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RESEARCH ARTICLE

Antiresorptive drug-related changes of the mandibular bone densitiy in medication-related osteonecrosis of the jaw patients

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Objectives: Medication-related osteonecrosis of the jaw (MRONJ) is a well known side-effect of anti-resorptive drugs. Changes in bone density might potentially constitute the development of ONJ. This study aimed to investigate, to which degree bisphosphonates (bp) and denosumab (db) induce changes in bone density that can be determined from routine diagnostic CT.
Methods: CT scans of 101 patients were investigated. MRONJ was present in 61 patients (n = 26: db-treated; n = 35 bp-treated). 40 patients were included as a reference group. Bone density was measured at two distinct locations in the mandible (M1: anterior of the mental foramen; M2: retromolar), each on the contralateral side to the necrosis.
Results: The bone density values measured at both locations were found to be significantly higher in the bp-group compared to the db-group (p = 0.027) and to the reference-group (p = 0.016). Almost no difference (p = 0.84) in bone density value was found between the db- and reference-groups.Investigating the effect of duration of treatment, none of the measured values showed significant differences in both locations of db- and bp-group.
Conclusion: The findings from this study suggest that that bisphosphonates change the microarchitecture of the alveolar bone by being embedded in the mandible, which may subsequently lead to a bp-specific corticalization, and a decrease in vascularization of the lower jaw. This process may be distinctive for bp-treatment and seems to induce the congestion of cancellous bone rather rapidly after the first administrations. This effect could not be determined in denosumab-treated patients.
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Keywords: Bone density; medication related osteonecrosis of the jaw; MRONJ; BMD; Osteonecrosis

Introduction

Bisphosphonates (bp) and denosumab (db) are widely and efficiently used in patients with increased bone resorption secondary to metastatic bone disease, osteoporosis, osteolytic lesions in multiple myeloma or Paget's disease of the bone.[1–3] However, concerns are raised by numerous reports of osteonecrosis of the jaw (ONJ) that has become a well-known severe side-effect of db and bp therapy.[4] Cumulative incidences of ONJ in patients receiving these agents are currently estimated at around 10% in subjects treated with high doses.[5,6] Clinical symptoms include exposed necrotic bone, gingival ulcerations, intra- or extraoral fistulas, swelling, cellulitis and pus exudation.[7] In 2014, the American Association of Oral and Maxillofacial Surgeons published a position paper. Here, the presence of medication-related

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osteonecrosis of the jaw (MRONJ) is defined by current or previous treatment with bp or db, exposed jawbone for at least 8 weeks and no previous radiation therapy of the jaw.[4] The pathogenesis of MRONJ is multifactorial but still remains not entirely understood. Several factors have been identified causing MRONJ. It is known that the inhibition of regular osteoclasts resulting in reduced bone remodelling is the fundamental pathophysiological process in the development of ONJ.[8] Additional factors have been investigated by numerous authors as being associated with progression and severity of the lesions.[9–11]

Insufficient vascularization induced by antiresorptive drugs' impact on bone remodelling inhibition appears to be pivot for the development of necrotic bone.[12–14] A recent study by Soares et al demonstrated a bisphosphonate induced corticalization and decrease of vascularization in the jaws of Wistar rats treated with zoledronic acid.[15] The authors assumed that zoledronic acid induced corticalization caused congestion of the microstructure of the bone, resulting in a decrease of blood supply and impaired healing capacity. Obliteration of nutritive canals inside the bone and a significant reduction of blood vessels were present. Likewise, other investigators presented additional data showing evidence of bisphosphonate induced decrease of blood vessels and reduction of vessel ramification in the bone.[13,14]

Dual-energy X-ray absorptiometry (DXA) is the most widely validated technique for bone mineral density (BMD) measurements.[16] Nonetheless, several recent studies allege that routine CT measurements, performed for different indications may detect changes in bone density, without additional costs or radiation exposure.[17] In CT the bone density is measured in Hounsfield units (HUs) and calculated for a certain region of interest (ROI). This method of bone density evaluation seems feasible and investigations underlined that ancillary application of contrast medium did not enhance CT performance.[18]

The aim of this study was to investigate changes in the alveolar bone density of patients suffering from MRONJ by analyzing CT scans of the mandible. Therefore, we evaluated differences between the bone density of patients either treated with bp or db. Presuming the hypothesis that we would detect denser bone using HU-based determination of bone density.

Methods and materials

Patients

Diagnostic CT scans of 101 patients (49 females, 52 males; mean age: 72.2 ± 10.7 years; age range: 41–91 years) were retrospectively evaluated. A total of 61 patients were diagnosed with MRONJ [n = 26 were treated with denosumab (Table 1); n = 35 were treated with bisphosphonates (Table 2)]. Another 40 patients were included in the study as a reference group. Inclusion criteria were the diagnoses of MRONJ based on the definition by the American Association of Oral and Maxillofacial Surgeons.[4] Additionally, we solely included patients that had been treated with either bps or db in the past. Consequently, we excluded patients with a medical history of recieving both groups of substances. Further exclusion criteria were previous radiation therapy of the jaw and osteolytic processes other than MRONJ. The reference group consisted of patients with no previous therapy of any antiresorptive medication. Our search algorithm created a gender balanced and age-matched group of patients with different diagnoses, each not affecting the mandible (Table 3).

Table 1 Patient characteristics of db-group

Db:	
n	26
Age	male = 14/female = 12
Years of treatment	3.4 ± 1.9
Drug name	
XGEVA	n = 25
Prolia	n = 1
Diagnoses	
Prostate cancer	n = 11
Breast cancer	n = 10
Lung cancer	n = 1
oOsteoporosis	n = 2
Kidney cancer	n = 1
Cancer of unknown primary	n = 1

db, denosumab.

CT

CT scans were performed on a routine clinical 256-slice CT scanner (Philips iCT, Best, The Netherlands). Images were obtained from the local Picture Archiving and Communication System (IMPAX, Agfa Healthcare, Belgium) and

Table 2 Patient characteristics of bp-group

Bps	
n	35
Age	male = 18/female = 17
Years of treatment	4.6 ± 2.7
Drug name	
Zoledronate	n = 24
Bondronate	n = 2
Alendronate	n = 7
Risedronate	n = 1
Ibandronate	n = 1
Diagnoses	
Prostate cancer	n = 6
Breast cancer	n = 7
Osteoporosis	n = 9
Kidney cancer	n = 1
Multiple myeloma	n = 12

Bp, bisphosphonates.

Table 3 Diagnosis of patients from the reference group

Diagnoses	*n*
Facial skin cancer	17
Mid face trauma	11
Intraoral SCC	4
SCC of the lip	3
Mucoepidermoid carcinoma	2
Sinus maxillaris pathology	2
Orbital tumor	1

SCC, squamos cell carcinoma.

reviewed on a standard radiologic workstation. Multiplanar reconstruction and assessment of HU-based determination of bone density was performed using standard clinical applications of the IMPAX software.

Slice thickness ranged from 1 to 5 mm. Bone density was assessed by placing circular click-and-drag ROIs constrained to the cancellous bone of the jaw in two distinct areas (Figure 1) and measuring mean HU values of the relevant ROI. For each measurement, a rotund ROI with an exact diameter of 10 mm was placed over an area of trabecular bone, excluding teeth, the cortical margins or areas in the course of the inferior alveolar nerve. The bone density was measured in two pre-defined locations of the mandible (M1: 10 mm anterior of the mental foramen; M2: retromolar region) (Figure 2). All measurements were performed on the contralateral side to the necrotic process within the mandible. Patients with necrotic areas on both sides of the mandible were excluded from the analysis. Images were assessed by a craniomaxillofacial surgeon and a radiologist.

Statistical analysis

All information was arranged electronically and analyzed (Microsoft Excel, v. 12.3.6; Microsoft Corporation, Redmond, WA). Measurements were described by the means and corresponding standard deviations (SDs). Unpaired *t*-tests were used for comparisons between the groups. p values ≤ 0.05 were regarded as statistically significant.

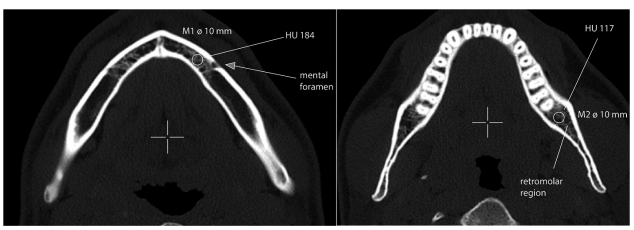

Figure 1 Location of bone density measurements M1: Measurement 1: anterior of the mental foramen; M2: retromolar region. Circle: ROI. ROI, region of interest.

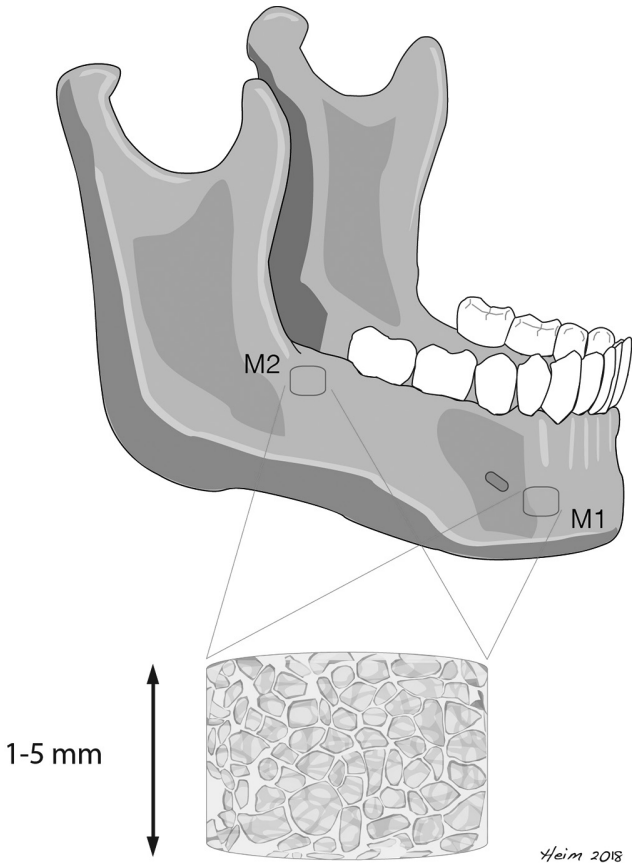

Figure 2 Defined locations of bone density measurements in the mandible Slice thikness in CT ranging from 1 to 5 mm.

Results

A total of 101 subjects were included in the study. The patients were either diagnosed with db-related osteonecrosis of the jaw (n = 26; 12 female and 14 male) with a mean age of 72.1 ± 12.6 years, ranging from 41 to 91 years; or bp-related osteonecrosis of the jaw (n = 35; 17 female and 18 male) with a mean age of 72.1 ± 9.3 years, ranging from 52 to 91 years; or referred to the reference group with various other diagnoses (n = 40; 20 female; 20 male) with a mean age of 72.5 ± 10.8 years, ranging from 50 to 91 years.

The mean duration of treatment for db-group was 3.4 ± 1.9 years, ranging from 1 to 8 years. Mean duration for bp-group was 4.7 ± 2.7 years, ranging from 1 to 13 years.

Bone density was measured for M1-location: db-group: 332.9 ± 161 HU, bp-group: 466.5 ± 300.5 HU, reference-group: 316.6 ± 168.2 HU. Measurements for M2-location: db-group: 208.7 ± 156.7 HU, bp-group: 286.4 ± 243.7 HU, reference-group: 219.6 ± 197.6 HU. Bone density values of both areas (M1 and M2) were added up in order to receive average values for the different groups (db-group: 274.3 ± 169.6 HU; bp-group: 376.5 ± 285.9 HU; reference-group: 268.1 ± 188.7 HU). Assessing the bone density values for M1 showed

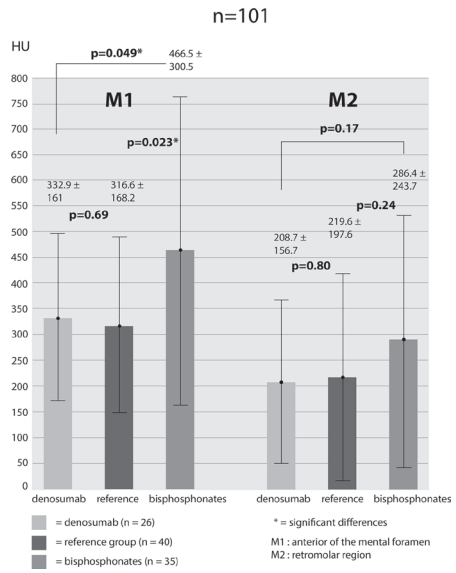

Figure 3 CT—measured bone density values in all of the three groups in two locations (M1 + M2). Values given in HU (mean ± standard deviation); *=significant differences ($p < 0.05$). HU, Hounsfield unit.

significantly higher HU-values in bp-group compared to db-group ($p = 0.049$) and bp-group to reference-group ($p = 0.023$). Differences between db-group and reference group showed no significance ($p = 0.69$). For M2-location, it emerged a distinct but not significant difference in bone density values between db- and bp-group ($p = 0.17$) and reference- to bp-group ($p = 0.24$). Furthermore, there was no significant difference between db- and reference-group ($p = 0.80$) (Figure 3). Added up values (M1 + M2) again showed a significantly higher bone density value of bp- to db-group ($p = 0.027$) and to the reference-group ($p = 0.016$). Bone density values of db- and reference-group showed almost no difference ($p = 0.84$) (Figure 4). For the purpose of investigating the impact of treatment duration on bone density values we subdivided each of the two groups. db-group was divided into treatment duration less than 4 years (<4y; $n = 13$) and more than 4 years (>4y; $n = 13$). None of the measurements at both locations showed significant differences in one density values (M1: 297.9 HU (<4y) *vs* 367.9 HU (>4y) [$p = 0.28$]; M2: 215.3 HU (<4y) *vs* 202.1 HU (<4y) [$p = 0.84$]). bp-group was subdivided into treatment duration less than 5 years (<5y; $n = 19$) and more than 5 years (>5y; $n = 16$). The measured values showed no significant differences in both locations (M1: 453.7 HU (<5y) *vs* 485.3 HU (>5y) [$p = 0.80$]; M2: 278.2 (<5y) *vs* 298.2 HU (>5y) [$p = 0.82$] (Figure 5).

Discussion

Recent studies investigated the development of sclerotic bone architecture with denser cancellous bone, thicker trabeculae and less complex structure in rat jaws treated with zoledronic acid. Subsequently, a significant reduction of blood vessel areas, smaller marrow spaces and nutritive canals were observed. Furthermore, bp-induced bone turnover suppression may induce bone corticalization and impact vascularization.[15] It becomes evident that bp-induced changes in bone microstructure plays a key role in ONJ-development.[19,20] Against the backdrop of these results, we expected increased bone

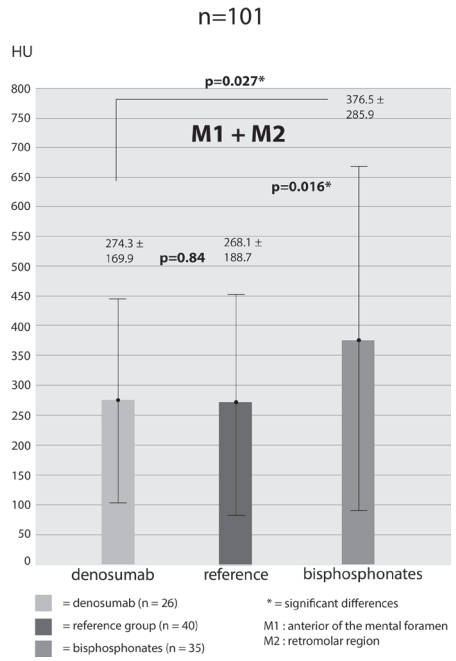

Figure 4 CT—measured bone density values (added M1 + M2) in all of the three groups. HU, Hounsfield unit.

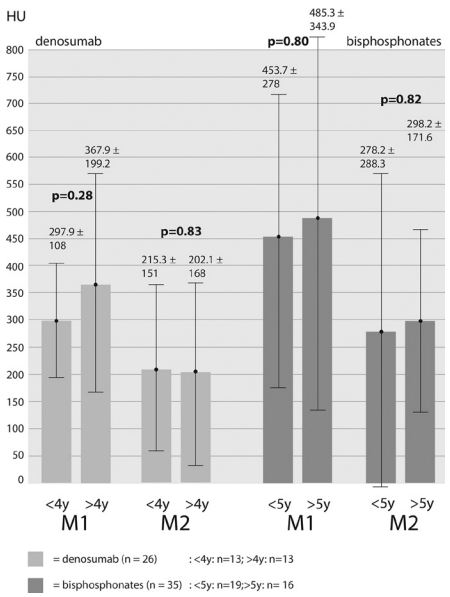

Figure 5 Differences in CT—measured bone density values with regard to duration of medication intake and location of measurement. <4y/<5y=under 4/5 years of treatment;>4y/>5y=over 4/5 years of treatment. HU, Hounsfield unit.

density measurements in CT-scans of mandibles in patients treated with antiresorptive drugs and suffering from MRONJ, compared to a gender- and age-balanced control group. Although, bisphosphonates and denosumab specifically target osteoclasts and both alendronate and denosumab lead to significant improvement in total bone density,[21] differences in structure, specific effects on osteoclasts and molecular targeting have to be respected.[8] Key target for the nitrogen-containing bisphosphonates is the farnesyl pyrophosphate synthase, which is needed for prenylation of proteins. Db is a fully human monoclonal antibody that inhibits RANKL to which it binds with high affinity and specificity. Thus, bps need to be taken up from bone matrix into osteoclast cytoplasm during bone resorption, while db works in the extracellular milieu, affects osteoclasts and their precursors which express the RANK protein and does not associate with bone tissue. Furthermore, db is not embedded within bone tissue and is cleared from the bloodstream through the reticuloendothelial system, with a half-life of approximately 26 days.[22]

Bps have a strong affinity to bone and become incorporated in the bone. There, the substance remains until the process of bone resorption releases the molecules, this process can extend over a period of weeks to years.[23] Nevertheless, the site-specific side-effects on the jaw (MRONJ) are similar in both classes of antiresorptive substances.[24] Interestingly, we observed no significant bone density differences within both groups (db and bp) regarding the duration of medication intake. In db group, the bone density values for M1 and M2 were higher in >4y-group than in <4y-group, but not significantly. In bp group, the bone density values for M1 were slightly higher in >5y-group than in <5y-group. In M2, values were even slightly lower in >5y-group. Differences showed no significance. The supposition of the authors is that structural changes in the bone that can be detected by CT scans proceed rather rapidly after the initial intake of bisphosphonates.

Comparing bone density values of all three groups showed significantly denser cancellous bone in patients treated with bp than db- and reference-group. However, db- and reference-group bone density values were almost measured equal in both locations (Figure 6). The mean age of the patients in every group was practically equal and the groups were almost gender balanced. Hence, two major biases with generally great effect on bone were eradicated.

In other CT studies of bone at the distal radius, effects in the cortical bone were measured.[21] Treatment over 12 months led to a significantly greater bone density increase with db than with alendronate. Other authors report alike results regarding the benefits of db over a greater duration of treatment.[8] Nonetheless, density gains of db are usually outlined for cortical bone and are not specifically addressing changes in the alveolar bone of patients suffering from MRONJ. Furthermore, existing studies investigated mostly the impaired bone healing and development of ONJ in the context of bisphosphonate intake.[19,20,25]

By taking into consideration the similar side-effects of db and bps on alveolar bone,[26] two presumptions arise on the backdrop of our results. Firstly, providing that previously demonstrated increased antiresorptive medication induced jaw bone density is directly associated with less blood perfusion in the jaw bone[27] and subsequent development of ONJ, this prediction can solely be sustained for bp therapy but not for db treatment. Secondly, significantly greater effects of db compared to bps on bone density and microarchitecture in bones are either constrained to the cortical and not the cancellous

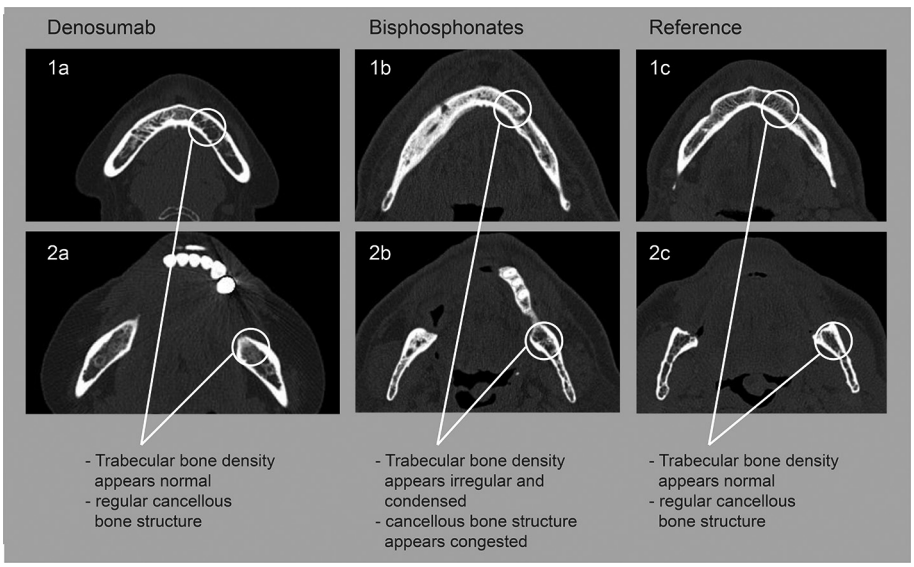

Figure 6 Examples of radiological findings of patients treated with denosumab (a), bisphosphonates (b) or reference group (c). 1 (a, b, c): anterior of the mental foramen; 2 (a,b,c) retromolar region.

bone or elsewise different conditions apply for mandibular bone density development.

However, our results have some limitations. CT scans for measuring bone density levels were used despite the fact that DXA is the most widely validated and preferred technique.[28] Although recent studies presented reasonable data comparing DXA and CT scans for bone density measurements,[29] alveolar bone was not implied in the settlement. Furthermore, the group of patients with bp-associated osteonecrosis of the jaw was very heterogeneous regarding the intake of different substances. Additionally, the exact doses of intake and administration intervals remained not fully clear in some cases.

In conclusion, we assume that bps change the microarchitecture of the alveolar bone by depositing in the bone in an additional different way than denosumab does. This may subsequently lead to a bp-specific corticalization and a decrease of vascularization in the jaw. Hence, the impairment of vascularization could compromise the alveolar bone and make it more vulnerable to infection and ONJ development.

Acknowledgements

We declare that we have no competing interests. The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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