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## Combined use of xenogeneic bone substitute material covered with a native bilayer collagen membrane for alveolar ridge preservation: A randomized controlled clinical trial

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**Abstract:** AIM The aim of this split-mouth randomized controlled study was to evaluate radiographic dimensional changes after tooth extraction in posterior sites treated with a ridge preservation technique or left for spontaneous healing. **MATERIALS AND METHODS** In a total of 18 patients, tooth extraction in posterior sites of the upper and lower jaw was performed in a split-mouth design. The post-extraction sockets were randomly assigned to the following two treatment modalities: deproteinized bovine bone mineral (DBBM) with 10% collagen (DBBM-C) covered with a native bilayer collagen membrane (NBCM) (test group) and spontaneous healing (control group). Cone beam computed tomography (CBCT) scans were performed after extractions, 3 and 6 months later. The following parameters were measured: the height of the buccal bone plate (BH), height of the palatal bone plate (PH), horizontal width of the extraction socket at 1 mm, 3 mm, and 5 mm (HW-1, HW-3, HW-5), and the horizontal width (thickness) of the buccal bone plate at 1 mm, 3 mm, and 5 mm (BHP-1, BHP-3, BHP-5). Statistical analysis was performed applying a nonparametric Wilcoxon signed-rank test. **RESULTS** The CBCT analysis showed a bone loss compared to baseline in test and control group. The measurements which have reached statistically significant differences at 6 months were BH (test: -2.31% vs control: -13.11%), PH (test: -2.07% vs control: -15.32%), HW-1 (test: -17.14% vs control: -32.47%), and HW-3 (test: -11.65% vs control: -28.47%). **CONCLUSIONS** The posterior ridge preservation technique using DBBM-C covered with a NBCM is a valid approach reducing the amount of the radiographic loss in alveolar ridge dimensions.

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**Combined use of xenogeneic bone substitute material covered with a native bilayer collagen membrane for alveolar ridge preservation: A randomized controlled clinical trial**

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Running title: Posterior ridge preservation

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## **Abstract**

**Aim:** the aim of the present split-mouth randomized controlled study was to evaluate radiographic dimensional changes after tooth extraction in posterior sites treated with a ridge preservation technique or left for spontaneous healing. **Materials and Methods:** In a total of 18 patients tooth extraction in posterior sites of the upper and lower jaw was performed in a split-mouth design. The post-extraction sockets were randomly assigned to the following two treatment modalities: deproteinized bovine bone mineral (DBBM) with 10% collagen (DBBM-C) covered with a native bilayer collagen membrane (NBCM) (test group) and spontaneous healing (control group). Cone Beam Computed Tomography (CBCT) scans were performed after extractions, 3 and 6 months later. The following parameters were measured: the height of the buccal bone plate (BH), height of the palatal bone plate (PH), horizontal width of the extraction socket at 1mm, 3mm, and 5mm (HW-1, HW-3, HW-5) and the horizontal width (thickness) of the buccal bone plate at 1mm, 3mm, and 5mm (BHP-1, BHP-3, BHP-5). Statistical analysis was performed applying a nonparametric Wilcoxon signed rank test. **Results:** The CBCT analysis showed a bone loss compared to baseline in test and control group. The measurements which have reached statistically significant differences at 6 months were BH (test: -2.31% vs. control: -13.11%), PH (test: -2.07% vs. control: -15.32%), HW-1 (test: -17.14% vs. control: -32.47%), and HW-3 (test: -11.65% vs. control: -28.47%). **Conclusions:** The posterior ridge preservation technique using DBBM-C covered with a NBCM is a valid approach reducing the amount of the radiographic loss in alveolar ridge dimensions.

## Introduction

After tooth extraction, spontaneous healing process causes bone remodeling and consequently shape and volume loss of the initial socket contour (Cardaropoli *et al.*, 2003; Araujo & Lindhe, 2005; Hämmerle *et al.*, 2012; Araújo *et al.*, 2015b) The remodeling process starts immediately after tooth extraction, and after 2 years an average of 40–60% bone loss is detected in vertical and horizontal dimensions (Johnson, 1969; Tan *et al.*, 2012). This amount of bone resorption in the alveolar process may interfere with the placement of dental implants.

Alveolar ridge preservation technique (ARP) has been proposed to reduce the bone resorption after tooth extraction (Darby *et al.*, 2009; MacBeth *et al.*, 2017). Several studies evaluated the ARP technique using different bone graft materials such as autogenous bone (Becker *et al.*, 1994), demineralized freeze-dried bone allograft (Froum *et al.*, 2002), mineralized freeze-dried bone allograft (Feuille *et al.*, 2003), deproteinized bovine bone (Artzi *et al.*, 2000), alloplastic polymers (Serino *et al.*, 2003) and bioactive glasses (Froum *et al.*, 2002). From all these bone graft materials deproteinized bovine bone (DBBM) might be the most often used material for ARP in the past years (Araújo *et al.*, 2015a). In recent randomized clinical trials (RCT), it has been demonstrated that DBBM with 10% collagen for ridge preservation in anterior sites (Jung *et al.*, 2013; Meloni *et al.*, 2015; Araújo *et al.*, 2015b) reduced the radiographic bone resorption.

However, the majority of these clinical studies focus on anterior single rooted teeth, ignoring the posterior region of the jaws, where the location of the maxillary

sinus or mandibular nerve limits the installation of dental implants.

Hence, the aim of the present split-mouth randomized controlled study was to evaluate, through Cone Beam Computed Tomography (CBCT) analysis, the dimensional changes after tooth extraction in posterior sites either treated with a ridge preservation technique or left for spontaneous healing.

## **Materials & Methods**

### Study design

This study is a prospective, randomized, controlled, clinical trial in a split-mouth design according to the Helsinki protocol. All procedures and materials were approved by the ethical committee of Peking University School and Hospital of Stomatology, China (Ref. N<sup>o</sup> PKUSSIRB-2012003). Twenty-four patients that visited the implant center of Peking University School and Hospital of Stomatology were included.

### *Inclusion criteria*

- i) Age: > 18 years;
- ii) Need of symmetric molar or premolar extraction within the same jaw;
- iii) Presence of one adjacent tooth at the extraction site;
- iv) Adequate oral hygiene (bleeding on probing <20%; plaque index <20%);
- v) Systemically healthy with no contraindication for oral surgical procedures;
- vi) Signed informed consent form.

### *Exclusion criteria*

- i) Pregnant or lactating women;
- ii) Existence of bone metabolic disease;
- iii) Currently taking drugs that influence bone metabolism;
- iv) Use of bisphosphonates in the last 4 years;
- v) Smokers (>10 cigarettes/day).

### Randomization

A computer-generated list was prepared (<http://www.randomizer.org/>) and concealed randomization envelopes were stored by an independent person unaware of the study protocol. The extraction sockets within the same jaw of each patient were randomly assigned to the test group and the control group.

### Surgical procedure

An experienced oral surgeon did all the extractions and alveolar ridge preservations. Extractions were performed under local anesthesia. Periotomes and elevators were used with great care to preserve the buccal bone plate and the surrounding soft and hard tissues. When it was necessary, the teeth were sectioned by a handpiece with diamond burs. No flap was elevated. After tooth extraction, the sockets were carefully debrided to remove all soft tissue remnants. Thereafter, the extraction sockets were randomly assigned to the following two treatment modalities:

- i) **Test group:** the sockets were completely filled with deproteinized bovine bone mineral with 10% collagen (DBBM-C; Geistlich Bio-Oss<sup>®</sup> Collagen, Geistlich Pharma AG, Wolhusen, Switzerland), then covered with a native bilayer collagen membrane (NBCM; Geistlich Bio-Gide<sup>®</sup>, Geistlich Pharma AG, Wolhusen, Switzerland). The membrane was shaped in a way to overlap the margins of the extraction sockets by 2-3mm and placed slightly underneath

the marginal mucosa. Subsequently, a cross suture was performed to keep the membrane in place.

- ii) **Control group:** the sockets healed spontaneously without any graft materials and with no sutures.

All the patients were instructed to rinse with 0.12% chlorhexidine for 1 minute, twice a day, for ten days. The sutures of the test site were removed 7-10 days after extraction.

#### Radiographic analysis

Cone Beam Computed Tomography (CBCT) was performed at baseline (immediately after teeth extraction), 3 months and 6 months after tooth extraction. The Field of View (FOV) of a cylinder measuring 8x8cm was selected and an image was acquired with 0.16 mm of resolution (Planmeca Promax, Planmeca Oy, Finland). The scan datasets (DICOM, Digital Imaging and Communications in Medicine) were compared using an open-source software (3D Slicer 4.5, [www.slicer.org](http://www.slicer.org)). The datasets were matched utilizing areas where no changes had taken place during the follow-up periods (e.g. the cranial base - maxilla - and the mandible – external and internal oblique ridge). Subsequently, images with an embedded ruler were taken in the center of the extraction socket of the mesial and distal roots at each time point. An image-editing software program (Adobe Photoshop CS6, Adobe Systems Incorporated, USA) was used to layer and delimit the following points at baseline according to figure 1. The most apical point of mesial and distal extraction socket, a

vertical reference line - parallel to the long axis of the tooth, or it's adjacent tooth - in the center of the extraction socket (crossing the apical reference point), two horizontal reference lines (perpendicular to the vertical line, crossing the top of the lingual/palatal bone plate and the most apical point of the extraction socket) and three reference lines with dots on the lingual/palatal wall of the root (at 1mm, 3mm and 5mm below the horizontal reference line) (Fig. 1). Another set of images from each patient were exported. Therefore, the measurements were made using the same reference points and lines defined in the baseline image for the 3 and 6 months follow-up. This method of analysis has been adapted according to a previous clinical study assessing single rooted tooth in the anterior region (Jung et al. 2013). The following images were calibrated with the embedded ruler and the measurements were taken using ImageJ software (ImageJ, Image J64, National Institute of Health, USA) by a single calibrated evaluator (V.M.S.):

- i) The Height of the Buccal (BH) and Palatal (PH) bone plate at baseline, 3 and 6 months' follow-up.
- ii) The Horizontal Width of the extraction socket measured at 1mm, 3mm and 5mm below the lingual bone crest at baseline, 3 and 6 months' follow-up (HW-1, HW-3, HW-5);
- iii) The Horizontal Width (thickness) of the buccal bone plate at 1mm, 3mm, and 5mm below the lingual bone crest at baseline (BHP-1, BHP-3, BHP-5);

#### Statistical analysis

The primary outcome of the present study was the Horizontal Width of the

extraction socket measured at 1mm (HW-1), with patient being the unit of analysis. The sample size was based on a previous publication (Jung *et al.*, 2013), considering a standard deviation of 0.7mm and a mean outcome of 1.1mm for control and 0.6mm for test group. The significance level was set at 5% and power of 60%. Twenty-four patients were included, considering a 20% drop-out rate. Intra-rater reliability was assessed by re-measuring more than 24 individual measurements from 10 patients. The corresponding intra-class correlation (ICC) and confidence intervals were calculated. Intra-rater reliability was excellent as confidence intervals for ICC were all above 0.95 for all parameters. The raw data have been checked for differences between the mesial and distal root. As there was no difference the dataset was first averaged over different roots of the same tooth, providing an average test and control value per patient. Descriptive statistics (mean value and standard deviation) were obtained and a nonparametric Wilcoxon signed rank test for paired data was employed to check for significant differences between the test and control groups. Tests and plots were done with the software R (R Core Team, 2015) and the significance level was set to  $\alpha=0.05$ .

## Results

A total of 24 patients were treated in the present study. During the healing period no graft loss or infection occurred. Four patients were excluded due to artifacts in the CBCT scans and two patients were excluded due to the fact, that it was impossible to set the reference lines. Finally, 18 patients with a split-mouth design were included for analysis (12 patients with upper jaw sites - 12 upper pre-molar, 12 upper molar - and 6 patients with lower jaw sites - 4 lower pre-molar, 8 lower molar) (Fig. 2 & 3).

The data are presented in figure 4. The CBCT analysis showed, in all measurements, a bone loss compared to baseline. The measurements which reached statistically significant differences between test and control group at 3 months were the BH (test: -1.96% / -0.56mm vs. control: -11.80% / -1,41mm), height of PH (test: -1.52% / -0.56mm vs. control: -13.21% / -1.16mm) and HW-3 (test: -7.81% / -0.72mm vs. control: -21.44% / -1.84mm). At 6 months, statistically significant differences between the test and control group were found in a vertical dimension at BH (test: -2.31% / -0.25mm vs. control: -13.11% / -1.25mm) and PH (test: -2.07% / -0.26mm vs. control: -15.32% / -0.89mm) (Fig. 4a), and at a horizontal dimension at HW-1 (test: -17.14% / -1.33mm vs. control: -32.47% / -2.78mm) and HW-3 (test: -11.65% / -0.82mm vs. control: -28.47% / -1.95mm) (Fig. 4b).

The percentage of bone loss in the upper jaw are presented in table 1. The measurements which have reached statistically significant differences between test and control group at 3 months were BH (test: -1.75% / -0.78mm vs. control: -7.67% /

-1.26mm), PH (test: -1.38% / -0,79mm vs. control: -10.35% / -0.94mm) and HW-3 (test: -6.72% / -0.87mm vs. control: -18.07% / -1.61mm) and at 6 months, were BH (test: -2.06% / -0.32mm vs. control: -7.17% / -0.84mm) and HW-3 (test: -11.73% / -0.91mm vs. control: -20.82% / -1.33mm).

The percentage of bone loss in the lower jaw are presented in table 2. The measurements which have reached statistically significant differences between test and control group at 3 months were BH (test: -2.95% / -0.15mm vs. control: -20.23% / -1.66mm) and PH (test: -2.16% / -0.15mm vs. control: -18.83% / -1.53mm) and at 6 months were BH (test: -2.18% / -0.12mm vs. control: -23.7% / -1.96mm), PH (test: -2.46% / -0.17mm vs. control: -19.84% / -1.60mm), HW-3 (test: -12.53% / -0.67mm vs. control: -43.74% / -2.97mm) and HW-5 (test: -5.07% / -0.21mm vs. control: -23.51% / -1.24mm).

The relationship between BHP-1 and the bone loss is presented in the following plots (Fig. 5). Independent of the treatment group no major bone loss (e.g. more than 30%) was observed when the buccal bone plate was wider than 1 mm.

## Discussion

The present CBCT analysis in posterior sites of both jaws demonstrated an overall reduction of the radiographic bone resorption after tooth extraction. However, the use of DBBM-C covered with a NBCM apparently reduced the radiographic loss in alveolar ridge dimensions in the horizontal and vertical direction, with statistically significantly less bone resorption at BH, PH, and HW-3.

There is a large body of literature evaluating the dimensional changes of the alveolar ridge in the anterior area after tooth extraction (Tan *et al.*, 2012; Avila-Ortiz *et al.*, 2014; Mardas *et al.*, 2015; MacBeth *et al.*, 2017). Recent randomized controlled clinical trials (RCTs) using xenografts for post-extraction socket preservation demonstrated a significant reduction of the alveolar bone contour in anterior sites (Jung *et al.* 2013; Araújo *et al.* 2015b; Meloni *et al.* 2015). One of these RCTs involving 40 patients, showed a reduction of 43% in the spontaneous healing group compared to 18% of xenograft groups at 1 mm below the crest (Jung *et al.*, 2013). Another RCT with 48 anterior extraction sockets assessing spontaneous healing vs. alveolar ridge preservation with xenograft demonstrated a considerable reduction in the amount of horizontal and vertical bone resorption in the xenograft group (Cardaropoli *et al.*, 2013). A recent RCT compared extraction sockets that have been preserved with the same xenograft but covered either by a porcine collagen matrix or an epithelial connective tissue graft. It has been concluded that both treatment modalities showed favorable and similar outcomes, however, the use of the porcine collagen matrix allowed simplification of the treatment because no

palatal donor site was involved (Meloni *et al.*, 2015).

In contrast to the previously mentioned literature on alveolar ridge preservation procedures (ARP) in anterior sites, the present RCT assessed exclusively posterior sites after tooth extraction. Due to the anatomic and morphologic differences, it seems that posterior sites demonstrate a different pattern of bone remodeling after tooth extraction. Considering the buccal bone plate height (BH), there is more resorption in posterior sites (Test: -2.31% posterior vs. -0.1% anterior; Control: -13.11% posterior vs. -5.5% anterior) compared to anterior single rooted sites (Jung *et al.* 2013). The changes taking place in the horizontal dimension of the extraction socket at 1mm (HW-1) below the crest demonstrated similar results in anterior and posterior sites receiving ARP (-17.14% posterior vs. -17.4% anterior). However, unassisted sockets healing in the posterior area revealed less resorption compared to the anterior region (-32.47% posterior vs. -43.3% anterior) (Jung *et al.*, 2013). Due to the larger dimensions in width compared to the anterior sites and the non-aesthetic appeal, the greater resorption in posterior sites might not cause a big impact for posterior implant placement. However, it might be speculated that the significantly higher amount of resorption in the vertical dimension could lead to more augmentative procedures during or before implant placement and, therefore, to more complex procedures and to an increased morbidity for sites receiving no ARP. Moreover, a recent RCT (Walker *et al.*, 2017) evaluating posterior ridge preservation also demonstrate a higher radiographic bone resorption at sites without ridge preservation procedure, especially at the buccal aspect.

Therefore, one of the main advantages of posterior ridge preservation, especially in the upper jaw, could be to avoid secondary bone regeneration procedures (e.g. minor GBR procedures, sinus elevation) to place implants. A systematic review (Mardas *et al.*, 2015) showed a decreased necessity for further augmentation procedures when ridge preservation was performed in anterior sites (Relative risk: 0.15, 95% CI: 0.07-0.3). Another recent RCT also demonstrated a reduced necessity of GBR procedure at implant placement in posterior sites when ridge preservation was performed (10% of implants needed GBR at implant placement at ridge preservation group against 25% on control group) (Walker *et al.*, 2017). The test group of the present study showed significantly less bone resorption on the height of buccal and palatal bone wall compared to the control group (BH Test: -2.31% vs. BH Control: -13.11%; PH Test: -2.07% vs. PH Control: -15.32%). Another important point is the relation between the maxillary sinus and the tip of the roots. Cases with a close relationship between the sinus and the tip of the root seem to suffer more from vertical resorption because of the sinus pneumatization (Sharan & Madjar, 2008). This has not been documented in the present split-mouth randomized clinical trial. The evaluated Chinese population presented a generous amount of bone between the tip of the root and the floor of the sinus (Fig. 2).

The correlation analysis between the horizontal width (thickness) of the buccal bone plate at 1mm (BHP-1) and the other parameters demonstrated a possible direct influence on the radiographic bone resorption rate. Cases with more than 1 mm of BHP-1 did not suffer extreme bone loss (e.g. more than 30%) in both groups. However,

the ridge preservation technique prevented a major bone remodeling, especially in height, even in cases with less than 1 mm of BHP-1.

The limitations of the present study were the low number of patients included, reducing the power of the present study to 60%, and consequently rising the chance of an “false negative” (Type II error). The difficulties regarding the CBCT analysis to identify the bone graft material due to the similar density compared to the other tissues in the extraction socket and the recurrent presence of artifacts in the CBCT scans (e.g. metal restoration, dental implants, etc.) were also considered a limitation of the present study. Although several studies have used native bilayer collagen membrane to seal the extraction socket, a possible drawback of the present study could be the use of this type of membrane, with an earlier breakdown compared to a non-cross-linked type I/III collagen-based material. The Chinese population is also a concern to the authors, as the anatomic characteristics are very singular and maybe not found in other populations. Moreover, there is a need for further RCTs comparing the ridge alterations after tooth extraction in posterior sockets. The necessity for secondary bone regeneration and the sinus floor alterations should be evaluated.

## **Conclusions**

The posterior ridge preservation technique, using DBBM-C covered with a NBCM, could be a valid approach reducing the amount of radiographic loss in alveolar ridge dimensions in the posterior area. Statistically significant differences were found between test and control group in bone height (buccal and palatal/lingual) and bone width (1 and 3 mm below the bone crest) 6 months after tooth extraction, in favor of the posterior ridge preservation technique.

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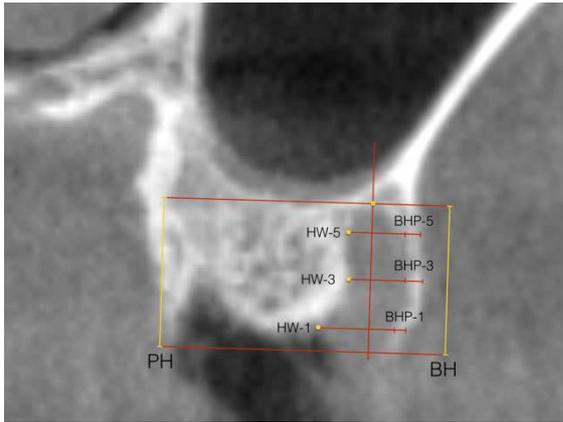


Figure 1. Slice section at baseline. HW-1 (at 1 mm), HW-3 (at 3 mm) and HW-5 (at 5 mm) represent the horizontal width of the extraction socket. BH and PH represent the height of the buccal (BH) and palatal (PH) bone plate. BHP-1 (at 1 mm), BHP -3 (at 3 mm) and BHP -5 (at 5 mm) represent the horizontal width (thickness) of the buccal bone plate.



Figure 2. Cone-beam computed tomography (CBCT) of test and control group of different patients at baseline, 3 and 6 months. Test group at baseline (a), 3 months' follow-up (b) and 6 months' follow-up (c). Control group at baseline (d), 3 months' follow-up (e) and 6 months' follow-up (f).

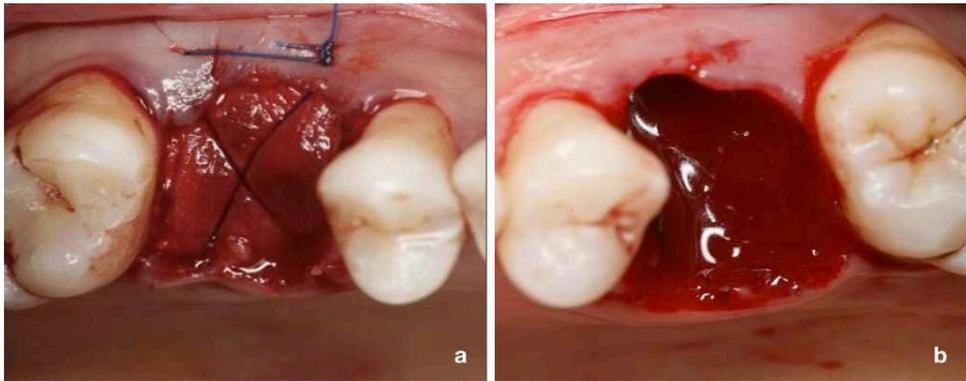


Figure 3. Clinical picture of test group with sockets completely filled with DBBM-C, covered with NBCM and a cross suture keeping the membrane in place (a). Clinical picture of control group without any graft materials and with no sutures (b).

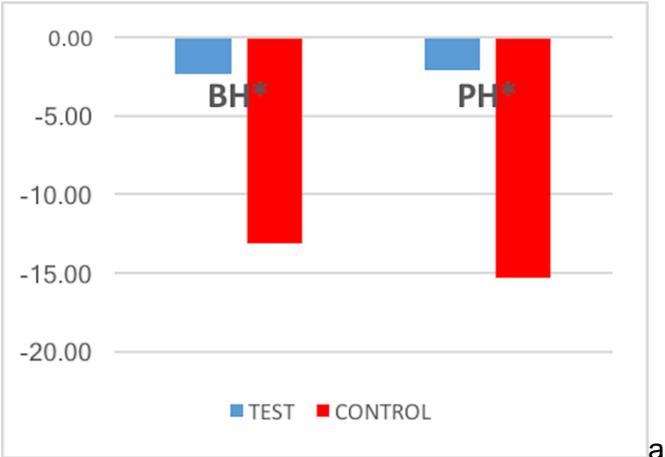


Figure 4. The Relative bone loss in height (%) over 6 months based on cone-beam computed tomography (CBCT) measurements (a). The Relative bone loss in width (%) over 6 months based on cone-beam computed tomography (CBCT) measurements (b).

Figure 4b

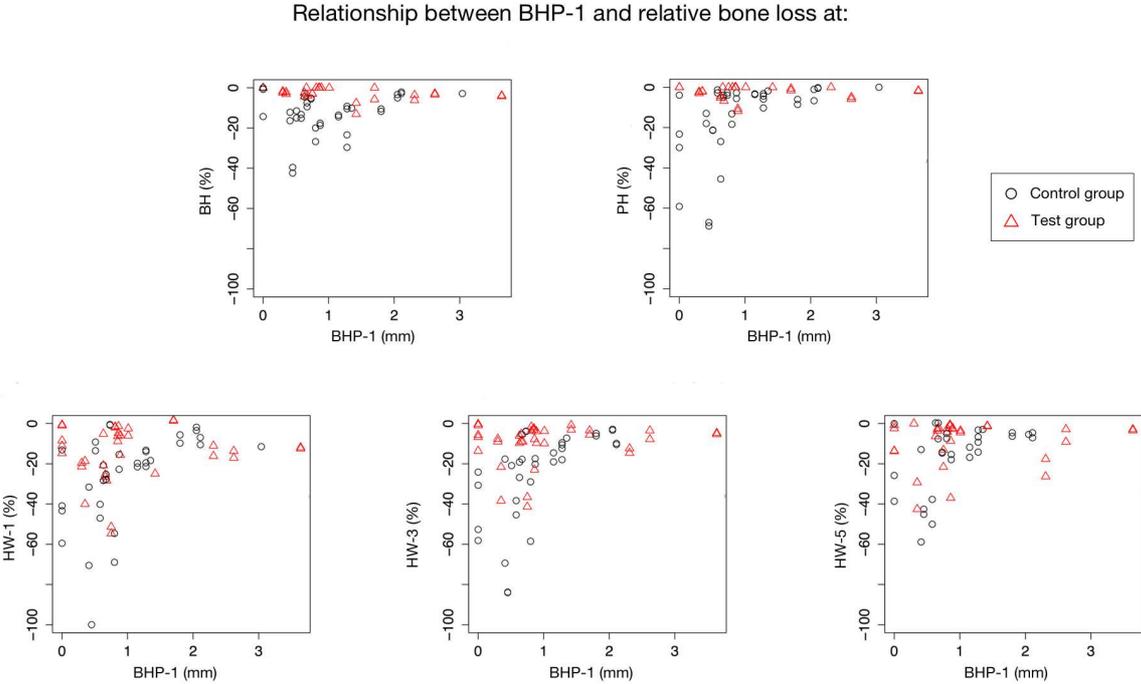


Figure 5. The relationship between BHP-1 and overall bone loss.