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A systematic review on the correlation between skeletal and jawbone mineral density in osteoporotic subjects.

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Running title: Are jaws and skeletal bone density related in osteoporosis?

Keywords: bone density; densitometry; osteoporosis; bone disease, metabolic; jaw; review

Abstract

Objectives The aim of this systematic review was to assess if the systemic skeletal reduction of bone mineral density (BMD) that characterizes osteoporotic subjects is also associated to a reduction of BMD in the jawbones.

Material and methods Two reviewers searched independently and in duplicate three databases up to May 2014 and assessed the risk of bias by using a tailored version of the Newcastle Ottawa scale (NOS). Only papers reporting either Pearson correlation coefficient or Spearman's rank correlation coefficient between skeletal and jawbone mineral density in more then five osteoporotic subjects were selected.

Results From 1763 citations, 64 full-text papers were screened and five papers that met the inclusion criteria were included in the final analysis. None of the included studies complied with all NOS criteria and since only two studies were eligible for meta-analysis, this was not performed..

Conclusions Only limited conclusions can be drawn from this systematic review, due to the small number of studies included, their heterogeneity and their high risk of bias. Future studies that take into consideration both upper and lower jaws, that use the same technique to measure skeletal and jaw BMD (ideally Dual-energy X-ray absorptiometry, DXA) and that account for confounding variables (such as medications/diseases affecting bone metabolism and demographics) are needed in order to provide more robust conclusions.

Introduction

Osteoporosis is a common skeletal disease that progressively reduces bone mass and changes its micro architectural structure, thus increasing the risk of fractures. The World Health Organization (WHO) has defined osteoporosis as a level of bone mineral density (BMD), calculated with DXA (Dual-energy X-ray absorptiometry) technique, 2.5 standard deviations (SD) or more below the average mean value for young healthy women (T-score $\leq$ -2.5) (Kanis, Melton et al. 1994, Kanis, McCloskey et al. 2013). The reference range recommended for calculating the T score is the National Health and Nutrition Examination Survey (NHANES) III database for femoral neck measurements in young Caucasian women (Looker, Wahner et al. 1998) and for this reason femoral neck is commonly used as the reference site. DXA scan is considered the gold standard for measuring BMD and diagnosing osteoporosis for its reproducibility, short scan times, large normative data and very low doses of radiation (Blake and Fogelman 2007), although other techniques such as quantitative ultrasound (QUS), quantitative computed tomography (QCT), peripheral DXA, digital X-ray radiogrammetry and radiographic absorptiometry are also commonly employed (Kanis, McCloskey et al. 2013).

Approximately 30% of all American and European post-menopausal women have osteoporosis and more than 40% of them are likely to experience one or more fragility fractures during their remaining lifetime (Melton, Chrischilles et al. 1992, Reginster and Burlet 2006). According to Johnell et al (Johnell and Kanis 2006), osteoporosis in Europe accounts for more deaths and morbidity than any other neoplastic disorder, save only for lung cancer, thus making the burden of osteoporosis extremely alarming.

As the number of osteoporotic patients requiring dental care is increasing, it would be important to know if osteoporosis is associated with a reduction of bone mass and density also in the jawbones. This could have important clinical implications, related for example to the success/survival and osseointegration of dental implants, to the success of bone regeneration therapies or to the risk of an increased bone loss in subjects affected by periodontitis (Blomqvist, Alberius et al. 1996, August, Chung et al. 2001, Gondim, Aun et al. 2013, Passos, Vianna et al. 2013). Although the evidence from the literature is only modest, it is plausible to hypothesize that osteoporotic-induced systemic bone loss may include also bone loss at the jaws, as bones of the skeleton. Pre-clinical studies in ovariectomized animals reported that estrogen deficiency could determine a decrease in bone volume and alterations in the trabecular structure of the mandibular condyle (Kuroda, Mukohyama et al. 2003, Kosugi, Yonezu

et al. 2013), in the inter-radicular septa of molar alveolar bone (Tanaka, Ejiri et al. 2002, Dai, Zhang et al. 2014) and also an increase in mandibular cortical porosity (Dvorak, Reich et al. 2011). A correlation between lumbar and alveolar bone density in ovariectomized monkeys has also been documented (Anwar, Tanaka et al. 2007). Some clinical studies reported that there is an increased alveolar bone resorption in osteoporotic versus non-osteoporotic edentulous patients (Hirai, Ishijima et al. 1993, Singhal, Chand et al. 2012) and that medications affecting systemic bone density (like hormone replacement therapy and bisphosphonates) are associated with a slower loss of alveolar bone (Graziani, Rosini et al. 2008) and improved periodontal parameters (Lane, Armitage et al. 2005, Lopez-Marcos, Garcia-Valle et al. 2005). However, other clinical studies did not confirm the influence of systemic bone mineral density on the resorption of edentulous jaws (Elders, Habets et al. 1992, Ozola, Slaidina et al. 2011, Springe, Slaidina et al. 2014).

Some clinical studies have investigated the relationship between bone density measured in different systemic skeletal sites and in the jawbones in subjects with different T scores. Although many of these studies have found a positive correlation (Horner, Devlin et al. 1996, Jonasson, Bankvall et al. 2001, Drozdzowska, Pluskiewicz et al. 2002, Takaishi, Okamoto et al. 2005, Erdogan, Incki et al. 2009, Vishwanath, Kumar et al. 2011, Makker, Singh et al. 2012, Esfahanizadeh, Davaie et al. 2013), others have reported that jawbone density is not, or only little, correlated to the density in other anatomic sites (Kingsmill and Boyde 1999, Jonasson 2009, Holahan, Wiens et al. 2011). A few studies did not manage to find differences in jawbone density between normal and osteopenic/osteoporotic subjects (Mohajery and Brooks 1992, Gulsahi, Paksoy et al. 2010).

The heterogeneity between the available studies may have contributed to this wide variability of results. In fact, in the published studies different techniques to measure bone density were adopted, dentate and edentulous areas were often pulled together and populations with different demographic characteristics were evaluated without accounting for confounding variables. In addition, the methods used for bone density measurement often had insufficient precision and accuracy.

Despite the contradicting results, a recent review suggested that osteoporotic bone should be regarded as equivalent to Type IV, according to Lekholm and Zarb classification (Lekholm, Zarb et al. 1985) and that, conforming to the limited available evidence, the clinician may also consider to allow a longer healing period for implant osseointegration before prostheses insertion in osteoporotic patients (Gaetti-Jardim, Santiago-Junior et al. 2011).

As a dedicated software for DXA measurement of the jaws does not exist, it has been proposed to adapt the forearm software to the mandible, despite evident practical difficulties (Horner, Devlin et al. 1996). Many other different techniques have been used to measure jawbone density, such as dual-photon absorptiometry (DPA), quantitative computer tomography (QCT), film densitometry, pixel intensity (PI), fractal dimension and visual inspection (von Wowern 1974, Klemetti, Kolmakov et al. 1993, Law, Bollen et al. 1996, Lindh, Horner et al. 2008), thus making comparisons among the studies very difficult. Bodic et al (Bodic, Amouriq et al. 2012) reported that computer tomography (CT) remains the most appropriate technique for the evaluation of mandibular bone density but they didn't find a correlation between mandibular and iliac bone in 20 human cadavers. On the contrary, a recent study of Chai et al (Chai, Chau et al. 2014) found that mandibular bone density measured in Hounsfield units (HU) with CT scans in edentulous subjects between 50 to 80 years of age has a modest but significant correlation with T scores and the authors suggested HU cut-offs for identifying osteoporotic subjects.

The aim of this systematic review was to summarize and critically appraise today's knowledge on the correlation between systemic skeletal BMD and BMD of the jaws in osteoporotic subjects. In other words, we were interested to clarify if osteoporosis could also affect the jawbones. Although previous literature reviews have addressed the potential detrimental effect of osteoporosis on jawbones, they mainly focused on the outcomes of dental implants in osteoporotic patients (Tsolaki, Madianos et al. 2009, Gaetti-Jardim, Santiago-Junior et al. 2011), without answering the question whether jawbones behave like the other bones of the skeleton in osteoporotic conditions. This will give us useful information in the attempt to consider osteoporosis from a multidisciplinary point of view and it may provide guidelines for future studies.

Materials & Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati et al. 2009) was followed.

Focused question

The question addressed was the following: "Is jawbone mineral density correlated to skeletal bone mineral density in osteoporotic subjects?"

Eligibility criteria

Observational studies assessing the correlation between jaw (either mandible or upper jaw) and skeletal BMD in osteoporotic subjects were considered. Only studies with at least 5 osteoporotic patients were selected, in order to exclude individual case reports. No restriction related to the technique adopted to measure bone density was initially applied in order to avoid omitting relevant data. However, since the sensitivity and specificity of the radiographic technique is crucial for reflecting bone density changes, it was taken into consideration and described in details for all the included studies in the quality data analysis of the result and discussion sections and in **Table** 3. The primary outcome of this review was to determine if in osteoporotic subjects the reduced systemic skeletal BMD is also associated with a reduced BMD in the jaws, therefore the studies had to report one of the following measures: the Pearson correlation coefficient or the non-parametric Spearman's rank correlation coefficient in osteoporotic subjects. Both coefficients measure the degree to which two variables are related, the first one applies to normally distributed variables and linear relations, whilst the second one is a nonparametric measure of statistical dependence and measures the monotonic relationship between two variables (Zou, Tuncali et al. 2003).

Search strategy, selection of trials and data abstraction

The research strategy included terms related to the population and the intervention investigated in this review and was performed in three databases, MEDLINE via OVID, EMBASE and The Cochrane Database (including the Central Register of Controlled Trials (CENTER)), updated to May 2014. In addition, bibliographies of review articles on this topic and of all the studies included for data extraction were screened and a hand search was performed in the major journals of the field (Bone, Journal of Bone and Mineral Research, Osteoporosis International, Menopause, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics, Journal of Prosthetic Dentistry). In an attempt to include also unpublished data, a specific theses database, www.theses.com/, was additionally screened and soon-to-be-published manuscripts were searched by contacting research groups with an interest in osteoporosis and in oral consequences of osteoporosis. Finally, Grey Literature was searched in opensigle.inist.fr. No language restrictions were applied. The search strategy for MEDLINE and EMBASE used a combination of MeSH terms and text words which were combined as Population AND Intervention (**Table 1**). Due to the large volume of literature on this topic, a three-stage screening was applied to increase the precision of screening. All stages (titles,

abstract, full-text) were carried out in duplicate and independently by two reviewers (EC and JCP) and the level of agreement at each of the three-stages was calculated using Kappa statistics. Any disagreement was resolved by discussion and, if necessary, a third reviewer (NM) was consulted. At the stage of full-text screening, a data extraction form was completed to check eligibility of the studies and, if eligible, to collect detailed information about population, intervention and outcomes. Reasons for study exclusion were also recorded (**Tab. 2**). Any ambiguous or incomplete data were further investigated by contacting the researchers responsible for the work.

Quality assessment

The methodological quality of the studies was assessed independently and in duplicate by two reviewers (EC, JCP), as part of the data extraction process. The Newcastle-Ottawa Scale (NOS) was applied. This tool arose by the combined efforts of the Universities of Newcastle and Ottawa to assess the quality of non-randomized studies and was endorsed for use in systematic reviews of non-randomized studies by The Cochrane Collaboration (Higgins and Green updated March 2011). The NOS provides predefined criteria covering three domains (selection of participants, comparability of study groups and ascertainment of exposure/outcome), some of which have to be further specified according to the aim of the review. We specified these criteria and tailored the tool for cross-sectional studies in a consensus meeting with all authors before assessing the studies.

Data synthesis and statistical analysis

Correlation coefficients were extracted from the studies meeting inclusion and exclusion criteria and confidence intervals were obtained through Fisher's z transformation. Following statistician's advice, we decided to perform meta-analysis only in case we found at least three papers that reported the Pearson correlation coefficient and which measured systemic skeletal BMD in the same anatomic site.

Results

Studies included

Four studies were identified through the database search and one additional study was retrieved through hand-search and bibliography check that met the inclusion/exclusion criteria (**Figure 1**). The reasons for exclusion of the studies at the level of full-text screening are reported in **Table 2**. Kappa statistics showed a high level of agreement between the reviewers (K> 0.90) at all three stages of

screening. All the included studies had a cross-sectional design and involved only post-menopausal osteoporotic women (**Table 3**).

The systemic skeletal sites evaluated by the studies and the techniques applied to measure BMD were pretty heterogeneous (**Table 3**). The first study of Kribbs et al (Kribbs, Smith et al. 1983) measured systemic skeletal BMD only at the forearm (at one tenth, S1, and one fifth, S2, of its length) by using single photon absorptiometry (SPA), while the second study from the same research group (Kribbs, Chesnut et al. 1989) considered also the lumbar spine, whose BMD was measured by using both dual photon absorptiometry (DPA) and computed Tomography (CT). Cakur et al (Cakur, Sahin et al. 2008) measured systemic skeletal BMD at the lumbar spine by using DXA, while the same group (Cakur, Dagistan et al. 2009) one year later and the group of Klemetti (Klemetti, Vainio et al. 1993) considered both lumbar spine and femur neck BMD and assessed them through DXA scan

Three studies used oral radiographs with an aluminum step wedge to measure mandibular density (Kribbs, Smith et al. 1983, Kribbs, Chesnut et al. 1989, Cakur, Sahin et al. 2008), and another one used a quantitative computed tomography QCT scan (Klemetti, Vainio et al. 1993). Cakur et al (Cakur, Dagistan et al. 2009) were the only ones that used the same technique (DXA scan) to measure skeletal and mandible BMD.

Two studies reported the use of Spearman's rank correlation coefficient, with pretty different results: the first study of Cakur et al (Cakur, Sahin et al. 2008) found a significant correlation between BMD at the lumbar spine and BMD at the mandible (r_s = 0.434, p=0.030), whilst the same group one year later did not manage to find a significant correlation between lumbar and femur BMD and mandibular BMD (r_s = 0.017 and r_s = -0.054 respectively) (Cakur, Dagistan et al. 2009). The remaining three studies used the Pearson correlation coefficient. Klemetti et al (Klemetti, Vainio et al. 1993) distinguished between the most and the average osteoporotic subjects according to the BMD values of the femur neck obtained by a dual-energy x-ray transmission apparatus. In particular, in the most osteoporotic group (BMD at femur neck <920 mg/cm^2), they reported significant correlation coefficients between cortical-buccal and cortical-lingual mandibular BMD and femur BMD (respectively r= 0.51, p <0.05 and r=0.54, p < 0.001). Conversely, they did not find a significant correlation between cortical-buccal/lingual mandibular BMD and lumbar BMD. Both studies of Kribbs et al (Kribbs, Smith et al. 1983, Kribbs, Chesnut et al. 1989) reported a significant correlation between BMD at the forearm and at the mandible (respectively r= 0.594 with p < 0.001 and r= 0.34 with p< 0.01).

All included studies measured the density of the jaws in the mandible and no study considered the maxilla. Cakur et al studies took into consideration a 10X10 mm^2 area of the mandible free of teeth and roots (Cakur, Sahin et al. 2008, Cakur, Dagistan et al. 2009), Klemetti et al measured the cortical and trabecular mandibular density distally to the mental foramen (Klemetti, Vainio et al. 1993) and Kribbs et al measured mandibular density either around mandibular teeth (dentate subjects) or distally to the mental foramen (edentulous subjects) (Kribbs, Smith et al. 1983, Kribbs, Chesnut et al. 1989). Previous studies assessing BMD of the mandible considered various areas of interest, located in the ramus (Horner, Devlin et al. 1996, Gulsahi, Paksoy et al. 2010, Esfahanizadeh, Davaie et al. 2013), the body of the mandible (Horner, Devlin et al. 1996, Drozdzowska, Pluskiewicz et al. 2002, Gulsahi, Paksoy et al. 2010, Makker, Singh et al. 2012, Esfahanizadeh, Davaie et al. 2013), the symphysis region (Horner, Devlin et al. 1996, Gulsahi, Paksoy et al. 2010) or the interdental areas (Jonasson, Bankvall et al. 2001, Takaishi, Okamoto et al. 2005, Erdogan, Incki et al. 2009, Jonasson 2009).

Assessment of methodological quality

There were no studies complying with all NOS criteria. Both studies of Cakur et al had the highest NOS score with seven out of eleven stars, whilst the two studies of Kribbs et al collected only three out of eleven stars (**Table 4**). Most of the quality issues were related to the selection of the subjects (either the osteoporotic condition or the representativeness of the subjects were not well-defined) and to the exposure (most studies did not use the same technique to measure skeletal and mandible BMD and they did not define if there was an appropriate interval of time between the two ascertainments).

Meta-analysis

Only three studies reported Pearson correlation coefficients (Kribbs, Smith et al. 1983, Kribbs, Chesnut et al. 1989, Klemetti, Vainio et al. 1993) (we assumed that both Kribbs studies used it), but only the two Kribbs studies compared BMD at the same skeletal site (forearm) with mandible BMD and, as a consequence, we had to exclude Klemetti study. Meta-analysis was therefore not performed.

Discussion

Four out of the five studies included in this review reported a significant correlation between BMD measured at different systemic skeletal sites and mandible BMD. Cakur et al (Cakur, Dagistan et al.

2009) study is the only one that did not confirm this correlation. However, we need to be very cautious on drawing conclusions, as these five studies were hardly comparable, since they used different techniques to measure skeletal and mandible BMD and they took into consideration different anatomic sites.

The meta-analysis was not performed, since we retrieved only on two studies that compared skeletal and jawbone BMD measured at the same anatomical sites and both did not have a high methodological quality..

Although there are no precise guidelines on how to interpret correlation coefficient results, the magnitude of correlation is usually considered in relation to the p-values (which is influenced by the sample size) and the r squared. The correlation coefficient can take values from -1 to 1, where 1 is the perfect correlation. The four included studies that found a positive correlation between mandible and skeletal BMD reported correlation coefficients ranging from 0.3 to 0.697 (Kribbs, Smith et al. 1983, Kribbs, Chesnut et al. 1989, Klemetti, Vainio et al. 1993) (**Table 3**). In the study that did not find a significant correlation, a Spearman's rank correlation coefficient ranging from -0.054 to 0.017 was reported (Cakur, Dagistan et al. 2009) (**Table 3**).

Several studies had also to be excluded during the screening stages because they did not distinguish between osteoporotic and healthy patients when reporting the correlation coefficients between skeletal and jaw BMD, thus further limiting the possibility of drawing robust conclusions.

Another limitation of this review is related to the fact that all studies considered only mandibular BMD, without taking into account the maxilla. It is well known that in osteoporotic subjects bone loss is not uniform and that the trabecular bone is earlier and more deeply affected than the cortical bone (Clarke and Khosla 2010, Khosla 2013). The mandible has a better resemblance with the femur neck (Devlin, Sloan et al. 1994, Devlin and Whelton 2013), where fractures are primarily caused by a loss in cortical rather than trabecular bone (Bell, Loveridge et al. 1999, Crabtree, Loveridge et al. 2001). Considering that the maxilla is mainly made of trabecular bone, it is likely that bone density measured at this site would have been better related to skeletal osteoporosis. However, the lack of stable referral points (like the mental foramen in the mandible) makes it challenging to evaluate standardized sites in the maxilla.

According to Gulsahi et al, BMD is the highest in the mandibular anterior region and lowest in the maxillary anterior and premolar regions (Gulsahi, Paksoy et al. 2010).

A recent study described a decrease in jawbone density assessed by DXA scan in osteoporotic subjects and observed the lowest level of density in the anterior region of the maxilla (Esfahanizadeh, Davaie et al. 2013). In addition, they found a positive correlation ($p< 0.05$) between BMD at various regions of the jawbones and femur and vertebrae BMD.

When dealing with jawbones it should also be borne in mind that they display unique anatomic characteristics in comparison with other bones of the skeleton, owing for example to their special relationship with teeth and the distinction between the more stable basal bone and the alveolar bone, which atrophies after teeth are lost (Tallgren 2003, Pietrokovski, Starinsky et al. 2007). Alveolar bone arises from the dental follicle (neural crest origin) and is therefore physiologically different from all other bones (Duailibi, Duailibi et al. 2006). It may be hypothesized that these and other anatomical/physiological peculiarities of the jaws can somehow account for differences in bone metabolism response (Seldin 2012). Therefore, applying the current reference standards for the diagnosis of skeletal osteoporosis (based on the NHANES III study (Looker, Wahner et al. 1998)) also to the diagnosis of jawbone osteoporosis, could be misleading. Further research on jawbone BMD in a large and representative population is necessary in order to develop a jawbone T score or Z score that could probably be used, similarly to the available skeletal scores, for the diagnosis of jawbone osteoporosis.

Some researchers pointed that the basal area of the mandible posterior to the mental foramen is probably the only part of the jaws with reasonably suitable characteristics to be a standard site for BMD measurements, since it has small inter- and intra-individual variations in anatomical size, shape, bone structure ad function (von Wowern 2001).

Among the five studies included in this review, three (Klemetti, Vainio et al. 1993, Cakur, Sahin et al. 2008, Cakur, Dagistan et al. 2009) took into consideration edentulous areas of the mandible and the last two studies (Kribbs, Smith et al. 1983, Kribbs, Chesnut et al. 1989) pulled together edentulous and dentate areas without distinguishing the results.

All the included studies recruited only osteoporotic post-menopausal women, therefore it is not possible to generalize the results to other forms of osteoporosis or to men.

Conclusions

The small number and heterogeneity of the retrieved studies did not allow clarifying if skeletal osteoporosis is associated also to osteoporosis in the jawbones. We recommend that future studies

should use the same technique to measure skeletal and jaw BMD (ideally DXA scan would be the best option, since it is considered the gold-standard for osteoporosis diagnosis), that they should possibly consider both upper and lower jaws and distinguish between basal and alveolar bone.

Since it is overall accepted to use hip and lumbar spine as references for diagnosing osteoporosis, it would be probably more useful to compare jawbone density with the density of these bones.

Future efforts should be dedicated to address this correlation not only in post-menopausal women but also in men and in patients with secondary osteoporosis, in order to have a wider picture of this possible association. Whether a correlation between jaws and other bones of the skeleton is confirmed, future studies may be able to identify customized thresholds for T and Z scores also for the jawbones.

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Table 1 Search strategy for Medline and Embase

Table 2 Reasons for exclusions of the 60 studies at the level of full-text screening

Table 3 Characteristics of the studies included in the systematic review. Correlation coefficient's confidence intervals were obtained through Fisher's z transformation. (r_s: Spearman's rank correlation coefficient; r: Pearson correlation coefficient; DXA: Dual-energy X-ray absorptiometry; QCT: Quantitative Computed Tomography; SPA: single photon absorptiometry; DPA: dual photon absorptiometry). * In the Klemetti et al study, the authors distinguished between the "most osteoporotic group", that had a BMD at femur neck <920 mg/cm^2, and the "average osteoporotic group", that had 920 <BMD< 1040 mg/cm^2.

Table 4 Assessment of methodological quality of the studies by the use of a tailored version of Newcastle-Ottawa Scale (NOS). A maximum of eleven stars could be assigned to each study.

Figure 1 Four-phase flow diagram of the article selection procedure, according to PRISMA statement (Moher, Liberati, Tetzlaff, Altman & Group 2009).

Table 1.

MEDLINE via OVID (For Ovid OLDMEDLINE 1946 to 1965, Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to May 2013.)			
	Mesh terms	**Free-text search**	**Limits**
Population	bone disease, metabolic/ or exp bone demineralization, pathologic/ or exp osteoporosis	osteoporo$ OR osteopeni$	NOT (animals NOT humans)
Intervention/Exposure	Bone Density OR exp Densitometry exp Jaw OR exp Jaw Edentulous	(bone adj2 densit$) OR (bone adj2 content) OR bmd OR bmc OR densitometr$ jaw$ OR mandib$ OR maxill$ or edentul$	
EMBASE (from 1980 to May 2013) and EMBASE Classic (from 1947 to 1979):			
	Emtree terms	**Free-text search**	**Limits**
Population	exp. osteoporosis OR osteopenia	osteoporo$ OR osteopeni$	NOT (animals NOT humans)
Intervention/Exposure	Bone Density OR Bone densitometry Jaw OR Edentulousness	(bone adj2 densit$) OR (bone adj2 content) OR bmd OR bmc OR densitometr$ jaw$ OR mandib$ OR maxill$ or edentul$	

Table 2

Author and year	Reasons for exclusion
(Alman 2012)	No primary outcome reported
(Alonso 2012)	No primary outcome reported
(Amorim 2006)	No primary outcome reported
(Amorim 2007)	Duplicate
(Ardakani 2012)	No primary outcome reported
(Bakalczuk 2006)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Bodic, Amouriq et al. 2012)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Bozic 2006)	No primary outcome reported
(Buyukkaplan 2012)	No primary outcome reported
(Byung 2005)	Duplicate
(Devlin 2007)	No primary outcome reported
(Drozdzowska, Pluskiewicz et al. 2002)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Erdogan, Incki et al. 2009)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Geraets 2008)	No primary outcome reported
(Gulsahi, Paksoy et al. 2010)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Hedstrom 2010)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Holahan, Wiens et al. 2011)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Horner 1992)	No primary outcome reported
(Horner, Devlin et al. 1996)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Horner 1998)	No primary outcome reported
(Jagelaviciene 2010)	No primary outcome reported
(Jonasson, Bankvall et al. 2001)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Jonasson 2007)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Jonasson 2009)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Kingsmill 1999)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Klemetti, Kolmakov et al. 1993)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Klemetti 1993)	No primary outcome reported
(Klemetti 1993)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Koh 2012)	No primary outcome reported
(Kribbs 1990)	No primary outcome reported
(Kribbs 1992)	No primary outcome reported
(Law, Bollen et al. 1996)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Lee 2005)	No primary outcome reported
(Lee 2013)	No primary outcome reported
(Li 2009)	No primary outcome reported
(Li 2011)	No primary outcome reported
(Lin 2010)	No primary outcome reported
(Lindh, Horner et al. 2008)	No primary outcome reported
(Makker, Singh et al. 2012)	No primary outcome reported
(Mohajery and Brooks 1992)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Mohammad 1996)	No primary outcome reported
(Munakata 2011)	No primary outcome reported
(Nackaerts 2008)	No primary outcome reported
(Naitoh 2007)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Nitta 2003)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Payne 1999)	No primary outcome reported

(Pluskiewicz 2000)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Ruttimann 1992)	No primary outcome reported
(Shi 1996)	No primary outcome reported
(Southard 1996)	No primary outcome reported
(Streckfus 1997)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Taguchi 1996)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Taguchi 1999)	No primary outcome reported
(Takaishi, Okamoto et al. 2005)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Tomaszewski 1997)	No primary outcome reported
(Tomaszewski 2002)	No primary outcome reported
(Tosoni 2006)	No primary outcome reported
(Vishwanath, Kumar et al. 2011)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Von Wowern 1988)	Osteoporotic and non-osteoporotic subjects pooled together when measuring the correlation coefficient
(Yasar 2006)	No primary outcome reported

Table 3

Study, year	No Osteoporotic subjects	Ethnicity	Gender	Age range (yrs)	Sites/ techniques of skeletal BMD measurement	Sites/techniques of jaws BMD measurement	Correlation coefficient (95% CI)	p value
Cakur 2008	25	Unclear	Women	50-59	Lumbar spine/ **DXA**	Mandible/ panoramic radiograph with **aluminium step wedge** (then converted in DXA measurement)	r_s = **0.434** (0.047; 0.708)	0.030
Cakur 2009	80	Unclear	Women	42-68	Lumbar spine/**DXA** Femur neck/**DXA**	Mandible/**DXA**	r_s = **-0.054** (-0.271; 0.168) (spine) r_s = **0.017** (-0.203;0.236) (femur)	0.884 0.637
Klemetti 1993	27 osteoporotic, 22 osteopenic*	Unclear	Women	48-56	Lumbar spine/**DXA** Femur neck/**DXA**	Cortical and trabecular mandible/**single-energy QCT**	Osteoporotic group (<920 mg/cm^2): **r** = **0.51** (cortical-buccal mandible/femur) **r** = **0.37** (cortical-buccal mandible/spine) **r** = **0.54** (cortical-lingual mandible/femur) **r** = **0.32** (cortical-lingual mandible/spine) Osteopenic group (920 <BMD< 1040 mg/cm^2): **r** = **0.59** (cortical-buccal mandible/femur) **r** = **0.25** (cortical-buccal mandible/spine) **r** = **0.32** (cortical-lingual mandible/femur) **r** = **0.22** (cortical-lingual mandible/spine)	 < 0.05 > 0.05(NS) < 0.05 > 0.05(NS) < 0.05 > 0.05 (NS) > 0.05 (NS) > 0.05 (NS)
Kribbs 1983	30	Unclear	Women	Unclear	Forearm (at one tenth, S1, and one fifth, S2, the length of the forearm)/**SPA**	Mandible/ peri-apical radiograph with **aluminum step wedge** attached to the occlusal surface	Whole population: **r** = **0.594** (S1) (0.297; 0.786) **r** = **0.657** (S2) (0.389; 0.823) Edentulous women (n=7): **r** = **0.632** (S1) (-0.231-0.938) **r** = **0.697** (S2) (-0.118-0.951)	 < 0.001 < 0.001 > 0.05 (NS) > 0.05 (NS)
Kribbs 1989	85	Unclear	Women	50-84	Forearm (at one tenth, S1, and one fifth, S2, the length of the forearm)/**SPA** Lumbar spine/**DPA** and **QCT**	Mandible/peri-apical radiograph with **aluminum step wedge** attached to the occlusal surface	**r** = **0.34** (0.137; 0.516) (mandibular BMD/SPA forearm) **r** = **0.41** (0.216; 0.573) (mandibular bone mass/SPA forearm) **r** = **0.33** (0.126; 0.507) (mandibular bone mass/DPA spine) **r** = **0.3** (0.093; 0.482) (mandibular bone mass/CT spine)	< 0.01 < 0.01 < 0.01 < 0.05

Table 4

		Cakur 2008	Cakur 2009	Klemetti 1993	Kribbs 1983	Kribbs 1989
SELECTION (max 2 stars)	**Ascertainment of the exposure (osteoporosis)**: a) Validated measurement tool for BMD (WHO guidelines or National Society guidelines) * b) Non-validated measurement tool/self-report/unclear	★	★			
	Representativeness of the subjects (osteoporotic subjects): a) Truly representative of the average in the target population. * (random or consecutive sampling) b) Potential for selection bias or no description of the sampling strategy					
COMPARABILITY (max 2 stars)	**Confounding factors are controlled.** a) The study controls for concomitant diseases affecting bone metabolism. * b) The study control for any additional factor (e.g. Medications). * c) No factors are controlled/Not specified	★	★	★		
EXPOSURE (max 7 stars)	**Ascertainment of jaw bone density:** a) The method is well-described, calibration of the technique is reported and the examiner(s) is blinded to skeletal BMD** b) The method is well-described but the blindness of operators and/or the calibration of the technique are not reported * c) Subjective evaluation/ Not specified	★	★	★	★ (reference to a previous paper)	★ (reference to a previous paper)
	Ascertainment of skeletal bone density: a) Validated measurement tool (DXA scan)** b) Non-validated measurement tool but the method is well-described and calibration is reported* c) Subjective evaluation/ Not specified/Not well described measurement tool	★★	★★	★★	★	★
	The same method of ascertainment was used to measure skeletal and jaw bone mineral density a) Yes * b) No/ Not specified		★			
	Statistical test: a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including the probability level (p value) * b) The statistical test is not appropriate, not described or incomplete/ insufficient	★	★	★	★	★
	Interval time between ascertainment of skeletal and jaw bone density: a) Reported and appropriate (within 12 months)* b) Not reported/Not appropriate	★				