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Alendronate or Zoledronic acid do not impair wound healing after tooth extraction in postmenopausal women with osteoporosis

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ABSTRACT

Background: Bisphosphonates (BPs) are widely used for the prevention or treatment of osteoporosis. One of the most serious complications associated with BPs is medication-related osteonecrosis of the jaw (MRONJ) but its incidence in patients with osteoporosis is very low ranging from 0.001–0.15%. A major predisposing factor for MRONJ is tooth extraction (TE). Controversies persist about the influence of current BP therapy regarding socket healing after TE. The aims of this study were to investigate prospectively, (i) alveolar bone healing, i.e., filling of the bony socket by new bone and (ii) mucosal healing, i.e., closure of the overlying mucosa, after TE in women receiving current BP therapy for the prevention or the treatment of postmenopausal osteoporosis. Methods: Women with osteoporosis under current treatment with BPs (BP+ group) or other anti-osteoporotic medications (BP- group) undergoing single TE were included in this study. No antibiotic prophylaxis was prescribed solely for the BP therapy, but antibiotic treatment may have been required for local infectious conditions. Chlorohexidine mouthwashes were systematically prescribed in all study patients for one week after TE. New bone height (NBH) and rate of socket filling (RSF) were recorded using intraoral standardized radiographs one month and 3 months after TE (T30 and T90 respectively). The closure of the overlying mucosa was assessed by measuring the wound extent with an electronic caliper at 1 week and at 1 month after TE (T7 and T30 respectively). Results: At T30, NBH was not statistically different between the BP+ and BP- groups ($p = .76$). At T90, more than a two-fold in NBH increase was recorded for both groups with no statistically significant difference between them ($p = .76$). At T30 and T90, RSF was similar in both groups ($p = .58$ and $p = .32$ respectively). More than a two-fold RSF increase was founded between T30 and T90 in both groups. No demographic or BPs-related factors were correlated with the RSF at T90. At T7, the mucosa wound extent was reduced by more than two-fold with no statistically significant difference between both groups ($p = .80$). At this time, mucosa healing was achieved in 11.9% of the BP+ group and 10% of the BP- group ($p = .99$). At T30, mucosal healing was achieved in all patients but two, and at T90 it was achieved in all patients. Conclusion: This study provides new insights into bone and mucosal healing in patients with osteoporosis taking BPs after TE. In this population, TE can be managed successfully with an appropriate surgical protocol and without discontinuation of BP treatment.

1. Introduction

Osteoporosis is a widespread systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, inducing a significant increase in bone fragility and susceptibility to fracture [1]. Osteoporotic fractures are a major cause of morbidity, and both severe fractures and refractures are associated with increased mortality [2]. Thus, it is widely recommended to treat individuals with

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a high risk of osteoporotic fractures.

The most commonly used agents to reduce the risk of fracture in postmenopausal women with osteoporosis are bisphosphonates (BPs). BPs, mainly nitrogen-containing BPs (NBPs), are potent inhibitors of bone resorption by reducing the recruitment and activity of osteoclasts, the bone-resorbing cells, and altering their survival [3].

One adverse event associated with these antiresorptive medications is osteonecrosis of the jaws also called medication related osteonecrosis of the jaw (MRONJ). The incidence of MRONJ is great in patients with cancer (1–15%) showing considerable variability related to type of malignancy being treated, dose and duration of NBP therapy [4]. In patients with osteoporosis treated with NBPs this incidence is estimated to be very low (0.001–0.15%) [4]. Among NBPs, alendronate (ALN) and zoledronic acid (ZOL) have a long retention in bone, and most data on MRONJ are available in populations receiving these drugs. Although it seldom occurs, there is a considerable awareness about MRONJ and therefore the prescription of NBPs to patients with osteoporosis is sometimes criticized [5].

A number of risk factors have been associated with the onset of MRONJ. Above all, the most significant predisposing factor is dentoalveolar surgery including tooth extraction (TE) [6,7]. Then, most task forces recommended strict limitations or even avoidance of TE in patients undergoing treatment with NBPs [4,8,9]. However, in some situations TE is necessary owing to infectious complications, dental fractures or significant discomfort in daily life.

Appropriate protocols for TE in patients with osteoporosis treated with oral NBPs can provide a predictable and favorable outcome [10]. However, the influence of current NBPs on wound healing is still debated. Some studies, but not all, suggest a longer wound healing period in patients treated with NBPs and correlate this with an increased risk of MRONJ onset [11].

Thus significant concerns remain regarding the risk of invasive dental procedures, TE in particular, in patients treated with NBPs. Therefore, prospective data about the healing process after this common invasive dental procedure are needed.

The aims of this study were to investigate prospectively, (i) alveolar bone healing, i.e., filling of the bony socket by new bone and (ii) gingival healing, i.e., closure of the overlying mucosa, after a single TE in women receiving current NBP therapy for the prevention or the treatment of postmenopausal osteoporosis.

2. Methods

2.1. Study design

This prospective controlled study was approved by the French data protection agency (agreement EudraCT n°2012-001756-19). All patients provided written informed consent before inclusion. They were recruited from 10 regional centers in France. All patients enrolled in the study were followed-up for 90 days after TE. Following the baseline visit (T0), scheduled visits were at 7, 30 and 90 days after TE (T7, T30 and T90 respectively).

2.2. Patient selection

Postmenopausal women aged 45 years and older currently receiving anti-osteoporotic treatment and requiring TE were recruited for this study. The indication for treatment was postmenopausal osteoporosis and high risk of fracture, according to current guidelines [1]. The women were divided in two groups:

- BP+: Patients receiving ALN at the appropriate dose for at least 1 year or at least one injection of ZOL 5 mg during the past year;
- BP-: Patients receiving either calcium and/or vitamin D, strontium ranelate, ralexifene, or hormone replacement therapy.

Corticosteroid intake was permitted only with current doses of less than < 10 mg prednisone (or equivalent) per day. Women with diabetes were also included and glycemic control was assessed according to the glycated hemoglobin (HbA1c) level. Glycemic control was considered to be good at HbA1c < 7% and poor if greater than this value. Individuals with previous head and neck radiotherapy were excluded.

Body mass index (BMI: kg/m^2) and risk factors for wound healing, i.e., oral status (considered good when no dental plaque, dental calculus, or active caries were discernible or moderate if this were not the case) and current tobacco use, were also recorded.

2.3. Tooth extraction

All procedures were reviewed and agreed upon before initiating the study during a meeting between investigators'.

Regarding TE, all patients were managed using a similar surgical protocol that did not include pre-extraction discontinuation of NBPs. The protocol comprised:

1) Preoperative management consisting of patient education of good oral hygiene and scaling. No antibiotic prophylaxis was prescribed solely for the NBPs therapy, but antibiotic treatment may have been required for local infectious conditions (amoxicillin 1000 mg b.id. or clindamycin 600 mg b.i.d. in the case of allergy to amoxicillin, for 6–7 days);
2) Atraumatic TE under local anesthesia (articaine 4% with adrenaline 1:200000) avoiding alveolar bone removal and/or tooth splitting as much as possible;
3) Tension-free wound closure with sutures was optional (complete mucosa closure was not mandatory);
4) Postoperative administration of oral analgesic (acetaminophen 1000 mg q.i.d. for up to 3 days) and prescription of chlorohexidine 0.12% mouthwashes t.i.d. up to the T7 follow-up visit; and
5) Follow-up visits at T7 with suture removal if applicable and then at T30 and T90.

2.4. Outcome assessment

Assessment of the alveolar bone healing i.e. filling of the bony socket by new bone, was based on radiographic investigations. The aim of the radiographic analysis was to determine on consecutive intraoral radiographs the new bone height (NBH given in mm) in the empty post-extractional tooth socket and thus the rate of socket filling (RSF given in %) by new bone which was calculated at T30 and T90. Periapical radiographs were taken perpendicular to the long axis of the alveolar socket with a long-cone parallel technique immediately after TE (T0) and at T30 and T90 and compared in terms of NBH and RSF. A bite block was fabricated for each patient, including at least one tooth anterior and posterior to the compromised tooth, to serve as a fixed reference guide and to allow for the repositioning of the radiograph in the same place at all time points. NBH was assessed from mesial and distal bone margins of the empty socket to the apical extent of the socket depth. The alveolar bone margins were considered the most coronal point of the alveolar bone on the mesial (Hm) and distal (Hd) sides of this socket. NBH is calculated according to the formula: NBH = Hm + Hd/2 (Fig. 1). The decrease in NBH at T30 and T90 indicated the gain in bone in the post-extractional socket. RSF is defined as the NBH at T30 or T90 relative to the NBH at T0.

Imaging modalities were standardized among investigators and a centralized reading of periapical images was used as described elsewhere [12]. Briefly, these radiographs were scanned in a digital format on a flatbed scanner (Epson expression 1680 Pro, France) at a resolution of 600 dpi. They were analyzed by a computerized measuring technique with an image analysis software (Digora Soredex, Finland) that measured the distance between two points. The precision of the measuring system was 0.01 mm. In order to improve the image

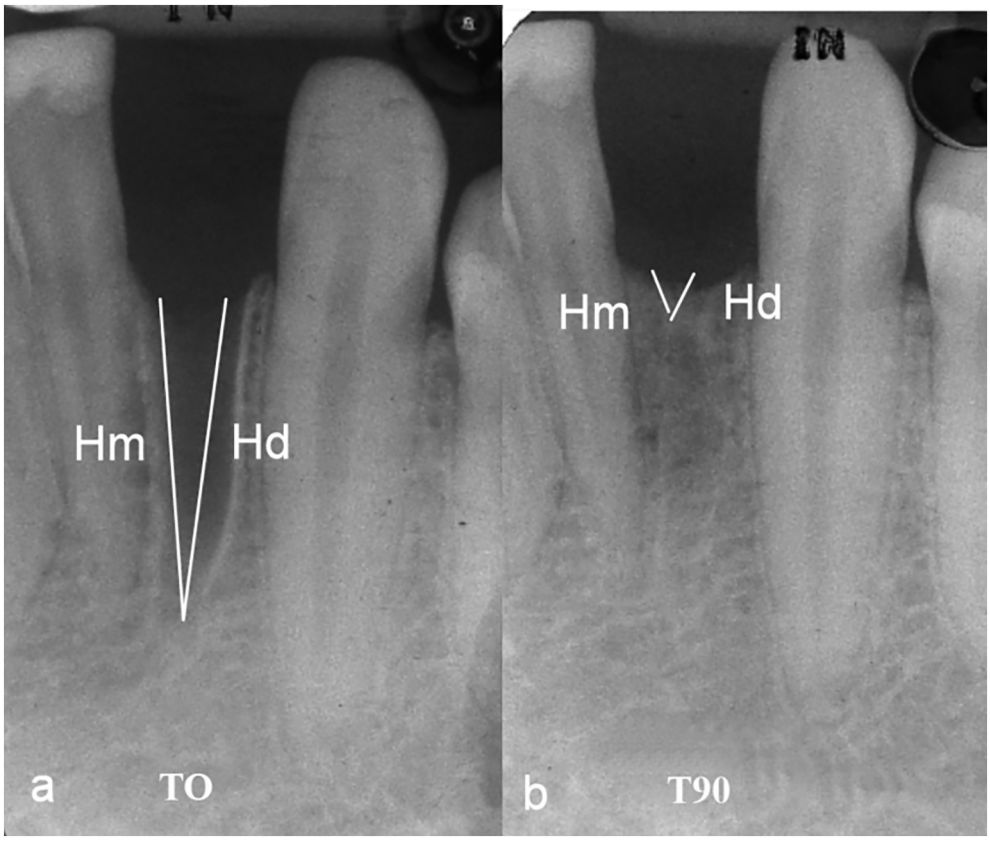

Fig. 1. NBH was assessed on standardized periapical radiograph from bone mesial and distal margins of the empty socket to the apical extent of the socket depth. NBH is an average calculated according to the formula: NBH = Hm + Hd/2. NBH = New Bone Height; Hm = Height mesial and Hd = Height distal. a: at T0 and b at T90.

analysis, an investigator not involved in the surgical procedure performed image enhancement operations when necessary including sharpening, brightness, contrast and gamma adjustments. Then, a pair of trained readers independently performed a blind evaluation (related to the clinical data and recruiting center) of the periapical images. The mean of the measures from these two readers was calculated. In the case of discordance of more than > 5%, a third trained reader was consulted and the mean of the two readers with the highest agreement was used.

Assessment of the gingival mucosa healing i.e., the closure of the overlying mucosa was based on clinical measurements made with an electronic caliper. Mucosa healing was defined as epithelial continuity obtained by granulation of the extraction socket with no fistulae connected to the underlying bone. Measurements of the gingival wound (given in mm) were made along the mesio-distal axis immediately after TE and before suture at T0, at T7 after suture removal when applicable, and at T30 if closure was not achieved at T7. An additional visit was planned 8 weeks postoperatively (T56) if complete epithelialization of the socket was not achieved at T30, to investigate and manage a potential MRONJ [5].

2.5. Statistical analysis

The initial sample size requirements were not met in this study. However, giving the actual sample size for the RSF primary outcome of 18 patients for the BP- group and 36 patients for the BP+ group, we could have detected a true difference in means between the two groups of 9% assuming a pooled standard deviation of 10%, a power of 80% and a two-sided level of significance of 5%.

Statistical analyses were performed using ad hoc routines implemented in R 3.4.4 software. Categorical data are summarized with numbers and percentages. Continuous data are described with median and interquartile range (IQR). Univariate analyses were performed in order to compare the baseline characteristics and the different endpoints between women with osteoporosis in the BP+ and BP- groups. Qualitative variables were compared using Fischer's exact test and quantitative variables were analyzed with the non-parametric Wilcoxon-Mann-Whitney test. Regarding the different outcomes, multivariate regression models (logistic or linear according to the variable studied) were run to adjust for the age of the women. All tests were two-sided at the 5% level of significance.

3. Results

3.1. Characteristics of the study population

Overall 66 women were enrolled in this study as shown in the consort diagram of the study, data were available at baseline for 44 women in the BP+ group and 21 in the BP- group. At T90, 36 BP+ patients and 18 BP- patients fully complied with the study protocol (Fig. 2).

No significant difference was found between the two groups regarding patient characteristics except for age (Table 1).

In the BP+ group, anti-osteoporotic treatment comprised ALN in 27 women and ZOL in 17 women. Eight women received NBPs for < 2 years, 15 between 2 and 5 years, 14 between 5 and 10 years, and 7 for > 10 years. In this BP+ group, 36.36% women received concomitant vitamin D ± calcium therapy. In the BP- group, anti-osteoporotic treatment was raloxifene for 3 women, hormonal therapy for 3, strontium ranelate for 1, and vitamin D ± calcium for 14.

3.2. Characteristics of tooth extraction

Extraction involved a monoradicular tooth (incisor, canine, premolar) in 63.6% of the patients from the BP+ group and in 76.2% of those from the BP- group (the rest of the TE involved a pluriradicular tooth: premolar and molar). There was an imbalance between the number of patients who received antibiotics in the BP+ and the BP-

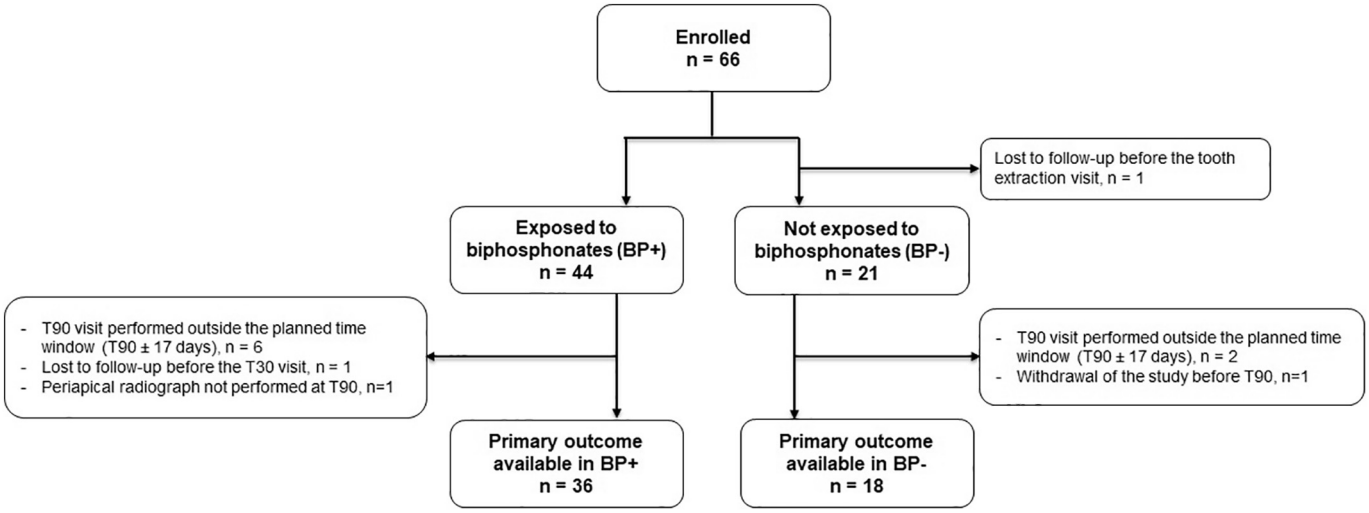

Fig. 2. Consort diagram of the study.

Table 1
Characteristics of the study population according to BP treatment. BP: bisphosphonates; BMI: body mass index.

	BP+ (n = 44)	BP- (n = 21)	p value
Age (year)	70.0 [64.0–77.0]	64.5 [57.0–85.0]	0.003
Current corticosteroid therapy (%)	11.4	9.5	0.99
BMI (kg/m^2)	23.7 [21.5–26.4]	23.1 [21.9–29.7]	0.59
Diabetes (%)	9.1	9.5	0.99
Current tobacco use (%)	9.1	14.3	0.68
Oral status (%)			0.15
• Good	88.6	71.4	
• Moderate	11.4	28.6	

group (p = .037). In the BP+ group, 30.6% of the women were treated with antibiotics for local infectious conditions, mainly severe periodontitis, at the time of TE compared with 16.7% of the women in the BP- group. No postoperative complication was recorded in the BP+ group at T7 and over. One local infectious complication was recorded in the BP- group at T7 that resolved with a 1-week antibiotic treatment (amoxicillin 1000 mg b.i.d.).

3.3. Bone healing

At T30, NBH was not statistically different in the BP+ group, median [IQR] 2.80 mm [1.84–4.2] versus 2.80 mm [1.65–3.77] in the BP- group (p = .76). At T90, NBH increased to 7.33 mm [4.40–10.1] in the BP+ group and 7.26 mm [5.99–7.85] in the BP- group with no statistically significant difference between the groups (p = .76) (Fig. 3). Thus, a more than two-fold increase in NBH was recorded between T30 and T90 in both groups, (+262% in the BP+ group and + 259% in the BP- group).

Fig. 4 presents the evolution in NBH profiles as a function of time since TE in both groups. It should be noted that these results remained unchanged after adjusting for age at baseline (p = .93 at T30 and p = .79 at T90).

At T30, RSF was similar in both groups, median [IQR] 32% [24–39] in the BP+ group and 32% [21–38] in the BP- group (p = .58). At T90, RSF was also similar in both groups, 75% [70–82] in the BP+ group and 73% [69–80] in the BP- group (p = .32) (Fig. 5). Thus, a more than two-fold increase in RSF was recorded between T30 and T90 in both groups (+234% in the BP+ group and + 228% in the BP- group). RSF at T30 and T90 remained not significantly different between both groups after adjusting for age at baseline in linear multivariate regression models (p = .82 and p = .31, respectively).

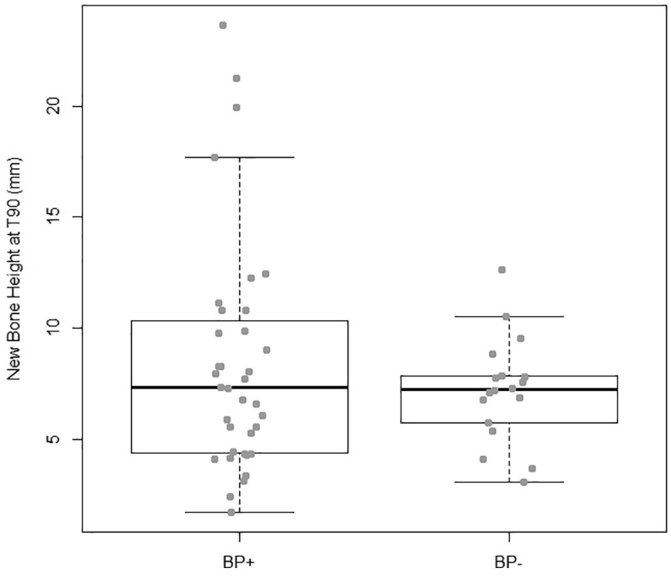

Fig. 3. Boxplot of new bone height (mm) at T90 between women with osteoporosis receiving bisphosphonates (BP+ group) or not (BP- group). No statistical difference was found. Gray points indicate the observed data.

Regarding RSF at T90, there was no difference between BP+ or BP- women who were treated or not treated with antibiotics (p = .06). No other factor was associated with RSF at T90, age (p = .43), corticosteroid intake (p = .99), diabetes (p = .60), tobacco use (p = .99), oral status (p = 1), or BMI (p = .87). No correlation was recorded between RSF at T90 and the anti-osteoporotic treatment regimen (p = .47) or the duration of the NBP therapy in the BP+ group (p = .37).

3.4. Mucosal healing

At T0, the size of the mucosal wound was not statistically different in the BP+ group, median [IQR] 5.59 mm [4.15–7.70] versus 6.16 mm [4.76–9.26] in the BP- group (p = .14). At T7, the size was 2.70 mm [1.68–3.70] in the BP+ group and 2.15 mm [1.45–4.04] in the BP- group (p = .80). This result remained unchanged after adjusting for age at baseline (p = .45) (Fig. 6). At that time, mucosal healing was achieved in 11.9% of the patients from the BP+ group and 10% of those from the BP- group (p = .99 and p = .54, respectively after

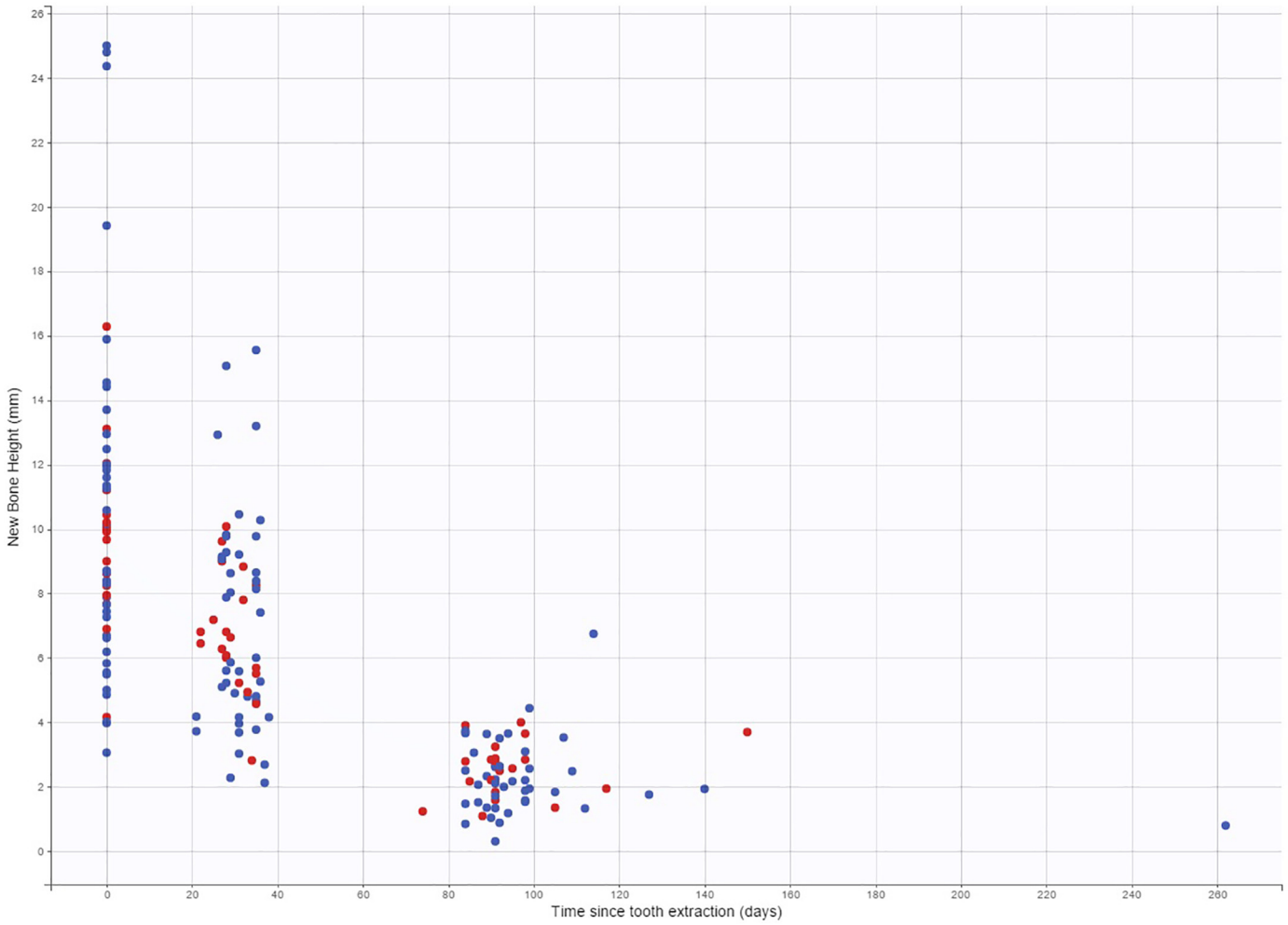

Fig. 4. New bone height as a function of time since the tooth extraction (days). Blue and red points indicate respectively the BP+ and BP- observations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

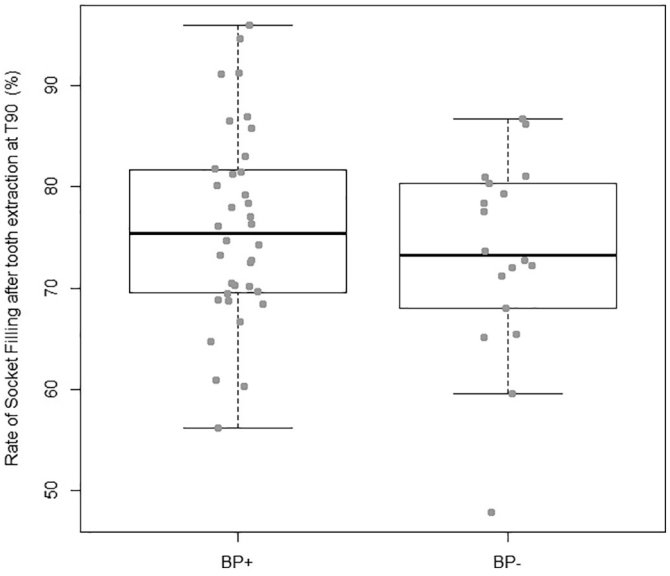

Fig. 5. Boxplot of socket filling rate after tooth extraction (%) at T90 between women with osteoporosis receiving bisphosphonates (BP+ group) or not (BP- group). No statistical difference was found. Gray points indicate the observed data.

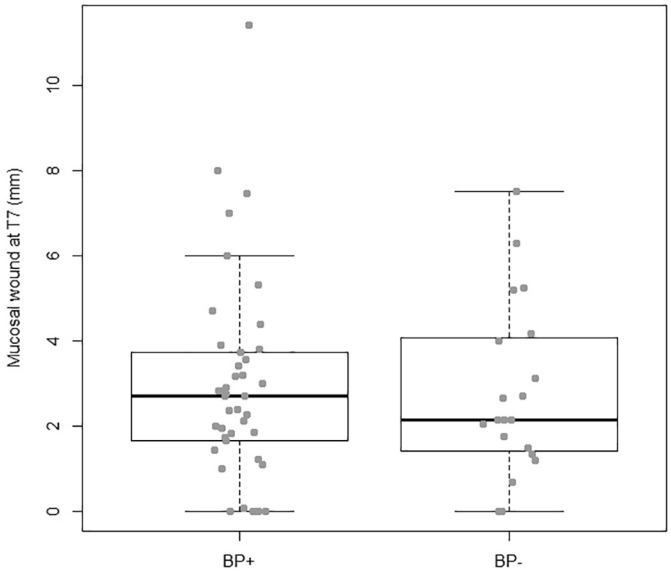

Fig. 6. Boxplot of the mucosal wound (mm) at T7 between women with osteoporosis receiving bisphosphonates (BP+ group) or not (BP- group). No statistical difference was found. Gray points indicate the observed data.

adjusting for age at baseline). This highlighted a more than two-fold decrease in the wound extent 1 week after TE.

At T30, mucosal healing was not complete in two women from the BP+ group but with no infectious features. Mouthwashes with 0.12% chlorhexidine were prescribed twice a day for 1 month and, according to the research protocol, an additional visit was planned at T56. At that time, mucosa healing was achieved in both patients. No MRONJ was diagnosed in this study.

4. Discussion

This study shows that current ALN or ZOL therapy for prevention or treatment of osteoporosis in postmenopausal women does not impair bone and mucosa healings after a single TE. This is evidenced for the first time with radiological and clinical data in humans. In this population, TE could be managed successfully with an appropriate surgical protocol without discontinuation of NBP treatment. These findings are pertinent since TE is commonly regarded as a major risk factor for MRONJ in NBP-treated patients [4,8]. Moreover, in our study NBP treatment in postmenopausal women did not appear to markedly delay wound healing after TE when compared with the RSF in healthy populations reported in the literature. Only three studies by one group of investigators assessed socket filling after TE. In a small cohort of patients, socket filling was monitored through recording clinical measurements of the distance from the coronal border of the buccal alveolar bone wall to the most apical end of the socket at T0 and 6 months after TE [13–15]. On average, this distance was reduced by 55% with a great interindividual variability (ranging from 40% to 75%). This is a little less than the 73–75% RSF recorded in our study 3 months after TE. This difference could be mainly explained by the traumatic surgical technique used for TE in these studies. TE was performed using circumferential, vertical and horizontal gingival incisions, elevation of full-thickness flaps and primary closure with sutures. However it is well established that, if primary closure of the mucosa requires the advancement of a full-thickness flap, then this may represent an additional inflammatory factor increasing resorption of alveolar bone and thereby possibly increasing the risk of MRONJ [16,17]. In addition, since delicate surgery with gingival incisions and full-thickness flaps to allow for primary socket closure was similarly effective to a less invasive TE technique without detachment of full-thickness flaps and wound healing via secondary intention, it is preferable to close the wound only to the extent possible using noninvasive methods rather than to force the wound closure [10]. Another study investigated osseous socket healing but not socket filling after TE in patients treated with current oral NBPs for > 24 months using orthopantomography [10]. One year after surgery, what the authors described as “normal alveolar bone healing” was discernible. In our study, using a much more accurate radiographic procedure, we did not record any difference in RSF 90 days after TE between women with osteoporosis who were treated with NBPs and those treated with other anti-osteoporotic therapies.

In fact, the vast majority of the literature related to NBP anti-osteoporotic therapy and TE is devoted to the risk of MRONJ onset. Only few studies have investigated bone and mucosal healing processes of the extraction socket and most of them used animal models treated.

In ZOL-treated rats, μCT scanning revealed a similar bone appearance and bone filling in the socket after extraction of a healthy molar to that in control animals but an impaired osseous socket healing after extraction of a molar with experimental periodontitis [18]. It is suggested that ZOL delayed wound healing of the TE socket by inhibiting osteogenesis and angiogenesis in mice [19]. ALN injection prior to molar extraction delayed wound healing in the extraction socket in rats, but in a few weeks it was progressively filled at a comparable rate to that of control animals [20,21]. These findings suggest that in these animal models NBPs could delay the bone healing process in the early stages after TE. Moreover, some authors agreed that short-term ALN monotherapy in rats or mice do not compromise but has the potential to enhance bone filling of the TE socket [22,23].

Some task forces suggest discontinuing oral NBP treatment for at least 2 months before invasive dental procedures in patients undergoing long-term therapy to minimize the influence of NBPs on the development of MRONJ [4,8,9]. However, there is no unified consensus concerning this issue for patients with osteoporosis as there is currently no evidence of the preventive effect of this recommendation. Moreover, considering the potential outcome of fracture caused by a withdrawal of the antiresorptive treatment, caution is warranted when deciding to discontinue a NBP treatment.

The effect of the duration of NBP treatment on the risk of MRONJ occurrence is debated, particularly over a 5-year period of treatment [11,24–26]. In our study, 46% of the BP+ women were treated for 5 years or longer and we did not find a negative effect on RSF.

Previous studies have reported that systemic factors such as glucocorticoid administration, tobacco use, and diabetes alter wound healing after TE and are thus considered to be risk factors for MRONJ onset [27,28]. But interestingly, these factors were not highlighted in patients with osteoporosis treated with NBPs [10,11,25]. In our study, no women with such potential risk factors, from both the BP+ and the BP- groups, had a significantly altered RSF.

Several studies reported that existing local infectious conditions such as periodontitis, periapical lesions or poor oral status were greater risk factors for MRONJ onset than TE itself [29–31]. Therefore, reducing local inflammation prior to TE through a professional oral hygiene and scaling session decreased the risk significantly and improved wound healing after invasive dental procedures such as TE [32,33]. Therefore this procedure was systematically followed for each patient 1 week before TE in our study.

Over the past decade, pre-operative serum level of carboxy-terminal collagen crosslink (CTX), a biomarker of bone resorption, has been presented as a predictor of the risk of developing post-operative MRONJ [34], as well as a prognostic factor [35]. However, this was rebutted by some task forces and a recent systematic review and meta-analysis and is not currently recommended in daily practice [4,8,36].

Antibiotic prophylaxis before TE is consensually recommended for oncology patients treated with NBPs but has been debated for patients with osteoporosis [4,8,9]. Some investigators speculated that prophylactic administration of antibiotics could prevent local infection and significantly reduced the risk of MRONJ onset while others did not report any positive effect of such prophylaxis [10,25]. Thus, except for local conditions, mainly periodontitis, and owing to increasing antibiotic resistance, no antibiotic prophylaxis was prescribed solely because of the NBPs therapy in our study. Moreover, in women from the BP+ and BP- groups taking antibiotic treatment for baseline local infectious conditions, mainly severe periodontitis, we did not evidence a shorter time of wound healing when compared with women of the BP+ and BP- untreated with antibiotics. Only one local infectious complication was recorded in a BP- woman (not previously treated with antibiotic for local infectious condition) at T7, which resolved with a 1 week amoxicillin treatment.

Regarding mucosal recovery of the empty alveolar socket after TE, some authors documented a delayed healing in oncology or osteoporosis patients treated with long-term NBP therapies [37], but others did not report this adverse influence of NBPs [10,11]. In vitro, high doses of NBPs exhibited cytotoxic effects on gingival cell types such as fibroblasts, endothelial cells, or keratinocytes that could be involved in impairment of mucosal healing [38,39]. In our study, the mucosal wound was not statistically different between the BP+ and BP- groups despite delays in two BP+ women at T30 (but which healed at T56). The daily mouthwashes with chlorhexidine 0.12% after TE up to the T7 follow-up visit may have positively influenced the healing since this antiseptic agent showed a positive effect on the healing activity of the periodontal tissue surrounding the TE wound [40]. Nevertheless, a close follow-up should be performed until the socket is completely

covered by the mucosa so as to intercept and manage a potential MRONJ as early as possible.

The main limitation of our study is due to the relatively small size of both the BP+ and BP- groups. Moreover our data are not generalizable to other antiresorptive drug such as denosumab. However, this is the first prospective and controlled study of the influence of NBPs on wound healing after TE in humans, using standardized quantitative parameters and centralized reading of imaging data. This study increases awareness concerning TE in such patients and could be a reliable source of information for physicians treating patients with osteoporosis.

In conclusion, bone and mucosal healing are not significantly altered by current ALN or ZOL treatment in women with osteoporosis after TE following optimal procedures. Thus, TE should not be withheld from patients with osteoporosis because of these therapies. Moreover, this study suggests that compliance with a combination of principles: reduce local inflammation prior to TE, perform atraumatic surgery, and prescribe local antiseptic care after TE until the complete closure of the mucosa over the bony socket has been clinically observed which involves close follow-up, may have positive effects on this healing.

CRediT authorship contribution statement

Philippe Lesclous: Conceptualization, Writing - original draft, Data curation. **Alexandra Cloitre**: Data curation, Writing - review & editing. **Sylvain Catros**: Data curation, Writing - review & editing. **Laurent Devoize**: Data curation, Writing - review & editing. **Béatrice Louvet**: Data curation, Writing - review & editing. **Cécile Châtel**: Data curation, Writing - review & editing. **Frantz Foissac**: Formal analysis. **Christian Roux**: Conceptualization, Writing - original draft.

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Declaration of competing interest

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