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

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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

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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.

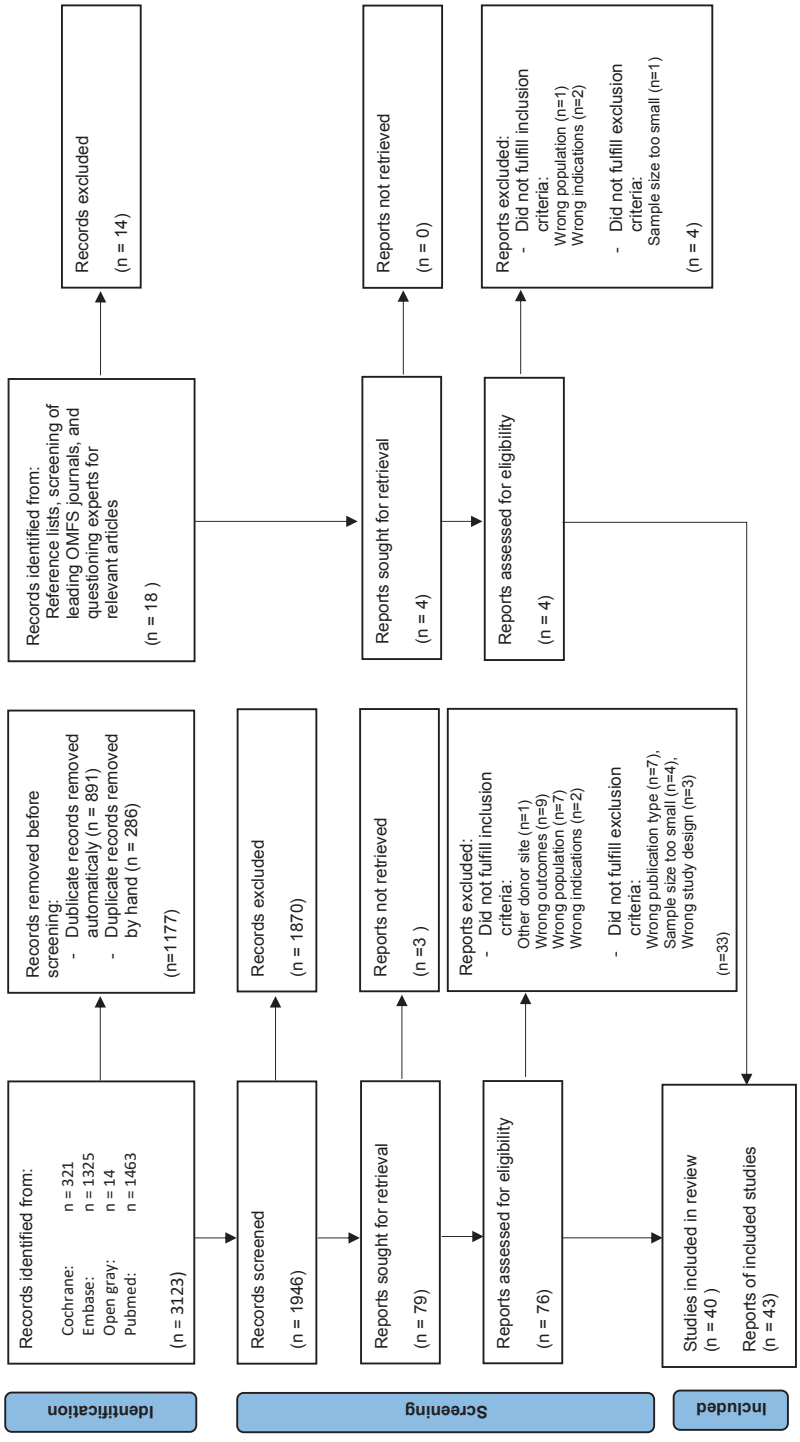

Figure 1. Flowchart presenting the identification of the literature and selection progress.

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.

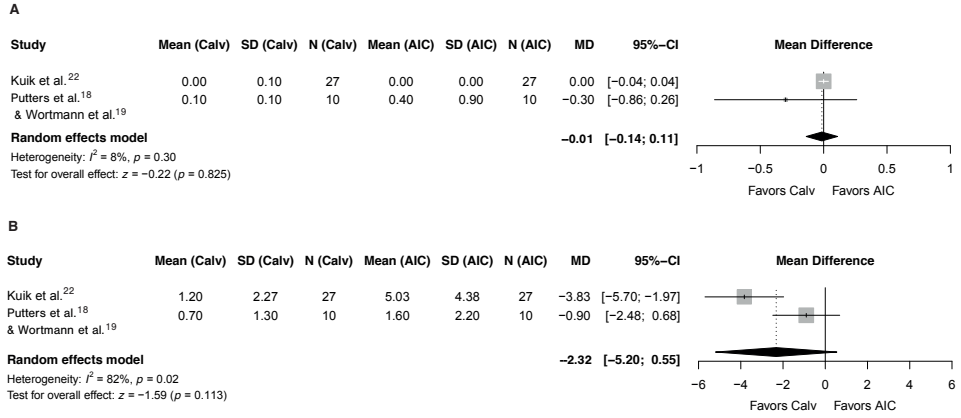

Figure 3 Forest plots of the secondary endpoints: pooled patient reported severity of postoperative pain after harvesting calvarium vs. anterior iliac crest grafts. (A) Direct postoperative pain; (B) late postoperative pain
Abbreviations: Calv: patients treated with calvarium grafts; AIC: patients treated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