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Efficacy of different forms of concentrated growth factors combined with deproteinized bovine bone minerals in guided bone regeneration: a randomized clinical trial

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Abstract

Objectives To explore the bone regeneration effect of different forms of concentrated growth factor (CGF) when combined with deproteinized bovine bone mineral (DBBM) for simultaneous implant-guided bone regeneration (GBR) and its impact on postoperative adverse reactions.

Methods Fifty-seven patients who underwent simultaneous implant GBR were selected for the study and divided into three groups. The study involved three groups: the gel phase concentrated growth factor (GPCGF) group, which used GPCGF-DBBM mixture; the liquid phase concentrated growth factor (LPCGF) group, which used LPCGF-DBBM mixture; and the control group, which used DBBM alone. The thickness of the buccal lateral bones was measured using cone beam computed tomography (CBCT), and patients were asked to complete questionnaires to assess primary adverse reactions during the first week after surgery. The data were analyzed using one-way ANOVA, Tukey test, and Kruskal-Wallis test.

Results The buccal lateral bone thickness in the GPCGF, LPCGF, and control groups decreased significantly at 6 months post-surgery compared to immediately after surgery. The change of bone thickness in the GPCGF group was lower than that in the control group ($p < 0.01$), and that in the LPCGF group did not differ from that in the control group ($p > 0.05$). During the postoperative week, statistically significant differences could be observed in bleeding, mouth opening, chewing, sleeping, speaking, daily routine, and pain ($p < 0.05$).

Conclusions Compared to the DBBM applied alone, the GPCGF-DBBM mixture has more positive implications for reducing bone resorption, promoting bone reconstruction and relieving certain postoperative adverse effects in dental implants with simultaneous GBR. The GPCGF-DBBM mixture was superior to the LPCGF-DBBM mixture in alleviating adverse effects in terms of bleeding and speaking after GBR.

Clinical trials registration number The Chinese Clinical Trial Registry, NO. ChiCTR2300070107 (03/04/2023).

Keywords Concentrated growth factors, Dental implants, Guided bone regeneration, Postoperative adverse reaction

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Introduction

Guided bone regeneration (GBR) is a common method for the repair of peri-implant bone defects [1] and offers the advantages of good bone formation predictability, a low long-term bone resorption rate, convenient filling and shaping, no secondary region, and few surgical complications when used for the restoration of damaged regions [2]. GBR uses granular graft material and barrier membrane and has become the standard procedure that has enabled sustained clinical success [3]. Various bone transplant materials are currently available, including autologous, allogeneic, and xenograft materials. One of the most popular xenografts is deproteinized bovine bone mineral (DBBM). DBBM is a xenograft derived from species genetically unrelated to the host. Due to the high temperature, the organic components in DBBM are removed, so the ideal biocompatibility can be achieved. Additionally, the crystal structure of DBBM closely resembles that of human cancellous bone, providing an excellent scaffold for new bone formation [4]. Compared to autologous bone grafts, DBBM minimizes surgical trauma, eliminates the need for a secondary surgical site, and reduces postoperative complications [5]. However, DBBM has certain limitations. For example, DBBM does not initiate new bone regeneration by itself and cannot synchronize with the osteogenic rate [6, 7].

Growth factors are pivotal in tissue regeneration and reconstruction [8]. Some research has shown that adding biological promoters containing the necessary growth factors to the graft material can accelerate tissue regeneration and improve the osteoinductive bone remodeling process [9–13]. As a third-generation platelet concentrate [14, 15], concentrate growth factor (CGF) includes a variety of growth factors, such as platelet-derived growth factors (PDGFs), transforming growth factor (TGF) b1 and b2, fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGFs), and insulin-like growth factors (IGFs), which have a positive role in promoting cell proliferation, matrix remodeling, and angiogenesis [16, 17]. In addition, they are widely used in oral and maxillofacial surgery procedures to promote tissue regeneration and repair owing to their convenient collection methods and risk-free clinical application [18].

CGFs exist in different forms, and were classified into two categories based on their state of existence: gel-phase concentrated growth factor (GPCGF) and liquid-phase concentrated growth factor (LPCGF). At present, GPCGF are used more frequently in the field of hard tissue regeneration, while LPCGF have been used in wound healing, periodontal tissue regeneration, and the treatment of temporomandibular joint disorders because of their excellent mobility [19–21]. Platelet concentrate has the potential for use in GBR. Işık [10] et al. concluded that Platelet-rich fibrin (PRF, the second-generation platelet concentrate) with Bovine-derived xenograft could successfully achieve peri-implant bone augmentation. Cheruvu [22] et al. found that PRF membranes could enhance peri-implant soft tissue healing. Xie [12] et al. found that CGF combined with bone powder particles could promote peri-implant bone regeneration compared to traditional GBR. However, investigations of the osteogenic effect of the combination of CGF and DBBM in implant placement and simultaneous GBR need to be supported by more research, and the research focused on the osteogenic effect of different forms of CGF is even more lacking.

Most patients are more concerned about short-term postoperative adverse events. However, most of the studies have focused on objective indicators such as reconstruction and healing of the defective tissue [23, 24] and have neglected to document and investigate patients' postoperative adverse reactions. This study also focused on the effect of different bone graft materials on the occurrence of postoperative adverse reactions in patients.

The objective of the present study was to explore the bone regeneration effect of various forms of concentrated growth factor (GPCGF/LPCGF) when used in combination with DBBM for implant placement and simultaneous GBR and their impact on postoperative adverse reactions. The null hypotheses were that LPCGF would have the ability to promote the formation of new bone and to relieve postoperative adverse effects better than GPCGF.

Methods

Study design

The study was designed as a parallel single-blinded randomized controlled clinical trial and was performed in accordance with the guiding principles of the Declaration of Helsinki revised in 2013 and was ethically approved by the committee of Affiliated Stomatological Hospital of Chongqing Medical University (No.2020-003). The study was registered with the Chinese Clinical Trial Registry (ChiCTR2300070107).

Power calculation

G*power3.1.9.7(University of Düsseldorf, Düsseldorf, Germany) was used to calculate the sample size. For the power analysis, the primary outcome was the buccal lateral bone thickness variation from the immediate postoperative period to 6 months postoperatively. Based on the preliminary experiment results, an effect size of 0.45 was obtained. The significance level was set at 0.05, and the power (1-β) at 0.8. The sample size was calculated to be 51. Taking into account a 10% loss to follow-up rate, we increased the sample size to 57 (19 per group).

Eligibility criteria

Fifty-seven patients with bone defects who were admitted to the Affiliated Stomatological Hospital of Chongqing Medical University between April 2023 and July 2023 were recruited for the study.

The inclusion criteria were as follows:

(1) Aged > 18 years.
(2) Teeth were removed at least 3 months before surgery.
(3) A single anterior tooth or premolar is missing, accompanied by a horizontal bone defect suitable for concurrent GBR for implantation, with a residual alveolar bone width>4 mm and ≤ 5 mm [10, 25].
(4) No systemic disease that could affect bone healing or render the patient unsuitable for dental surgery.
(5) Periodontal health.

The exclusion criteria were as follows:

(1) Inability to understand the experimental content or withdrawal in the middle of the experiment.
(2) Local or systemic contraindications for implant surgery.
(3) Severe periodontitis or poor oral hygiene.
(4) Heavy smokers (≥ 10 cigarettes per day).

An informed consent form was signed by each included patient for participation in the study.

Randomization and allocation concealment

Simple randomized grouping was adopted in the present study. The patients were grouped by computer-generated random numbers and the grouping information was hidden in sealed envelopes. The envelopes were opened by the operator prior to surgery. Patients were randomly assigned to the control group, GPCGF group, and LPCGF group, with 19 individuals in each group. The control, GPCGF and LPCGF groups were subjected to GBR using DBBM, GPCGF-DBBM mixture and LPCGF-DBBM mixture, respectively. Individuals who were unfamiliar with the trial served as outcome evaluators, data monitors, and statistical analysts.

GPCGF/LPCGF preparation

Of venous blood, 9 mL was drawn into sterile vacuum centrifuge tubes of two types (Greiner Bio-One, GmbH, Kremsmünster, Austria): one with serum clot activator (red centrifuge tube, 454092) for gelatinous GPCGF, and the other with no additive (white centrifuge tube, 4550001) for LPCGF. The samples underwent immediate centrifugation (Medifuge, Silfradenstr, S. Sofia, Italy) following a variable-speed centrifugation procedure: 30 s at 2700 rpm, 2 mins at 2400 rpm, 4 mins at 3000 rpm, and finally, 36 s of deceleration to complete the separation, with a total centrifugation duration of 12 mins [26].

After centrifugation of the red tube, three distinct layers were observed: the erythrocyte layer, the GPCGF layer, and the serum layer. The second GPCGF layer was extracted using sterile scissors to obtain the gelatinous GPCGF. The centrifugation of the white tube resulted in three separate layers: the erythrocyte layer, the LPCGF layer, and the platelet-poor plasma layer. The LPCGF were collected in a 5 ml disposable sterile syringe [26].

Following the manufacturer's instructions, the GPCGF was pressed into a membrane and cut into small particles. The GPCGF was mixed with 0.25 g of DBBM (Bio-Oss, Geistlich Pharma AG, Wolhusen, Switzerland) and then placed in a blender (Roundup, Silfradenstsr, S. Sofia, Italy) for 15 s to obtain sticky bone which is the GPCGF-DBBM mixture. Mixing the LPCGF with 0.25 g of DBBM to obtain the sticky bone which is the LPCGF-DBBM mixture. (Fig. 1)

Surgical procedure

The surgeries were performed by experienced clinicians who were qualified for implant bone augmentation surgery. The surgeries were performed at the Affiliated Stomatological Hospital of Chongqing Medical University. Prior to surgery, patients gargled using 0.12% chlorhexidine for 1 min, and routine disinfection of the face was performed. 4%Articaine with 1/100,000 epinephrine was used for local anesthesia during the procedure. A mucoperiosteal triangular flap was elevated at the surgical site and extended to both adjacent teeth. Under digital guidance, the implant sites were prepared in the surgical area and implant placement was completed according to the instructions of the manufacturers. Implants were inserted while maintaining a minimum thickness of 1 mm for the lingual cervical bone and were placed in a prosthetically desirable position. Intraoperatively, dehiscence of the lateral labial bone due to the presence of a horizontal bone defect was observed, which resulted in exposure to the implant.

An overlay screw was attached to the implant. In order to increase the blood supply to the area of bone regeneration, a round drill was used to drill holes in the bone cortical on the buccal side of the implant area.

The sticky bone (DBBM, GPCGF-DBBM mixture or LPCGF-DBBM mixture) was applied to the bone deficiency, which raised the buccal lateral bone thickness by at least 2 mm [27]. The bone deficiency was subsequently covered with collagen membrane (Bio-Gide, Geistlich Pharma AG, Wolhusen, Switzerland) and finally sutured. (Fig. 2).

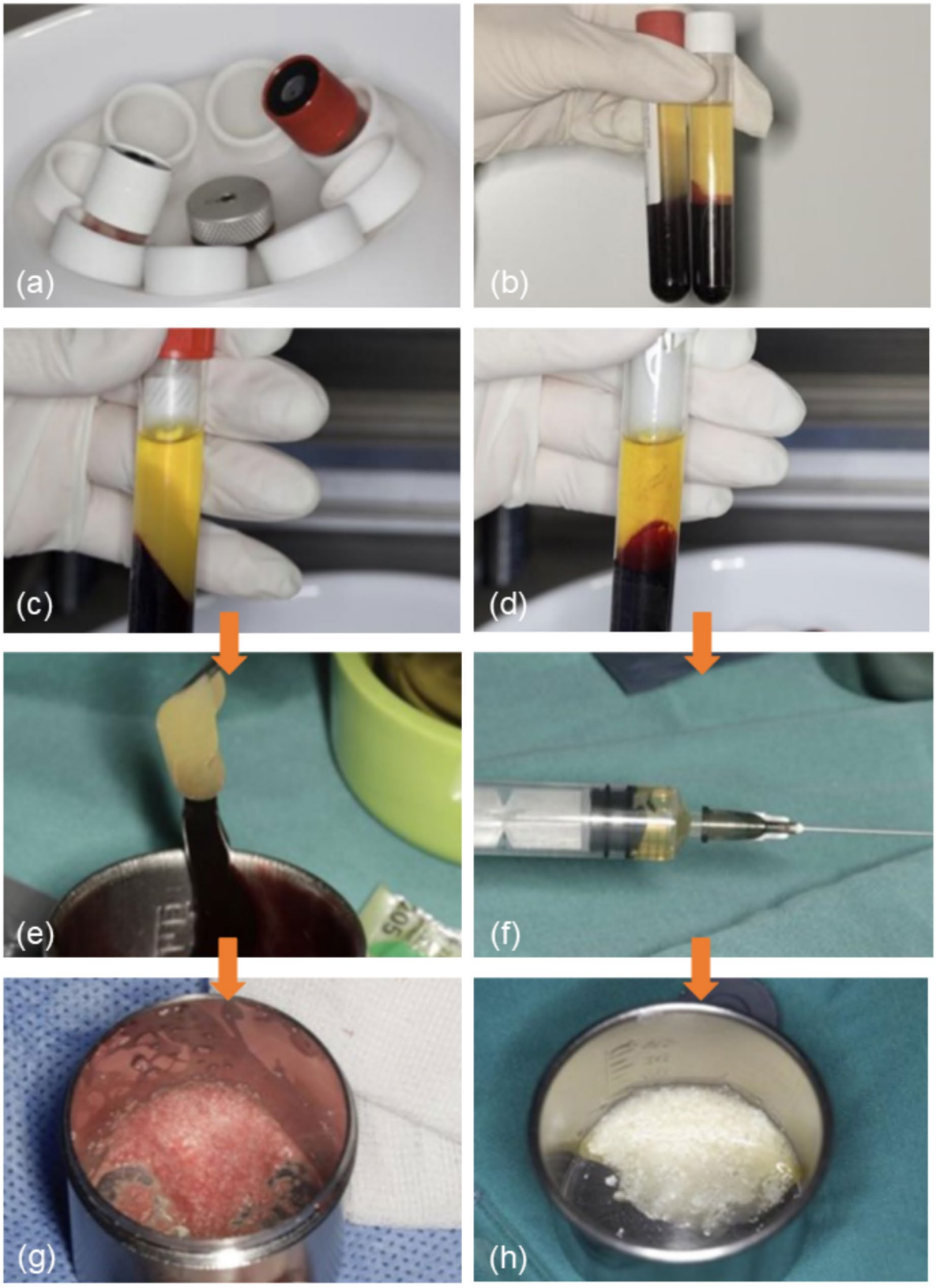

Fig. 1 Preparation of GPCGF-DBBM mixture and LPCGF-DBBM mixture. (**a**) CGF centrifuge equipment. (**b**) After centrifugation. (**c**) The red tube after centrifugation. (**d**) The white tube after centrifugation. (**e**) The product of the red tube: GPCGF. (**f**) The product of the white tube: LPCGF. (**g**) GPCGF-DBBM mixture. (**h**) LPCGF-DBBM mixture

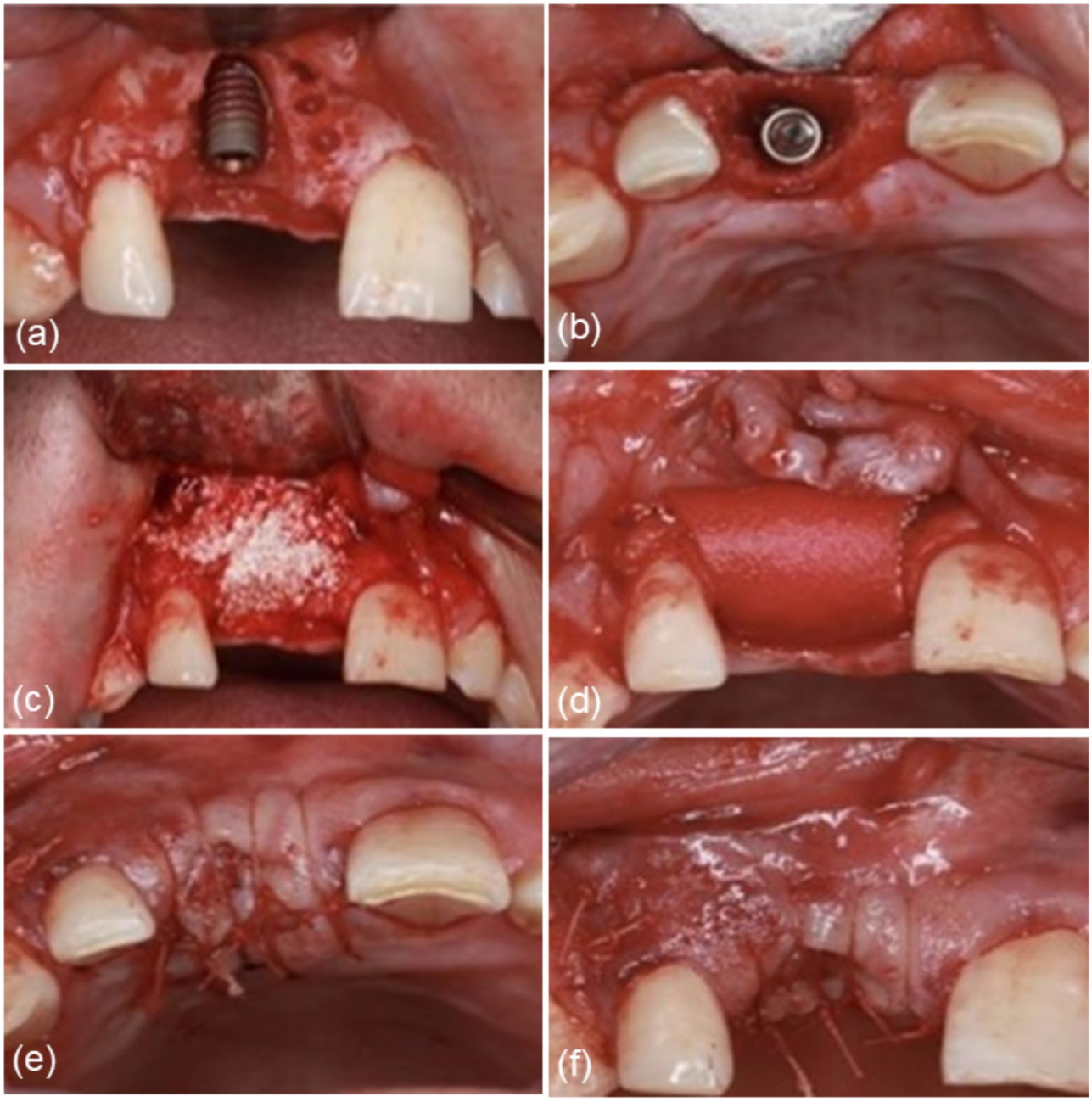

Fig. 2 Surgical procedure. (**a**-**c**) Filled the bone graft material in the bone defected region. (**d**) Trimmed the collagen membrane to a size matching of the defect region. (**e**-**f**) Using absorbable front sutures firmly sutured

Outcome measures

CBCT (Kavo-3D-eXam High-Quality CBCT, Kavo, USA; 80 mA, 80 kVp, and 8.9-s scan time) was performed under the same predicted conditions immediately postoperative and 6 months postoperatively. All CBCT scans were performed by senior radiologists on the same machine. Imaging analysis was performed using the 3D image software (KaVo 3D eXam Vision, Kavo, USA). The same anatomical structure and implant structure were used as reference points during measurement to match images immediately after surgery and 6 months after surgery [10]. Three horizontal lines were generated perpendicular to the central axis of the implant. Buccal lateral bone thickness was measured at three different levels, which were 2 mm (L1), 4 mm (L2), and 6 mm (L3) apical to the implant shoulder at immediately postoperative and at 6 months postoperatively on CBCTs [10, 27]. The same trained and experienced researcher performed all measurements, and the measurements were repeated 3 times at all sites and averaged. (Fig. 3)

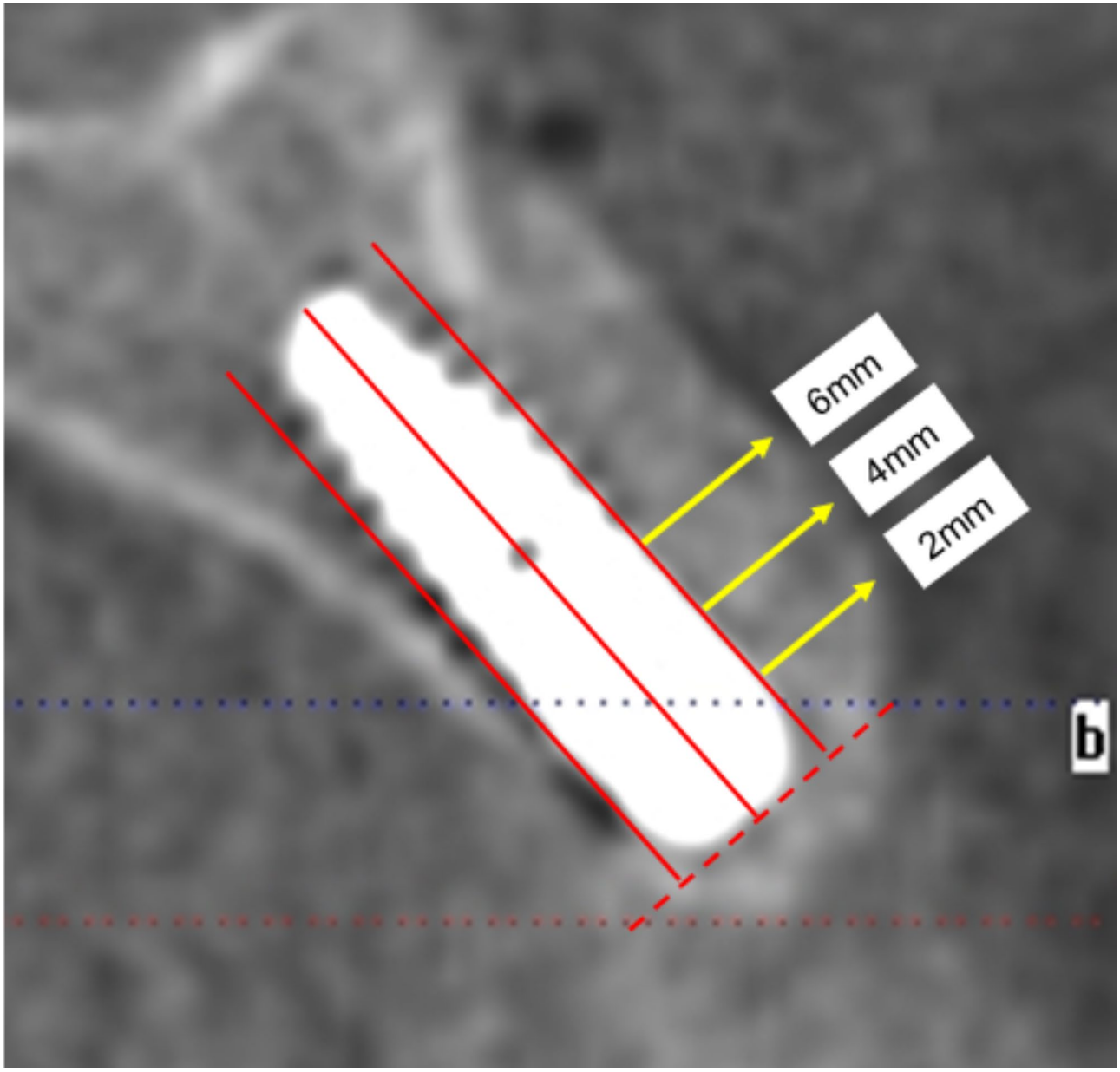

Fig. 3 Measurement of buccal lateral bone thickness at three different levels. Measurement of buccal lateral bone thickness at three different levels: 2, 4, and 6 mm apical to the implant shoulder

The sutures were removed during a one-week follow-up visit after surgery to evaluate healing. Each day during the first postoperative week, the patients completed questionnaires, which were subsequently used for assessing postoperative limitations. The data on the postoperative limitations of mouth opening, swelling, chewing, speaking, sleeping, daily routines and bleeding were provided by the patients through questionnaires [28]. Postoperative adverse effects were measured by the five-point numerical rating scales (NRS), in which 0 indicated 'not at all' and 4 indicated 'very', with the severity increasing from 1 to 4. The patients were then asked whether they had used any painkillers every day after the surgery. Finally, visual analog scale (VAS) scores were used to measure oral pain [29].

Statistical analyses

IBM SPSS statistics 22.0 (IBM Corp., New York, USA) was used to conduct the statistical analysis of the resulting data. The differences among groups were analyzed by one-way ANOVA, and post hoc tests were analyzed using the Tukey test. The NRS scores and VAS scores for postoperative adverse effects were not normally distributed, so they were analyzed using the Kruskal-Wallis test. The

means, standard deviations (SD), and 95% confidence intervals (95% CI) of the data are reported. All the data were summarized using descriptive statistics, and $p < 0.05$ was used as the threshold for statistical significance.

Results

Research population

Fifty-seven patients were recruited for the trial, all of whom participated throughout the trial. 19 were treated with conventional DBBM, 19 with GPCGF + DBBM, and 19 with LPCGF + DBBM, and all patients were evaluated by CBCT after implant placement as well as 6 months after implantation. Figure 4 shows CBCT images of three patients, one patient treated with DBBM, one patient treated with GPCGF + DBBM, and one patient treated with LPCGF + DBBM. This study is reported according to the CONSORT guidelines, and Fig. 5 provides a CONSORT flowchart illustrating the study design.

The present trial included 57 patients (29 males and 28 females, age range 19–76 years, mean age 44.6 ± 14.4 years). No statistically significant differences were observed in the general statistics for sex, age, implant site, or different implant brands among the three groups ($p > 0.05$, Table 1). In all 57 GBR procedures (57 implants in total), each implant was radiologically confirmed to have healed uneventfully.

Buccal lateral bone thickness

In the immediate postoperative period, the buccal lateral bone thickness (mean ± SD) at the three measurement levels were 3.41 ± 0.66 mm(L1), 3.74 ± 0.79 mm(L2), and 3.77 ± 0.87 mm(L3) in the control group; 2.95 ± 0.72 mm(L1), 3.13 ± 0.89 mm(L2) and 3.23 ± 0.93 mm(L3) in the GPCGF group; and 3.24 ± 0.76 mm(L1), 3.58 ± 0.87 mm(L2) and 3.79 ± 1.02 mm(L3) in the LPCGF group, without any significant difference between the buccal lateral bone thickness of the three groups ($p > 0.05$) (Table 2).

The period immediately after surgery, the buccal lateral bone thickness in the GPCGF group, the LPCGF group, and the control group decreased to different degrees at 6 months after surgery. In the control group, the changes(mean ± SD) were 0.98 ± 0.39 mm(ΔL1), 0.87 ± 0.43 mm(ΔL2) and 0.78 ± 0.51 mm(ΔL3); in the

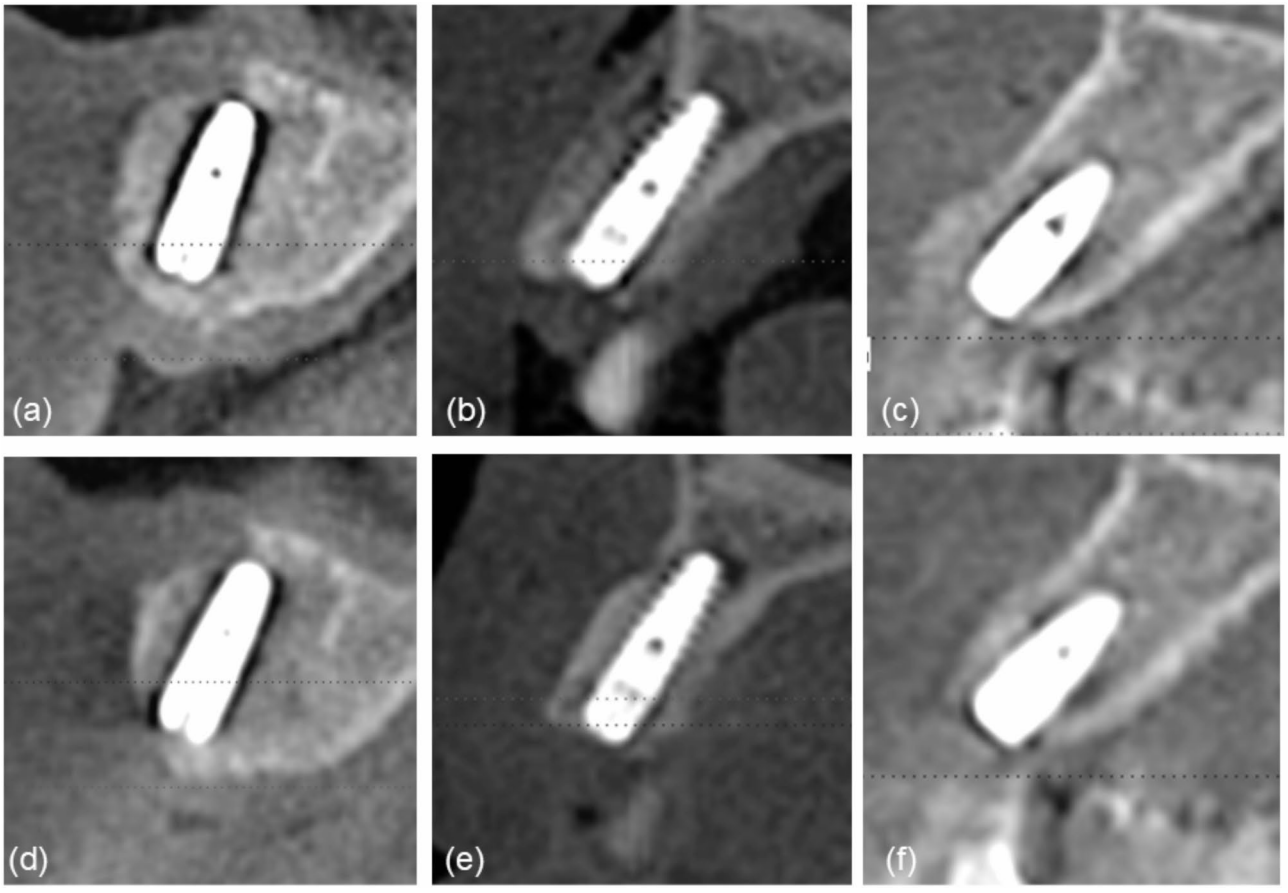

Fig. 4 CBCT images of the three patients above the immediate postoperative CBCT image and below the 6-month postoperative CBCT image. (**a**-**c**) CBCT images of the immediate postoperative period in the control, GPCGF, and LPCGF groups, respectively. (**d**-**f**) CBCT images at 6 months postoperatively in the control, GPCGF, and LPCGF groups, respectively

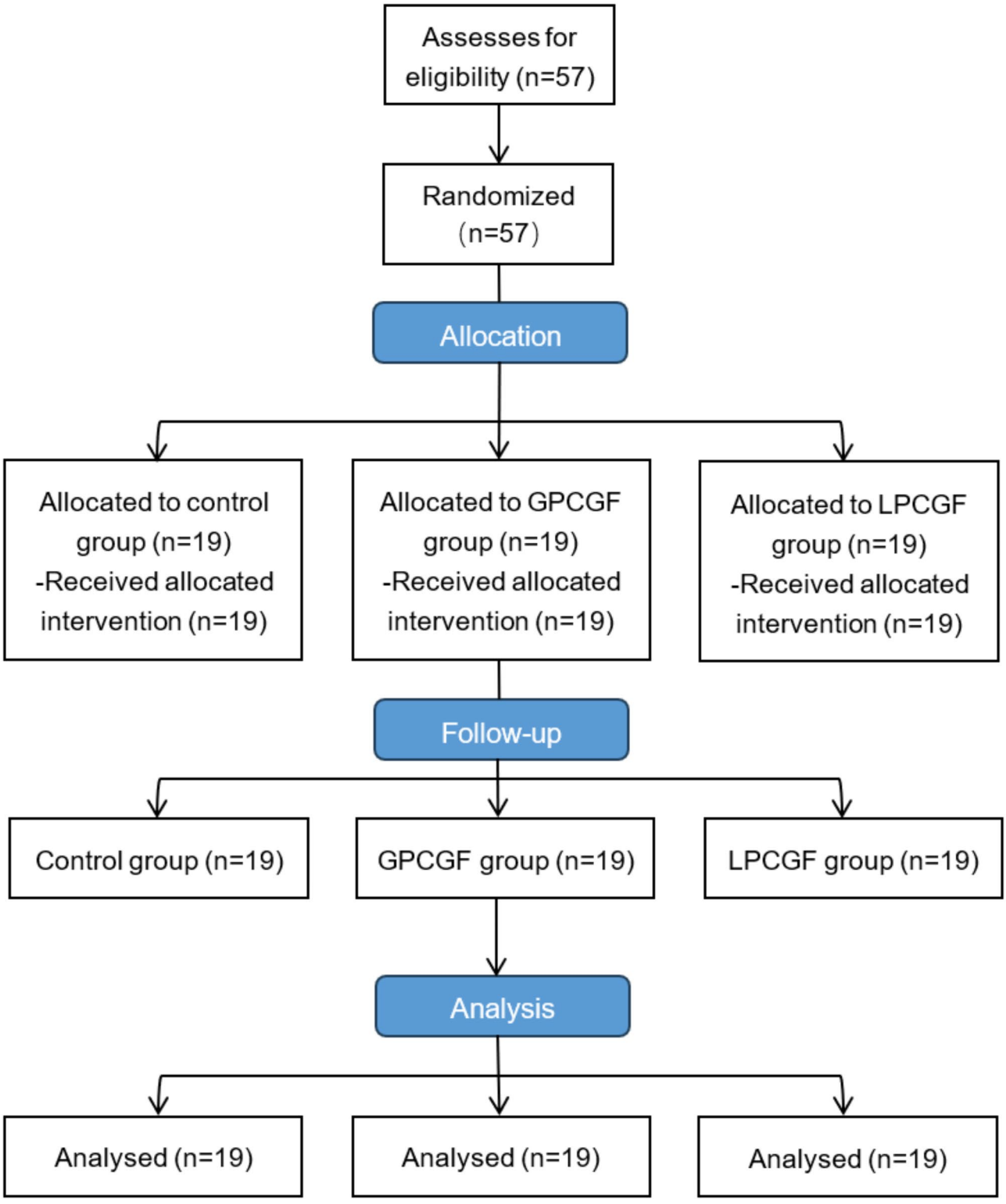

Fig. 5 Consort flow diagram

Table 1 Patient clinical and demographic characteristics

Variable	Control $n=19$ n(%)	GPCGF $n=19$	LPCGF $n=19$	Total $n=57$	p-value[a]
Sex					
Male	11(58.9)	11(58.9)	7(36.8)	29(50.9)	0.325
Female	8(42.1)	8(42.1)	12(63.2)	28(49.1)	
Age (mean ± SD)	45.3 ± 11.5	41.2 ± 15.0	47.2 ± 16.3	44.6 ± 14.4	0.431
Implant site					
Anterior teeth	16(84.2)	13(68.4)	15(78.9)	44(77.2)	0.498
Premolars	3(15.8)	6(31.6)	4(21.1)	13(22.8)	
Implant brand					
OSSTEM	3(15.8)	4(21.1)	6(31.6)	13(22.8)	0.229
Straumann	5(26.3)	10(52.6)	7(36.8)	22(38.6)	
Anthogyr	11(57.9)	5(26.3)	6(31.6)	22(28.6)	

a: One-way ANOVA for age; chi-square test for sex, implant site, and implant brand

Table 2 Buccal lateral bone thickness immediately after surgery involving GBR and 6 months after surgery in the three groups (mean ± standard deviation)

	Control		GPCGF		LPCGF		p-value			
	Immediate (a)	6 months (b)	Immediate (c)	6 months (d)	Immediate (e)	6 months (f)	(a) vs. (b) [a]	(c) vs. (d) [a]	(e) vs. (f) [a]	(a)vs (c)vs (e) [b]
L1	3.41 ± 0.66	2.43 ± 0.76	2.95 ± 0.72	2.49 ± 0.80	3.24 ± 0.76	2.50 ± 1.05	<0.001	<0.001	<0.001	0.139
L2	3.74 ± 0.79	2.87 ± 0.87	3.13 ± 0.89	2.74 ± 0.91	3.58 ± 0.87	2.98 ± 1.23	<0.001	<0.001	<0.001	0.085
L3	3.77 ± 0.87	2.99 ± 1.03	3.23 ± 0.93	2.97 ± 1.05	3.79 ± 1.02	3.34 ± 1.13	<0.001	0.011	<0.001	0.126

a: Paired samples t-test; b: One-way ANOVA

GPCGF group, the changes were 0.45 ± 0.28 mm(ΔL1), 0.39 ± 0.32 mm(ΔL2), and 0.27 ± 0.41 mm(ΔL3); and in the LPCGF group, the changes were 0.74 ± 0.51 mm(ΔL1), 0.60 ± 0.64 mm(ΔL2), and 0.50 ± 0.50 mm(ΔL3). The results of one-way ANOVA showed that the change reached a level of statistical significance in all three groups (ΔL1: $p<0.001$; ΔL2: $p=0.013$; ΔL3: $p=0.004$) (Fig. 6).

Based on the results of the Tukey test, compared to those in the control group, the changes in buccal lateral bone thickness at 6 months postoperatively were smaller in the GPCGF group (ΔL1: $p<0.001$; ΔL2: $p=0.009$; ΔL3: $p=0.003$), while no statistically significant difference existed between the LPCGF and control groups ($p>0.05$). Furthermore, no significant difference in the change in buccal lateral bone thickness was observed between the GPCGF group and the LPCGF group. (Fig. 6)

Postoperative adverse effects

The data presented in Fig. 7 revealed that within one week after surgery, statistically significant differences could be observed in restricted bleeding, mouth opening, chewing, sleeping speaking, daily routine, and pain ($p<0.05$). In terms of postoperative pain, the patients in the GPCGF group exhibited lower pain scores than those in the control group on days 0–4 (day0: $p=0.004$; day1: $p=0.004$; day2: $p=0.019$; day3: $p=0.004$; day4: $p=0.024$.) (Fig. 7-a) In terms of postoperative bleeding, the GPCGF group had significantly lower NRS scores than the control group on days 2–6 (day2: $p=0.017$; day3: $p=0.008$; day4: $p=0.007$; day5: $p=0.021$; day6: $p=0.043$), whereas the LPCGF group showed a significant difference from the control group on day 5 ($p=0.005$). The GPCGF group exhibited a lower bleeding NRS score than LPCGF group on day 5 ($p<0.001$). (Fig. 7-b) In terms of speaking, the adverse effects in the GPCGF group were less pronounced than those in the control group on days 0, 1, 3, 4, 5, and 6 (day0: $p=0.006$; day1: $p=0.027$; day3: $p=0.034$; day4: $p=0.008$; day5: $p=0.028$; day6: $p=0.005$), and the GPCGF group outperformed the LPCGF group in speaking ability on day 5 ($p=0.039$). (Fig. 7-c) Compared with the control group, the GPCGF group showed milder restrictions on mouth opening on days 4 and 5 (day4: $p=0.029$; day5: $p=0.044$), and the LPCGF group showed milder restrictions on mouth opening on day 5 ($p=0.044$). (Fig. 7-d) The GPCGF group experienced less chewing discomfort than did the control group from days 4–6 (day4: $p=0.021$; day5: $p=0.039$; day6: $p=0.037$). (Fig. 7-e) The GPCGF group exhibited reduced sleep impacts on days 0 and 4 (day0: $p=0.030$; day4: $p=0.002$) (Fig. 7-f) and the GPCGF group demonstrated a statistically notable variance in daily living scores solely on day 4 ($p=0.028$) when contrasted with the control group (Fig. 7-g).

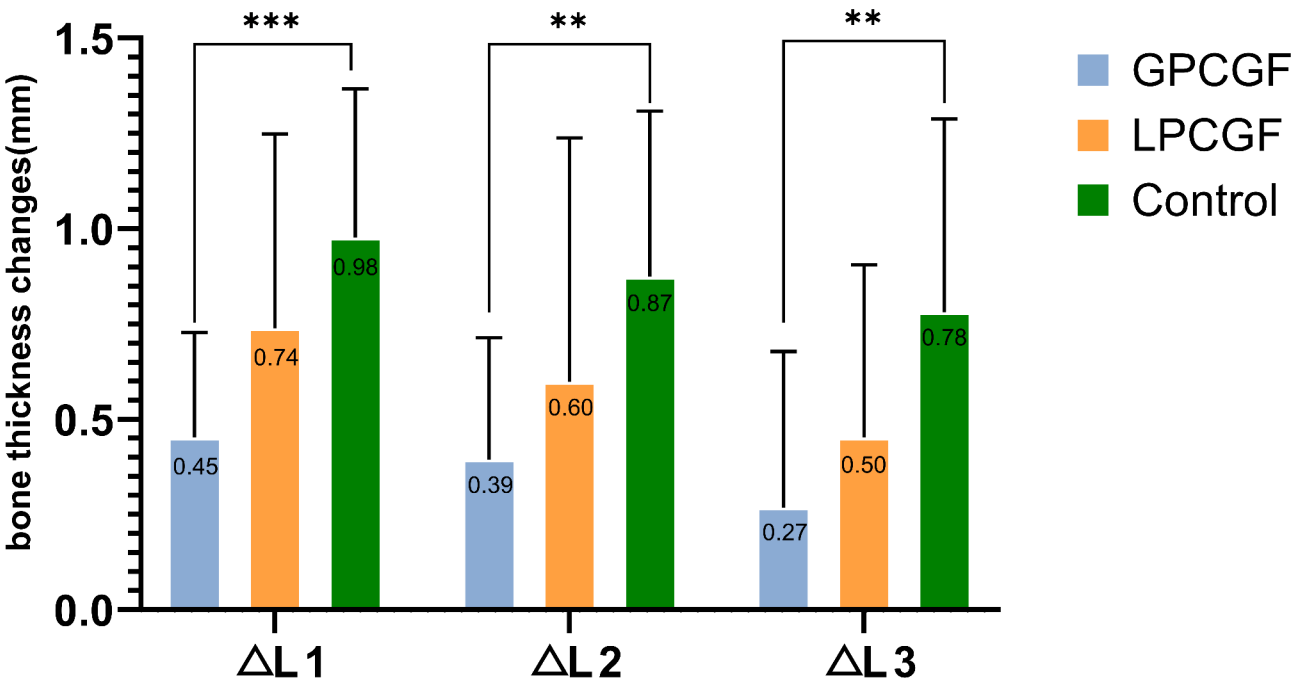

Fig. 6 Buccal lateral bone thickness changes immediately after surgery with GBR and 6 months after surgery in the three groups
Histogram of the results illustrating the mean and standard deviation (SD)
The *p*-value represents the significant difference among the test groups (**Significant at the 1% level, ***Significant at the 0.1% level)

Discussion

This study explored the clinical outcomes of various forms of concentrated growth factors when used in combination with DBBM for simultaneous implant-guided bone regeneration and their impact on postoperative adverse reactions. Compared with DBBM applied alone, GPCGF combined with DBBM as a bone grafting material for the implantation of contemporaneous GBR can achieve better bone regeneration results. In addition, the use of CGF is effective in reducing adverse reactions in patients after surgery. LPCGF is not as effective as GPCGF in mitigating certain adverse effects (bleeding and speaking). Thus, the null hypothesis of this research was rejected.

DBBM is a commonly used graft material, which is an inorganic component in bovine bone, and the main component is porous hydroxyapatite. Since the porous structure of DBBM is similar to that of human bone, it can provide good support for new bone formation. In addition, the porous structure of DBBM can also provide a large surface area to promote the formation of new blood vessels, thereby promoting osteogenesis [5]. DBBM can not only reduce patient trauma and simplify surgical procedures, but also achieve the osteogenic effect that is close to or even better than autogenous bone transplantation [30] and is widely used in GBR, maxillary sinus lifting, and alveolar ridge preservation [31]. On the premise of retaining the original advantages of DBBM, the mixture of CGF and DBBM adds growth factors that promote cell proliferation differentiation and angiogenesis, and its osteogenic effect has also been confirmed by a large number of studies [32].

Our study showed that at 6 months postoperatively, the amount of change in buccal lateral bone thickness was less in the GPCGF group than in the control group. Currently, GPCGF is the most widely used form of CGF, and most CGF studies have focused on GPCGF. With regard to bone tissue regeneration, our findings closely agreed with those of Dai et al. [33], who demonstrated that GPCGF has a positive role in promoting bone defect repair in implant-contemporaneous GBR. Although there are few studies on the application of GPCGF in contemporary GBR implantation, several studies have confirmed its potential to enhance bone tissue regeneration in dentistry. In alveolar preservation, the use of GPCGF helps preserve the horizontal width and height of the alveolar ridge while stimulating new bone growth [34, 35]. Ghasemirad et al. [36] utilized GPCGF for maxillary sinus floor augmentation surgery and observed a greater osteogenesis rate in the GPCGF group than in the control group at 6 months post-surgery.

The potential of CGFs to promote bone regeneration involves fibrin networks containing platelets, leukocytes, and growth factors. Fibroblasts are involved in angiogenesis and tissue remodeling, while endothelial cells provide the matrix for cell migration. Platelets are particularly significant because they produce large amounts of bioactive proteins that promote cell morphogenesis, growth,

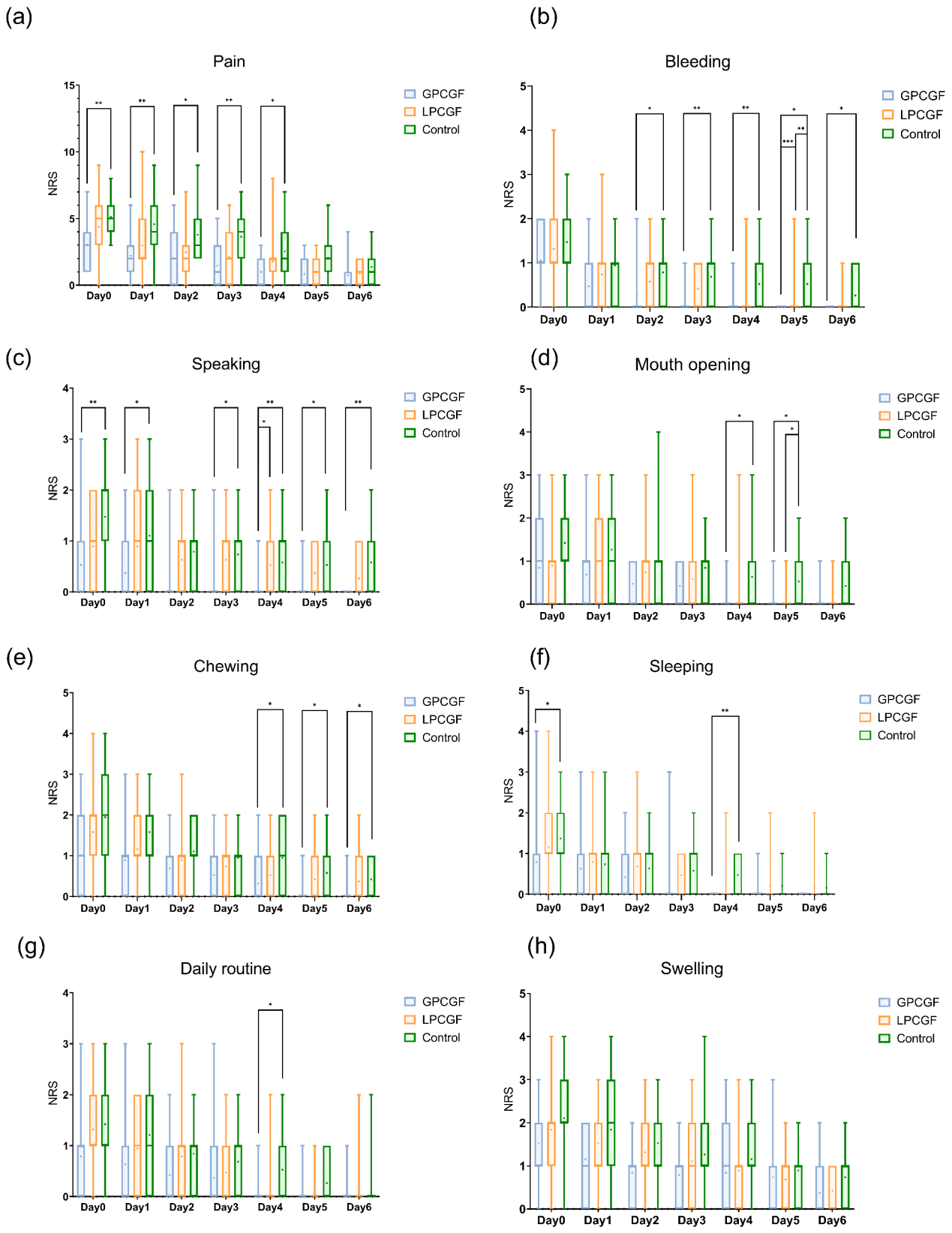

Fig. 7 The adverse reactions in the three groups at 7 days after surgery
Box plots of the results illustrating the median, quartile, min, and max
The *p*-value represents the significant difference among the test groups (*Significant at the 5% level, **Significant at the 1% level, ***Significant at the 0.1% level)

and recruitment [37, 38]. According to previous studies, CGF contains CD34-positive cells, as well as TGF-β1 and VEGF, and these growth factors exert favorable effects on blood vessel maintenance, neovascularization, and anti-adhesive angiogenesis [39]. In addition, these factors stimulate the differentiation of mesenchymal stem cells into osteogenic cells, promote cell proliferation and migration, prevent bone resorption, and accelerate bone tissue repair through the regulation of gene expression [14, 38].

In preparing LPCGF, we opted for white centrifuge tubes without any additional ingredients instead of the green tubes recommended, which contained sodium heparin. We were concerned that this component could hinder the osteogenic effect. Before this study, we hypothesized that LPCGF with a liquid morphology and without any additional ingredients could eliminate other extraneous components and establish a more uniform and effective connection with BMMD, thereby enhancing osteogenesis. Although the osteogenic effect of the LPCGF group was not statistically different from the control group, it is shown by our findings that the mean resorption of buccal bone thickness in the LPCGF group was less than that in the control group in the postoperative period, and we hypothesized that there was some osteogenic effect of the LPCGF, but it was just not as pronounced as that of the GPCGF, so much so as to fail to produce a statistically significant difference.

LPCGF did not play a sufficiently active role in bone regeneration in the implantation of contemporaneous GBR as GPCGF for the following possible reasons. The osteogenic mechanism of GPCGF is that various growth factors contained in GPCGF can promote the proliferation of fibroblasts, osteoblasts and endothelial cells, stimulate the production of extracellular matrix (such as collagen and elastin), and promote the regression of inflammation, inhibit excessive inflammation, and create a positive environment for tissue regeneration [32]. VEGF and other growth factors play an active role in stimulating new angiogenesis [40]. Although LPCGF also contains growth factors that promote tissue regeneration, such as TGF-β and VEGF [41], the levels of growth factors in LPCGF may be lower than those of GPCGF [19]. Ma et al. [19] pointed out that compared with LPCGF, GPCGF can more effectively enhance the proliferation and migration of bone marrow mesenchymal stem cells, and also has better osteogenic induction activity and stability. In addition, the main difference between GPCGF and LPCGF in the preparation process is that GPCGF uses centrifuge tubes containing coagulation promoters, while the centrifuge tubes of LPCGF do not use any additives, and the coagulation promoter of the centrifuge tubes of GPCGF used in the present experiments is silica. Silicon is an important trace element in the human body. It promotes bone calcification, increases bone density, and promotes bone growth [42]. Silica nanoparticles are also widely used as drug delivery systems to promote bone regeneration [43, 44]. Although silica was mainly used as a procoagulant coated on the walls of the centrifuge tubes in this experiment, and its content in GPCGF was probably low, it may still play an active role in the promotion of osteogenesis in GPCGF.

Most patients treated with implants experience postoperative adverse reactions [45, 46]. To investigate the kinds of materials that would provide better relief for patients' postoperative discomfort, we used the NRS and the VAS to investigate the adverse reactions of patients at 7 days postoperatively. In the present study, at the beginning of the postoperative week, all patients experienced varying degrees of discomfort and limited activity. The use of GPCGF reduces the postoperative adverse effects of pain, bleeding, speaking, mouth opening, chewing, sleep, and daily routine after surgery for patients. There are few reports on the use of GPCGF to alleviate postoperative adverse effects on simultaneous implant GBR, but some studies using GPCGF in other oral treatments have shown similar results to our study [47, 48]. Lu et al. [49] noted that the application of GPCGF can reduce pain and accelerate healing after mandibular impacted wisdom tooth extraction. Koyuncu et al. [50] also reported that patients in the GPCGF group experienced less postoperative discomfort in the first seven days.

Compared with the control group, the study revealed that GPCGF was more effective in reducing postoperative adverse effects after surgery. This difference primarily to the ability of GPCGF to promote the healing and regeneration of soft tissues at surgical sites [51]. The beneficial effects of GPCGF on mouth opening restriction, mastication, sleep, and daily living were primarily observed between postoperative days 4 and 6. This may be linked to the soft tissue healing process. Days 4–6 are in the angiogenic phase [52], during which the proangiogenic and tissue migration abilities of growth factors in CGF start to increase, leading to improved healing with fewer adverse effects compared to those in the control group. By day 7 post-procedure, only a few patients still experienced mild adverse effects, and the difference in tissue healing was no longer evident through adverse effects.

Compared with the control group, the efficacy of LPCGF in reducing postoperative patient discomfort was demonstrated by bleeding on day 5 and mouth opening on day 5 after surgery. Currently, research on LPCGF has focused primarily on soft tissues. Yu et al. [53] demonstrated the ability of LPCGF to promote the proliferation, migration, and differentiation of human dental pulp cells. Zhan et al. [21] applied LPCGF to the surface of roots affected by periodontitis and found that it promoted

cell attachment, growth, migration, and differentiation. Because of the potential of LPCGF in soft tissue regeneration, it can be hypothesized that LPCGF may be able to promote the healing of gingival tissues and thus achieve relief of adverse postoperative reactions.

Compared with GPCGF, LPCGF has no desirable role in reducing certain postoperative adverse effects(bleeding and speaking), which could be attributed to the following reasons. Firstly, as a result of differences in internal bracket construction, LPCGF has a higher rate of excretion and a worse gradual release rate during the same interval [19]. Furthermore, the fibronectin structure in GPCGF is richer and denser, which may provide an improved scaffold for tissue reconstruction. Secondly, the growth factor content in GPCGF and its ability to promote cell growth and migration were considered superior to LPCGF in some studies [19]. Thirdly, since no obvious boundary between the LPCGF layer and the PPP layer exists, some of the liquid with less growth factor content may be extracted during the extraction of LPCGF, which may lead to the deviation of the growth factor content in LPCGF. Moreover, GPCGF was placed in a special mixer when it was mixed with DBBM, and the content of GPCGF per unit of DBBM could be more uniform and better than that of the artificial mixture of LPCGF. Although more research is needed to explore the prospects for the application of LPCGF in GBR, we believe that GPCGF is more advantageous in this regard.

Our study also has several limitations. Firstly, to honor the preferences of the patients and accommodate the individual alveolar bone conditions of the patients, the brand and size of the implants were not standardized, although this variation was maintained within a specific range. Another limitation was that the study did not include more objective clinical outcomes, such as implant stability. In addition, the conclusions above were only conjectured based on the present study, and although the experiment achieved clinical osseointegration, no histological analysis was conducted to reveal the characteristics of the tissue in contact with the implant. The application of different forms of CGF in other implant surgeries (e.g., internal maxillary sinus lift, external maxillary sinus lift, etc.) also needs to be explored with more experiments. Moreover, a follow-up after implant loading may allow for a more comprehensive evaluation of different treatment options by assessing bone resorption after implant loading.

Conclusions

From randomized clinical trials, we have drawn the following conclusions:

- In promoting bone regeneration after GBR, the GPCGF-DBBM mixture was superior to the DBBM applied alone.
- In relieving certain postoperative symptoms, the CGF-DBBM mixture was superior to the DBBM, in which the GPCGF-DBBM mixture was superior to the LPCGF-DBBM mixture(bleeding and speaking).

Supplementary Information

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Supplementary Material 1

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Author contributions
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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This randomized controlled clinical trial was approved by the ethically committee of Stomatological Hospital of Chongqing Medical University (No.2020-003). This randomized controlled clinical trial was performed in accordance with the guiding principles of the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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