removal of the corticocancellous bone block piece by piece from the inner table, additional cancellous bone was harvested with gouges and curettes. Care was taken not to perforate the lateral cortex.

All the operations were performed at UMCG by an experienced oral and maxillofacial surgeon. After harvesting the calvarial or iliac crest bone, sinus elevation surgery was performed according to the procedure described by Raghoebar et al.[14].

Broad-spectrum antibiotics (amoxicillin–clavulanic acid) and non-steroidal anti-inflammatory drugs (NSAIDS) (ibuprofen) were prescribed for 1 week post-surgery. Patient instructions included a soft diet and not wearing the maxillary denture for 2 weeks.

After 4 months, the dental implants were placed in the augmented maxilla. All of the patients were enrolled for a dental hygiene protocol.

2.4 Outcome measures

The primary outcome measure was donor site morbidity (perioperative, early, and late postoperative). The secondary outcome measures were patient satisfaction, self-reported postoperative pain, and implant survival.

For the assessment of perioperative donor site morbidity, the presence (reported as yes/no) of each of the following items was recorded during the grafting procedure: dura exposure, dural tear, accidental falling of the graft, graft fracture during removal and/or bicortical perforation of the iliac crest, and size of the graft. The duration of the harvesting procedure was measured (min). The hospitalization period was also recorded in days. During implant placement, bone loss or signs of bone resorption (yes/no) were recorded.

With regard to early postoperative donor site morbidity, the morbidity data of both groups were recorded by the surgeon at 1, 2, 6, 16, 20, and 28 weeks postoperative. The following items were each assessed with regard to the donor site (reported as yes/no): scar aspects (dehiscence, erythema, swelling, and pain), hair loss, localized pain, and contour deficit. If contour deficits were present, the patient was asked whether or not this was bothersome (yes/no). With regard to the receptor site, the presence of dehiscence, fistula, erythema, loss of implant, and gingivitis were also recorded (reported as yes/no).

Late postoperative donor site morbidity was assessed at 1 year after prosthetic loading. All patients were invited for a physical examination by an independent investigator at UMCG. The following variables were investigated: contour deficits, sensitivity, tenderness, and length of the scar. In addition, alopecia around the donor site, defined as evident hair loss next to the scar, was assessed for the calvaria group.

The assessments of the donor site contour changes were standardized for both groups. The operated parietal surface of the head was palpated, or the contour of the operated anterior

superior iliac crest was dorsally palpated after localizing the iliac spine. Subtle or evident deficits were reported. The patients were asked to report tenderness or pain accompanying the examination.

Tactile sensitivity of the donor site was determined by touching the skin lightly with a piece of cotton wool. Patients were asked to identify the number of contacts. Sensitivity was established by touching with a dull cotton bud and a sharp needle, and the participants had to discriminate between them. The patients were blinded for both tests.

For the assessment of postoperative pain, the participants graded the donor site pain experienced (skull or iliac crest region) following augmentation and implantation surgery for 30 days at 12:00 a.m. each day. Twelve months after prosthetic construction, the participants were asked to score their current pain. This was measured using a 10-cm visual analogue scale (VAS), ranging from 'no pain' (0) to 'the worst pain imaginable' (10).

Patient satisfaction was assessed at 12 months post-augmentation. This was measured with a VAS, with 0 representing 'a bad outcome' and 10 'a good outcome'.

Implant survival was investigated by assessing loose and lost implants, which were recorded at any time after placement.

2.5 Statistical analysis

The data management and analysis were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). The Student *t*-test, Mann–Whitney *U*-test, and Pearson c^2 test were used to compare the outcomes of the parametric variables, non-parametric variables, and categorical sex variable, respectively, between the groups. Concerning the outcome data, the Pearson c^2 test (or, if necessary, Fisher's exact test) was used to compare any dichotomous variables. Categorical variables with an outcome scale greater than 2 were compared with the Fisher–Freeman–Halton exact test. The means of continuous variables, pain experience, scar length, and satisfaction rate were compared with the Mann–Whitney *U*-test. With regard to pain experience, a Pearson's *r* test was used to assess the correlations with age, body mass index (BMI), and duration of follow-up. Significance was set at an α level of 0.05.

3 RESULTS

3.1 Clinical characteristics

Table 1 describes the baseline characteristics of the study patients. One patient in each group had minor intraoral wound dehiscence. Both were closed with a pedicle mucosal flap and they healed without further complaints.

3.2 Implant survival

In all cases, the augmentation procedure resulted in sufficient bone volume for implant placement at the prosthodontically preferred sites. A total 44 implants were placed in each group. One patient in each group lost an implant because of mobility during the osseointegration phase, resulting in a 1-year implant survival rate of 97.7%.

3.3 Perioperative morbidity

The harvesting of calvarial bone took an average of 53 ± 13 min. One monocortical bone strip fractured during harvesting, but without hampering the augmentation procedure (Tables 2 and 3). The mean graft surface was 13.5 ± 1.8 cm^2.

The harvesting of anterior iliac crest bone took an average 42 ± 8 min. The mean graft surface was 18.3 ± 3.6 cm^2.

Table 1. Characteristics of the calvaria and anterior iliac crest groups[1].

	Calvaria group ***n*** **= 10**	**Anterior iliac crest group** ***n*** **= 10**
Sex		
Male	5	4
Female	5	6
Age at implant placement (years)	65.9 ± 8.7	63.5 ± 7.0
BMI (kg/m^2)	30.6 ± 7.9	28.5 ± 6.13
Time between augmentation and implant placement (years)	0.5 ± 0.2	0.4 ± 0.1

BMI, body mass index.

[1]*Results are presented as the number, or the mean ± standard deviation.*

Table 2. Complications in the calvaria and anterior iliac crest groups.

	Calvaria group *n* **= 10**	**Anterior iliac crest group** *n* **= 10**	***P*-value[1]**
Perioperative complications			
Dura mater exposure without dura tear	0	-	
Dura mater tear with leakage of CSF	0	-	
Accidental bicortical perforation of the iliac crest	-	0	
Breakage of graft	1	0	0.317
Early postoperative complications			
Donor site haematoma	0	0	
Need for extra surgical interventions	0	0	
Need for extra non-surgical interventions	0	0	
Referral to physiotherapy because of persistent pain during movement	0	0	
CT scan because of prolonged tenderness of the scalp	0	0	
Antibiotics because of oedema and prolonged tenderness of the scalp	0	0	
Late postoperative complications[2]			
Difficulties in daily functioning at 12 months postoperative			
Walking	0	1	0.317
Climbing stairs	0	1	0.317
Cycling	0	0	
Persistent headache episodes	0	0	
Difficulties with wearing			
Headgear	0	0	
Pair of trousers	0	1	0.317
Belt	0	1	0.317
Tenderness during palpation	1	0	0.317
Sensory disturbances	1	1	
Hyperalgesia in combination with hypoalgesia	0	1	0.317
Solitary hypoalgesia along the scar	1	0	0.317
Solitary hyperalgesia along the scar	0	0	
Localized alopecia	0	0	
Contour examination			
Evident deficit	2	0	0.146
Subtle deficit	5	3	0.170
Normal contour	3	7	0.089
Contour alteration (subjective)	1	1	
Implants			
Participants with 4 implants	8	8	
Participants with 6 implants	2	2	

CSF, cerebrospinal fluid; CT, computed tomography.
[1]*Mann–Whitney U-test.*
[2]*Assessed at the 12-month follow-up meeting.*

3.4 Early morbidity

In the calvaria group, no dura mater exposure or dura tear occurred during the bone harvesting procedures (Table 2). There was no case of donor site haematoma. No extra (non)surgical interventions were needed at the donor site.

In the anterior iliac crest group, no bicortical perforation of the iliac crest occurred. No donor site haematoma was observed. There was no requirement for extra (non)surgical interventions or for referral to a physiotherapist because of persistent pain during movement.

3.5 Late morbidity

None of the patients in the calvaria group reported difficulties in daily functioning (walking, climbing the stairs, or cycling) at 12 months postoperative (Tables 2 and 3). Persistent episodes of headache did not occur. One patient reported a subjective contour alteration. Physical examination revealed five subtle and two explicit contour deficits (including the patient who reported the contour alteration). The mean scar length was 9.6 ± 2.5 cm. Solitary hypoalgesia along the scar was observed in one patient.

With regard to the anterior iliac crest group, difficulties in daily functioning were reported by two patients at 12 months postoperative. Difficulties with wearing a pair of trousers or a belt were each reported once. Persistent headache episodes did not occur. One patient reported a subjective contour alteration, whereupon a physical examination revealed that a subtle contour deficit was indeed present. No contour defects were observed in the other patients. The mean scar length was 5.7 ± 2.2 cm. Sensory disturbances at the donor site were noted by one patient (hyperalgesia in combination with hypoalgesia).

3.6 Postoperative pain

In the assessment of the calvaria group patients, direct postoperative pain scores in relation to sex, age, and BMI were not significantly correlated, as determined by a Pearson product-moment correlation test ($P > 0.05$, Pearson's r). At the 1-year follow-up, the mean VAS score for current pain of the skull was 0.1 ± 0.1. The participants were highly satisfied with the result of the procedure after 12 months (mean score of 8.0 ± 2.9 on a 0-10 VAS, Table 3).

For the anterior iliac crest group, the Pearson product-moment correlation test revealed a relationship between BMI and the direct postoperative pain scores. After excluding one outlier, the BMI and post-augmentation pain scores for the hip region were significantly correlated ($r = 0.830$, $n = 9$, $P = 0.006$). Direct postoperative pain scores were not correlated with sex or

age ($P > 0.05$, Pearson's r). At the 1-year follow-up, the mean VAS score for current pain of the skull was 0.4 ± 0.9. The participants in this group were very satisfied with the results after 12 months (mean VAS score 9.4 ± 0.5, Table 3).

3.7 Calvarial versus anterior iliac crest bone

The operating time was significantly shorter for the anterior iliac crest group than for the calvaria group ($P = 0.03$, independent samples t-test). Grafts taken from the skull were significantly smaller in surface area than the grafts from the iliac crest ($P = 0.001$, independent samples t-test), but the harvested bone volume from both procedures was sufficient for all the augmentation procedures applied. There were no significant differences in early and late complications between the two groups.

The physical examination at the 1-year follow-up revealed more contour alterations in the calvaria group ($P = 0.089$, Mann–Whitney U-test), and the scars after calvarial bone grafting were significantly longer than the scars after anterior iliac crest grafting ($P = 0.003$, independent sample t-test). Although these results seem unfavourable for the calvaria group, the subjective outcomes of the contour alterations and scar formation were similar in the two groups.

On comparing the pain diaries of the two groups, it was evident that there was a difference in postoperative pain development. Fig. 1 shows that post-augmentation pain was similar until day 5, following which the anterior iliac crest group experienced more pain at the donor site and intraorally than the calvaria group. The pain reported for both procedures was minor, which may explain the observation of no significant differences between the groups over the 30-day postoperative period in this patient cohort (Independent sample t-test, p-values ranging from $p = 0.047$ to $p = 1.00$). Also, the pain curves of the two groups were similar after implantation (Fig. 2).

Table 3. Grafting aspects, scar length, postoperative pain, and patient satisfaction in the calvaria and anterior iliac crest groups.

	Calvaria group Mean ± SD	Anterior iliac crest group Mean ± SD	P-value[1]
Grafting			
Graft surface (cm^2)	13.5 ± 1.8	18.3 ± 3.6	0.001*
Graft operation time (min)	53 ± 13	42 ± 8	0.033*
Visible scar length (cm)	9.6 ± 2.5	5.7 ± 2.2	0.003*
Postoperative pain score (0–10) at long-term follow-up	0.1 ± 0.1	0.4 ± 0.9	0.270
Patient satisfaction (0–10)	8.0 ± 2.9	9.4 ± 0.5	0.142

SD, standard deviation.
[1]*Independent samples t-test*
**significant difference.*

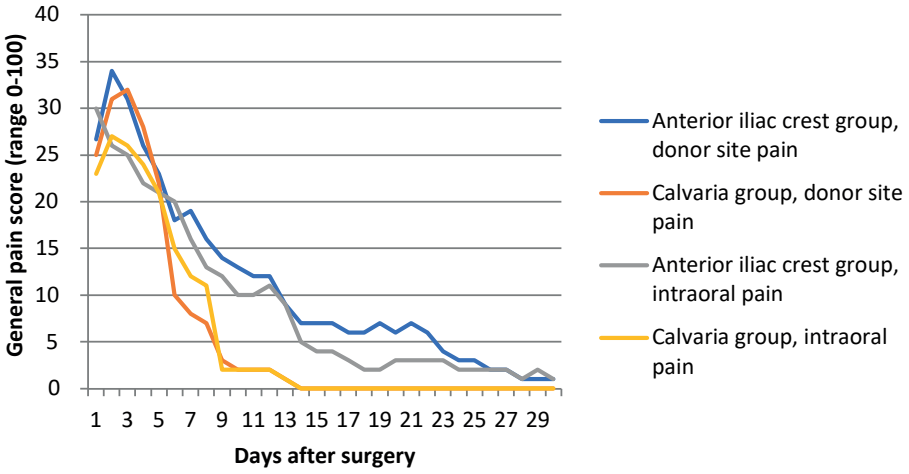

Figure 1. Pain scores following augmentation surgery. The figure shows the mean pain scores (VAS) after augmentation surgery for anterior iliac crest (blue) and calvarial (red) bone graft harvesting. To compare, the mean intra-oral pain is shown as well (gray for anterior iliac crest group and orange for the calvarial group). The figure demonstrates that the pain levels take a similar course for both donor locations, however the pain following calvarial harvesting deceases after two weeks whereas some patients from the anterior iliac crest group perceive pain for almost 30 days post-surgery.

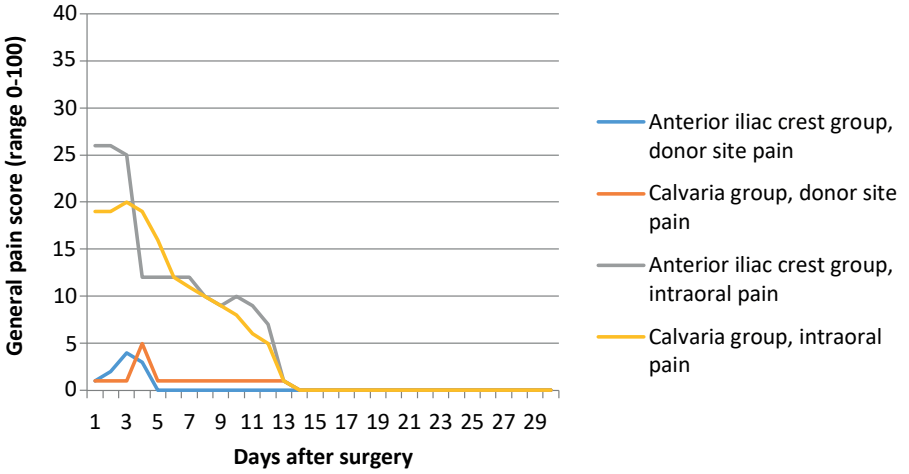

Figure 2. Pain scores following implantation surgery. After 4 months healing, the implants were places. Again, patients were asked to score the pain perceived at donor site and intra-orally. The figures shows that the pain at donor site was very low for both groups.

4 DISCUSSION

No apparent difference in short- or long-term donor site morbidity between calvaria and anterior iliac crest harvesting was evident. This study revealed that few complications occurred and that the pain experienced was very minor, hence patient satisfaction was high.

As mentioned, the complication rate was negligible for both calvaria and iliac crest harvesting. This result is somewhat different from the morbidity reported in the literature, as iliac crest harvesting is commonly associated with a higher rate of minor complications than calvaria harvesting[7,8]. Furthermore, any complications occurring following calvaria harvesting are generally more severe, especially dura exposure [2,5,8,9,11]. The fact that no complications were observed after calvaria harvesting may be due to the technique applied, which prevents dura exposure[4].

Regarding late morbidity, the postoperative mobility assessment showed that two patients in the iliac crest bone harvesting group had minor gait problems, but this did not interfere with their daily activities. This observation is in line with the reported postoperative impaired mobility following iliac crest and calvaria harvesting[9,15–19].

Furthermore, any pain experienced by patients is commonly reported to be higher following iliac crest bone harvesting[8,9]. A similar pattern was observed in the present study, as shown in Fig.1, but the postoperative pain experienced was rather low, hence the lack of a significant difference between the two groups with regard to postoperative pain up to 30 days after treatment. However, postoperative pain levels in the iliac crest region and BMI were strongly correlated. This may be due to accessibility of the donor site and forces on the operated area during rehabilitation.

The occurrence of sensory disturbances did not differ significantly between the groups. Such sensory alterations, probably due to the transection of local nerve endings, are well known consequences of both procedures: Kalk et al.[13] described sensory loss after iliac crest harvesting, and Kuik et al. [7], Scheerlinck et al.[9], and Touzet et al.[11] have described several presentations of altered sensitivity after calvaria harvesting. The changes after calvaria harvesting are thought to be more prominent when a coronal incision is used, as nerves supplying the scalp follow a parasagittal course. Hence, a parasagittal incision of the scalp was used to minimize the chance of cutting through the sensory nerves[10,11]. Some sensitivity could have been due to the described correlation between the extensive use of electrocautery and postoperative hyperalgesia[20] and/or the strong correlation between electrocautery and alopecia[11].

Several studies have described contour alterations after calvarial bone harvesting. To prevent an aesthetically undesirable outcome, reconstruction using biomaterials directly after obtaining the graft is generally advised. In the current study, the bone alterations in the calvaria group patients were reconstructed with bone cement. Despite this, contour deficits were seen on physical examination in more than half of the participants at the 12-month follow-up. However, this was reported as bothersome by only one patient. Kuik et al. described similar results[7]. Hence, this raises the question of whether objectively reported contour changes are relevant in the context of calvarial bone harvesting. Furthermore, the anatomical differences between the two donor sites might explain the different results on examination: irregularities in the skull are easier to identify than alternations to the inner table of the anterior iliac crest.

Furthermore, the restoration of the skull defect caused by the harvesting of calvarial bone was performed with the bone cement Palacos. Although the reconstruction is aesthetically favourable, the cement itself may cause complications such as allergic reactions and infection. However, no such complications were observed. Furthermore, as pointed out by Zanotti et al.[21], all currently available materials for cranial reconstruction have their inherent advantages and disadvantages, and none of these materials lacks an infection risk or potential biological toxicity.

The aim of this study was to make a fair comparison between bone grafting techniques. Some limitations can be pointed out. Although postoperative pain and mobility were primary parameters, the presurgical level of daily physical functioning and usage of pain medication were not assessed at inclusion. It is possible that the frequent use of NSAIDs was a confounding factor. Furthermore, the participants were only followed-up for 1 year postoperatively. Long-term effects could have been analysed better by extending this follow-up period. Moreover, the differences in functionality of the grafts in the long term were not assessed. Specific assessments of bone metabolism at a microscopic level could provide further information about the sustainability and stability of the grafts. The patient-reported outcomes in the present study consisted of pain levels and general satisfaction with the procedure. Following the current trend towards patient-centred decision-making in medical science, the assessment of patient experiences deserves a more prominent role when considering treatment options for pre-implantation surgery. Future studies should pay special attention to this point.

To conclude, both the calvaria and anterior iliac crest are appropriate options for pre-implantation maxillary augmentation with regards to donor site morbidity. The complication rate is low for both procedures and the level of patient satisfaction is high. Therefore, when deciding between these two options, it is recommended that patient-specific factors be taken into account. Pain following calvaria harvesting is apparently lower than that after anterior iliac crest harvesting, especially in those with a higher BMI. Furthermore, the findings of this

and previous studies advocate taking the patient's daily mobility into account when choosing a procedure: calvaria harvesting might be more favourable for highly active patients. However, in the case where large bone volumes are required or limited surgical time is available, the iliac crest (two-team approach) might be the donor site of choice. Furthermore, due to the frequently described contour changes after harvesting, the use of the calvaria as a donor site requires a direct reconstruction with biomaterial. Finally, to reduce the risk of alterations in sensitivity and alopecia, it is recommended that the use of electrocautery is minimized.

5 DECLARATIONS

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Competing interests

There is no conflict of interest in this study.

Ethical approval

The study protocol was approved by the Medical Ethics Committee of the University Medical Centre of Groningen (reference number NL48614.042.14).

Patient consent

Written consent was obtained from all participants.

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CHAPTER 4

Patients' appreciation of pre-implant augmentation of the severely resorbed maxilla with calvarial or anterior iliac crest bone: a randomized controlled trial

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Background: Little is known about the impact of bone graft harvesting for pre-implant augmentation of the maxilla from a patient's perspective. To assess patient reported outcome measures (PROMs) related to augmentation of the extremely resorbed edentulous maxilla with calvarial or anterior iliac crest bone.

Materials and methods: For this randomized controlled trial, twenty consecutive edentulous patients needing extensive pre-implant surgery of the maxilla were randomly assigned to either anterior iliac crest (n=10) or calvarial (n=10) bone harvesting. Patient reports on procedure related satisfaction, questionnaires on oral functionality (Denture Satisfaction, Chewing Ability) and oral health related quality of life (OHIP-49NL) and subjective donor site related outcomes (eg, of post operative pain, scar formation, physical mobility) were assessed.

Results: Irrespective of the harvesting site, patients were generally satisfied (median VAS-score 93(86-99) mm, p=0.400) with the procedure and its final results. Post-operative pain was mild (median 40(20-40) mm) and deceased within 14 days. Early post-operative pain was significantly higher following anterior iliac crest harvesting (p<0.00). Impact on physical mobility, daily functioning and satisfaction with the scar formation were similar in both groups.

Conclusions: The assessed PROMs confirmed that bone graft harvesting from the calvarium or anterior iliac crest are appropriate procedures, reflected by high levels of satisfaction, minor long-term sequela and improvement of perceived oral health. For clinical decision-making, decisions can be based on individual features and preferences.

Key words: patient satisfaction; PROM; autogenous bone graft; edentoulous atrophic maxilla; RCT; iliac crest; calvarium

1 INTRODUCTION

Pre-implant augmentation of the maxilla using extra orally grafted bone has been studied objectively on medical indicators, such as surgical complication rate, donor site morbidity and physical characteristics[1–4]. Little is known about the patients' perceptions of the applied bone harvesting techniques for reconstruction of the maxilla[5]. Moreover, the studies performed thus far assessing patients' perspectives have been mainly retrospective[6–10].

The use of objective outcome measures strikes to the modern view on clinical research that appropriate judgments on the outcome of therapeutic procedures come from those who experience them from beginning to end i.e., the patients themselves[11]. Hence, the use of patients' reported measures (PROMs) to assess patients' opinion on healthcare has been set as a standard in treatment evaluation. As a result, patient satisfaction ratings have become important indicators for therapeutic efficacy[12].

PROMs have shown that an edentate state is associated with a significant decrease in oral health related quality of life (OHRQoL)[13,14], and that adequate prosthetic treatment results in improvement in OHRQoL and patients' satisfaction[5,13,14]. The introduction of implant supported overdentures has been a great asset in resolving problems related to a maxillary denture[13–15]. Implant placement in the extremely resorbed maxilla usually requires, however, augmentation with extra orally grafted bone. While there is ample evidence that the PROMs are favorable regarding replacement of a conventional maxillary denture with a maxillary overdenture on implants, scarce information is available in terms of how patients experience the bone harvesting procedure enabling maxillary augmentation surgery. Therefore, the aim of this prospective study was to assess patient satisfaction and patient reported morbidity of patients needing calvarial or anterior iliac crest bone harvesting to reconstruct an extremely resorbed edentulous maxilla before being treated with an implant-retained maxillary overdenture.

2 METHODS

2.1. Patient population

A total of 20 consecutive eligible patients was asked to join the study. These patients were referred to the Department of Oral and Maxillofacial Surgery of the University Medical Centre Groningen (UMCG), Groningen, the Netherlands, having problems with wearing an upper denture (pain, mobility, loss of retention). These problems were a result of severe resorption of the edentulous maxilla. Patients were included when insufficient bone volume was available for reliable implant placement, that is, <3 mm bone height in the maxillary sinus area and <2 mm bone width in the anterior maxillary area. The bone height and width were assessed using

cone beam computed tomography (CBCT) scanning. For temporal bone, the thickness in the area between the articular tubercle and the end of the mastoid bone had to be >5mm to allow for harvesting calvarial bone. None of the participants had undergone an operation at the donor site before.

2.2 Design of the study

20 patients gave written consent to participate in the study. Randomization software was applied to divide them into two groups based on the location for harvesting the bone grafts: the anterior iliac crest (n=10) or the calvarium (n=10). All patients were subjected to a bilateral maxillary sinus floor augmentation and reconstruction of the width of the maxilla. The surgeries took place between November 2014 and September 2016. Each patient was followed -up until at least 12 months.

PROMs were assessed at several moments in time (Figure 1). To control for equality between groups and determine improvement in perceived oral health, OHRQoL, denture satisfaction and chewing ability were assessed at baseline and 12 months post-treatment. Furthermore, postoperative pain was assessed during the first 30 postoperative days. At the 12-month follow-up meeting, patient reported satisfaction and donor site related outcomes were assessed too.

The study protocol was reviewed and approved by the medical ethical committee of the UMCG, reference NL48614.042.14. Written consent was obtained from all participants.

2.3 Surgical procedures

For harvesting anterior iliac crest bone, an incision was made from 1 cm behind the anterior superior iliac spine toward posteriorly, following the iliac crest. It was continued sharply to the midcrest, separating the aponeurosis of the fascia lata and the oblique abdominal muscles. By reflecting the iliac muscle sub-periosteally, the bony ilium was exposed. A retractor was used to expose the donor site. Two horizontal and five vertical cuts were made to harvest corticocancellous bone. The upper horizontal cut was placed midcrestal using a reciprocating saw. 4 cm inferior, in the inner table, the other cut was made with a curved osteotome. These were connected by the vertical cuts using a reciprocating saw. After piece-by-piece removal of the corticocancellous bone blocks, additional cancellous bone was harvested with gouges and curettes[2]. To harvest calvarial bone, a full-thickness flap was raised, followed by marking the outer table graft with a burr until the diploe was encountered. With a bone scraper (SafeScraper Twist; META, Reggio Meilia, Italy) a bevel was created through around the calvarial outer table graft to facilitate its removal with a reciprocating saw. The scraper was used to collect copious amounts of cancellous like bone. To remove the graft without breaking,

parallel saw cuts were made in situ[16]. Next, the graft was removed piece by piece. The ensuing defect in the skull was reconstructed with bone cement (Palacos®, Zimmer Biomet, Warsay, Iniana, USA).

All the operations were performed by the same experienced oral and maxillofacial surgeon at the UMCG. After harvesting the calvarial or iliac crest bone, maxillary augmentation surgery was performed according to the procedure according to Raghoebar et al. (2001)[17].

Broad-spectrum antibiotics (amoxicillin/clavulanic acid, 625 mg t.i.d) and non-steroidal anti-inflammatory drugs (ibuprofen, max. 600 mg t.i.d.) were provided for one week post-surgery. Patient instructions included a soft diet and chlorhexidine mouth rinse (1 min, two times daily) for 2 weeks. Two weeks after surgery, the dental prostheses were corrected and the patients were allowed to wear them again.

The implants were placed in the augmented maxilla after a period of 4 months. All the patients were enrolled in a dental hygiene protocol. The final maxillary overdenture was made after a 3 month osseointegration phase.

2.4 Patient reported outcomes

2.4.1 OHRQoL assessment: OHIP-49

OHRQoL was assessed using the validated Dutch version of the Oral Health Impact Profile-questionnaire (OHIP-49) (Slade and Spencer, 1994; Slade, 1998; Van Der Meulen et al., 2008). This 49-item questionnaire assesses improvement or regression in a patient's OHRQoL, enabling an analysis of any changes in OHRQoL over time. The questions are divided into seven domains describing different oral health impact problems: functional limitations, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. Patients must complete five categories per question (graded 0-4) indicating how frequently a certain situation occurs (never, hardly ever, sometimes, fairly often or very often). A high OHIP-49 score corresponds to a low OHRQoL. In this study, the OHIP scores were analysed according to an ordinal scale. The internal reliability, test/retest reliability and OHIP-49 validity have been previously established[19,21]. The Dutch version of the questionnaire, that has been evaluated for reliability and validity[18], was used for the current study.

2.4.2 Denture satisfaction questionnaire

Patient reported denture satisfaction, including functional problem complaints in general, specific features related to facial and denture aesthetics and accidental lip, cheek, and tongue biting, were assessed using a validated questionnaire[22]. The patients were asked to report the

applicability of 40 denture-related complaints to their situation using a four-point scale (0 = no complaints, 1 = few complaints, 2 = moderate complaints, 3 = severe complaints), with a lower score indicating a higher satisfaction.

2.4.3 Chewing ability questionnaire

Patients' eating ability was assessed by a validated chewing ability questionnaire[23]. This questionnaire focuses on how patients experience eating soft, tough, and hard foods and has three answer options: 0 = good, 1= moderate and 2 = bad. A lower score equals a better outcome as it indicates better chewing ability.

2.4.4 Direct post-operative pain

Each patient was asked to score the postoperative pain felt at the donor site during each of the first 30 days after harvesting surgery was performed. A 10 cm vertical visual analogous scale (VAS-)score was used, with the bottom anchor representing 'No pain' and the top anchor as 'Worst pain imaginable'. Assessments took place at 12 o'clock each day. By measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the patient's mark, the score is determined on a range from 0–100. For interpretation of the scores, the following cut points on the pain VAS were used: no pain (0-4mm), mild pain (5-44mm), moderate pain (45-74 mm) and severe pain (75-100mm).

2.4.5 Patient satisfaction with the procedure and outcomes

A three-item list questioned several aspects of the patient's experience with the procedure. The patient's satisfaction with the end result was assessed using a 10 cm VAS-scale with the bottom anchor representing "very unsatisfied" and the upper anchor "very satisfied". The other two items questioned (yes/no) whether the patient would recommend the procedure to other patients with the same problem and whether the patient would be willing to undergo the same operation if needed. Furthermore, satisfaction with the outcomes was assessed regarding the scar aesthetics at the donor site (yes/no) and whether the altered donor site contour was bothersome (yes/no).

2.4.6 Long-term sequela

Twelve months after the implant-based prostheses' were placed, the patients were seen for the final follow up. They were asked to rate the current pain at the donor site (VAS-score). In addition, the patients were questioned regarding difficulties with wearing clothes (wearing a hat/cap, a belt or a pair of trousers) and difficulties with functional mobility (complaints during walking, climbing stairs or cycling). Patients were asked whether they had perceived such

difficulties during the seven days prior to the follow-up meeting and whether these problems had been present before surgery. If the latter was positive, the results were excluded from the evaluation. The items were formulated as two-choice questions (yes/no).

2.5 Statistical analysis

The data were collected by one observer (ABE). Data management and analysis were performed using SPSS 23.0. Data were tested for normal distribution with a Shiparo-Wilk test and checked visually using a histogram with a distribution curve. If required, the outcomes of a non-normally distributed variable were transformed into a normal distribution using a Log10-transformation. The Student-*t* test, the Mann-Whitney-U test and the Pearson-c^2 test compared the outcomes of the parametric variables, nonparametric variables and the categorical gender variable between groups, respectively. Concerning the outcome data, the Pearson-c^2 test compared dichotomous variables. For the post-operative pain dairy, a mixed ANCOVA was performed. Medians instead of means were calculated for non-normally distributed continuous variables such as the general satisfaction (VAS-score) and questionnaire-scores. A significance level of 0.05 was chosen for all tests.

3 RESULTS

All consecutive eligible patients that were referred to our department between November 2014 and March 2016, and met the inclusion criteria, were willing to join the study. The augmentation surgery resulted in sufficient bone volume for implant placement at the prosthodontically preferred sites in all cases. No peri-operative complications occurred. A total of 44 implants was placed in each group. In each group, one patient lost an implant because of mobility during the osseointegration phase, resulting in a 1-year implant survival rate of 97.7%. The clinical characteristics of both groups are listed in Table 1.

3.1 OHIP-49NL, Denture satisfaction and chewing ability

3.1.1 OHIP-49NL

For both groups, the OHIP-49NL sum scores and scores on all seven domains improved between baseline and 12-months post denture placement (Wilcoxon signed-rank test, p=0.001-0.003, Table 2). The functional limitation and physical disability domains showed the largest improvements whereas psychological discomfort, social disability and handicap improved the least. The OHIP-49-scores showed no significant differences in improvement scores between the groups (Mann-Whitney U-test, u=34.00-49.50, p=0.23–0.98, Table 3).

3.1.2 Denture satisfaction

The scores improved significantly after treatment (median score 61.00 (IQR 56.38,74.30) (Wilcoxon signed-rank test, *p*=0.001, Table 2) and were similar in both groups (Mann-Whitney U-test, u=27.00, *p*=0.09, Table 3).

3.1.3 Chewing ability

Chewing ability improved from 16.00 (IQR 13.00, 18.00) at baseline to 11.00 (IQR 9.00, 13.00) 12 months after overdenture placement (Wilcoxon signed rank-test, *p*<0.0001, Table 2), and the group-outcomes were also similar (Mann-Whitney U-test, respectively u=27.00, *p*=0.09 and u=43.00 *p*=0.61, Table 3).

Table 1. Characteristics of the study group

	Total n = 20	**Anterior iliac crest group n = 10**	**Calvarium group n = 10**	**Comparing groups**	
				Test statistic	***p*-value[1]**
Sex				Pearson-c^2-test	
Male	9	4	5	0.202	1.000
Female	11	6	5		
Number of implants placed					
Participants with 4 implants	10	8	8		
Participants with 6 implants	10	2	2		
Number of implants lost	2	1	1		
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Mann-Whitney U**	
Age at implant placement (years)	65.4 (56.4;71.1)	63.5 (56.5;69.3)	68.4 (54.6;72.7)	41.000	0.529
Time between augmentation and implant placement (days)	133 (126;145)	126 (119;133)	140 (131;152)	17.500	0.011

Results are presented as the number or the median (interquartile ranges: IQR).
[1]Exact sig. (2-sided)

Table 2. OHIP-49NL, Denture satisfaction and chewing ability scores before and after treatment

		Anterior iliac crest group n=10		Calvarium group n=10	
Questionnaire	**Max.[1]**	**Pre-treatment Median (IQR)**	**Post-treatment**	**Pre-treatment Median (IQR)**	**Post-treatment**
OHIP-49					
Functional limitations	36	17.4 (15.0;25.3)	3.2(1.1;7.0)	18.0(14.8;24.3)	4.0(1.8;14.5)
Physical pain	36	15.5(11.5;25.5)	2.5(0.8;11.3)	14.5(9.0;20.5)	4.0(1.5;14.5)
Psychological discomfort	20	11.0(6.0;16.5)	0.0(0.0;1.8)	11.5(10.0;16.3)	4.5(0.0;8.3)
Physical disability	36	15.0(9.8;21.0)	0.0(0.0;4.8)	16.5(9.8;25.8)	4.5(0.0;9.5)
Psychological disability	24	7.0(1.0;12.5)	0.0(0.0;1.5)	10.0(6.8;18.3)	2.5(0.0;7.3)
social disability	20	3.5(0.0;8.5)	0.0(0.0;0.0)	3.5(1.5;11.3)	3.0(0.0;5.3)
Handicap	24	4.0(1.0;9.8)	0.0(0.0;0.0)	3.2(0.8;12.3)	0.5(0.0;3.5)
Summary scores OHIP	196	78.8(48.0;125.7)	10.5(2.5;27.7)	77.4(55.5;128.1)	24.3(5.1;57.5)
Denture satisfaction	216	111.1(85.4;126.4)	58.0(55.1;69.9)	90.3(72.3;113.5)	65.8(58.1;78.3)
Chewing ability	27	15.5(12.8;126.5)	9.0(9.0;12.0)	16.0(12.3;20.3)	12.5(9.0;16.2)

[1]*Maximum score possible on test/domain*

Table 3. Score changes following treatment for OHIP-49, denture satisfaction and chewing ability

	Anterior iliac crest group n = 10 Median (IQR)	**Calvarium group n = 10 Median (IQR)**	**Comparing groups Mann-Whitney U**	***p*-value[1]**
OHIP-49				
Functional limitation	13.44(9.66; 20.41)	9.69 (5.50; 15.75)	34.00	0.24
Physical pain	12.00(1.50; 22.75)	5.19 (-2.00; 15.85)	39.00	0.42
Psychological discomfort	11.00(5.50; 13.25)	9.00 (1.75; 12.00)	36.00	0.30
Physical disability	10.50(9.00;19.50)	12.50(0.75;17.50)	43.50	0.64
Psychological disability	5.00(1.00;12.25)	5.00(1.50;11.25)	49.50	0.98
Social disability	2.00(0.00;8.50)	1.50(-0.25;4.00)	39.50	0.44
Handicap	4.00(1.00;9.75)	1.50(0.00;5.25)	34.00	0.23
Summary scores	61.80(26.08;92.14)	51.39(14.67;85.79)	39.00	0.44
Denture satisfaction	39.02(27.95; 70.40)	12.34(4.37; 54.80)	27.00	0.09
Chewing ability	4.50(2.75; 7.50)	5.00(-0.75;7.28)	43.00	0.61

[1]*Exact sig. (2-sided)*

3.4 Direct post-operative pain

For the anterior iliac crest group, the mean VAS-scores for pain ranged from 34.0±14.3 mm (day 2) to 1.0±3.2mm (day 30). For the calvarium group, the highest mean pain score was 32.0±22 (day 3) and this deceased to 0.0±0.0 on day 14 (figure 2). After a Log10-transformation of the data to correct for skewness, a Linear Mixed Model was run to determine to compare the course of pain scores between the treatment groups. There was a significant difference between treatment groups with an estimated effect of 0.09 (standard error=0.015) for the anterior iliac crest group (G=31.3, p=0.00), meaning the pain scores of anterior iliac crest group are higher than the calvarium group scores (F=31.30, p<0.00).

To determine the effect of time and covariates such as age, gender and BMI on the VAS-scores, a repeated measures ANCOVA was run. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated (X^2=0.000, p<0.0005) and therefore, a Greenhouse-Geisser correction (ε=0.11) was used. There was a significant effect of time on VAS-scores, F(3.1;55.3)=32.6, p<0.0005. (Figure 2). Furthermore, an interaction was found between BMI and VAS-scores of the anterior iliac crest group (Greenhouse-Geisser, ε=0.14, F(3.3;26.4)=2.9, p=0.04), but not for the calvarium group (Greenhouse-Geisser, ε=0.084, F(2.4;19.5)=0.1, p=0.93)

3.5 Patients' satisfaction

The results on general patient satisfaction are listed in Table 4. All the participants (n=20) confirmed that they would undergo the same procedure again if needed and that they would recommend the procedure to others. The overall level of satisfaction with the end result was high with a median of 93 (IQR 86, 99) on a 100 mm VAS-scale (n=20).

On separating the results according to treatment group, the median VAS-score of the calvarium group was 87mm (IQR 74, 100) and of the anterior iliac crest group, 95mm (IQR 90, 100) (Mann Whitney U-test, U=34.5, p=0.247). The VAS-scores on satisfaction with the end result contained one outlier (VAS-score: 4mm) in the calvarium group. The final appearance of the prosthetic device did not match this patient's expectations. The complaint was directed at the prosthetic technique and not at the surgical procedure. On excluding this case from the analysis, the remaining scores provided a median score of 93mm (IQR 86, 99) for the entire study group (n=19) and 89mm (IQR 81, 100) for the calvarium group (n=9). There was no significant difference either when the median VAS-scores were compared without the outlier (Mann-Whitney U-test, U=34.00, p=0.400).

3.5.1 Donor site appearance

Regarding changes at the donor site, one patient from each treatment group noticed an alteration in the contour. Two patients from the anterior iliac crest regarded the scar aesthetics as being acceptable instead of satisfactory (Pearson c^2-test, 2.222, *p*-value = 0.474).

3.6 Long-term sequelae

3.6.1 Pain

The median VAS-scores for current donor site pain at the calvarium and anterior iliac crest site were 1mm (IQR 0, 1mm) and 2mm (IQR 1, 3), respectively. (Mann Whitney U-test, U=30.500, *p*=1.000 for the current pain at donor site) (Table 5).

3.6.2 Difficulties in daily functioning

None of the participants in the calvarium group reported difficulties with wearing clothes or functional mobility (Table 5). One participant in the anterior iliac crest group reported difficulties with wearing clothes. Furthermore, two participants from the anterior iliac crest group noted they had problems with functional mobility. One of these two patients reported pre-surgical problems with walking as well. It was unclear whether the complaints were stable or had worsened or improved. The differences between the groups were not statistically significant (Pearson *c*2-test, *p*-values 0.31-1.00, Table 2).

Table 4. Patient reported outcomes on general satisfaction regarding the treatment procedure

	Iliac crest group *n* = 10 Median (IQR)		**Calvarium group *n* = 9[1] Median (IQR)**		**Comparing groups**	
					Mann-Whitney U	***p*-value[2]**
How satisfied are you concerning the end result? (VAS-score in mm)	95(90;95)		87(74;100)		34.500	0.247[2]
	Yes	*No*	*Yes*	*No*		
Would you recommend the procedure to other patients with the same problem?	10	0	10	0		
Would you be willing to undergo the same operation when needed?	10	0	10	0		

Results are presented as the number or the median (interquartile ranges: IQR).
[1]*After excluding one outlier from the calvarium group who reported a VAS-score of 4mm*
[2]*Exact sig. (2-sided)*

Table 5. Patient reported outcomes on donor site pain (VAS-score), difficulties in daily functioning and satisfaction with the procedure; assessed after bone graft harvesting surgery

	Iliac crest group *n* = 10		**Calvarium group *n* = 10**		**Comparing groups**	
	Median (IQR)		**Median (IQR)**		**Mann-Whitney U**	***p*-value[1]**
Donor site pain (VAS-scores)						
How would you rank the current pain felt at the donor site?	2(1;3)	1(0;1)			30.500	1.000
Donor site related complaints in daily functioning	Yes	Yes	No	No	Pearson-c[2] test	
During the past week, did you perceive any of the following						
Headache	2	2	8	8	.000	1.000
Difficulties with wearing cloths[2]	1	0	10	9	1.053	0.305
Difficulties with functional mobility [3,4]	1	0	10	9	1.053	0.305
Are you satisfied with the scar aesthetics at the donor site?	8	10	0	2	2.222	0.474
Do you consider the altered contour of the donor site bothersome?	1	1	9	9	0.000	1.000

Results are presented as the number or the median (interquartile ranges: IQR).

[1]*Exact sig. (2-sided)*

[2]*Difficulties with wearing daily cloths such as a hat, cap, belt or pair of trousers*

[3]*Difficulties with getting around in daily living, such as with walking, climbing the stairs or cycling*

[4]*Statistical test performed exclusive of one case with pre-surgical difficulties on functional mobility*

FIGURES

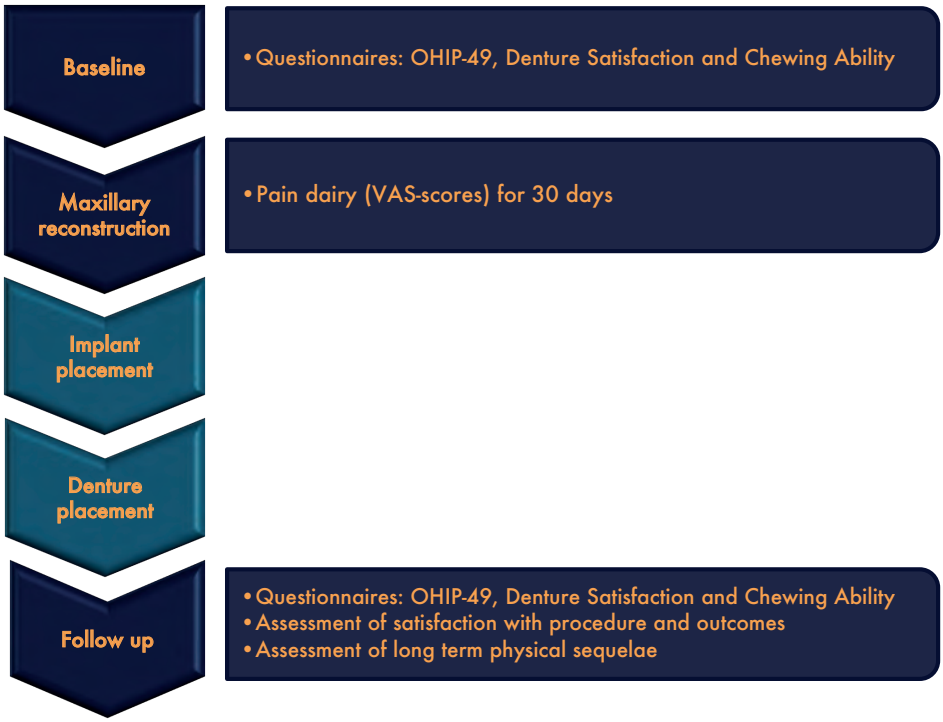

Figure 1. The PROMS were assessed at pre-defined steps in the treatment program of an individual participant. First, when a participant was included for the study but before an intervention had taken place, the OHIP-49, Denture Satisfaction and Chewing Ability questionnaires were administered to determine the baseline level of oral health related quality of life, satisfaction with the current denture and perceived ability to chew food, respectively. Next, directly following the reconstruction surgery that included the bone graft harvesting from either calvarium or anterior iliac crest, the post-operative pain was assessed by asking participants to report the perceived pain at donor site on a 100 mm VAS-score for 30 days. Following a four months osseointegration phase, the implants were placed in the reconstructed maxilla. Another four months later, the patients received their implant retained denture. No PROMs were assessed during these two steps as they were not related to the bone graft harvesting surgery. Finally, at a 12-months follow up meeting, again the OHIP-49, Denture Satisfaction and Chewing Ability questionnaires were administered again to measure improvement or decrease in scores. Moreover, patient satisfaction with the procedure and the outcomes were assessed as well as presence of long-term physical sequelae resulting from the bone graft harvesting procedure.

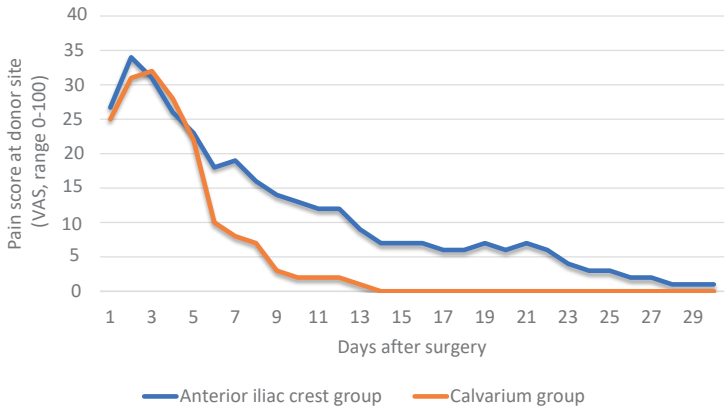

Figure 2. During the first 30 days following maxillary reconstruction with either calvarial (n=10) or anterior iliac crest (n=10) bone grafts, participants scored the pain felt at donor site using a 100 mm VAS-scale ('0' represents 'no pain' and '100' represents 'worst pain ever'). For the anterior iliac crest group, the mean VAS-scores for pain ranged from 34.0±14.3 mm (day 2) to 1.0±3.2mm (day 30). For the calvarium group, the highest mean pain score was 32.0±22 (day 3) and this deceased to 0.0±0.0 on day 14. A Linear Mixed Model determined a significant difference between treatment groups with an estimated effect of 0.09 (standard error=0.015) for the anterior iliac crest group (G=31.3, *p*=0.00), meaning the pain scores of anterior iliac crest group are higher than the calvarium group scores (F=31.30, *p*<0.00).

5 DISCUSSION

PROMs are a core aspect in treatment program evaluations[24]. Therefore, patients' appreciation of extra oral bone graft harvesting, used for pre-implant augmentation of the edentulous maxilla, was assessed. The bone graft harvesting surgery itself and the complete procedure enabled by the bone grafting showed a high patient reported satisfaction with the course and its results. The PROMs imply a successful treatment, and apart for the higher post-operative pain scores following harvesting anterior iliac crest bone the outcomes are similar for calvarial and iliac crest bone harvesting.

This study's results are in accordance with previous findings in literature on OHRQoL, denture satisfaction and chewing ability, procedure related satisfaction and long-term donor site related outcomes[9]. The prospective, controlled design of this study enables confirmation of the suggested similarites between the procedures from a patients point of view. For clinical decision making, the interaction between direct post-operative pain and BMI can be taken into account. Futhermore, the minor differences in satisfaction with the outcomes at donor site and problems with physical mobility should be considered as well.

Another previously described phenomenon was found: the surgery comes a long with moderate direct post operative pain and with high levels of satisfaction[14]. High pain levels following extra oral bone harvesting[8], especially when it comes the the anterior iliac crest[3,25], is frequently mentioned as a major disadvantage from a patients perspective and the coexistence with high satisfaction with the procedure is a frequent subject of debate[26]. This discussion might result from the way the patient satisfaction construct is interpreted. A complete model of this construct can explain this coexistence. Patient satisfaction covers all aspects of care quality, that is appropriate access to health services, provision of health information, relationship between patient and health care staff, participation in making choices regarding health treatment, satisfaction with the treatment provided, effectiveness of treatment including the extent to which the treatment meets the patient's expectations of care, and general satisfaction[27]. Thus, a patient's satisfaction with treatment is not dictated exclusively by physical parameters[27] and therefore, it can be high despite moderate post-operative pain.

This study assessed satisfaction at the final follow up to assure the patients' appreciation would entail each step in the treatment program. However, the course that patients' satisfaction makes was not registered. Furthermore, not all dimensions of patients' satisfaction were assessed as this study focused on the patients' appreciation of the technical procedure. Future research on these two points can help improving the treatment program.

To conclude, prosthetic rehabilitation programs, encompassing maxillary augmentation with extra-oral bone grafts from either the calvarium or anterior iliac crest, are reliable pre-implant surgery procedures for extremely resorbed maxilla cases, as they are associated with high patient satisfaction in terms of both treatment procedure and end results. As patient satisfaction is determined by the patient's expectations and provision of information, an explanation of the procedure and the course of postoperative complaints deserves special attention in clinical practice.

LIST OF ABBREVIATIONS

PROM:	Patient Reported Outcome Measures
OHRQoL:	Oral Health Related Quality of Life
OHIP-49NL:	Oral Health Impact Profile, 49 item version in Dutch
UMCG:	University Medical Centre Groningen
CBCT:	Cone Beam Computed Tomography
VAS:	Visual Analogues Scale
IQR:	Inter quartile range

6 DECLARATIONS

Ethical approval and patient consent

The study protocol was approved by the Medical Ethics Committee of the University Medical Centre of Groningen (reference number NL48614.042.14). Written consent was obtained from all participants.

Availability of data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

JS and GMR conceived and planned the work. DEW, CG and AV contributed to analysis and interpretation of the data for the work. DEW wrote the manuscript with consultation of CG, JS, AJ and GMR. DEW, CG, JS, AJ and GMR provided critical feedback and helped shape the research, analysis and manuscript. DEW, CG, JS, AJ and GMR approved the current version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any parts of the work are appropriately investigated and resolved.

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CHAPTER 5

Histomorphometric and micro-CT analyses of calvarial bone grafts used to reconstruct the extremely atrophied maxilla

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This chapter is an edited version of the manuscript: D.E.Wortmann, J. Klein-Nulend, L. J. Van Ruijven, A. Vissink, G.M. Raghoebar, J. Schortinghuis. Histomorphometric and micro-CT analyses of calvarial bone grafts used to reconstruct the extremely atrophied maxilla

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Background: Calvarial bone grafts are successful in reconstruction of the severely atrophied maxilla as a pre-implant procedure. However, not much is known about graft incorporation at microscopic level.

Purpose: This study aimed to assess calvarial bone conversion 4 months after being grafted in edentulous maxillary bone.

Materials and methods: In 13 patients (age:65.3±8.7 years) the atrophic maxilla was reconstructed with autologous calvarial bone. Biopsies were taken from fresh calvarial bone grafts and from the reconstructed maxillae after 4 months healing. Micro-CT, histomorphometric, and histological analysis were performed. From 3 patients biopsies were obtained after 9, 11 or 45 months.

Results: The micro-CT analysis revealed that in the maxilla the calvarial bone was well preserved even after 45 months. Histology showed progressive incorporation of grafted bone within maxillary bone. Osteoid and osteocytes were present in all biopsies indicating new bone formation and vital bone. Histomorphometrically, the percentage of grafted bone volume over total volume decreased from 79.8% (IQR78.7-83.3) in fresh calvarial grafts to 59.3% (IQR44.8-64.6) in healed grafts. The biopsies taken after 9, 11 and 45 months showed similar values.

Conclusions: Calvarial bone grafts results in stable and viable bone, good incorporation into native maxillary bone, and minor decrease in bone volume after healing. Consequently, they provide a solid base for implant placement in severely atrophied edentulous maxillary bone.

1 INTRODUCTION

Autologous bone grafts are widely used to reconstruct bony defects in the craniofacial region. They are still the most favourable grafting material for reconstructions due to their unique osteogenic, osteoinductive, and osteoconductive properties.[1-3] The long-term structural integrity and quality of the grafted bone depend on the donor site the bone graft is harvested from. Several sites are used to harvest autologous bone. These sites can be classified according to their embryological origin, i.e. endochondral or intramembranous. The iliac crest, tibia, and ribs are endochondral in origin, while the maxilla, mandible, and skull (calvaria) are intramembranous in origin.[1,4] A major difference between the two is that the resorption rate of intramembranous bone is less than that of endochondral bone.[4,5] As a result, intramembranous bone is presumed to have better long-term results with regard to three-dimensional reconstructions of severely atrophied ridges.

Intra-oral sites are frequently used as graft donor sites for bony reconstructive procedures prior to implant placement, but the amount of bone that can be harvested from the chin, mandibular ramus and maxillary tuberosity is limited. When large volumes are needed, other intramembranous bone sites can be used as a donor, for example the calvarium.[1,5] Although calvarial bone grafting bears the hazard of inducing severe complications, technique improvements have made its harvesting a safe and straightforward procedure.[6-10]

The success of a bone graft is often assessed indirectly based on implant survival and macroscopic volumetric changes,[11] An important drawback of these approaches is that qualitative and quantitative factors, such as relative volumetric changes, mineral density, and maturation of the graft, remain out of scope, even though these parameters provide insight into the long-term outcomes of the reconstruction. Current advancements in imaging technology have led to a significant improvement in the resolution of the skeletal structural architecture *in vivo* and *ex vivo*, enabling a more in-depth analysis of bony reconstructions. Micro-CT scanning provides a 3D image with a very high resolution which can be used for quantitative analysis of the calcified tissue to assess graft site healing. Histomorphometric analysis provides insight into the cellular properties of the calcified tissue .[12] Utilising a combination of these techniques facilitates the evaluation of the mineral and bioactive properties of bone. The aim of this study was to use micro-CT and histomorphometric analyses to assess the material properties and incorporation of calvarial bone grafts into the reconstructed atrophied maxilla.

2 MATERIAL AND METHODS

2.1 Patient selection

Consecutive eligible patients who were referred to the department of Oral and Maxillofacial Surgery of the Treant Scheper Hospital in Emmen, the Netherlands, and who suffered from problems with wearing an upper denture due to severe resorption of the edentulous maxilla, were asked to join this study. Inclusion criteria were an insufficient bone volume for reliable placement of dental implants as assessed on a computed tomography (CT) scan, i.e. <3 mm bone height in the maxillary sinus area, and <2mm bone width in the anterior maxillary area. In order to harvest calvarial bone, the patients' parietal bone in the skull had to be at least 5 mm thick in the area between the articular tubercle and the end of the mastoid bone. Exclusion criteria were patients with an American Society of Anaesthesiologists (ASA) score of III or higher[13], a history of radiotherapy in the head and neck region, former or current use of intravenous bisphosphonates, and previous cranial surgery.

2.2 Study approval

The study was approved by the Medical Ethical Committee (REF SH20141) of the Scheper Hospital, Emmen, the Netherlands.

2. 3 Surgical procedure

The technique described by Schortinghuis et al. was used to harvest the calvarial bone grafts.[6] In short, after raising a full-thickness flap from the parietal skull, the outer table graft was marked with a burr until the diploe was encountered. A bevel was created with a bone scraper around the calvarial outer table graft area to harvest cancellous bone and to facilitate piece-by-piece removal of the cortical bone grafts with a reciprocating saw. The remaining defect in the skull was reconstructed with bone cement (Palacos®, Zimmer Biomet, Warsay, IN, USA).

Maxillary sinus floor elevation surgery was performed with the cancellous calvarial bone on both sinuses. The cortical bone grafts were positioned at the exposed maxillary alveolar process as buccal onlay grafts. The cancellous portion of the graft was placed towards the recipient maxilla. The grafts were fixed with 1.3 mm osteosynthesis screws (Synthes, Wolhusen, Switzerland). The sharp bone edges were rounded to allow for smooth coverage of the grafted area with the overlying mucosa. Subsequently, dental implants (Straumann, Wolhusen, Switserland) were placed immediately in the reconstructed maxilla and the remaining gaps were covered with cancellous bone. Primary wound closure was accomplished using resorbable 4-0 polyglactine sutures (Ethicon, Somerville, NJ, US).

2.4 Bone biopsies

Bone biopsies were obtained from the calvarial bone area immediately after harvesting and from the fresh grafts as well as 4 months later from the native and grafted bone in the reconstructed maxilla, whereby a small bone wedge of the reconstructed alveolar process was taken between two adjacent implants. A photograph and a schematic drawing of each biopsy were made to record the spatial orientation of the specimen (Figure 1). The biopsies were preserved in 4% phosphate-buffered formaldehyde solution (Klinipath BV, Duiven, the Netherlands) for 24 h and then stored in 70% ethanol until used for micro-CT and histomorphometric analyses.

2.5 Micro-computed tomography evaluation

All the biopsies were scanned with a high-resolution micro-CT (mCT 40, Scanco Medical AG, Brüttisellen, Switzerland). This system was calibrated every two weeks using phantoms with densities of 0, 100, 200, 400 and 800 mg HA/cm^3. Before scanning, the biopsies were fixed with synthetic foam in a polyetherimide tube (inner diameter, 28.5 mm; length, 75 mm). Then the tube was filled with 70% ethanol and covered with Parafilm M (SPI Supplies, West Chester, PA, US) to prevent evaporation during scanning. The scanner settings were voltage, 70 kV; intensity, 113A; integration time, 1000 ms; isometric resolution, 0.015 mm. 3D reconstructions were made with a cone-beam reconstruction algorithm. All reconstructions were smoothed with a Gauss filter (0.8/1) and segmented with a visually determined threshold of 559.2 mg HA/cm^3 (Figure 2). This threshold visualises bone in the same way as it appears on histological sections. Orientation of the biopsy and transition zone were identified for each bone biopsy using the photographs and schematic drawings of the biopsies.

To perform evaluations, volumes of interest (VOIs) were set by manually tracing the contours of the fragment of bone. For all biopsies, the VOI included the entire fragment of bone. Then for each of the biopsies taken after 4 months, one VOI was drawn including only grafted bone and one including only native bone. For each VOI, the tissue mineral density (TMD, mg HA/cm^3), defined as the mean mineral density of the whole volume of interest, was calculated. TMD can be used as a qualitative measure for the mineral density of compact bone. The bone mineral density (BMD, mg HA/cm^3), defined as the mean mineral density of the segmented bone volume in the VOI, was also calculated[14]. Finally, the bone volume fraction (BVF), which is a quantitative measure defined as the ratio of the segmented bone volume to the total volume of the VOI (%), was assessed. In other words, BVF represents the percentage of biopsy volume, or tissue volume, that is occupied by bone volume.

2.6 Histology and histomorphometric analysis

After micro=CT scanning and dehydrating in ascending alcohol series, the bone biopsies were embedded without prior decalcification in low-temperature polymerizing methyl methacrylate

(MMA, Merck Schuchardt OHG, Hohenbrunn, Germany). 3D-orientation of the biopsies was assessed using the clinical pictures. Longitudinal 5 µm thick sections were cut with a Jung K microtome (Reichert Jung, Heidelberg, Germany). Midsagittal histological sections of each biopsy were stained with Goldner's trichome to distinguish mineralized bone (green) and unmineralized osteoid tissue.[15] Digital images of the sections were acquired at 100x magnification.

First, a qualitative histological analysis was performed. The 2D-orientation, completeness, and outstanding features, such as signs of inflammation, were identified for each section. The orientation was determined from the notes and photographs taken during the surgery as well as the 3D-reconstructions made by the micro-CT-software (Figure 3). The cortical bone percentage was determined for the fresh biopsies. Regarding the biopsies taken after 4 months, the native maxillary bone and grafted calvarial bone were identified visually. The presence and 2D distribution of bone, osteoid and osteocytes was measured per section (presence and location). Bone is defined here as mineralized bone matrix excluding osteoid.[16] Osteoid is bone matrix that was not yet mineralized.[16] The presence of osteoid indicates new bone formation. Osteocytes are mature osteoblasts located with their cell bodies in lacunae and with their cellular processes running through the canaliculi. They are encased by a mineral matrix and are normally supplied by vessels lying in the bone's canal system. Osteocytes are the mechanosensors of bone, and as such they have an important regulatory function in bone resorption and bone formation. The presence of vital osteocytes in the grafted bone indicates that the canalicular system has been able to remain viable and functional. [17]

Histomorphometry was performed by dividing the sections into three pre-defined zones, i.e. (1) the cortical zone of the graft, which is the cortical outer side of the graft just underneath the periosteum; (2) the cancellous zone of the graft, which is the side of the graft towards the alveolar process; and (3) the transitional zone, which is the contact zone between the calvarial graft and the alveolar process onto which the graft is fixed. For each zone, three regions of interest (ROIs) were determined for every biopsy zone following a pre-defined pattern (Figure 4). The mean result of each zone was used to compare the biopsies.

For each ROI, histomorphometrical measurements were manually performed using a computer with an electronic stage table and a Leica DC 200 digital camera. The computer software used was Leica QWin (Leica Microsystems Image Solutions, Rijswijk, The Netherlands). The primary variables bone area, osteoid area, and osteocyte number were determined. The percentage of bone area, percentage of osteoid, and osteocyte number per mm^2 of tissue area were derived from these primary outcomes.[16-18]

2.6 Statistical analysis

Data management and analysis were performed using SPSS 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) The data were tested for normal distribution with a Shiparo-Wilk test and checked visually using a histogram with a distribution curve. Data are presented as mean ± standard deviation, or in case of non-normal distribution, as median and interquartile range. A dependent student T-test, or the non-parametric paired Wilcoxon Signed Rank-test, was used to determine differences in TMD, BMD, and BVF between the fresh calvarial bone and the grafted calvarial bone in the biopsy obtained after four months healing from the same patient, and to determine differences between the grafted and native bone in the biopsies obtained after four months healing, within the same biopsy. A Friedman Test, or in case of non-parametric data, a Kendall's W test, was used to determine differences in histomorphometric results between the three zones (cortical, cancellous, and transition zone) of the same section. A significance level of 0.05 was chosen for all tests.

3 RESULTS

3.1 Study population characteristics

The 13 participating patients were either male (7) or female (6) (Table 1). The mean age of all participating patients at the time of bone graft harvesting surgery was 65.3±8.7 years. Three participating patients were smokers.

3.2 Clinical results

All 13 participating patients received reconstructive surgery of the maxilla. In 3 participating patients, the process involved a double plating technique, i.e. both buccal and palatinal bone grafting was applied. There were no differences in clinical outcomes or micro-CT, histological, and histomorphometric results between the patients that received buccal bone plating only and those that received both buccal and palatinal platings. It was possible to place all 66 implants immediately during the reconstruction. In total 6 implants were lost in 2 patients (one patient lost 5 implants, and one patient lost one implant) after one-year follow up. Both patients were smokers.

3.3 Biopsies

A total of 28 bone biopsies was obtained. Thirteen biopsies came from the freshly harvested calvarium, 15 were taken from the reconstructed maxillary alveolar wall after the grafted bone had healed. In 12 participants, biopsies were taken after four months of healing, and one participant's biopsy was taken after 9 months of healing due to a prolonged stay abroad. This biopsy's analysis was not added to the other results from the specimens that were taken after

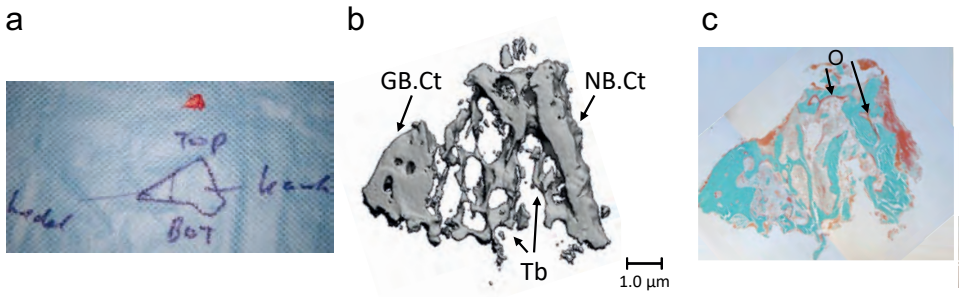

Figure 1. Method of micro-CT and histomorphometrical analysis of biopsies taken from the edentulous maxillary alveolar process that was reconstructed using calvarial bone grafts, four months after reconstruction took place. (a) Direct per-operative notes. Biopsy obtained from the alveolar process, four months after it was reconstructed using calvarial bone grafts, with the orientation indicated by pencil marker. (b) Micro-CT image of the same biopsy. The thick cortical part (GB.Ct) (left) represents the grafted bone. In the middle, trabeculae (Tb) connect the grafted and native bone. (c) Histological section of the same biopsy. New bone formation is observed, as red non-mineralized osteoid aligning mature bone between native and grafted bone. Magnification: a, 2x; b, 20x; c, 20x. Top: top of the alveolar process; bot: maxillary jaw bone cranial from the alveolar process; Kaak: native maxillary bone; schedel: grafted calvarial bone used to reconstruct the alveolar process; GB.Ct: cortical part of grafted calvarial bone; NB.Ct: cortical part of native maxillary bone; Tb: trabeculae; O: osteoiZie opmerking bij figuur hierboven, tekst klopt maar figuren moeten worden omgedraaid.

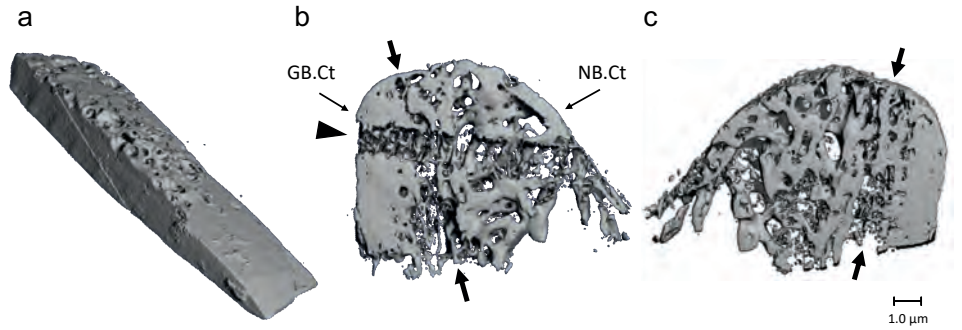

Figure 2. Micro-CT scans of fresh calvarial bone biopsy and bone biopsy obtained from an edentulous maxillary alveolar process, four months after it was reconstructed using a calvarial bone graft. (a) Fresh calvarial bone biopsy consisting mainly of cortical bone. The diploic bone is the more porous part of the piece. (b) Biopsy after 4 months healing seen from distal perspective. The left side exists of grafted bone. The compact cortex of the calvarium can be identified based on morphology and density of the bone. Native maxillary bone is more porous, contains more trabeculae, and the cortical wall is thinner compared to the bone in grafted area. (c) Biopsy after 4 months healing seen from mesial perspective. Arrows: border between grafted and native bone. The horizontal path through the calvarial part and the native bone part of the removed fixation screw is clearly visible (arrowhead). Magnification: a, 40x; b, 20x; GB.Ct: cortical part of grafted calvarial bone; NB.Ct: cortical part of native maxillary bone.

4 months. From two participants, a biopsy could be obtained at a later point in time. One biopsy obtained after 11 months, was taken during surgical treatment of a peri-implantitis, from a healthy area of the reconstructed maxilla. The other bone biopsy was taken 45 months after the calvarial bone grafting when this patient was surgically treated for a non-dental related sinusitis condition.

3.4 Micro-CT

In the CT scans the original orientation and the transition zone were identified on the 3D-reconstruction by the same investigator (DW) and double checked (JS). Figure 2 shows a 3D-reconstruction of a fresh block of calvarial bone graft and a specimen harvested during implant placement after a 4 month healing period.

In the fresh calvarial bone grafts, smooth transition from dense cortical bone towards more cancellous diploic bone was seen. The trabecula of the diploic part were thick and short. In the biopsies obtained after four months, the grafted bone could be identified easily based on the compact cortical bone and morphology of the graft. The grafted bone looked as dense as the fresh biopsies. A more in-depth observation of the biopsies revealed that the transition towards cancellous bone started similar to the fresh biopsies, but the trabeculae became thinner and longer towards the native maxillary bone. At the transition between both bone types, more space was seen between the trabeculae, while they were irregular in form and thickness indicating remodelling of the grafted bone. Further towards the native bone, the trabeculae remained thin and long, but became more packed together. The cortical zone of the native bone was thinner compared to the calvarial bone.

All biopsies were included for micro-CT analysis and the results are depicted in Table 1. The tissue mineral density measurements revealed that the density of the grafted bone after four months of healing was comparable to the fresh calvarial bone (Wilcoxon Signed Rank Test, Z=-.87, p=.43, Table 1). Comparison of the BMD between fresh biopsies and the grafted bone VOI of biopsies taken after 4 months showed no significant differences either (Wilcoxon Signed Rank Test, BMD: Z=-1.9, p=.06). In addition, the volume of the grafted bone (BVF) showed no significant decrease (Wilcoxon Signed Rank Test, Z=-.62, p=.58). Thus, calvarial bone grafts remain their volume and bone mass after being incorporated in the maxilla.

When grafted and native bone from the same biopsy were compared, the tissue mineral density of the grafted bone was significantly less compared to the maxillary bone (TMD: Wilcoxon Signed Rank Test, Z=-2.5, p=.01). The inorganic bone mass (BMD) and the volume fraction occupied by bone (BVF) were significantly lower in native bone as well (Wilcoxon Signed Rank Test, BMD: Z=-2.1, p=.02; BVF: Z=-2.5 p=.01, Table 1). In other words, after four months healing, the grafted bone seemed to adapt to the maxillary bone with slight changes.

The TMD, BMD, and BVF values of the grafted bone biopsies taken at later moments (9, 11 and 45 months) lie within the confidence intervals of the biopsies taken after 4 months: the TMD was 768.6, 406.8 and 597.8 mg HA/cm^3, the BMD was 990.3, 1009.1, and 867.5 mg HA/cm^3, and the BVF was 49%, 32% and 58% for the 9, 11 and 45 months biopsies, respectively. This suggests that calvarial bone grafts also remain stable over a longer time period than four months.

Table 1. Microcomputed tomography analysis of tissue mineral density (TMD), bone mineral density (BMD) and bone volume fraction (BVF) in biopsies taken from fresh calvarial bone grafts and from reconstructed maxillary alveolar ridges with calvarial bone graft four months after reconstruction and prior to implant placement.

	Fresh calvarial bone biopsies (n=13)		Healed reconstructed alveolar process biopsies							
			Native bone (n=12)		Grafted bone (n=12)		*P* value[a]		*P* value[b]	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Z**	***p***	**Z**	***p***
TMD (mg HA/cm^3)	617.9	510.3-784.5	373.9	300.5-484.9	596.3	444.4-756.1	-2.5	.01*	-.87	.43
BMD (mg HA/cm^3)	983.4	962.9-1016.2	866.7	823.7-909.7	919.4	827.5-985.1	-2.1	.04*	-1.9	.06
BVF (%)	59.8	51.6-72.7	30.5	24.4-43.8	62.6	35.3-74.1	-2.5	.01*	-.62	.58

**Significant difference between native and grafted bone within the same biopsy obtained after four months healing, p<0.05. [a]Equality of medians tested between native and grafted bone within the same biopsy using a Wilcoxon Signed Rank test. [b]Equality of medians tested between fresh calvarial bone and grafted calvarial bone after four months of healing. IQR: interquartile range.*

3.5 Histology

The fresh calvaria sections consisted of highly mineralized bony tissue, appearing dark green in the histological sections. The sections contained mostly dense cortical bone, but several sections showed both cortical and diploic bone, with a smooth transition from one type to the other bone type. The diploic bone consisted of short, thick trabeculae. Numerous osteocyte lacunae were visible throughout the sections (Figure 4A). In the sections obtained from biopsies taken at 4 months, the original alveolar process, transition zone, and grafted bone could still be identified in the bone morphology, irrespective of bone maturation. Several trabeculae were present at the transition zone between the grafted and native bone. These trabeculae connected the two bony parts, thus representing new bone formation. The trabeculae at the transition zone were irregular and thin, and appeared more like maxillary bone. Next to these trabeculae, soft, mostly fat, tissue was seen between the graft and the native bone, and sometimes signs of inflammation. Moreover, low mineralized bony tissue was observed, possibly the result of the cancellous bone particles that were used to fill the gaps between the grafted and native bone. Apart from mineralized bone tissue, osteoid was present foremost in the transition zones (Figure 4B). Osteocytes were seen throughout the biopsies, but they were more concentrated in the

transition zone and cancellous parts of the grafted bone than in the cortical part of the graft. In the biopsies taken at later time points, the osteocytes were more evenly distributed throughout the grafts (Figure 4C), indicating further maturation of the bone. The visual difference between the graft and the alveolar bone was less obvious in the later biopsies.

3.6 Histomorphometry

Histomorphometry was used to measure the cortical part and the cancellous zone of the graft, and the transition zone between the graft and the alveolar process. It was possible to set the nine ROIs following the pre-defined pattern in 9 out of 11 biopsies taken after 4 months and all three late biopsies. In two biopsies, only two ROIs per zone were possible. Another two biopsies could not be measured due to inadequate orientation of the sectioning.

During the four-month healing period, the median bone percentage significantly decreased from 79.8 % (IQR 78.7-83.3%) in fresh biopsies and to 59.3% (IQR 51.5-64.1%) in biopsies taken at 4 months (Wilcoxon Signed Rank Test, Z=-2.5, *p*=.01). Within the biopsies taken at 4 months, the median osteoid percentage was highest at the transition zone between the grafted and native bone, and lowest at the cortical zone (Kendall's W test, W=.412, *p*=.004, Table 2). As osteoid indicates new bone formation, it seems that bone had formed throughout the grafted bone. However, the highest activity took place at the border between the grafted and native bone. The median osteocyte count over the bone area was similar among the biopsies, i.e. the highest number of osteocytes was found at the border between the grafted and native bone, and the lowest number of osteocytes was observed at the cortical part of the grafted bone (Kendall's W test, W=.05, *p*=.473, table 2).

Table 2. Histomorphometric analysis of bone percentage (Bp), osteoid percentage (Op) and osteocyte number per volume (OcN/Ba) in biopsies from grafted sites after 4 months in patients undergoing reconstruction of the edentulous maxilla prior to implant placement.

	Cortical bone of calvarial graft		**Cancellous bone of calvarial graft**		**Transition zone between calvarial graft and native maxillary bone**		**Significance***	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**W**	***P* value**
Bp (%)	59.3%	44.8-64.6%	36.2	29.5-43.3	29.4%	23.7-34.6%	.387	.001
Op (%)	.7%	.3-1.5%	.7%	00-1.3	1.6%	.9-2.1%	.412	.004
OcN/Ba (1/ mm^2)	159	87-291	158	46-506	316	83-432	.05	.473

**Significant difference between Bp, Op or OcN/Ba measured in the cortical calvarial bone, cancellous calvarial bone or transition zone between grafted calvarial bone and native maxillary bone, within the same section (Kendall's W test). IQR: interquartile range.*

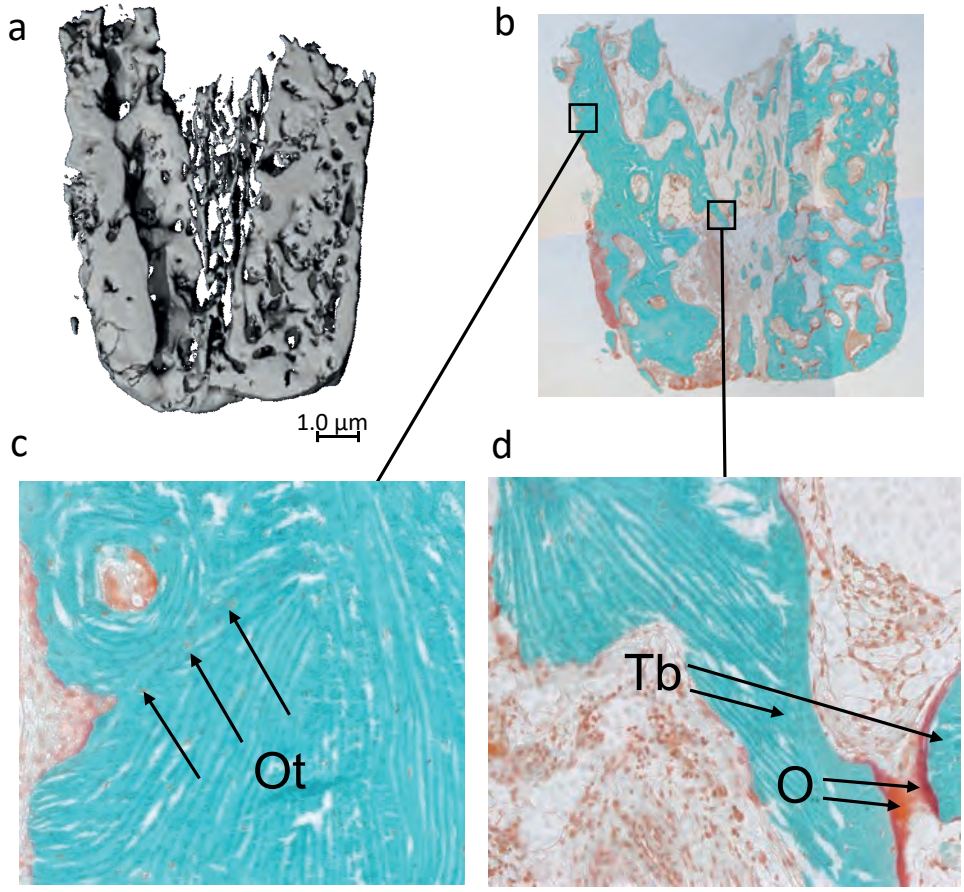

Figure 3. Histological and micro-CT analysis of a biopsy taken from a double plated very thin knife edge alveolar ridge of an edentulous patient who received a reconstruction of the maxilla using calvarial bone grafts. (a) Image of micro-CT scan. Only bone with a mineral density of >559.2 mgHA/cm^3 is visible. Magnification 20x. (b) Histological section of the biopsy stained with Goldner's trichome to distinguish mineralized bone tissue (green) and unmineralized osteoid (red). Viable, mineralized mature bone(green) is visible. Osteoid is red. The morphology of the bone graft is still visible. Magnification 20x. (c) Cortical region of interest (ROI), showing compact lamellar bone with several osteocytes visible as tiny black dots inside the green mineralized tissue, indicating vital bone. In the upper left corner, a haversian channel is visible. Magnification, 100x. Ot, osteocyte. (d) Cancellous bone at the transition between grafted and native bone, the presence of osteoid (red; lower right corner) indicates the formation of new bone. Probably, the two trabeculae will be connected after maturation (mineralization) of the osteoid. Magnification, 100x. Tb: trabecula; O: osteoid.

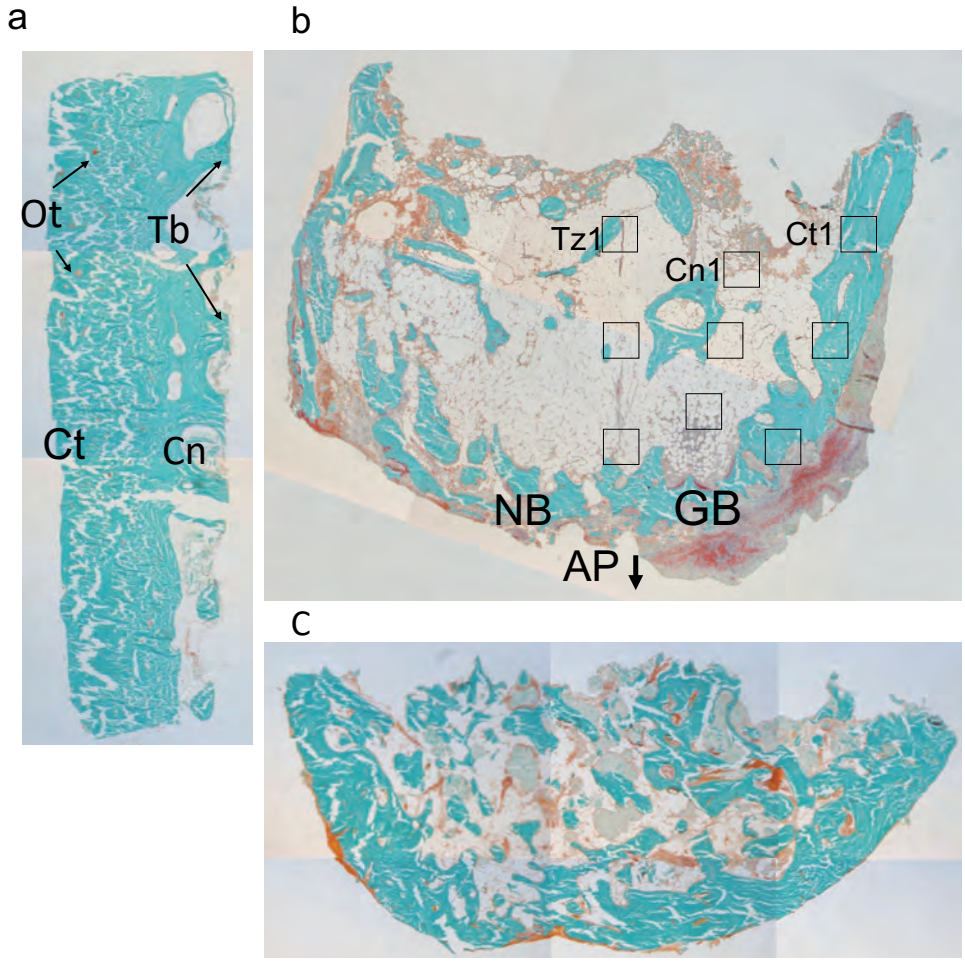

Figure 4. Histologal sections of biopsies obtained from one edentulous patient who received reconstruction of the maxilla using calvarial bone grafts: fresh calvarial bone biopsy and biopsies from the maxillary alveolar ridge, four and 45 months post reconstruction surgery. (a) Fresh calvarial bone showing dense cortical bone (Ct) and several thick trabeculae (Tb) on the right, where the more cancellous diploic bone (Cn) starts. (b) Biopsy 4 months after grafting with native maxillary bone (NB; left), and grafted calvarial bone (GB; right). The cortical part of the calvarial bone is denser compared to the native bone. Between the native bone and calvarial grafted bone, crossing trabeculae are scarce and non-mineralized connective tissue is present. (c) Biopsy 45 months after grafting. The border between grafted and native bone has disappeared, and there is more homogenous mineralized, hard bone tissue visible throughout the section compared to the section obtained after four months of graft healing. Staining: Goldner's trichome to distinguish mineralized bone tissue (green) and unmineralized osteoid (red). All bone/biopsies are from 1 patient, showing progression from fresh calvarial bone towards a healed, reconstructed alveolar process. Magnification, 20x. Ot: osteocyte; Tb: trabecula; Ct: cortical bone; Cn: cancellous bone; NB: native (maxillary) bone; GB: grafted (calvarial) bone; AP: alveolar process; Tz1: first region of interest of transition zone between grafted and native bone; Cn1: first region of interest of cancellous zone of grafted bone; Ct1: first region of interest of cortical zone of grafted bone.

In the 9, 11 and 45 month biopsies, the cortical bone percentage was highest with 57.3%, 68.2%, and 66.9%, respectively, and the transition zone bone percentage was lowest, with 36.2%, 29.4%, and 20.3%, respectively. The osteoid percentage was highest at the transition zone (1.6%, 1.0% and 0.2%, respectively), and lowest at the cortical part of the grafted bone (0.6%, 0.9% and 0.1%, respectively). The osteocyte count over bone volume was highest at the transition zone (326.0, 1260.1 and 561.6 per mm^2 bone), and lowest at the cortical part of the grafted bone (86.0, 135.9, and 395.3 per mm^2 bone). These results lie within the confidence interval of the results from the biopsies obtained after four months.

4 DISCUSSION

The aim of this study was to provide insight into the incorporation of calvarial bone grafts into native maxillary bone following reconstruction of the severely resorbed edentulous maxilla. Histomorphometrical and micro-CT analyses of bone biopsies revealed that (i) after four months of healing, calvarial bone grafts were viable and well incorporated as shown by the presence of living osteocytes throughout the histological sections, the presence of osteoid around the transition zone, and the formation of bony connections between grafted and native bone; (ii) calvarial bone was well preserved even after 45 months (iii) compared to maxillary bone, calvarial grafts were less porous, contained a higher mineral density, and had a higher volumetric fraction that was occupied by bone, providing a more stable base for implant placement; (vi) calvarial bone graft resorption was low as shown by the persistent high values for bone volume fraction and bone percentage.

Micro-CT analyses demonstrated that the calvarial grafts consisted of bone with a large and strong mineral component. In other words, the grafts were a stable basis for implant placement. When compared to native maxillary bone, it seems as if the graft adapted to the native bone, but its superior features remained in terms of strength. Based on the similarities between the fresh biopsies, the biopsies taken at 4 months, and the biopsies obtained after more than 4 months, it can be surmised that these results are stable over time.

Histological analysis of the biopsies revealed bone graft viability and signs of the three important properties of autologous bone grafts namely, osteogenesis, osteoconduction, and osteoinduction, in the calvarial bone blocks. Osteogenic acitivity, the production of osteoid by osteoblasts in the grafted bone, was proven by presence of osteoid in the histological biopsy sections taken after 4 months. Bone trabeculae in the transition zone between grafted and native bone were a sign of osteoconduction, as this is the formation of new bone from adjacent bone or from the periosteum through a matrix that acts as a scaffold. Osteoinduction, the formation of bone by the biochemical transformation and stimulation of stem cells into bone-

producing cells, was not specifically assessed in this study. However, in the biopsies taken after more than 4 months, the border between the grafted and native bone had faded away, contained less voids, had no signs of inflammation and the bone volume had not changed much. This is a sign of the formation of new bone.

A decrease in BVF and BMD is considered normal as this results from resorption that comes along with bone graft healing.[17] Due to its dense microarchitecture, cortical bone will start its healing in conjunction with osteoclastic activity, which is important to allow the revascularization of the haversian channels. This process will start two weeks after grafting and is at its highest about six months after transplantation.[19-21] Bone apposition starts around twelve weeks post-surgery.[20-22] In the biopsies obtained in this study, bone apposition had only just started. This theory is in line with the results found in the biopsies obtained after 9, 11, and 45 months, which showed negligible (later) loss of native bone.

Several theories have arisen in the attempt to understand why calvarial bone demonstrates high volume maintenance after grafting to craniafacial bones.[21,23] Although some theories have focused on embryologic origin, a specific mechanism to support this has not been identified, and the concept of innate embryological bone graft behaviour continues to be a matter of controversy.[21] Others state that the microarchitecture of a bone graft is perhaps the most important determinant of graft volume maintenance.[21,23] In this theory, cortical bone serves as a space maintaining membrane, and cancellous bone facilitates a framework for rapid revascularization and contains marrow bone tissue with precursors of bone forming cells. Subsequently, graft incorporation and osteogenic and osteoconductive activity have been mainly addressed using cancellous bone.[20] Interestingly, the calvarial bone grafts in this study contained copious amounts of cortical and minor amounts of marrow bone and were well incorporated with signs of osteogenesis and osteoconduction. The explanation for high bone volume maintenance in calvarial bone is, therefore, not due to the microarchitecture.

It is also hypothesized that the low resorption of cranial bone grafts results from high mechanosensitivity. Due to specific mechanosensitive features of the local osteocytes, the parietal skull has efficient physiological load bearing and volume maintenance despite its relative mechanical disuse.[24,25] Possibly, calvarial osteocytes have the ability to successfully orchestrate bone apposition and resorption even after transplantation[24,25], resulting in proper incorporation of a viable graft in combination with the preservation of its material properties. This theory seems to fit the findings in our study since the morphology of the grafted bone had only changed slightly during the healing period. The similarities are obvious between the biopsies taken at 4 months and at 45 months from the same patients.

The bone graft harvesting technique used for the current study, has been proven to be safe and effective [6-10]. However, it is not recommended to perform the technique without prior training, as the low level of post operative morbidity and high level of success of the procedure are reported in studies using the technique of Schortinhuis et al[6]. Furthermore, although the current study shows results after 45 months as well, studies with larger sample sizes and longer follow up time are needed to confirm the conclusions based on our results.

On attempting to clarify the incorporation of calvarial bone grafts into native maxillary bone following the reconstruction of the severely resorbed edentulous maxilla, this study revealed that (i) calvarial bone grafts were viable and well incorporated after 4 months of healing; (ii) calvarial bone was well preserved even after 45 months (iii) calvarial grafts were less porous than native maxillary bone, contained a higher mineral density and had a higher volume fraction; and (iv) areas grafted with calvarial bone showed less resorption.

5 DECLARATIONS

Conflict of interest

All authors have no conflict of interest

Author contributions

Concept/design: DEW, JKN, LvR, AV, GMR, JS; Data analysis/interpretation: DEW, JKN, LvR, AV, GMR, JS; Drafting article: DEW, JKN, LvR, AV, GMR, JS; Critical revision of article: DEW, JKN, LvR, AV, GMR, JS; Approval of Article: DEW, JKN, LvR, AV, GMR, JS, Statistics: DEW, Funding secured by: JS, Data collection: DEW, LvR, JS; Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any parts of the work are appropriately investigated and resolved: DEW, JKN, LvR, AV, GMR, JS.

Non-author contributions

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CHAPTER 6

Incorporation of anterior iliac crest or calvarial bone grafts in reconstructed atrophied maxillae:

A randomized clinical trial with histomorphometric and micro-CT analyses

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Background: Autologous bone grafts have been applied successfully to severely atrophied maxilla via a pre-implant procedure. Differences in graft incorporation at the microscopic level can be the decisive factor in the choice between anterior iliac crest and calvarial bone.

Purpose: To compare conversion of anterior iliac crest bone and calvarial bone four months after grafting of the edentulous maxilla.

Materials and methods: Twenty consecutive patients were randomly assigned to either anterior iliac crest (n=10) or calvarial (n=10) bone harvesting to reconstruct their atrophied maxillae. Biopsies were taken from both fresh bone grafts and reconstructed maxillae after four months healing, at time of implant placement. Micro-CT, histomorphometric and histological analyses were performed.

Results: Micro-CT analysis revealed that both the anterior iliac crest and calvarial bone grafts retained their volume and bone mass after being incorporated in the maxilla, but with a favour for calvarial bone grafts: calvarial bone grafts had a higher mineral density before and after incorporation. Both bone grafts types were well incorporated after four months of healing with preservation of bone volume and mineral density. Although the fresh bone biopsies were similar histomorphometrically, after four months of graft incorporation, the osteoid percentage and osteocyte count remained higher in the anterior iliac crest bone whereas the percentage of bone was higher in the calvarial bone grafts compared to the anterior iliac crest bone grafts.

Conclusions: Both donor sites, i.e., anterior iliac crest and calvarial bone, are well suited to provide a reliable and stable basis for implant placement four months after grafting with mineral density, porosity, and resorption rate in favor of calvarial bone grafts.

1 INTRODUCTION

Due to their unique osteogenic, osteoinductive and osteoconductive properties, autologous bone grafts are still the preferred grafting material for craniofacial reconstructions prior to placement of dental implants.[1-3] Although several sites are used to harvest autologous bone, the properties of the grafts derived from these sites differ such as long-term structural integrity and tissue quality.

The donor sites can be classified according to their embryological origin, i.e., endochondral or intramembranous. The iliac crest, tibia and ribs are endochondral in origin, while the maxilla, mandible and skull (calvaria) are intramembranous in origin.[1,4] A major difference between the two embryological origins is that the resorption rate of intramembranous bone is less than that of endochondral bone.[4,5] As a result, intramembranous bone is presumed to have better long-term results with regard to three-dimensional reconstructions of severely atrophied ridges of the maxilla or mandible.

Intra-oral sites are frequently used as graft donor sites for bony reconstructive procedures prior to implant placement, but the amount of bone that can be harvested from the chin, mandibular ramus and maxillary tuberosity is limited. The anterior iliac crest is traditionally the most frequently used donor site for harvesting autologous bone when large volumes are needed. The major drawbacks of iliac crest bone harvesting are post-operative pain and gait problems, as perceived by the patients[6]. The calvarium is an alternative donor site when there is a demand of copious amounts of bone.[1,5] Although calvarial bone grafting bears the hazard of inducing severe complications, technique improvements have made its harvesting to a safe and straightforward procedure.[7-11]

The success of a bone graft is mostly assessed indirectly based on implant survival and macroscopic volumetric changes.[12] Unfortunately, qualitative and quantitative factors, such as relative volumetric changes, mineral density and maturation of the graft, are not within the scope of these approaches, even though these parameters provide insight into the long-term outcomes of the reconstruction. Current advancements in imaging technology, however, have led to a significant improvement in the resolution of the skeletal structural architecture *in vivo* and *ex vivo*, thus enabling a more in-depth analysis of bony reconstructions. Utilising a combination of micro-CT scanning and histomorphometric analysis facilitates the evaluation of the mineral and bioactive properties of bone.[13] Therefore, the aim of this study was to compare the material properties and incorporation of anterior iliac crest and calvarial bone grafts when applied to reconstruct atrophied maxillae by means of micro-CT and histomorphometric analyses.

2 MATERIAL AND METHODS

2.1 Patient selection

Twenty consecutive eligible patients who were referred to the department of Oral and Maxillofacial Surgery of the University Medical Center Groningen (UMCG), the Netherlands, and who suffered from problems with wearing an upper denture due to severe resorption of the edentulous maxilla, were asked to join this study. Inclusion took place between November 2014 and March 2016. Inclusion criteria were an insufficient bone volume for reliable placement of dental implants as assessed on a cone beam computed tomography (CBCT) scan, i.e., <3 mm bone height in the maxillary sinus area and <2mm bone width in the anterior and posterior maxilla. The patients were randomly assigned to either the anterior iliac crest group (n=10) or calvarial bone group (n=10) using computer-generated random numbers. Also, in order to be able to harvest the calvarial bone, the patients' parietal bone in the skull had to be at least 5 mm thick in the area between the articular tubercle and the end of the mastoid bone on the CBCT scan. Exclusion criteria were patients with an American Society of Anaesthesiologists (ASA) score of III or higher[14], a history of radiotherapy in the head and neck region, former or current use of intravenous bisphosphonates, and previous surgery at one of the two donor sites (iliac crest or cranium).

The anticipated effect size of bone volume reduction in the calvarium group compared to the anterior iliac crest group was 1.6, which is in agreement with other studies[5,13,15-17]. Using an A-priori sample size calculator for student t-test with the anticipated effect size (Cohens d) of 1.6 with a two-sided 5% significance level and a power of 80%, a sample size of 8 patients per group was necessary. To compensate for error, it is reasonable to include 10 per group.

2.2 Study approval

The study was approved by the Medical Ethical Committee (REF NL48614.042.14) of the University Medical Centre Groningen, the Netherlands.

2.3 Surgical procedure

A monocortical iliac crest bone graft was taken from the medial surface of the anterior ilium using a technique that was based on the procedure described by Kalk et al.[6]. The incision began 1 cm behind the anterior superior iliac spine and continued posteriorly, following the iliac crest. It was carried down sharply to the mid crest, dividing the musculotendinous aponeurosis of the tensor muscle of the fascia lata and the oblique abdominal muscles, without transecting any muscle fibres. The bony ilium was exposed directly by reflecting the iliac muscle subperiosteally, and the donor site was exposed with a retractor. The corticocancellous bone blocks were harvested by making two horizontal and five vertical cuts. The superior horizontal

cut was made midcrestal with a reciprocating saw. The inferior horizontal cut was made 4 cm inferior in the inner table with a curved osteotome. The horizontal cuts were connected by verticals cuts using a reciprocating saw. After removing the corticocancellous bone blocks, piece by piece from the inner table, additional cancellous bone was harvested with gouges and curettes. Care was taken not to perforate the lateral cortex.

The technique described by Schortinghuis et al.[7] was used to harvest the calvarial bone grafts. In short, after raising a full-thickness flap from the parietal skull, the outer table graft was marked with a burr until the diploe was encountered. A bevel was created with a bone scraper around the calvarial outer table graft area to harvest cancellous bone and to facilitate piece-by-piece removal of the cortical bone grafts with a reciprocating saw. The defect in the skull was reconstructed with bone cement (Palacos®, Zimmer Biomet, Warsay, IN, USA).

All the operations were performed at the UMCG by an experienced oral and maxillofacial surgeon (GMR). After harvesting the iliac crest or calvarial bone, maxillary sinus elevation surgery was performed with the cancellous bone on both sinuses. The cortical bone grafts were positioned on the exposed maxillary alveolar process as buccal onlay grafts. The cancellous portion of the graft was placed facing the recipient maxilla. A maxillary sinus augmentation and buccal plating was performed in all patients on both sides. If necessary, a double plating with both a buccal and a palatinal graft was performed or bone particles were added to gain enough bone volume. In all patients, a minimum crest width of the alveolar process of 6 mm was strived for. The grafts were fixed with 1.3 mm osteosynthesis screws (Synthes, Wolhusen, Switzerland). The sharp bone edges were rounded to allow for smooth coverage of the grafted area with the overlying mucosa. Primary wound closure was accomplished with resorbable 4-0 polyglactine sutures (Ethicon, Somerville, NJ, USA). After a 4-month healing period, dental implants (Straumann Standard SLA® implants; Ø 4.1 mm, Institut Straumann AG, Basel, Switzerland) were placed in the reconstructed maxilla in a one-stage procedure. The wound was closed with resorbable 4-0 polyglactine sutures (Ethicon, Somerville, NJ, USA).

2.4 Bone biopsies

Bone biopsies were obtained from the donor bone area immediately after harvesting the fresh grafts as well as four months later from the native and grafted bone in the reconstructed maxilla, whereby a small bone wedge of the reconstructed alveolar process was taken between two adjacent implants. The biopsies were preserved in 4% phosphate-buffered formaldehyde solution (Klinipath BV, Duiven, the Netherlands) for 24 h and then stored in 70% ethanol until used for micro-CT and histomorphometric analyses. The analysis were performed by DEW, JS, LvR and MAD and they were blinded for the allocation sequence until all outcomes were assessed.

2.5 Micro-computed tomography evaluation

All the biopsies were scanned with a high-resolution micro-CT (mCT 40, Scanco Medical AG, Brüttisellen, Switzerland). This system was calibrated every two weeks using phantoms with densities of 0, 100, 200, 400 and 800 mg HA/cm^3. Before scanning, the biopsies were fixed with synthetic foam in a polyetherimide tube (inner diameter, 28.5 mm; length, 75 mm). Then the tube was filled with 70% ethanol and covered with Parafilm M (SPI Supplies, West Chester, PA, USA) to prevent evaporation during scanning. The scanner settings were: voltage, 70 kV; intensity, 113 µA; integration time, 1000 ms; isometric resolution, 0.015 mm. A cone-beam reconstruction algorithm was used to make 3D reconstructions. All the reconstructions were smoothed with a Gauss filter (0.8/1) and segmented with a visually determined threshold of 559.2 mg hydroxyapatite (HA)/cm^3 (Figure 1). This threshold visualises bone in the same way as it appears on histological sections. The biopsy and transition zone orientations were identified for each bone biopsy using per operatively obtained photographs and schematic drawings of the biopsies.

The volumes of interest (VOIs) evaluations were performed by manually tracing the contours of the entire freshly biopsied fragments of bone. Then, three VOIs were drawn for each of the biopsies taken from the grafted bone and native bone after 4 months: a VOI including the entire biopsie and VOIs including only grafted and only native bone. The tissue mineral density (TMD, mg HA/cm^3), defined as the mean mineral density of the whole volume of interest, was calculated for each VOI. TMD can be used as a qualitative measure of the mineral density of compact bone. The bone mineral density (BMD, mg HA/cm^3), defined as the mean mineral density of the segmented bone volume in the VOI, was also calculated[18]. Finally, the bone volume fraction (BVF), which is a quantitative measure defined as the ratio of the segmented bone volume to the total volume of the VOI (%), was assessed. In other words, BVF represents the percentage of biopsy volume, or tissue volume, that is occupied by bone volume.

2.6 Histology and histomorphometric analysis

After micro-CT scanning and dehydrating in ascending alcohol series, the bone biopsies were embedded without prior decalcification in low-temperature polymerizing methyl methacrylate (MMA, Merck Schuchardt OHG, Hohenbrunn, Germany). The biopsies 3D-orientations were assessed using the micro-CT reconstructions. Longitudinal 5 µm thick sections were cut with a Jung K microtome (Reichert Jung, Heidelberg, Germany). Midsagittal histological sections of each biopsy were stained with Goldner's trichome to distinguish mineralized bone (green) and unmineralized osteoid tissue (red).[19] Digital images of the x100 magnified sections were acquired.

First, a qualitative histological analysis was performed. The 2D-orientation, completeness, and outstanding features, such as signs of inflammation, were identified for each section. The orientation was determined from the notes and photographs taken during the surgery as well as the 3D-reconstructions made by the micro-CT-software. The cortical bone percentage was determined for the fresh biopsies. Regarding the biopsies taken after four months, the native maxillary bone and grafted bone were identified visually. The presence and 2D distribution of bone, osteoid, and osteocytes was measured per section (presence and location). Bone is defined here as mineralized bone matrix without any osteoid.[20] Osteoid is bone matrix that is not mineralized yet.[20] The presence of osteoid indicates new bone formation. Osteocytes are mature osteoblasts located with their cell bodies in lacunae and with their cellular processes running through the canaliculi. They are encased by a mineral matrix and are normally supplied by vessels lying in the bone's canal system. Osteocytes are the mechanosensors of bone and, as such, they have an important regulatory function in bone resorption and bone formation. The presence of vital osteocytes in the grafted bone indicates that the canalicular system is viable and functional.[21]

The histomorphometry was performed by dividing the sections into three pre-defined zones, i.e., (1) the cortical zone of the graft, which is the cortical outer side of the graft just underneath the periosteum; (2) the cancellous zone of the graft, which is the side of the graft towards the alveolar process; and (3) the transitional zone, which is the contact zone between the calvarial graft and the alveolar process onto which the graft is fixed. Three regions of interest (ROIs) were determined for each biopsy zone following a pre-defined pattern. The mean result of each zone was used to compare the biopsies.

Histomorphometrical measurements were manually performed for each ROI using a computer with an electronic stage table and a Leica DC 200 digital camera. The computer software used was Leica QWin (Leica Microsystems Image Solutions, Rijswijk, the Netherlands). The primary variables, in terms of the bone area, osteoid area, and osteocyte number were determined. The percentage of bone area, percentage of osteoid, and osteocyte number per mm^2 of tissue area were derived from these primary variables.[20-22]

2.7 Statistical analysis

Data management and analysis were performed using SPSS 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp., NY, USA). The data were tested for normal distribution with a Shiparo Wilk-test and checked visually using a histogram with a distribution curve. The data are presented as mean ± standard deviation, or in case of non-normal distribution, as median and interquartile range. A dependent student t-test, or the non-parametric paired Wilcoxon Signed Rank-test, was used to determine differences in the micro-CT parameters (tissue mineral density, bone mineral density, bone volume fraction) and the

histomorphometric parameters (bone percentage, osteoid percentage, osteocyte number per volume of bone) between the fresh iliac crest and calvarial bone biopsies and between the grafted iliac crest and calvarial bone biopsies obtained after four months healing from the same patient. Also, the differences between the grafted and native bone within each biopsy obtained after four months of healing, were determined as were the differences between the fresh and 4 months grafts An independent t-test, or in case of non-parametric data, a Mann Whitney U-test, was used to determine the differences between both groups. A significance level of 0.05 was chosen for all tests.

3 RESULTS

3.1 Study population characteristics

The 20 participating patients were either male (9) or female (11), with an equal distribution between the groups (Table 1). No patients were lost to follow-up. There were no smokers. The mean body mass index was comparable in both groups.

Table 1. Characteristics of the calvarial and anterior iliac crest groups.

	Anterior iliac crest bone n = 10		**Calvarial bone n = 10**		**Students T-test**	
					t	***p***
Gender						
Female	6		5		-0.43	0.673
Male	4		5			
	Mean	**SD**	**Mean**	**SD**		
Age at implant placement (years)	63.5	7.0	65.9	8.7	-0.67	0.509
BMI (kg/m^2)	28.5	6.13	30.6	7.9	0.64	0.532
Time between augmentation and placement of implants (years)	0.4	0.1	0.5	0.2	-1.63	0.120
Number of implants placed	44		44			

SD: standard deviation of the mean; BMI: Body Mass Index

3.2 Clinical results

In all cases, the augmentation procedure resulted in sufficient bone volume for implant placement at the prosthodontically preferred sites. In each group, 44 implants were placed. One patient in each group lost an implant because of mobility during the osseointegration phase resulting in a 1-year implant survival rate of 97.8%.

3.3 Biopsies

A total of 40 bone biopsies was obtained. Twenty biopsies came from the freshly harvested bone grafts (10 per group) and 20 were taken from the reconstructed maxillary alveolar wall of the grafted bone after 4 months of healing (10 per group).

3.4 Micro-CT

The original orientation and the transition zone were identified on the 3D-reconstructions of the CT scans by the same investigator (DW). Figure 1 shows a 3D-reconstruction of fresh blocks from anterior iliac crest and calvarial bone grafts and of a specimen harvested during implant placement after a 4-month graft healing period.

The fresh anterior iliac crest biopsies contained a thin layer of very dense, compact cortical bone. This compact layer merged into the cancellous bone with a small transition zone. The numerous trabeculae of the cancellous bone were thin and round, extending in all directions. The original anatomy of the anterior iliac crest was reflected in the form of the grafts since the cortical layer was slightly concave. In the biopsies obtained after four months of anterior iliac crest bone graft healing, the transition from the grafted bone towards the native bone could be identified by the small impression in the cortical layer of the biopsies. Furthermore, the cancellous bone was less dense at the junction. The grafted bone still appeared as a dense, thin cortical layer at the grafted site. The cancellous bone was less dense compared to the fresh anterior iliac crest bone and the orientation of the trabeculae appeared slightly disorganized.

The fresh calvarial bone grafts demonstrated a smooth transition from dense cortical bone towards more cancellous diploic bone. The trabecula of the diploic part were thick and short. In the biopsies obtained after four months, the grafted bone could be identified easily based on the compact cortical bone and the morphology of the graft, and since they looked as dense as the fresh biopsies. A more in-depth observation of the biopsies revealed that the transition towards cancellous bone started similar to the fresh biopsies, but the trabeculae had become longer and thinner towards the native maxillary bone. Both bone types' transition area demonstrated more space between the trabeculae, which were irregular in form and thickness indicating remodelling of the grafted bone. Further towards the native bone, the trabeculae remained long and thin but were more packed together. The cortical zone of the native bone was thinner compared to the calvarial bone.

All the biopsies underwent micro-CT analysis and the results are depicted in Table 2. When the fresh bone graft outcomes regarding tissue mineral density of the grafted bone (TMD), inorganic bone mass (BMD) and volume fraction occupied by bone (BVF) were compared with the outcomes in grafted bone obtained from the same participants after four months of bone graft healing, a slight decrease was seen for TMD and BVF and an increase for BMD

in the anterior iliac crest group. However, these inter-group differences were not statistically significant (TMD: anterior iliac crest group: Z= -1.572, *p*=0.116, calvarium group: Z =-0.76, *p*=0.445; BMD: anterior iliac crest group: Z=-1.07, *p*=0.285, calvarium group: Z =-1.78, *p*=0.074; BVF: anterior iliac crest group: Z= -0.15, *p*=0.878, calvarium group: Z= -0.15, *p*=0.878) (Wilcoxon Signed Ranks-test). Thus, both the anterior iliac crest and calvarial bone grafts keep their volume and bone mass after being incorporated in the maxilla.

A comparison of both groups' micro-CT parameter outcomes showed that fresh calvarial bone had a higher tissue density value (BMD, Mann Whitney U-test, U=11.00, *p*=0.002) and a higher fraction of the volume that is occupied by bone (BVF, Mann Whitney U-test, U=25.00, *p* =0.049) than the anterior iliac crest bone. After four months of graft healing, the tissue mineral density, the inorganic mass and the bone volume fraction had higher values in calvarial bone (TMD, Mann Whitney U-test, U=14.50, *p*=0.007; BMD, Mann Whitney U-test, U=22.00, *p*=0.035; BVF, Mann Whitney U-test, U=7.00, *p*=0.001). In other words, inorganic tissue density was higher in calvarial bone before and after graft incorporation.

The two groups' native maxillary bone TMD, BMD and BVF outcomes did not differ (Mann Whitney U-test, TMD: U=35.00, *p*=0.414; BMD: U=35.50, *p*=0.438; BVF: u=32.00, *p*=0.288). Furthermore, irrespective of the type of graft, the native bone's TMD, BMD, and BVF values were lower compared to those measured in the grafted bone. It seems that since the TMD, BMD, and BVF had decreased after four months of graft incorporation, the grafted bone had adapted to the maxillary bone.

Table 2. Microcomputed tomography analysis of tissue mineral density (TMD), bone mineral density (BMD) and bone volume fraction (BVF) in biopsies taken from fresh anterior iliac crest and calvarial bone grafts and from reconstructed maxillary alveolar ridges with either of these bone grafts four months after reconstruction and prior to implant placement.

	Fresh bone biopsies (n=20)				**Healed reconstructed alveolar process biopsies (n=20)**			
			Mann Whitney U-test				**Mann Whitney U-test**	
	Anterior iliac crest Median (IQR)	**Calvarium Median (IQR)**	**U**	*p*	**Anterior iliac crest Median (IQR)**	**Calvarium Median (IQR)**	**U**	*p*
TMD (mgHA/cm^3)	399.3 (341.2-814.4)	743.6 (500.1-889.6)	22.0	0.329[1]	365.2 (264.5-530.6)	509.9 (372.4-621.9)	14.5	0.007
BMD (mgHA/cm^3)	860.8 (819.2-887.9)	1028.4 (987.7-1112.1)	11.0	0.002[1]	892.9 (832.8-943.0)	929.6 (877.7-956.9)	22.0	0.035[2]
BVF (%)	39.3 (13.7-61.6)	69.4 (69.4-79.1)	25.0	0.049[1]	38.7 (21.3-52.0)	47.5 (33.2-60.6)	7.0	0.001[2]

[1]*Significant difference between freshly harvested calvarium and anterior iliac crest bone obtained at bone graft harvesting surgery, p<0.05, Mann Whitney U-test*
[2]*Significant difference between calvarium and anterior iliac crest bone grafts obtained after four months of healing, p<0.05, Mann Whitney U-test.*
IQR: interquartile range.

Table 3. Histomorphometric analysis of bone percentage (Bp), osteoid percentage (Op) and osteocyte number per volume (OcN/Ba) in biopsies from fresh harvested bone grafts and from the grafted sites after 4 months in the patients undergoing reconstruction of the edentulous maxilla prior to implant placement.

		Anterior iliac crest bone Median (IQR)	Calvarium Median (IQR)	Mann Whitney U-test[1]	
				U	*P*
Fresh bone graft		**N=10**	**N=10**		
All regions combined	Bp (%)	51.5 (46.3-56.7)	51.2 (46.0-69.5)	37.0	0.790
	Op (%)	0.3 (.1-.6)	0.44 (0.1-.8)	34.0	0.594
	OcN/Ba (1/mm^2)	114 (90-190)	215 (64-273)	30.0	0.374
Cortical bone	Bp (%)	68.3 (58.3-79.7)	59.9 (37.4-79.7)	29.0	0.328
	Op (%)	0.1 (0.2-0.5)	0.2 (0.3-1.0)	31.0	0.423
	OcN/Ba (1/mm^2)	98 (107-117)	126 (57-201)	34.0	0.594
Trabecular bone	Bp (%)	33.7 (24.0-55.8)	37.4 (28.6-59.6)	33.5	0.563
	Op (%)	0.1 (0.0-0.6)	0.15 (0.35-1.0)	35.0	0.651
	OcN/Ba (1/ mm^2)	101.9 (80.4-164.3)	127 (57-201)	32.0	0.477
Grafted bone after four months of healing		**N=8**	**N=8**		
All regions combined	Bp (%)	27.5 (25.1-38.5)	49.7 (42.1-57.7)	5.0	0.005*
	Op (%)	1.1 (0.6-1.5)	1.3 (0.5-1.9)	27.0	0.600
	OcN/Ba (1/mm^2)	369 (284-402)	278 (239-370)	22.0	0.293
Cortical bone of graft	Bp (%)	45.6 (22.6-54.3)	51.9 (49.2-59.2)	16.0	0.093
	Op (%)	1.0 (0.5-1.7)	1.7 (0.4-2.3)	30.0	0.834
	OcN/Ba (1/mm^2)	399 (223-437)	302 (231-438)	27.0	0.599
Cancellous bone of graft	Bp (%)	34.8 (15.8-45.7)	50.2 (28.8-61.7)	15.0	0.074
	Op (%)	0.5 (0.1-1.7)	1.7 (0.4-2.3)	26.0	0.528
	OcN/Ba (1/mm^2)	318 (116-427)	234 (195-405)	34.0	0.847
Transition zone	Bp (%)	36.5 (25.2-38.0)	45.5 (40.2-50.5)	4.0	0.003*
	Op (%)	1.0% (0.8-1.3%)	0.6% (0.4-2.4%)	26.0	0.528
	OcN/Ba (1/mm^2)	284 (93-410)	258 (90-190)	14.0	0.065

[1] Equality of the median between the anterior iliac crest and calvarial bone grafts after four months of healing using a Mann Whitney U-test.

** Significant difference between Bp, Op or OcN/Ba measured in the cortical bone, cancellous bone, or transition zone between of grafted bone and native maxillary bone, in sections obtained from participants' from the anterior iliac crest group and calvarial bone graft group.*

IQR: interquartile range.

3.5 Histology

The sections with fresh anterior iliac crest consisted of highly mineralized bony tissue, appearing dark green in the histological sections (Figure 2). The sections contained a dense cortical layer and an adjacent network of numerous thin trabeculae surrounding fatty tissue. The transition area from the compact cortex towards the spongious bone was irregular and abrupt. Osteoid, appearing as clear red lines adjacent to green, mineralised bone, was present throughout the sections, as were osteocytes, which were visible as dark dots within the white lacunae in the mineralized bone.

The fresh calvaria sections appeared dark green as well. The sections mostly contained mostly dense cortical bone, but several sections showed both cortical and diploic bone, with a smooth transition from one to the other bone type. The diploic bone consisted of short, thick trabeculae. Numerous osteocyte lacunae were visible throughout the sections (Figure 2). In the sections obtained from biopsies taken after four months of healing, the original alveolar process, transition zone and grafted bone could still be identified from the bone morphology, irrespective of bone maturation. Several trabeculae were present at the transition zone between the grafted and native bone. These trabeculae connected the two bony parts, thus representing new bone formation. The trabeculae at the transition zone were thin and irregular, and appeared more like maxillary bone. Next to these trabeculae, soft, mostly fat tissue was seen between the graft and the native bone, and sometimes signs of inflammation were observed. Moreover, poorly mineralized bony tissue was observed, possibly the result of adding cancellous bone particles to fill the gaps between the grafted and native bone. Apart from mineralized bone tissue, osteoid was highly present in the transition zones (Figures 2b and 2f). Osteocytes were seen throughout the biopsies, but they were more concentrated in the transition zone and cancellous parts of the grafted bone than in the cortical part of the graft. In the biopsies taken at later time points, the osteocytes were more evenly distributed throughout the grafts indicating further maturation of the bone.

3.6 Histomorphometry

Histomorphometry was used to measure the cortical part and the cancellous zone of the graft, and the transition zone between the graft and the alveolar process. It was possible to set the nine ROIs following the pre-defined pattern in 16 out of the 20 biopsies taken after four months. In two biopsies, one per group, only two ROIs per zone could be set. Another two biopsies, again one per group, could not be measured due to inadequate orientation of the sectioning.

There were no significant differences between the bone percentage, osteoid percentage, or osteocyte number over bone area of the fresh bone graft biopsies (Table 3). Then, the median bone percentage in the anterior iliac crest group sections decreased significantly from 51.5% (IQR 46.3-56.7%) in the fresh biopsies to 27.5% (IQR 25.1-38.5%) in the biopsies taken 4 months later (Wilcoxon Signed Rank-test, Z=-2.24, p=0.025). The median osteoid percentage increased significantly from 0.3% (IQR 0.1-0.6%) to 1.1% (IQR 0.6-1.5%) (Wilcoxon Signed Rank-test, Z=-2.38, p=0.017) and the median number of osteocytes over bone volume increased significantly from 114 (IQR 90-190) to 369 (IQR 284-402) (Wilcoxon Signed Rank-test, Z=-2.24, p=0.025.) In the calvarium group, the median bone percentage decreased from 51.2% (IQR 46.0-69.5%) in fresh biopsies to 49.7% (IQR 42.1-57.7%) in biopsies taken at four months (Wilcoxon Signed Rank-test, Z=-1.15, p=0.249), the median osteoid percentage

increased from 0.44 % (IQR 0.1-0.84%) to 1.3% (IQR 0.5-1.9%) (Wilcoxon Signed Rank-test, Z=1.57, *p*=0.116 and the number of osteocytes over bone volume also increased somewhat, from 215 (IQR 64-273) to 278 (IQR 239-370) (Wilcoxon Signed Rank-test, Z=-1.78, *p*=0.075).

There were no significant differences between the bone percentage, osteoid percentage or osteocyte number over bone area in the fresh bone graft biopsies. On comparing the two groups' sections obtained four months post reconstruction, the bone percentage in the transition zones was significantly higher in the calvarium bone graft group (median (IQR) bone percentages in the transition zone: 45.5(IQR 40.2-50.5)% for the calvarium group and 25.2(IQR 25.2-38.0)% for the anterior iliac crest group; Mann Whitney U-test: U=4.50, *p*=0.004). There were no significant differences between the other histomorphometry outcomes, but what stood out was that the osteocyte number over bone volume was clearly higher in all the anterior iliac crest group's section zones (median OcN/Ba in entire sections: 302 (IQR 231-428) per mm^2 for the calvarium group and 399 (223-437) per mm^2 for the anterior iliac crest group; Mann Whitney U-test, U=22.00, *p*=0.293)(Table 3).

Thus, all the fresh bone biopsies' histomorphometric outcome values were similar. During the four-month healing period, the median bone percentage decreased, whereas the median osteoid percentage and number of osteocytes increased in both groups and the changes were of statistical significance in the anterior iliac crest group (Bone percentage, anterior iliac crest group: Z=2.24, *p*=0.025 and calvarium group: Z=-1.15, *p*=0.25; osteoid percentage, anterior iliac crest group: Z=-2.38, *p*=0.116; number of osteocytes per bone area: anterior iliac crest group: Z=2.24 *p*=0.025 Z=-0.73, *p*=0.463). After four months of graft incorporation, the amount of bone per graft volume was higher, and the number of osteocytes per volume of bone was lower, in the calvarial bone graft compared to the anterior iliac crest bone graft group (Table 3).

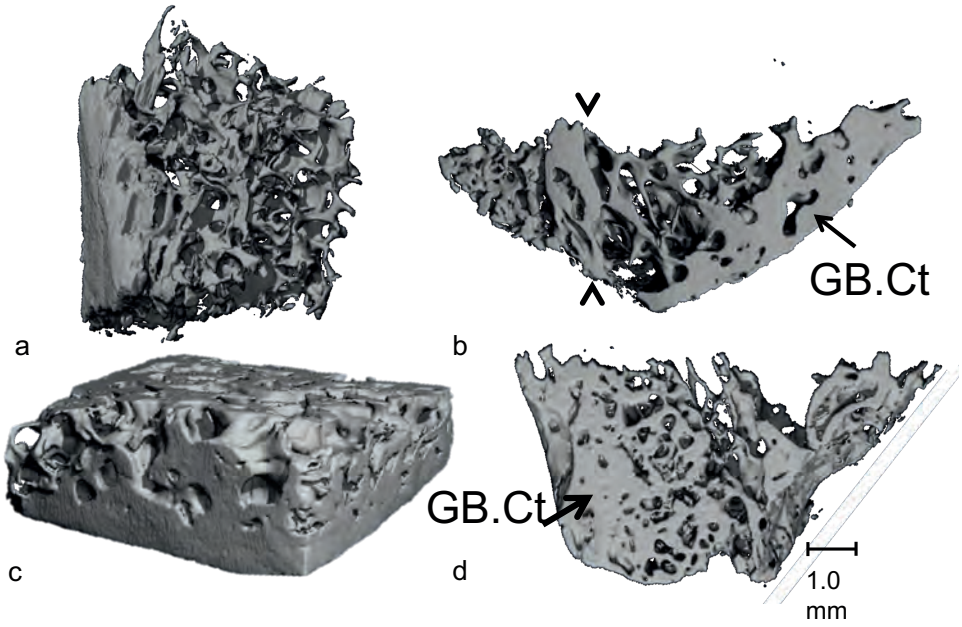

Figure 1. Micro-CT scans of fresh bone biopsies and bone biopsies obtained from edentulous maxillary alveolar processes four months after being reconstructed with an anterior iliac crest or calvarial bone graft. Only bone with a mineral density of >559.2 mg HA/cm^3 is visible. (a) Fresh anterior iliac crest biopsy consisting of a thin, dense cortical layer and a major spongious bone part. The thin trabeculae are numerous and form a dense network. (b) Biopsy obtained after four months of anterior iliac crest bone graft healing. The right side consists of grafted bone. The compact cortex of the anterior iliac crest can be identified based on morphology and bone density. The native maxillary bone is more porous, contains more trabeculae, and the cortical wall is thinner compared to the bone in the grafted area. In this biopsy, the palatinal cortical wall is hard to identify from this perspective. (c) A fresh calvarial bone biopsy consisting mainly of cortical bone. The diploic bone is the more porous part of the piece. (d) Biopsy after four months of healing seen from the mesial perspective. The left side consists of grafted bone. The compact cortex of the calvarium can be identified based on morphology and bone density. The native maxillary bone is more porous, contains more trabeculae, and the cortical wall is thinner compared to the bone in the grafted area. Magnification: a and c, 40x; b and d, 20x; Arrow heads: border between grafted and native bone; GB.Ct: cortical part of grafted iliac crest or calvarial bone.

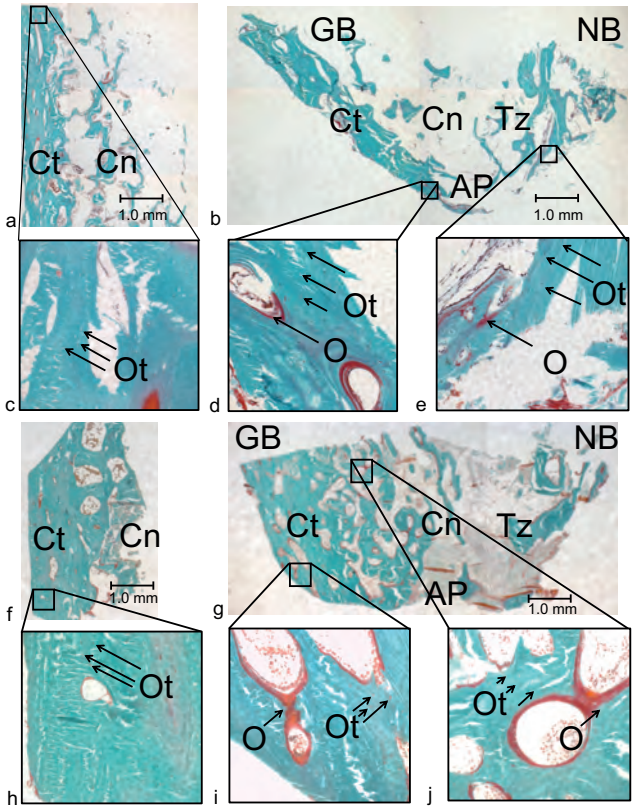

Figure 2. Histologic sections of biopsies obtained from edentulous patients whose maxilla were reconstructed with either anterior iliac crest or calvarial bone grafts: fresh anterior iliac crest and calvarial bone biopsies and biopsies from the maxillary alveolar ridge, four months post reconstruction surgery. (a) Fresh anterior iliac crest bone showing dense cortical bone (Ct) and several thick trabeculae (Tb) on the right where the copious amount of cancellous trabecular bone (Cn) starts. (b) Biopsy 4 months after grafting the native maxillary bone (NB; right) with anterior iliac crest bone (GB; left). The cortical part of the anterior iliac crest bone is denser compared to the native bone. Crossing trabeculae are scarce between the native and grafted bones and non-mineralized connective tissue is present. (c) Detail of (a), containing cortical bone with osteocytes (Ot). (d) Detail of (b), taken from the border between the grafted and native bones, including osteoid (O) and osteocytes (Ot). (e) Detail of (b), taken from the cortical part of the grafted bone, including osteoid (O) and osteocytes (Ot). (f) A fresh calvarial bone graft biopsy demonstrating a thick and dense cortical layer (Ct) with a smooth transition towards cancellous diploic bone months after grafting. The border between the grafted and native bone has disappeared, and there is more homogenous mineralized, hard bone tissue visible throughout the section compared to the section obtained after four months of graft healing. (g) Biopsy 4 months after grafting the native maxillary bone (NB; right) with anterior iliac crest bone (GB; left). The cortical part of the calvarial bone is denser compared to the native bone. Several crossing trabeculae are present between the native bone and grafted bone and non-mineralized connective tissue is present. (h), (i) and (j): Details of, respectively, (f) and (g). Staining: Goldner's trichome to distinguish mineralized bone tissue (green) and unmineralized osteoid (red). All the bone biopsies are from 1 patient, showing the progression from fresh calvarial bone towards a healed, reconstructed alveolar process. Magnification: a and b 20x, c and d 100x. Ot: osteocyte; Tb: trabecula; Ct: cortical bone; Cn: cancellous bone; O: osteoid; NB: native (maxillary) bone; GB: grafted (anterior iliac crest or calvarial) bone; AP: alveolar process; Tz: transition zone between grafted and native bone; Cn: cancellous zone of grafted bone; Ct: cortical zone of grafted bone.

4 DISCUSION

This study revealed that the histomorphological and radiographic characteristics make both graft types very suitable for pre-implant graft procedures, showing that (i) both bone graft types become well incorporated after four months of healing. The bone volume and mineral density are well preserved, the grafted bone is well connected to the native bone and the grafts are vital and showed signs of new bone formation; (ii) calvarial bone grafts are less porous, have a higher volume of mineralized tissue, and showed less resorption over time compared to anterior iliac crest bone grafts; (iii) anterior iliac crest bone grafts show a higher percentage of a osteoid and higher number of osteocytes per bone volume compared to calvarial bone grafts.

The major differences between both donor sites lie in the mineral density, bone percentage, osteoid percentage and osteocyte number of the grafts. The calvarial grafts show a higher mineral density measured with micro-CT and a higher percentage of bone per tissue surface as shown by histomorphometry, which corresponds with the thick cortical layer and overall dense structure calvarial bone is known for. Anterior iliac crest bone contained more osteoid and a higher number of osteocytes after four months healing. This reflects a high metabolic activity in anterior iliac crest bone grafts. These outcomes suggest that the number of osteocytes per volume in anterior iliac crest does not add to bone mass preservation when compared to calvarial bone, since the calvarial bone grafts showed less decrease in bone percentage without an increase in osteoid or osteocyte number. It is therefore hypothesized that on the long term, calvarial bone grafts show less resorption compared to anterior iliac crest grafts.

This hypothesis is supported by previous clinical studies which have shown more bone resorption in anterior iliac crest bone grafts compared to calvarial bone grafts[5,23]. The three-dimensional volume reduction after reconstructions with iliac crest bone ranges from 24% [24] after 6 months to 60% [12] after one year. When calvarial bone grafts are used, the resorption is reported to be 0-15%[12] , viz., 8.44% after 6 months[24], and 10%[25] to 19.2%[2] after one year. These observations are in line with differences we found between both graft types at baseline and four months after grafting in terms of mineral density, bone percentage and metabolic activity. Higher volume preservation of the alveolar bone after augmentation using calvarial grafts compared to using anterior iliac crest grafts should be taken into account in clinical decision making, as it might benefit the prosthetic outcomes of the procedure.

The higher number of osteocytes in combination with lower bone mass and mineral density in anterior iliac crest bone compared to calvarial bone matches with previously described differences in flat bone and long bone osteocyte networks that arise from adapting to different physiological loading patterns, which suggest different networks activities[26]. In other words,

the bone percentage of bone after four months of graft incorporation might result from the specific features of the osteocytes instead of the number of these cells per volume of bone. Osteocytes are mechanosensitive cells that play a key role in bone remodeling, facilitating an increase or decrease in bone resorption and formation depending on the prevailing loading conditions.[27,28] Previous studies have suggested that differences in the fate of the endochondral and intramembranous bone grafts are caused by differences in osteocyte function whereby the to specific mechanosensitive features of the local osteocytes in the parietal skull bone means it has efficient physiological load bearing and volume maintenance properties despite its relative mechanical disuse.[27,28] Possibly, calvarial osteocytes have the ability to successfully orchestrate bone apposition and resorption even after transplantation,[27,28] resulting in proper incorporation of a viable graft in combination with the preservation of its material properties. This theory seems to fit the findings in our study since the morphology of the grafted calvarial bone had only changed slightly during the healing period. In other words, the previously described higher metabolic activity of anterior iliac crest compared to calvarial bone[5,12,23], is likely to result from differences in osteocyte functioning rather than osteocyte number. This theory explains the previously described clinical findings supporting the hypothesized long term volume preservation seen in calvarial bone grafts. Furthermore, as osteocytes seem to play a key role in the fate of reconstructed alveolar ridges, future research on these procedures should focus on the optimal use of osteocytes.

The current micro-CT analyses demonstrated that both types of bone graft adapt to the native maxillary bone, as their features in terms of mineral density and porosity changed towards values measured in native bone. However, both graft types continued to show favourable features in terms of strength when compared to native maxillary bone. Previous research suggests that after a longer healing period, calvarial bone grafts still show favourable features that are as least as favourable as native bone when it comes to bone density, bone mass and bone volume[29]. Long term studies on a larger scale are needed to further analyse the functioning of bone grafts compared to native maxillary bone, in terms of bone volume and bone strength as this has consequences for the placement of implants for prosthodontic rehabilitation.

In the quest to an ideal bone graft, the current study is of great value due to its randomized controlled design. This design allows for thorough comparison of both bone grafts despite their differences in anatomical location and subsequent burdens the bone was exposed to before harvesting. Both groups were equal in age distribution, male/female ratio and presence of known comorbidities.

The current study analyzed effects after four months of healing in terms of bone mineral density and microscopic bone volume. In clinical decision making, long term evaluations on macroscopic alveolar crest volume, implant survival and prosthetic outcomes should be

included. Medium term studies on bone volume resorption report that, in line with the current results, anterior iliac crest shows a higher resorption rate than calvarial bone[5,12,17,25,30-33]. However, it the outcomes might converse to some extent with time as anterior iliac crest has a steep initial resorption curve which flattens after several months whereas calvarial bone shows a more gradual resorption pattern[17]. To answer questions on differences in clinical outcomes, an analysis on macroscopic bone volume, for example by means of CBCT imaging, is needed.

In conclusion, the results of this study show that both donor sites, i.e., anterior iliac crest and calvarial bone, are both well suited to provide a reliable and stable basis for implant placement four months after grafting with mineral density, porosity, and resorption rate being in favor of calvarial bone grafts. Future studies with a longer follow up period are needed to test the hypothesis that calvarial bone grafts will show less resorption on the long term, therefore providing a more favorable and more durable outcome from a prosthodontic point of view.

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CHAPTER 7

General discussion and conclusions

Patients in need for an implant retained denture due to severe resorption of the edentulous jaw often require bone reconstruction for reliable implant placement. For years, anterior iliac crest has been widely used to perform these reconstructions. Calvarial bone grafts are a possible alternative. The PhD research in this thesis aimed to compare the clinical, radiological, and histological outcomes of anterior iliac crest and calvarial bone graft harvesting.

Patient reported outcomes and morbidity

The current thesis revealed that bone graft harvesting surgery from both the calvarial bone, and the anterior iliac crest is associated with high patient appreciation (Chapter 2, 3 and 4). When interpreting the outcomes, several considerations can be made. It has been shown that the construct of patient satisfaction is most strongly affected by fulfillment of expectations and experiences of the patient[1]. The high overall satisfaction observed in the studies described this thesis, also may reflect high fulfillment of expectations, and limited negative experiences for patients. Another factor affecting the patient's satisfaction with harvesting surgery, is satisfaction with other aspects of the treatment[1]. For instance, when patients are highly satisfied with the improvement of their denture function, differences in satisfaction with donor site related outcomes might be overshadowed[2]. Thus, expectations, experiences, and acceptance of other aspects of the treatment might affect the patient reported satisfaction with bone graft harvesting surgery. Therefore, to enable truly patient's appreciation, sources of dissatisfaction like postoperative pain, sensory alterations, esthetic outcomes, and complications have to be assessed as well. The studies in this thesis reflected that postoperative pain was low for both donor sites with a slight favor for calvarial harvesting (Chapter 2 and 3). Also, independently from the donor site, sensory alterations were limited and mostly not noticed by patients, esthetic outcomes were generally not bothersome to patients (Chapter 2 and 4) and complication rates were low (Chapter 3).

For anterior iliac crest harvesting, pain is postulated as a major source of gait disturbances. It is the most frequently mentioned drawback of anterior iliac crest harvesting[3,4]. Moreover, pain and gait disturbances have been reported as a major source of dissatisfaction for patients[5]. In attempt to limit these complaints, several authors studied the mechanism and possible measures to avoid pain following anterior iliac crest harvesting. The pain is either musculoskeletal or neurogenic, secondary to the stripping of abductors from the ilium or neurogenic secondary to sensory nerve injury. Recommendations to reduce morbidity of iliac crest harvesting, i.e., a skin incision 2 cm medially to the iliac crest with an appropriate length for adequate exposure; avoidance of excessive stretching of the tissues and damage to the superficial sensory nerves; respect for fascial planes and minimal dissection of muscles and harvesting only the required amount of bone, leaving distance from the anterior superior iliac spine, are shown to reduce donor-site complications, in particular reduce the incidence and severity of pain[3]. Further

reduction in pain and gait disturbances can be achieved by treating the cortices following the harvest, e.g by using bone wax or other hemostatic materials[3,4,6], or post-harvest reconstruction of the iliac crest. These adjustments in operative techniques are advised to reduce postoperative gait disturbances.

Several studies have focused on which factors predict the level of postoperative pain. In general surgery, pain severity and duration were found higher in patients with younger age, female sex, smoking habits, history of depressive symptoms, anxiety symptoms or difficulties, presence of preoperative pain, especially in the same region, and the use of preoperative analgesia[7-10]. However, the clinical relevance of these associations is unclear[11] as the effects on pain following iliac crest harvesting are limited. Another factor that has been associated with pain[7-9,12,13] and adverse events[14,15] following surgical treatments, is BMI. When iliac crest is harvested, elevated pain and gait disturbances in patients with higher levels of BMI were demonstrated as well[13,16]. This probably results from compromised accessibility of this donor site, thereby strengthening the above-described mechanism of stretching of the tissues causing postoperative pain and gait disturbances. These patients may profit from choosing another donor site like calvarial bone.

Sensory disturbances[3,4,17] and unfavorable esthetics are frequently mentioned drawbacks from harvesting extra-oral bone. For calvarial and anterior iliac crest, the impact of these outcomes seems limited (Chapter 2). In fact, sensory alterations are mostly temporary and barely noticed by patients, and patients reported to appreciate the cosmetic outcomes at donor site. To further optimize the outcomes of harvesting surgery with regards to sensory alterations and esthetics at donor site, several technical steps have been suggested. Sensory disturbances following iliac crest harvesting can be avoided by limiting direct trauma of the lateral cutaneous nerve[3,4,17]. When harvesting from the calvarium, a parasagittal incision and limited use of electrocautery have been proposed to limit sensory nerve damage[18-20]. Considering contour alterations, calvarial harvesting is associated with more prone deficits[21-23], which is probably due to the superficial location of the harvesting site. To limit the contour alterations for both harvesting locations, it is advised to reconstruct the defect with an osteoconductive biomaterial[24,25]. With regards to esthetic outcomes following calvarial harvesting, alopecia is reported as well. This late complication may be avoided by using a 30° angle incision to the follicles[19], a very low use of electrocoagulation[19,20], and the use of low tension sutures[26,27].

Other potential sources of dissatisfaction by patients includes complications associated with harvesting calvarial or anterior iliac crest grafts. While pain and gait disturbances do frequently occur, but are mostly temporary, most other complications can be considered minor[3,4,18,19,28-36], in particular for calvarial harvesting. In fact, a previous study on subclinical complications following calvarial harvesting, such as punctate intracranial bleeding or cerebral contusions,

did not identify such sequelae on computed tomographic scans[37]. However, when it comes to major complications, trepanation of the skull when harvesting calvarial bone might occur with significant sequelae such as sagittal sinus injury, brain injury, cerebrospinal fluid leak and meningitis as a result[19,29,30,38]. However, cases of dura exposure are generally quickly recognized and treated adequately[28-30], thus the patients do not suffer from permanent neurologic sequelae. Several authors declare that safe and successful calvarial harvesting is highly dependent on the training, technique[30,39,40] and expertise of the surgeon [28-30,39,40], but recent developments in the harvesting technique drastically have reduced, or perhaps even eliminated, this risk[16,41,42].

Specific major complications when harvesting anterior iliac crest bone include deep infection, iliac fracture, sacroiliac joint injury, arterial, nerve or ureteral injuries, meralgia paresthetica, hernias, pelvic instability and major hematomas[3,4,43]. Incidence of fracture of the iliac crest is low (0.7-1.2%) and invasive treatment is not needed in most cases[3,4]. Generally, patients recover well from these fractures.

To conclude from the above, particularly harvesting calvarial bone seems to be accompanied by a favorable outcome when applying the modified technique, and anterior iliac crest harvesting seems to be accompanied with similar results with mostly mild and temporary effects.

Microscopic properties of anterior iliac crest and calvarial bone grafts

The current comparison of anterior iliac crest and calvarial bone grafts by means of imaging technology (histology/histomorphometry and microCT) revealed differences in terms of quantity (volume) and quality (bone structure): both fresh harvested and incorporated calvarial grafts were denser and more contained a greater portion of cortical bone compared to the highly cancellous anterior iliac crest (Chapter 6). The incorporation and resorption rates of both graft types reflect these differences in micro-architecture.

In general, cancellous bone is very osteogenic, easily revascularized, and rapidly incorporated at the host site due to the large surface area covered with dormant and active osteoblasts[44-46]. Indeed, the highly cancellous anterior iliac crest grafts demonstrated these properties (Chapter 6). Calvarial grafts exhibited adequate incorporation of the grafted bone as well, despite their low proportion of cancellous bone. A drawback of highly cancellous bone grafts is the lack of mechanical strength, demonstrated by the decrease in bone volume in the anterior iliac crest grafts[46,47]. Cancellous bone exhibits high induction and production of new bone, thus providing early stability at the recipient site, but the space maintaining ability of cancellous bone is limited and this overrules its biologic activity, resulting in more volume loss of the grafted site over time[47-49].

With regards to cortical bone in general, it is often stated that revascularization is hampered by the dense architecture of the graft[44-46]. Also, a relatively scarce number of endosteal cells is available for the formation of end-to-end anastomoses. Thus, to enable revascularization and the recruitment of osteoblasts, incorporation of cortical bone is initiated by osteoclasts instead of osteoblasts[44-46]. Indeed, the cortical parts of anterior iliac crest grafts showed decrease of the bone percentage after four months incorporation. The cortical parts of calvarial grafts showed high percentages of bone even after four months healing, despite the thicker and denser cortical layer of calvarial bone.

The findings on microarchitecture and bone preservation correspond to features associated with the embryogenic origin of calvarial and iliac crest grafts, that is, intramembranous and enchondral origin, respectively[17,50-53]. Intramembranous bone is known to exhibit high bone preservation compared to enchondral bone[54-59]. Some state this results from the microscopic architecture of the tissue[58], others suggested differences in vascularization networks[59]. However, recent in vitro analysis has proposed a key role for osteocytes in bone regeneration[54-57,60]. Osteocytes account for 90–95% of all bone cells and they are thought to sense mechanical loads and accordingly transmit the signals to osteoblasts and osteoclasts through the osteocyte network, and thus regulate bone remodeling [58,59,60,61]. Likely, intramembranous osteocyte networks have a better bone preserving and regenerating ability in case of reconstruction of severe defects of the jawbone prior to implant placement. The current findings as well as previous reports[61] correspond to the findings from in vitro[54,56,57] and animal studies[48]: cortical bone of calvarial grafts showed a high efficiency in bone remodeling (demonstrated in Chapters 2 and 6) and are minimally resorbed, and show high viability and good incorporation. Additionally, the mesenchymal calvarial grafts exhibit more space maintaining properties, resulting in a higher bone volume preservation compared to enchondral bone grafts.

Autologous bone grafts versus bone tissue engineering

Bone graft harvesting surgery bears risks of donor site morbidity and complications. Therefore, several attempts have been made to optimize bony reconstructions by means of bone tissue engineering. A variety of materials have been used over time to substitute bone tissue, such as animal derived substitute materials (xenografts)[47,62-64]. Clinical studies on these xenografts to reconstruct severe defects are lacking. Histologic studies reported that xenografts demonstrate poor absorption and vascularization[47,64-67]. Poor absorption and vascularization hampers replacement of the graft by newly formed bone and compromise bone quality of the reconstructed jaw. In case of small reconstructions, such shortcomings are compensated by the regenerative capacities of the native bone. For large (horizontal and vertical) defects, this still must be shown. For example, only under the condition of mixation with autogenous bone and application of a membrane to cover the graft site, onlay grafting with bovine bone

mineral block was successful for reconstructions of intermediate defects of the anterior maxilla in partially dentate patients, however reconstructions with bovine bone alone failed[68]. Thus, reconstructions of large defects with bovine bone alone seems challenging with the current techniques and there is still an important place for autologous bone grafts.

Some authors have pointed out the clinical advantages of combining regenerative procedures with platelet-rich fibrin (PRF) to enhance bone[69]. However, a systematic review on the application of PRF in the dental field found very little to no data available directly investigating the effects of PRF on new bone formation in horizontal/vertical bone augmentation procedures[69]. Others mention the lack of evidence for using such substances in large defects as well[70-73]. Furthermore, several approaches have been made to optimize the vascularization in bone regeneration attempting to improve graft incorporation and bone regeneration. Human adipose tissue-derived stromal vascular fraction (SVF) and microvascular fragments (MF) are promising examples here. However, the usability of such substances in case of large bony defects has not been determined[70-72].

Future studies

The current thesis aimed to compare the augmentation of the maxilla using either calvarial or anterior iliac crest bone grafts from a clinical, radiological, and histological perspective. To further optimize the reconstruction of the severely resorbed maxilla for prosthetic rehabilitation, future studies are needed. The following topics have still to be addressed:

- Long term evaluations of the clinical outcomes of anterior iliac crest and calvarial bone harvesting to reconstruct large defects, including patient reported outcomes with a specific focus on sources of dissatisfaction;
- Long term evaluations of microstructure and volume maintaining properties of the bone grafts;
- More basic experiments on osteocyte level to elucidate the mechanisms of bone preservation between anterior iliac crest osteocytes and calvarial osteocyes
- Economic aspects of both procedures such as intraoperative costs and postoperative infirmity.

Long term (>5 years) RCTs are needed to compare the clinical bone volume maintenance and implant survival. Also, since postoperative complaints can affect patient reported satisfaction, studies should also assess patient satisfaction. Special attention should be placed at the impact of dissatisfying factors like pain, sensory disturbances, esthetic outcomes and complications bearing consequences for patients.

Long term evaluations of the microarchitecture and volume maintaining properties of the grafts are needed. The current results suggest that calvarial grafts are more favorable in terms of bone quality and bone quantity, but Carinci et al[74] postulated that the outcomes might approximate each other over time[74]. As the course of bone quality and quantity affects implant survival and prosthetic functioning, long term studies comparing the regeneration of maxillary bone augmented with either anterior iliac crest and calvarial bone grafts can add in selecting the most reliable and predictable treatment planning for a particular case.

Considering economic outcomes, several aspects are frequently discussed. First, it is often stated that anterior iliac crest harvesting is economically more favorable from a surgical perspective as a two-team approach can be employed, thereby reducing the duration of the surgery. On the contrary, the costs associated with a longer period of impaired independency in daily activities or unemployment of the patient following iliac crest bone harvesting[75-77] might outweigh this benefit. In other words, calvarial harvesting requires some extra surgical time, but patients recover more quickly. Some reports on the costs of anterior iliac crest harvesting for reconstruction of the severely resorbed edentulous maxilla exist[22,78], but not for calvarial bone graft harvesting. Also, a fair comparison is hampered as the management of inpatient care, including time management of operation rooms and nursing wards depend to a major extent on local standards and facilities. To weigh the costs of anterior iliac crest and calvarial bone grafts, future studies should be performed in which the sources of bias are reduced for example by performing a randomized controlled trial.

CONCLUSION

Clinical and histological studies have demonstrated that a severely resorbed maxillary alveolar ridge can be augmented effectively and predictably with both calvarial or anterior iliac crest bone grafts. The morbidity of a second surgical site required for both graft types should be weighted correctly: patients' report high satisfaction on various parts of the procedure and donor site related morbidity is temporary. However, the early postoperative complaints are a bit lower for calvarial bone, but one-year results are comparable. It thus can be concluded that calvarial grafts are a viable alternative to anterior iliac crest bone grafts for reconstruction of the severely resorbed edentulous maxilla.

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CHAPTER 8

Summary

Patients in need for an implant retained denture due to severe resorption of the edentulous jaw, often require bone reconstruction for reliable implant placement. For years, anterior iliac crest has been widely used to perform these reconstructions. However, anterior iliac crest harvesting is associated with postoperative pain and gait disturbances. Also, bone grafts derived from the iliac crest exhibit high resorption rates. Calvarial bone grafts form a potential alternative here, because of presumed low morbidity as well as favorable bone regeneration properties demonstrated by this bone type. The research described in this thesis aimed to compare patient reported outcomes, morbidity, microradiography, and histology of anterior iliac crest and calvarial bone graft harvesting.

In Chapter 2, knowledge on patient satisfaction associated with anterior iliac crest or calvarial bone graft harvesting for reconstruction prior to dental implant placement was systematically reviewed. MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases were searched. Outcomes measured included patient satisfaction, pain, disturbances in daily functioning, sensory alterations, esthetics at donor site, and complication rates. 40 out of 1946 articles fulfilled the inclusion criteria (2 comparative, 29 prospective cohort and 9 retrospective cohort studies). Meta-analysis (2 studies, 74 patients) showed no differences in satisfaction (standard mean difference (SMD) -0.13, 95% CI: -1.17;0.92; p =0.813) and postoperative pain between donor sites (direct postoperative: SMD, -2.32; 95% CI: -5.20;0.55; p=0.113; late postoperative: -0.01; CI -0.14;0.11, p =0.825). For anterior iliac crest, postoperative gait disturbances were highly prevalent. The incidence and prevalence of sensory disturbances and other complications were low for both groups. Esthetic outcomes at donor site were favorable for both graft types. To conclude, harvesting bone grafts from the calvarium or anterior iliac crest for augmentation of the severely resorbed edentulous jaw results in similar patient satisfaction.

In the study described in Chapter 3, it was aimed to assess calvarial conversion to maxillary bone after grafting the edentulous maxilla. In 13 patients (age: 65.3 ± 8.7 years) the atrophic maxilla was reconstructed with autologous calvarial bone. Biopsies were taken from fresh calvarial bone grafts and from the reconstructed maxillae after 4 months of healing. Micro-computertomography (CT), and a histomorphometric and histological analysis were performed. From three patients, biopsies were obtained after 9, 11, or 45 months. Micro-CT analysis revealed that in the maxilla the calvarial bone was well preserved even after 45 months. Histology showed progressive incorporation of grafted bone within a maxillary bone. Osteoid and osteocytes were present in all biopsies indicating new bone formation and vital bone. Histomorphometrically, the percentage of grafted bone volume over total volume decreased from 79.8% (IQR 78.7-83.3) in fresh calvarial grafts to 59.3% (IQR 44.8-64.6) in healed grafts. The biopsies taken after 9, 11, and 45 months showed similar values. Thus,

calvarial bone grafts result in stable and viable bone, good incorporation into native maxillary bone, and a minor decrease in bone volume after healing. Consequently, they provide a solid base for implant placement in severely atrophied edentulous maxillary bone.

Subsequently, in Chapter 4 a randomized controlled trial is described in which the morbidity associated with calvarial and anterior iliac crest bone graft harvesting are compared. For this randomized controlled trial, 20 consecutive edentulous patients needing extensive pre-implant surgery of the maxilla were randomly assigned to either calvarial (n = 10) or anterior iliac crest (n = 10) bone harvesting. All patients underwent a maxillary sinus floor elevation procedure combined with widening of the alveolar process using buccal bone blocks with calvarial or iliac crest bone. Donor site morbidity was assessed before, during, and at 1year after the surgery through patient questionnaires, physical examination and medical records. No perioperative complications occurred. The anterior iliac crest group reported minor postoperative pain after harvesting. The scars after calvaria harvesting were significantly longer (p =0.003), but this was not reported as bothersome by patients. Long-term pain was negligible and satisfaction was high in both groups. Both the calvaria and anterior iliac crest are associated with low long-term donor site morbidity and high patient satisfaction. Thus, patient-centred decision-making is appropriate when selecting the preferred harvesting method for that patient.

In Chapter 5, the results of this trial from a patient perspective were described. Patient-reported outcome measures (PROMs) related to augmentation of the extremely resorbed edentulous maxilla were compared. Patient reports on procedure-related satisfaction, questionnaires on oral functionality (denture satisfaction, chewing ability) and oral health-related quality of life (OHIP-49NL) and subjective donor site-related outcomes (e.g., of post-operative pain, scar formation, physical mobility) were assessed. Where applicable, a 100 mm visual analogue (VAS) score was used. Irrespective of the harvesting site, patients were generally satisfied (median VAS score 93, IQR 86-99 mm, p =0.400) with the procedure and its final results. Post-operative pain was mild (median VAS score 40, IQR 20-40 mm) and decreased to no pain (median VAS score 4, IQR 0-16 mm) within 14 days. Early post-operative pain was significantly higher following anterior iliac crest harvesting ($p<0.00$). Impact on physical mobility, daily functioning and satisfaction with the scar formation were similar in both groups. Thus, the assessed PROMs confirmed that bone graft harvesting from the calvarium or the anterior iliac crest is an appropriate procedure, reflected by high levels of satisfaction, minor long-term sequela and improvement of perceived oral health. For clinical decision-making, decisions can be based on individual features and preferences.

In Chapter 6, the histological and micro-CT changes of anterior iliac crest and calvarial bone grafts from this trial were compared. Biopsies were taken from both fresh bone grafts and reconstructed maxillae after 4 months healing, at time of implant placement. Micro-CT,

histomorphometric and histological analyses were performed. Micro-CT analysis revealed that both the anterior iliac crest and calvarial bone grafts retained their volume and bone mass after being incorporated in the maxilla, but with a favor for calvarial bone grafts: calvarial bone grafts had a higher mineral density before and after incorporation. Both bone graft types were well incorporated after 4 months of healing with preservation of bone volume and mineral density. Although the fresh bone biopsies were similar histomorphometrically, after 4 months of graft incorporation, the osteoid percentage and osteocyte count remained higher in the anterior iliac crest bone whereas the percentage of bone was higher in the calvarial bone grafts compared to the anterior iliac crest bone grafts. In conclusion, both anterior iliac crest and calvarial bone are well suited to provide a reliable and stable basis for implant placement 4 months after grafting with mineral density, porosity, and resorption rate in favor of calvarial bone grafts.

The results of the various studies are discussed in a broader context in Chapter 7. It can be concluded that:

- Calvarial and anterior iliac crest harvesting for reconstruction of the severely resorbed edentulous jaw prior to implant placement are both associated with high patient appreciation.
- With regards to morbidity and complications, harvesting bone grafts from either of the sites is safe. However, a slight favor is seen for calvarial grafts with regards to postoperative pain and gait disturbances.
- Calvarial and anterior iliac crest bone both provides a reliable and stable basis for implant placement four months after grafting. However, mineral density, porosity and resorption rate are in slight favor for calvarial bone.
- When extensive augmentation is needed in severely resorbed maxilla to allow for future preimplant surgery, the choice between crista iliac anterior or the calvarium as donor site depends on several factors, boldness, gait problems and preference of the patient.

CHAPTER 9

Samenvatting

Patiënten met een volledige gebitsprothese kunnen klachten ondervinden bij het dragen van en het functioneren met de prothese. Het is bewezen dat ondersteuning van een gebitsprothese door implantaten het draagcomfort en de functie kunnen verbeteren. In sommige gevallen dient eerst de kaak te worden gereconstrueerd om het plaatsen van implantaten op de gewenste plaats mogelijk te maken. De gouden standaard hiervoor is een lichaamseigen bottransplantaat, zeker als de kaak sterk geslonken is. Tot voor kort werd vooral bot dat werd geoogst uit het voorste deel van de bekkenkam, de crista iliaca anterior, gebruikt voor deze reconstructies. Het uitnemen van een stuk bot uit de voorste bekkenkam gaat echter gepaard met postoperatieve pijn en bewegingsbeperkingen. Tegenwoordig wordt ook bot uit het schedeldak, het calvarium, gebruikt voor kaakreconstructies. In het algemeen wordt aangenomen dat het uitnemen van bot uit het schedeldak weinig ongunstige neveneffecten heeft. Daarnaast is het gebruik van schedeldakbot mogelijk gunstiger voor het plaatsen van implantaten vanwege de goede kwalitatieve en regeneratieve eigenschappen in vergelijking met bot uit de bekkenkam Het in dit proefschrift beschreven promotieonderzoek had als doel te onderzoeken of schedeldakbot een effectief en betrouwbaar alternatief is voor een bottransplantaat uit de bekkenkam wanneer dit bottransplantaat wordt toegepast voor reconstructie van de sterk geslonken bovenkaak ten behoeve van het plaatsen van implantaten. Hierbij werd zowel gekeken naar door de patiënt gerapporteerde uitkomsten van de ingreep als naar de regeneratieve eigenschappen van beide bottypes.

De literatuur over patiënttevredenheid na het oogsten van bekkenkam- of schedeldakbot werd systematisch onderzocht (**Hoofdstuk 2**). Een literatuuronderzoek werd verricht in MEDLINE, EMBASE en Cochrane Central Register of Controlled Trials. De uitkomstmaten waren patiënttevredenheid (primaire uitkomst), postoperatieve pijn, problemen bij het dagelijks functioneren, postoperatieve gevoelsstoornissen in het operatiegebied, esthetische uitkomsten (donorlocatie) en complicaties. In totaal werden 1946 artikelen gevonden. Veertig van de 1946 artikelen voldeden aan de inclusiecriteria voor studie type (gerandomiseerde of niet-gerandomiseerde klinische studies ≥5 patiënten per groep, case series ≥5 patiënten), populatie (patiënten die een reconstructie van de ernstig geslonken onder- of bovenkaak ondergaan) en uitkomsten (ervaringen van de patiënt, morbiditeit). Deze 40 geïncludeerde studies bestonden uit 2 vergelijkende, 29 prospectieve cohortstudies, 9 retrospectieve cohortstudies. Twee studies kwamen in aanmerking voor een meta-analyse (74 patiënten). In de meta-analyse konden geen verschillen in de tevredenheid van patiënten (gestandaardiseerd gemiddeld verschil, SMD -0,13, 95% CI: -1,17;0,92; p=0,813) of postoperatieve pijn (direct postoperatief: SMD -2,32; 95% CI: -5,20;0,55; p=0.113; laat postoperatief: SMD -0,01; CI -0,14;0,11, p=0,825) worden aangetoond, of bot nu geoogst werd van de voorste bekkenkam of van de schedel. Er werden frequent problemen bij het lopen gemeld door patiënten bij wie bekkenkambot werd geoogst. Deze waren echter van tijdelijke aard. . Gevoelsstoornissen en andere complicaties werden weinig gemeld in beide groepen. Ook de esthetische uitkomsten

en tevredenheid van de patiënt waren gunstig en vergelijkbaar voor beide donorlocaties. Op basis van deze resultaten werd geconcludeerd dat de schedeldakbot een goed alternatief vormt voor bekkenkambot.

In **Hoofdstuk 3** wordt een studie beschreven waarin de genezing van het kaakbot werd onderzocht nadat deze was gereconstrueerd met schedeldakbot. Bij 13 patiënten (leeftijd: 65,3±8,7 jaar) met een tandeloze, sterk geslonken bovenkaak werd deze gereconstrueerd met schedeldakbot om het plaatsen van implantaten mogelijk te maken. Er werden biopten vergeleken die waren genomen van het schedeldakbot direct na het oogsten en van de gereconstrueerde bovenkaak na een genezingsinterval van 4 maanden. De biopten werden geanalyseerd door middel van micro-computertomografie (CT), histologie en histomorfometrie. Bij drie patiënten waren tevens biopten genomen na 9, 11 of 45 maanden. Analyse middels micro-CT toonde dat het schedeldakbot herkenbaar aanwezig bleef, ook na 45 maanden. Histologisch onderzoek liet een progressieve omzetting van het getransplanteerde bot naar maxillair bot zien. Bij alle biopten werden osteoïd en osteocyten aangetroffen wat duidt op vitaal bot en de vorming van nieuw bot. Histomorfometrisch daalde het botvolume van 79,8% (IQR 78,7-83,3) in verse schedeldaktransplantaten tot 59,3% (IQR 44,8-64,6) na een genezingsduur van vier maanden. De biopten die waren genomen na 9, 11 en 45 maanden toonden overeenkomstige waarden. Uit bovenstaande blijkt dat schedeldaktransplantaten stabiel en betrouwbaar kunnen worden toegepast bij het reconstrueren van de tandeloze bovenkaak. De biopten worden omgezet naar maxillair bot waarbij er een gering volumeverlies optreedt. Derhalve vormen ze een solide basis voor het plaatsen van implantaten.

In **Hoofdstuk 4** wordt een gerandomiseerde, gecontroleerde studie beschreven waarin de morbiditeit van het oogsten van bot uit de voorste bekkenkam of het schedeldak wordt vergeleken. Voor deze studie werden 20 patiënten geïncludeerd bij wie de tandeloze bovenkaak was gereconstrueerd met bekkenkam- of schedeldakbot. De patiënten waren willekeurig verdeeld over een groep waarbij schedeldakbot (10 patiënten) of bekkenkambot (10 patiënten) geoogst. De morbiditeit geassocieerd met de donorlocatie werd onderzocht met behulp van vragenlijsten en lichamelijk onderzoek zowel vóór, direct na de ingreep en na 1 jaar. Perioperatief werden geen complicaties gezien. Patiënten uit de bekkenkamgroep ervaarden milde postoperatieve pijn kort na het oogsten van het transplantaat. De littekens na het oogsten van schedeldakbot waren langer, maar patiënten vonden dit niet storend. De pijn op lange termijn was nihil en patiënten waren zeer tevreden in beide groepen. Op grond van deze uitkomsten werd geconcludeerd dat zowel het gebruik van schedeldakbot als bekkenkambot een lage morbiditeit met zich meebrengt. Bij het maken van een keuze dient de patiënt betrokken te worden bij het kiezen van de donorlocatie.

In **Hoofdstuk 5** werd een analyse van verschillende door patiënten gerapporteerde uitkomsten gepresenteerd van dezelfde patiënten als in hoofdstuk 4. Het betrof uitkomsten als tevredenheid met de procedure, vragenlijsten over de mondfunctie zoals de tevredenheid met het kunstgebit en het kauwen, de mondgezondheid gerelateerde kwaliteit van leven en subjectieve donorlocatie-gerelateerde uitkomsten zoals postoperatieve pijn, littekenvorming en eventuele klachten bij lichamelijke activiteiten. Onafhankelijk van de donorlocatie waren patiënten zeer tevreden met de procedures: op een schaal van 0-100 werd een score van 93 gegeven voor beide groepen. De vroege postoperatieve pijn was mild, maar significant hoger wanneer bekkenkambot werd geoogst. De tendens van de impact op lichamelijke activiteiten en het dagelijks functioneren was vroeg postoperatief eveneens groter wanneer bekkenkambot werd geoogst. De tevredenheid met het litteken verschilde niet tussen beide groepen. Op basis van de hoge patiënt tevredenheid, de weinige nadelige uitkomsten op de lange termijn en de verbetering van de mondgezondheid na afronding van de procedure, werd geconcludeerd dat het oogsten van bot uit het schedeldak en de voorste bekkenkam, beide veilige procedures zijn vanuit het perspectief van de patiënt.

Om op microscopische niveau schedeldakbot en bekkenkambot te vergelijken, werden bij de patiënten uit de in de vorige twee hoofdstukken beschreven studie tevens biopten verzameld (**Hoofdstuk 6**) Bij alle patiënten werd een biopt genomen van het bottransplantaat direct na aanbrengen en 4 maanden nadat de reconstructie was uitgevoerd. De biopten werden röntgenologisch (micro-CT) en middels lichtmicroscopie (histologie, histomorfometrie) geanalyseerd. De micro-CT analyse toonde aan dat beide donorlocaties hun volume en botmassa behielden. De dichtheid van de schedeldakbiopten was zowel voor als na de genezing hoger. Lichtmicroscopisch onderzoek toonde dat beide typen bottransplantaat goed waren geïncorporeerd vier maanden na het aanbrengen, maar dat de omzetting van het bot in de bekkenkamtransplantaten actiever was dan bij de schedeldaktransplantaten, terwijl het behoud van botvolume bij schedeldaktransplantaten hoger was. Op basis van deze resultaten kon ook hier worden geconcludeerd dat schedeldakbot en bekkenkambot een betrouwbare en stabiele bases vormt voor implantaten, waarbij schedeldakbot gunstigere uitkomsten had op het gebied van dichtheid en volumebehoud.

In **Hoofdstuk 7** worden de resultaten in een bredere context besproken. De belangrijkste conclusies die kunnen worden getrokken, zijn:

- Gebruik van schedeldak- en bekkenkambot voor reconstructies van de geresorbeerde tandeloze bovenkaak ten behoeve van het plaatsen van implantaten wordt gekenmerkt door een hoge mate van tevredenheid onder patiënten;

- Beide donorplaatsen zijn veilig met betrekking tot morbiditeit en complicaties, met een klein voordeel wanneer schedeldakbot wordt gebruikt: op korte termijn is de postoperatieve pijn geringer en de patiënt ervaart op korte termijn minder problemen bij lichamelijke activiteiten. Op langere termijn verdwijnen deze verschillen;
- Schedeldakbot en bekkenkambot vormen beide een stabiele basis voor het plaatsen van implantaten. De hogere dichtheid en de hoge mate van volume behoud vormen mogelijk een voordeel wanneer schedeldakbot wordt gebruikt;
- De keuze voor schedeldak-_of bekkenkambot is afhankelijk van verschillende factoren, zoals haardracht, preexistente problemen bij lichamelijke activiteit en voorkeuren van de patiënt.

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ABOUT THE AUTHOR

Dagmar Wortmann

Dagmar Edith Wortmann was born on April 15th 1991 in Veldhoven, the Netherlands, and grew up in nearby Eindhoven. When she was 12 years old her family moved to Glimmen, a village in countryside in the North of The Netherlands. In 2009, she obtained her gymnasium degree at the Maartenscollege, Haren.

Dagmar continued her education by studying Medicine at the University of Groningen. During her study, she was actively involved in several extracurricular organizing committees. Also, she followed a minor course in Clinical Pharmacology. She performed her clinical internships at the University Medical Centre Groningen and the Isala Hospital in Zwolle. She alternated her study in the Netherlands with internships in Cameroon and Indonesia. During a five month internship in South Sulawesi, Indonesia, she decided to focus her further career on Oral & Maxillofacial Surgery. She did her final internships at the departments of Oral & Maxillofacial Surgery and Ear, Nose & Throat, and Head & Neck Oncology in the Amsterdam University Medical Centre. She obtained her Master's degree of Medicine in 2017. That same year, she started as a PhD-candidate at the University Medical Centre in Groningen, supervised by prof. dr. G.M. Raghoebar and prof. dr. A. Vissink. This project was performed in cooperation with the Academic Centre for Dentistry in Amsterdam, where prof. dr. J. Klein Nulend was her supervisor. Meanwhile, Dagmar obtained her Doctor of Dental Surgery degree at the University of Groningen and worked as a clinical resident at the department of Oral and Maxillofacial Surgery of the Medical Centre Leeuwarden.

Currently, Dagmar has started her residency in Oral & Maxillofacial Surgery at the University Medical Center Groningen. She lives together with Erwin Koning.