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Greater bone regeneration required for implants following periodontal extraction: a retrospective cross-sectional study

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Abstract

Background We evaluated cone beam computed tomography images to compare the complexity of dental implant surgery after alveolar ridge preservation in damaged versus intact sockets resulting from severe periodontitis-related tooth extraction.

Methods In a retrospective analysis of 165 alveolar ridge preservation sites among 116 patients, we categorized 72 sockets as damaged and 93 as intact. Using cone beam computed tomography, we measured bone width at three vertical levels and compared bone regeneration needs for subsequent dental implant surgery between socket types.

Results Despite no difference in bone width between damaged and intact sockets, implant placement revealed differing regenerative needs. Mandibular teeth and non-drinkers required less regeneration. Damaged sockets exhibited 3.02 times higher regeneration requirements compared to intact ones.

Conclusions The complexity of implant surgery following alveolar ridge preservation is influenced by alcohol consumption, tooth position, and periodontitis-related tooth extraction.

Clinical trial registration The ClinicalTrials.gov Identifier: NCT05657223, 20/12/2022.

Keywords Periodontitis, Alveolar ridge preservation, Implant surgery

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Background

Alveolar ridge resorption is an unavoidable consequence of tooth extraction and poses a substantial problem in implant and restorative dentistry. Postextraction maintenance of the alveolar ridge minimizes residual ridge resorption and enables the placement of an implant that meets both esthetic and functional criteria. Alveolar ridge preservation (ARP) is a promising therapeutic option because it significantly reduces postextraction dimensional changes of the ridge [1]. Several studies have demonstrated that tooth extraction leads to significant changes in the residual alveolar bone [2, 3]. Specifically, the extraction of a tooth triggers notable bone alterations in the remaining alveolar ridge, causing pronounced changes in both height and width. The buccal wall typically experiences a decrease in height, along with the disappearance of bundle bone [4, 5]. Bone remodeling following tooth extraction along the buccal aspects of the sockets may result in aesthetic concerns due to the reduction in tissue volume. Bone remodeling following tooth extraction along the buccal aspects of the sockets may result in aesthetic concerns due to the reduction in tissue volume. Schropp et al. reported that up to 50% reduction in residual alveolar ridge may occur 12 months after tooth extraction [3].

Periodontally compromised extraction sockets exhibit cortication and slow healing [6, 7]. Severe loss of alveolar bone height and width can occur following teeth removal in advanced periodontitis. In animal studies, buccal bone deficiency leads to significant volume reduction after tooth extraction along the entire length of the socket [8]. Preservation and reconstruction of alveolar ridge volume in extraction sockets affected by severe periodontitis present clinical challenges. Systematic reviews have confirmed that, compared with natural socket healing, ridge preservation is more effective in attenuating the dimensional reduction of the alveolar ridge in intact sockets [9, 10]. Many studies on ARP have excluded patients who underwent tooth extraction due to severe periodontitis. However, outpatient tooth extraction due to severe periodontitis is frequently performed by clinicians, and reconstruction after extraction remains challenging.

The diverse applications of different materials used for ARP. Various materials are used for ARP by filling or covering the alveolar sockets with biomaterials. These include autologous granulated bone, allogeneic decalcified bone, allograft bone, other bone biomaterials [11], and platelet concentrates. Each material has its own advantages and disadvantages. Mineralized freeze-dried bone allograft (FDBA) is a widely accepted and commonly utilized product aimed at minimizing alterations in ridge dimension following tooth extraction. It facilitates the generation of sufficient new vital bone for effective implant placement [12–15]. FDBA preserves

the socket space and serves as a scaffold for host osteo-progenitor cells throughout the healing phase [16, 17]. Autologous platelet concentrates, derived from the patient's venous blood, usually have a platelet concentration three to five times higher than that of normal whole blood. Platelet-rich fibrin (PRF) is abundant in fibrin, platelets, white blood cells, growth factors, cytokines, and other beneficial components that promote tissue repair [18–20]. The interactions of growth factors, tissue factors, antimicrobial peptides, and other active proteins can promote the proliferation and differentiation of various tissue cells. ARP utilizing a membrane effectively prevents epithelial downgrowth, facilitating the defect's colonization by host bone-forming cells [10, 21–23]. However, premature membrane exposure can result in infection, adversely affecting new bone formation [21]. PRF has found application in clinical practice for preserving alveolar sites and addressing defects in alveolar bone, affirming its effectiveness in stimulating bone tissue regeneration [24–27].

Although periodontitis is the primary cause of tooth loss in adults, only a few articles have been published on the immediate reconstruction of periodontitis-induced severely compromised molar alveolar sockets [28–30]. Zhao et al. reported that compared with natural healing alone, ridge preservation at periodontally compromised molar extraction sites may compensate for ridge width reduction and buccal bone resorption after tooth extraction [29].

To the best of our knowledge, no study has compared the effect of ARP on tooth extraction performed due to different conditions, such as periodontitis. Therefore, this retrospective study assessed the cone beam computed tomography (CBCT) images to evaluate the differences in the complexity of dental implant surgery following ARP between damaged and intact sockets. Our study hypothesis is that there will be no difference in alveolar bone width on CBCT and subsequent implant reconstruction techniques between intact and damaged sockets after ARP.

Methods

IRB approval

The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E[I]-20210023) and conformed to follow up the Declaration of Helsinki. The ClinicalTrials.gov Identifier: NCT05657223. This study retrospectively collected past dental treatment history of participants and restoration upon dental implants. Due to the retrospective characteristics, all participants did not sign the informed consent before inclusion.

Inclusion criteria

We enrolled patients who underwent tooth extraction; ARP and CBCT 4 months following tooth extraction. The dental implant treatment was between January 2015 and the end of December 2019. This work has been reported in line with the STROCSS criteria [31].

This study included patients aged more than 20 years, with the requirement for teeth extraction in the premolar and molar regions, who underwent flapless tooth extraction with ARP and filling with FDBA and PRF, who underwent CBCT followed by dental implant surgery after tooth extraction, and with adequate oral hygiene. The patients were divided into two groups. In the damaged socket group, the requirement for tooth extraction was due to stage III or IV periodontitis, type III socket classification [32] and severe periodontal attachment loss, as determined by two periodontists. The intact socket group presented with untreatable tooth decay or root fractures in the root area. The alveolar bone around the teeth with intact without obvious damage.

Patients with untreated periodontitis, systemic disease, or the of medication that influences bone metabolism were excluded.

Clinical procedures

The flapless tooth extraction procedure was performed using a periosteal elevator and elevators. If necessary, the root was sectioned using a handpiece and diamond burs to prevent any trauma to the alveolar walls. Granulation tissue inside the socket was meticulously removed, followed by irrigation with copious amount of sterile saline solution. PRF is obtained by drawing blood from the patient's arm vein, placing it into a BD Vacutainer, and centrifuging it at 700× g for 12 min. Sockets were grafted with FDBA and covered with PRF for sealing the top of the extraction sockets. A description of the surgical steps is shown in Fig. 1. A cross-mattress suture secured the PRF and bone graft in place. Medication prescribed to all patients included systemic antibiotics (amoxicillin 500 mg, Q8H for 5~7 days).

A prosthodontically-driven surgical stent indicating the future dental implant position was placed at tooth

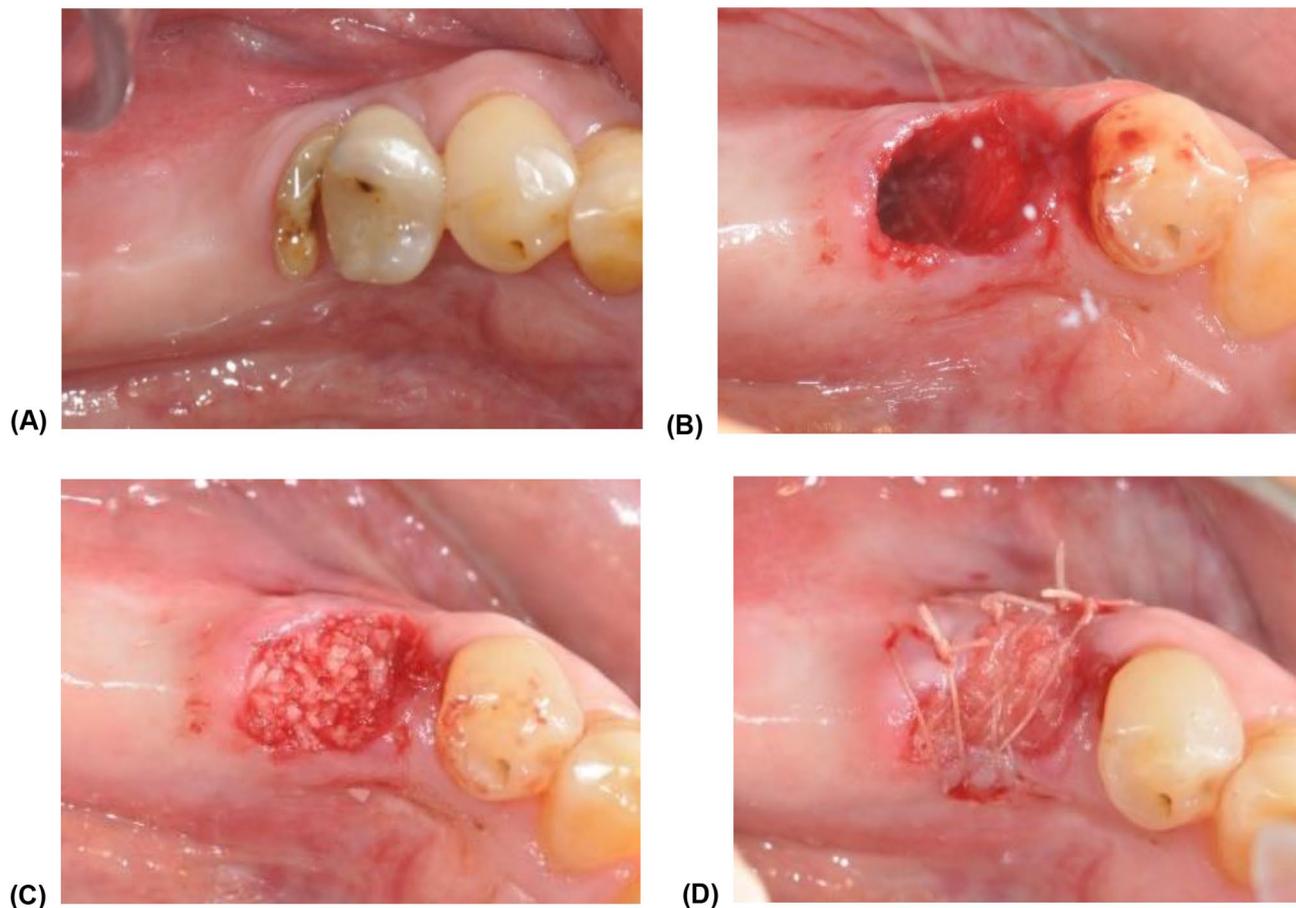


Fig. 1 The surgical procedures of tooth extraction and ARP. (A) Tooth 45 fracture and planned to extraction. (B) Tooth 45 flapless extraction socket. (C) Socket with FDBA grafting. (D) PRF is placed on the extraction wound and sutured

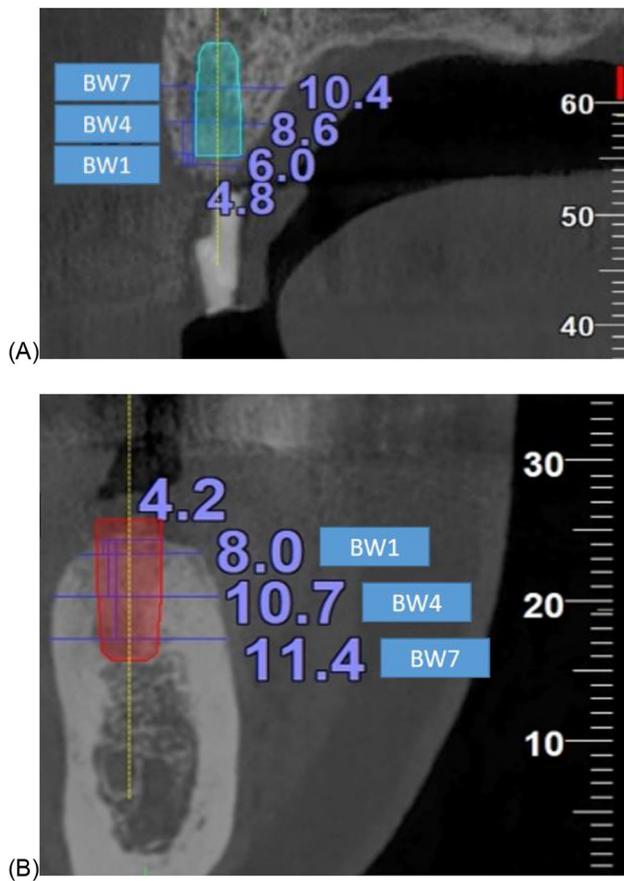


Fig. 2 Measurement of maxillary (A) and mandibular (B) subcrestal bone widths in CBCT. The horizontal alveolar bone over three levels. BW1: subcrestal width 1mm. BW4: subcrestal width 4mm. BW7: subcrestal width 7mm

extraction site before the patients underwent CBCT. CBCT and implant or guided bone regeneration (GBR) surgery were performed 4 to 6 months after extraction. The surgical treatment plan for dental implant placement was designed according to the alveolar bone width

calculated based on the basis of CBCT images. The treatment modalities were classified into three groups. In Group I, implant placement without adjuvant bone grafting augmentation was performed. In Group IGBR, implant placement combined with GBR was performed, whereas in Group adGBR, GBR was performed before implant placement. The implant diameter ranged from 4.1 mm to 4.8 mm, whereas the length from 8 to 10 mm.

Alveolar bone width measurement

To ensure measurement consistency, the bone width for pre-implant CBCT was measured by a single blinded well-trained examiner. CBCT images were captured using Picasso Trio (Vatech, Korea) with EzImplant (version 4) viewer software and VGi evo (NewTom, Italy) with NNT study viewer software. Alveolar bone width measurements were performed using the integral tool of the software program.

The long axis of the tooth on a CBCT image was marked by the surgeon on the basis of the long axis of the implant to be implanted. The horizontal alveolar bone width was measured at three different vertical levels: subcrestal width 1 mm (BW1), subcrestal width 4 mm (BW4), and subcrestal width 7 mm (BW7; Fig. 2) [33]. The study process and grouping is shown in Fig. 3.

Statistical analysis

All calculations were conducted by one blinded examiner. To assess intraexaminer reproducibility, 30% of the measurements were randomly recalculated on two occasions at a 2-week interval. The intraclass correlation ranged between 0.94 and 0.92.

Numerical data are presented as mean ± standard deviation, and frequency distributions within each group are indicated using numbers and proportions. A two-sample t test, the chi-square test and multivariable logistic regression analysis were used to compare intergroup

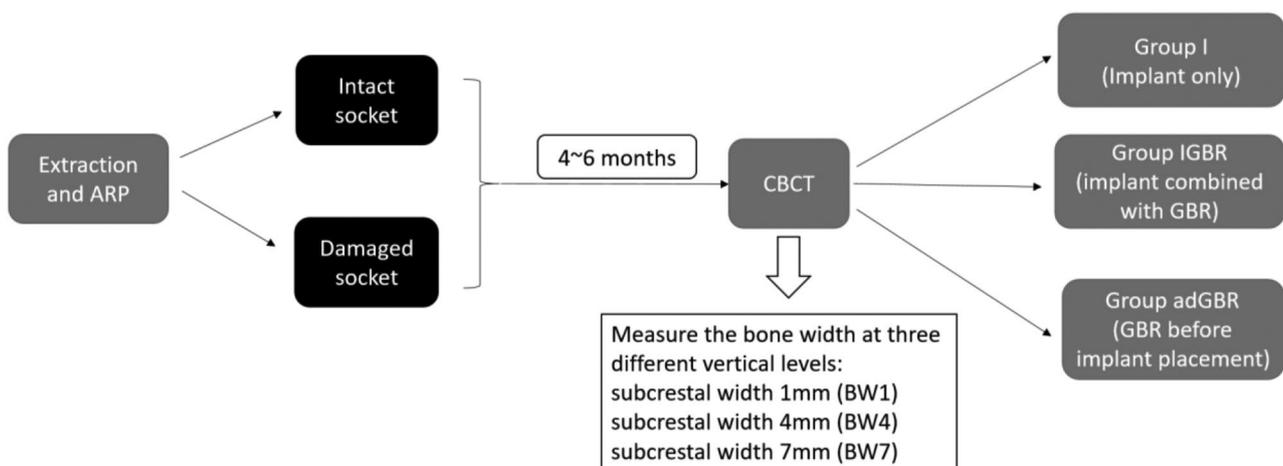


Fig. 3 Study process and grouping

Table 1 Demographic data of the included patients

		Damaged sockets n = 72	Intact sockets n = 93	p value
		n (%)	n (%)	
Gender	Female	43 (59.7)	61 (65.6)	0.439
	Male	29 (40.3)	32 (34.4)	
Age		55.99 ± 9.45	51.80 ± 11.47	0.011*
Location	Maxillary	38 (38.9)	35 (37.6)	0.869
	Mandibular	44 (61.1)	58 (62.4)	
Alcohol (n = 151)	No	50 (71.4)	56 (69.1)	0.759
	Yes	20 (28.6)	25 (30.9)	
Betel nut (n = 151)	No	70 (100)	81 (100)	-
	Yes	0	0	
Cigarette (n = 151)	No	61 (87.1)	71 (87.7)	0.925
	Yes	9 (12.9)	10 (12.4)	
BMI (n = 150)	< 24	34 (48.6)	45 (56.3)	0.347
	≥ 24	36 (51.4)	35 (43.8)	
Systemic diseases (n = 152)	No	38 (53.5)	54 (66.7)	0.098
	Yes	33 (46.5)	27 (33.3)	

Age: years old

BMI: body mass index, kg/m²

p value were assessed using two-sample t test and the chi-square test

differences in distribution means and proportions, respectively. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using JMP version 13 software (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

We examined 165 alveolar ridge preservation (ARP) sites in 116 patients post-tooth extraction via CBCT. Data on demographics, habits, diseases, and socket types were collected. Among these, 156 sites underwent dental implant surgery, with 72 damaged sockets and 93 intact sockets analyzed. The intact socket group had a lower average age compared to the damaged socket group (51.80 ± 11.47 vs. 55.99 ± 9.45 years), while other demographic factors were similar between the groups (Table 1).

Comparison of the different socket types in the bone width after ARP

We measured the bone width on CBCT images at three subcrestal levels; the images were obtained during pre-implant evaluation following ARP. The damaged sockets exhibited greater bone widths at these levels compared to intact sockets (Table 2). However, statistical analysis revealed no significant differences in bone widths between damaged and intact sockets at the three subcrestal levels ($p = 0.257, 0.396,$ and 0.602 for BW1, BW4, and BW7, respectively). Even after adjusting for age, the differences in width measures remained nonsignificant between the groups ($p = 0.431, 0.175,$ and 0.528 for BW1, BW4, and BW7, respectively; data not shown in the table).

The distribution of dental implant surgery performed in different socket groups

Out of 165 sites, dental implant surgery was not performed in 9 cases due to unnecessary occlusion reconstruction. Thus, 156 implant surgeries were carried out, with 63 implants in damaged sockets and 93 in intact sockets. Both damaged and intact sockets had similar proportions requiring additional staged GBR (12.7% and 12.9%, respectively). However, a significantly higher proportion of simple dental implantations occurred in the intact socket group compared to the damaged socket group (71% vs. 52.4%, $p = 0.022$; Fig. 4).

Table 2 Comparison of the different socket type in the bone width after alveolar ridge preservation

	Damaged sockets n = 72		Intact sockets n = 93		p value	
	Mean	SD	Mean	SD		
Bone width (BW, mm)	BW1	9.18	2.20	8.76	2.37	0.257
	BW4	11.56	2.20	10.47	2.34	0.396
	BW7	12.75	2.41	11.61	2.57	0.602

p value were assessed using two-sample t test

BW1: subcrestal width 1 mm

BW4: subcrestal width 4 mm

BW7: subcrestal width 7 mm



Fig. 4 The distribution of dental implant surgery performed in different groups. Group I: implant placement without any adjuvant bone grafting augmentation procedure. Group IGBR: implant surgery combined with simultaneous GBR. Group adGBR: additional staged GBR before implant

Comparison of the surgical condition after ARP

Further analysis revealed that socket type, implant location, and patient drinking habits influenced the need for additional bone grafting (IGBR or ad GBR) (Table 3). Simple implant surgery was performed in 52.4% of damaged sockets and 71% of intact sockets ($p=0.018$). Among these, 70.7% of mandibular teeth were reconstructed without additional bone filling, compared to 50.9% of maxillary teeth ($p=0.007$). Notably, a significantly higher proportion of patients with a drinking habit underwent simple dental implant surgery compared to those without (79.5% vs. 55.6%, $p=0.006$).

The risk factors for extra GBR of implant

The adjusted odds ratio (AOR) for extra GBR (IGBR or adGBR) was 3.02 in damaged sockets compared to intact sockets ($p=0.009$; Table 4). Additionally, the AOR for extra GBR in lower jaw implants was 0.35 compared to upper jaw implants ($p=0.011$). Patients with drinking habits had an AOR of 0.32 for extra GBR compared to those without ($p=0.028$). Thus, socket type, implant location, and drinking habit were identified as significant factors influencing the need for extra GBR in implant reconstruction.

Discussion

Alveolar ridge healing patterns [1] and preservation [10] after tooth extraction for non-periodontal reasons have been well investigated. However, healing patterns following posterior teeth extraction in advanced periodontitis remain unknown. Healing dynamics in compromised extraction sockets are different from those in extraction sockets unaffected by periodontitis [6, 34–37]. Cha et al. [36, 38] reported that in reconstruction surgeries following tooth extraction due to severe periodontal disease,

among the cases undergoing ARP, 42.9% did not require any additional sinus augmentation procedure for implant placement, while 100% of cases in the spontaneous healing group required additional sinus augmentation procedures during implant placement.

This retrospective study evaluated the effect of ridge preservation following posterior teeth extraction in damaged (severe periodontitis, stage III–IV periodontitis) and intact sockets (fracture teeth or untreatable caries) by using CBCT images. The results revealed a similar bone widths after flapless ARP with FDBA and autogenous PRF in the damaged and intact sockets at the BW1, BW4 and BW7 levels. Although the bone width in the damaged sockets was slightly larger than that in intact sockets, no statistical difference was noted. As observed in actual dental implant surgery, the bone width in the damaged sockets was slightly larger than that in the intact sockets after ARP healing. However, in the damaged socket group, the proportion of sites at which implantation without extra GBR could be performed was significantly lower than those in the intact socket group (the difference was approximately 20%; 52.4% vs. 71%). Therefore, even if the width on CBCT images is sufficient, simple dental implant surgery could not be performed; moreover, the texture of the bone may affect the complexity of dental implant surgery. A 2021 study on ARP for periodontally compromised teeth reported that ARP can effectively improve dimensional loss, but histologically, less mineralized tissues is observed in these extraction sockets, especially in the extraction sockets with >50% bone loss [39]. This explains the similar bone width on CBCT images between the damaged and intact socket in this study; however considerable significant differences were observed in clinical surgical procedures between the groups.

Table 3 Comparison of the surgical condition after alveolar ridge preservation

	Surgical condition		χ^2	P-value
	Implant	Implant with extra GBR		
	n (%)	n (%)		
Socket type			5.596	0.018*
Destructive	33 (52.4)	30 (47.6)		
Intact	66 (71.0)	27 (29.0)		
Gender			1.206	0.272
Female	59 (60.2)	39 (39.8)		
Male	40 (69.0)	18 (31.0)		
Age			1.217	0.270
< 54	49 (68.1)	23 (31.9)		
≥ 54	50 (59.5)	34 (40.5)		
Location			7.215	0.007*
Upper	29 (50.9)	28 (49.1)		
Lower	70 (70.7)	29 (29.3)		
Alcohol			7.516	0.006
No	55 (55.6)	44 (44.4)		
Yes	35 (79.5)	9 (20.5)		
Cigarette			0.123	0.726
No	78 (62.4)	47 (37.6)		
Yes	12 (66.7)	6 (33.3)		
BMI			1.378	0.240
< 24	43 (58.1)	31 (41.9)		
≥ 24	46 (67.6)	22 (32.4)		
Systemic diseases			0.008	0.930
No	54 (62.8)	32 (37.2)		
Yes	36 (62.1)	22 (37.9)		
BW1			0.002	0.964
Narrow	49 (63.6)	28 (36.4)		
Wide	50 (63.3)	29 (36.7)		
BW2			0.908	0.341
Narrow	46 (59.7)	31 (40.3)		
Wide	53 (67.1)	26 (32.9)		
BW3			1.355	0.245
Narrow	46 (59.0)	32 (41.0)		
Wide	53 (67.9)	25 (32.1)		

Age: years old

BMI: body mass index, kg/m²

BW1 median: 8.7 mm. Wide BW1 ≥ 8.7 mm; narrow BW1 < 8.7 mm

BW4 median: 10.8 mm. Wide BW1 ≥ 10.8 mm; narrow BW1 < 10.8 mm

BW7 median: 12.5 mm. Wide BW1 ≥ 12.5 mm; narrow BW1 < 12.5 mm

GBR: guided bone regeneration

Implant with extra GBR: IGBR (implant surgery combined with simultaneous GBR) or adGBR (additional staged GBR before implant)

p value were assessed using the chi-square test

* p value < 0.05

Table 4 The risk factors for extra GBR of implant by multivariable logistic regression analysis

	Risks of extra GBR		
	AOR	95% CI	p-value
Socket type (reference: intact socket)	3.02	1.32–7.32	0.009*
Gender (reference: male)	0.51	0.21–1.20	0.125
Age (reference: < 54)	1.01	0.41–2.49	0.977
Location (reference: upper)	0.35	0.15–0.79	0.011*
Alcohol (reference: no user)	0.32	0.10–0.89	0.028*
Cigarette (reference: no user)	1.68	0.41–6.82	0.468
BMI (reference: < 24)	0.76	0.33–1.78	0.534
Systemic diseases (reference: healthy)	0.89	0.37–2.12	0.800
BW1 (reference: < 8.7 mm)	2.10	0.72–6.62	0.179
BW4 (reference: < 10.8 mm)	1.15	0.26–4.97	0.851
BW7 (reference: < 12.5 mm)	0.33	0.08–1.22	0.095

CI: confidence interval

AOR: Adjusted Odds Ratio

Age: years old

BMI: body mass index, kg/m²

GBR: guided bone regeneration

extra GBR: IGBR (implant surgery combined with simultaneous GBR) or adGBR (additional staged GBR before implant)

BW1 median value: 8.7 mm; BW4 median value: 10.8 mm; BW7 median value: 12.5 mm

p value was analyzed by multiple logistic regression

* p value < 0.05

In 2020, Fok et al. [40] reported that during dental implant reconstruction performed 6 months after the extraction or exfoliation of first molars with severe periodontitis, approximately 37.8%~45.9% of sites did not require additional bone grafting. In the posterior teeth with severe periodontitis, the implant diameter in our study was similar to that the study by as Fok et al. study (4.1 to 4.8 mm). We observed that a high proportion (52.4%) of implant reconstruction did not require additional bone grafting. This may be because the ARP procedure was performed at the same time as tooth extraction, thereby reducing the requirement for bone filling during the subsequent dental implant surgery. Clinical guidelines on the management of posterior teeth extraction sites in patients with stage III or IV periodontitis are lacking. Previous animal studies have demonstrated that PRF displays strong osteogenic potential and has the ability to reduce inflammation in soft tissues [41, 42]. Flapless ARP combined with FDBA and autologous PRF filling may be an effective method to simplify subsequent implant procedures.

A previous study [40] revealed that mandibular teeth require less bone augmentation than maxillary teeth. Moreover, the proportions of the mandibular teeth and maxillary teeth that received simple implant surgery were 43.5%~60.9% and 35.3%~39.2%, respectively. In our study, 70.7% of the mandibular teeth could be directly implanted after ARP without additional bone repair,

whereas approximately half (50.9%) of the maxillary teeth could be directly implanted.

In addition to socket type and tooth position, the complexity of implant surgery is affected by drinking habit. A study reported that alcoholism is associated with implant failure, mainly due to poor oral hygiene [43]. In our study, a higher proportion of the patients with drinking habit could undergo dental implant surgery without bone graft replacement than the patients without drinking habits. We adjusted for possible factors; however, the AOR was still 0.32 ($p=0.028$); drinking habit may be associated with wound healing after tooth extraction. In 2020 Brian et al. [44] reported that compared with no alcohol consumption, mild and moderate consumption was associated with 47% ($p<0.0223$) and a 75% ($p<0.0250$) decreases in peri-implantitis. Moreover, high alcohol consumption was associated with a nearly threefold increase in peri-implantitis ($p<0.0001$). A 2022 study also reported that mild alcohol consumption was associated with a decrease in late dental implant failures, and high alcohol consumption was associated with an increase in late dental implant failure [45]. Most alcoholic beverages used in this study are consumed socially (95.3%) and, therefore, come under mild alcohol consumption.

In our study, the average age of the drinking group was 51.32 ± 10.52 years, while the non-drinking group had an average age of 53.99 ± 10.6 years. Although the drinking group was younger, there were no statistically significant differences between the damaged socket group and the intact socket group ($p=0.605$ and $p=0.879$). Previous research [46] has indicated that excessive alcohol consumption beyond a certain threshold can impact the occurrence of periodontal disease due to the dysfunction of immune cells, particularly T cells and neutrophils. In this study, among the 45 individuals in the drinking group, 20 (44.44%) had damaged sockets and 25 (55.56%) had intact sockets. However, since this study only categorized the extracted tooth sockets as either intact or damaged, it does not provide a comprehensive understanding of the relationship between alcohol consumption and periodontitis. However, more randomized controlled studies are required to determine the relationship between alcohol consumption and periodontal treatment response.

The main limitation of this retrospective study is the nonquantification of the remaining bone thickness and defect patterns in the groups. In addition, of 165 sites received, incomplete basic information was available for approximately 15 sites, thereby slightly reducing the sample size in subsequent analyses. While dental CBCT is currently one of the most precise examinations used in implant imaging, it still only yields a detail visibility of 500 microns, which is 0.5 millimeters [47]. Therefore, in clinical applications, accuracy cannot be expected to

be finer than half a millimeter. Therefore, other factors, such as different materials and methods, associated with socket morphology must be identified in a larger and longer-term clinical trial. Due to the broad categorization of anatomical factors, materials used, and patient-related factors in this study, future research will focus on a more detailed classification of these items.

In the future interpretation of CBCT, in addition to numerical measurements, such as width at different sub-crestal levels, bone quality data should be considered for the accurate prediction of surgery complexity. Moreover, the correlation between alcohol consumption and periodontal healing should be evaluated in our follow-up research. Bone quality (not bone width) on CBCT images, alcohol consumption, tooth position, and periodontitis-related tooth extraction affect the complexity of dental implant surgery.

Conclusion

No differences in the bone width were detected between the damaged and intact sockets, however in subsequent implant reconstructive surgery, different regenerative requirements were observed in the damaged and intact sockets. There is a gap between the bone width on CBCT images and the complexity of implant surgery. The mandibular teeth and drinking habit were associated with less requirement for regeneration during dental implant surgery, and the teeth extracted due to periodontitis exhibited 3.02 times higher requirement for implant bone regeneration than did fracture or irreparable teeth. Therefore, alcohol consumption, tooth position, and periodontitis-related tooth extraction affect the complexity of dental implant surgery rather than the bone width on CBCT images.

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Author contributions

All authors contributed to the study conception and design. Conceptualization, K.-F.H. and Y.-H. C.; resources, C.-C.L.; methodology, P.-F.L.; software, C.-C.L.; formal analysis, K.-F. H. and Y.-H. C.; validation, P.-S. H. and C.-J.T.; data curation, K.-F. H. and Y.-H. C.; supervision, P.-F.L. and C.-J.T.; writing—original draft, K.-F. H.; writing—review and editing, Y.-H. C. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due patients' privacy but are available from the corresponding author on reasonable request.

Declarations**Ethical approval**

The study protocol was approved by the Institutional Review Board of the Kaohsiung Medical University Hospital, Taiwan (KMUHIRB-E[1]-20210023). All methods were carried out in accordance with relevant guidelines and regulations. Due to the retrospective nature of the study, Institutional Review Board of the Kaohsiung Medical University Hospital, Taiwan has waived need for informed consent.

Human ethics and consent to participate declarations

Not applicable.

Permission to reproduce material from other sources

Not applicable.

Competing interests

The authors declare no competing interests.

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