A prospective study of mandibular trabecular bone to predict fracture incidence in women: A low-cost screening tool in the dental clinic

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ABSTRACT

Bone structure is the key to the understanding of fracture risk. The hypothesis tested in this prospective study is that dense mandibular trabeculation predicts low fracture risk, whereas sparse trabeculation is predictive of high fracture risk. Out of 731 women from the Prospective Population Study of Women in Gothenburg with dental examinations at baseline 1968, 222 had their first fracture in the follow-up period until 2006. Mandibular trabeculation was defined as dense, mixed dense plus sparse, and sparse based on panoramic radiographs from 1968 and/or 1980. Time to fracture was ascertained and used as the dependent variable in three Cox proportional hazards regression analyses. The first analysis covered 12 years of follow-up with self-reported endpoints; the second covered 26 years of follow-up with hospital verified endpoints; and the third combined the two follow-up periods, totaling 38 years. Mandibular trabeculation was the main independent variable predicting incident fractures, with age, physical activity, alcohol consumption and body mass index as covariates. The Kaplan–Meier curve indicated a graded association between trabecular density and fracture risk. During the whole period covered, the hazard ratio of future fracture for sparse trabeculation compared to mixed trabeculation was 2.9 (95% CI: 2.2–3.8, p < 0.0001), and for dense versus mixed trabeculation was 0.21 (95% CI: 0.1–0.4, p < 0.0001). The trabecular pattern was a highly significant predictor of future fracture risk. Our findings imply that dentists, using ordinary dental radiographs, can identify women at high risk for future fractures at 38–54 years of age, often long before the first fracture occurs.

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Introduction

Although osteoporosis is associated with a high fracture risk, roughly 73% of all fractures occur in women who test negatively for osteoporosis [1]. Bone mineral density (BMD) only partly explains bone quality and fracture risk, and bone strength is also dependent on variables such as geometry (bone shape and size) and microstructural features (e.g., collagen fibres, crystal size) [2]. Clinical fracture risk factors such as lifestyle (smoking, high alcohol consumption, physical inactivity), medication predisposing to low bone mass, and conditions increasing the risk of falls have been identified [3,4]. Bone structure is now considered the key to understanding fracture risk [5]. Trabecular bone structure can be assessed by measuring trabecular volume, spacing, and connectivity by computed tomography and magnetic resonance [2]. Although progress has been made in assessing trabecular bone structure, the cost and complexity of these methods limit their utility for routine use.

However, trabecular bone structure can be visually evaluated in plain dental radiographs. A large proportion of the population visits a dentist on a regular basis every 1–2 years and dental radiographs have been performed routinely [6]. The intra-oral and panoramic radiographs provide information about the mandibular and maxillary bone at low cost to the patient and without undue exposure to radiation. Therefore, research teams throughout the world have tried to develop methods for using the jawbones to predict skeletal BMD [7]. The alveolar process of the mandible develops as a result of tooth eruption
and elongation. It is subject to physiologic remodeling throughout life, and can be influenced by masticatory demands, orthodontic movements and may undergo more or less progressive resorption after tooth extraction. The mandibular alveolar process undergoes the same aging processes as other bones [8], and the thickness of the trabeculae, spacing between the trabeculae, and the trabecular connectivity in the jaw are altered in patients with osteoporosis compared to normal subjects [9].

A dense alveolar trabecular pattern in the mandibular alveolar process is a reliable sign of normal BMD in dentate middle-aged subjects, whereas a sparse trabecular pattern indicates osteopenia [10–12]. We have previously found that mandibular sparse trabeculation, evaluated visually using dental intra-oral radiographs in a small study group, was associated with an increased likelihood of previous fracture, and in this context performed better than BMD [13]. However, ascertainment of fracture was retrospective, i.e. we investigated the association between current trabecular bone pattern and previous fractures, not incident fractures [13]. In the current study our aim was to test alveolar trabecular bone structure as a predictor of future, incident, post-cranial bone fractures.

Materials and methods

Participants

The Prospective Population Study of Women in Gothenburg, Sweden, is an ongoing longitudinal study of women initiated in 1968/69, in which medical and dental examinations have been performed on multiple occasions until 2010. To ensure selection of a representative sample of women in Gothenburg in 1968/69, women were chosen randomly from the Revenue Office register, according to their date of birth, on dates of the month divisible by six (five cohorts born 1908, 1914, 1918, 1922, and 1930). Ninety percent of women invited underwent a medical examination, 97% of whom also participated in the dental part of the study, which corresponded to an 87% participation rate [14]. At the second phase of the study in 1980/81, 73% of those who had taken part in the baseline study in 1968/69 participated [15]. A non-participation analysis was performed in the 24 year follow-up, and the women who declined to participate in the first study did not differ significantly from the participants except for the long-term survival which showed to be lower in the initial refusers [16].

The present report is based on 917 women born 1914, 1922 and 1930 and aged 54, 46 or 38 at baseline (from three of the original five age-cohorts). The study was designed to study women before, during and after menopause. Women born in 1908 and 1918 were not included in this special study. A group of 151 women was only examined in 1968 and 28 of them were excluded because the panoramics did not have a fully acceptable quality. Furthermore, 73 edentulous women were excluded. Thus, of those with panoramic radiographs taken in 1968/69, 816 had sufficient alveolar bone for evaluation of trabecular pattern.

All women were invited for dental re-examinations in 1980/1981 and 579 women, including 76 new participants, had sufficient trabecular bone for inclusion. Seventy-three edentulous women from the first examination had been excluded and six more women from the second examination had to be excluded because they had too little alveolar trabecular bone left for evaluation (Fig. 1). This is a consequence of tooth extraction where resorption of the alveolar trabecular bone starts at the extraction site [17]. In addition to medical history data collected during the health examinations, verified fracture data were obtained after 1980 from the hospitals and date of death from the National Swedish Death Registry. Before 1980 registry data from hospital care was not possible to obtain, and fractures were ascertained by questionnaire only, as described in next section.

The Ethics Committee of University of Gothenburg approved the study (T 453-04 and T 075-09), and participants gave their informed consent in accordance with the Helsinki Declaration.

Fracture ascertainment

Self-reported information on fractures was collected from the 1968/69, 1974/75, and the 1980/81 questionnaires. Fifty-five percent of the fractures were forearm fractures, 17% hip fractures, 14% clinical spine fractures, and 14% upper-arm fractures. We had information from a few women concerning the reason for self-reported fractures. No fractures of fingers and toes were recorded, and no attempt to separate fragility fractures from other fractures was made. Thirty-one women had two fractures, twenty had three and 12 had more than three fractures. Women who sustained fractures on more than one occasion were included only with the first fracture. Women with a fracture in childhood (<20 years old) were registered as not fractured. Before the main analysis was performed, 85 women with self-reported fractures were excluded (19 fracture cases from before 1968 and 66 undated fracture cases).

Women examined in 1968/69, with dated, self-reported, incident fractures between 1968 and 1980 were included in the proportional hazards regression analysis for the first period of 1968–1980. Sixty-one of 731 women with sufficient trabecular bone 1968/69 reported an incident fracture with a date during the period 1968–1980 (Fig. 1, Table 1).

Västra Götaland County (VGR) (unification of Gothenburg and three other counties) is the largest Health Care Organization in Sweden, including 18 hospitals. Hospital-verified fracture data from the whole region was available from the VGR Patient Register for the period 1980–2006. Almost all “medical” radiography and all fracture treatment are performed at the hospital. It means that very few fracture cases were missed. Verified, incident fracture cases occurring between 1980 and 2006 were used in the second regression analysis. For the second analysis, all previous fracture cases were excluded leaving 518 “fracture-free” women with panoramics from 1980/81 for evaluation. They had a total of 136 dated and hospital-verified, incident fractures from 1980 to 2006 (Fig. 1, Table 1).

The final, third analysis included 731 women, starting “fracture-free” from baseline (1968) and experiencing 222 incident fractures. Analysis 3 combines the two periods 1968–80 and 1980–2006. In the first period we only have available self-reported fractures. In the second period we only include hospital verified ones. These 2 groups are mutually exclusive (Fig. 1).

The 61 fractures in analysis #1 and the 136 in analysis #2 do not add up to the 222 in analysis # 3 because 25 of the dated fractures in the final analysis were found in women who were not examined in 1980.

Ordinal classification of the radiographic mandibular alveolar trabecular pattern

The panoramic radiographs have been performed at two different time periods using different panoramic machines. The exposure factors were set individually according to the size of the probands. However, these small variations have no influence on the visual evaluation of the trabecular pattern. The panoramic radiographs were placed over a light-box in a darkened room, extraneous light was masked, and magnifying lenses (×2) were used. Crestal bone around teeth with marginal bone loss due to periodontitis and sclerotic bone around apices of problematic teeth was disregarded in the evaluation. With the help of three panoramic reference radiographs (Fig. 2 shows intraoral radiographs which better visualize the trabeculation in a journal) and a visual index proposed by Lindh et al. [18] and modified by Jonasson et al. [10], the alveolar trabeculation was classified as either sparse (value 1), mixed dense plus sparse (value 2), or dense...
When the trabecular pattern was evaluated as sparse, the criterion was large intertrabecular spaces in most of the alveolar process, especially in the cervical, dentate, premolar area. When the trabecular pattern was evaluated as dense, the whole radiographed alveolar premolar area had small intertrabecular spaces. When the trabecular pattern was assessed as mixed dense plus sparse, the trabeculation was mostly dense cervically and sparse apically [10]. The assessments were blinded for fracture status.

Densitometric measurements

In order to validate the visual index used in this study, objective densitometric measurements in the premolar area of the panoramics were performed in a subsample of 192 panoramics. The optical density was measured with a densitometer (Macbeth TD-500 with an aperture of ~2 mm, Macbeth Division of Kolmorgen Co., Newburgh, N.Y., USA). The optical density is a measure of the darkening of the exposed and processed radiograph. When the bone mass is reduced optical density increases. The optical density was assessed at a location between the first and second premolar if possible or as close to that location as possible. The locations were positioned at least 3 mm apical to the crestal lamina dura, avoiding roots, lamina dura, and apical area. The radiographs from 2005/06 and 1992/93 were chosen because the quality was excellent and the processing procedures better controlled than 1968/69.

Reproducibility

Three dentists, one experienced in classifying the trabecular pattern in oral radiographs in earlier research (observer A), an oral and maxillofacial radiologist (B), and one general practitioner (C) from a department of oral and maxillofacial radiology, performed a study of the intra and inter-individual agreement concerning the assessment of the pattern of the bone trabeculation for panoramic radiographs using a test-retest evaluation. A
radiographs are intra-oral radiographs with better sharpness than panoramic radiographs; note that in the investigation we had only panoramic radiographs available.

Assessment of potential confounders

At each examination, all women answered questions concerning smoking, physical activity, and alcohol consumption (all three discrete numerical variables). Anthropometric measurements were taken including height and weight. Descriptions of these procedures have been published previously, including group means and prevalences for these potential confounders in 1968/69 [19–21]. All hazard ratios are adjusted for these variables, as described below. Another known risk factor for future fracture is previous fracture, but we only used the first fracture. Cortisone medication was noted in 2.4% of the women (constant during the period), and none received other medication for osteoporosis than calcium supplementation, which increased from 5% to 20% during the period, whereas hormone replacement therapy decreased from 22.8% to 13.6%.

Statistical analysis

The time from the 1968/69 baseline examination to first fracture or censoring (until 2006) was calculated for each individual. Cox proportional hazards regression was used to model the dependence of time to fracture on the exposure (sparse, mixed sparse plus dense, and dense trabecular pattern) and confounding factors for “fracture-free survival” by censoring at date of death or at the end of 2006. Three different proportional hazards regression analyses were performed based on:

#3: dental examinations in 1968/69 and self-reported fractures 1968–1980 plus verified fractures 1980–2006 (Fig. 1, Tables 1 and 2).

In all Cox proportional hazards analyses, mixed dense plus sparse trabeculation was used as a reference group because approximately 50% of the women had this mixed trabecular pattern. Time to fracture was the dependent variable, and the independent variables were trabeculation (categories 1 and 3, versus 2), age, smoking, physical activity, drinking habits, and body mass index (BMI).

Kappa-statistics was used to calculate the intra and interindividual agreements. The statistical program SAS version 9.2 (SAS Institute Inc., Cary, NC) was used.

Results

Radiographic mandibular alveolar trabecular pattern in 1968/69 and 1980/81

In 1968/69, sparse trabeculation was observed in 18.2% of the women with sufficient trabecular bone for inclusion (Table 1). Twelve years later, in 1980/81, a larger fraction, 27.6%, now had sparse trabeculation. Somewhat fewer had dense trabeculation in 1980/81 compared to 1968 (23.6% versus 31%). In 1980/81, the majority of subjects were re-examined, new participants were added, and previous fracture cases were excluded. The risk estimates, presented in three parts below are all based on the same model including trabeculation, age, and other potential confounders.

Results for 1968–1980

In the first analysis (Tables 1 and 2), only age and dense versus mixed trabeculation significantly explained the risk time for self-reported fracture. The hazard ratio was 0.39 (95% CI: 0.18–0.81, total of 30 panoramics were evaluated twice 4 weeks apart by the three observers.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Dense</th>
<th>Mixed</th>
<th>Sparse</th>
</tr>
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<tbody>
<tr>
<td>Analysis 1: 1968/1980</td>
<td>n = 731, cases 65</td>
<td>n = 227, cases = 9</td>
<td>n = 371, cases = 37</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.386 (0.184–0.807)*</td>
<td>1.0</td>
<td>1.453 (0.816–2.59)</td>
</tr>
<tr>
<td>Analysis 2: 1980/2006</td>
<td>n = 518; cases = 136</td>
<td>n = 122, cases = 2</td>
<td>n = 253, cases = 49</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.07 (0.017–0.292)***</td>
<td>1.0</td>
<td>3.63 (2.54–5.18)***</td>
</tr>
<tr>
<td>Analysis 3: 1968/2006</td>
<td>n = 731, cases = 222</td>
<td>n = 227 cases = 17</td>
<td>n = 371, cases = 114</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.21 (0.13–0.36)***</td>
<td>1.0</td>
<td>2.87 (2.17–3.80)***</td>
</tr>
</tbody>
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*p<0.05, **p<0.01, ***p<0.001.

Included variables in the model besides trabeculation: age, smoking, physical activity, drinking habits and body mass index.

a Self-reported fractures.

b Hospital-verified fractures.

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results for 1980–2006

In the second analysis, 518 women with 136 verified incident fractures from 1980 to 2006 were included. Again, age and trabecular pattern explained the risk time for fracture (Table 2). The hazard ratio for a fracture of sparse trabeculation compared to mixed trabeculation was 3.63 (95% CI: 2.54–5.18, \( p \leq 0.0001 \)). Consistent with the first observation period, we also observed a significant protective association for dense versus mixed trabeculation, with hazard ratio for fracture of 0.07 (95% CI: 0.02–0.29, \( p = 0.0003 \), Table 2). The hazard ratio for age was 0.92 (95% CI: 0.89–0.95, 0.0001).

Results for 1968–2006

Finally, in the third analysis including the same variables, 731 women with 222 reported and/or verified incident fractures were included. Again, age and trabecular pattern explained the risk time for fracture (Table 2). The hazard ratio for a fracture with sparse trabeculation compared to mixed trabeculation was 2.87 (95% CI: 2.17–3.80, \( p < 0.0001 \)), and 0.21 (95% CI: 0.13–0.36, \( p < 0.0001 \)) for a fracture of dense versus mixed trabeculation (Table 2). The Kaplan–Meier curve for risk time for fracture during the combined observation period is shown in Fig. 3, where a graded effect of dense, mixed, and sparse trabeculation is illustrated. The hazard ratio for age was 0.92 (95% CI: 0.90–0.94, \( p < 0.0001 \)).

Densitometric measurements

Significant differences were found between the optical density of radiographs from individuals with sparse trabeculation (1.78, 95% CI: 0.96–2.60), mixed trabeculation (1.42, 95% CI: 0.70–2.20), and dense trabeculation (1.25, 95% CI: 0.60–1.80, \( p < 0.0001 \)).

Reproducibility

Inter-observer agreement was at least good (Kappa: 0.73, 0.72, and 0.84, Table 3) and so was intra-observer agreement (Kappa: 0.65, 0.76, and 0.92, Table 3).

Discussion

The results of the present investigation indicated that mandibular trabeculation was a powerful predictor of fracture risk. The percentage of women with sparse trabeculation increased considerably with age as did the fracture rate. The regression analyses, confirmed with Kaplan–Meier survival curve, clearly show the protective effect of dense trabeculation and the excess risk for sparse trabeculation. Despite variations in bone mass and trabecular pattern in different regions within a single mandible, it seems that mandibular trabecular pattern in the premolar region is a useful predictor of post-cranial fractures [13]. The hazard ratio for fracture with sparse trabeculation relative to mixed trabeculation was highest in the second period from 1980 to 2006 compared to the first period (1968–1980). This can be explained by the higher age of participants in the second period compared to the first, or alternatively could be due to longer follow-up time and better ascertainment of endpoints available after 1980. The higher age in the second period implies that fractures were more

Fig. 3. Kaplan–Meier survival curve showing cumulative survival and risk time for fracture in three different trabeculation groups; \( \times \) 1: survival of women with sparse trabeculation, \( \square \) 2: mixed trabeculation and \( \bigcirc \) 3: dense trabeculation. Risk time represents the time interval between baseline assessment and the fracture event. All 731 participants included, started “fracture-free” at baseline (1968) and experienced 222 first, incident fractures during the period 1968–2006.
likely osteoporotic than fractures at a younger age. In all three periods, regression models consistently show significant protection in the dense trabeculation group, regardless of whether endpoints are reported or verified. It is likely that secondary causes of osteoporosis may influence fracture rate, but in our investigation physical activity, medication, alcohol consumption, or smoking were neither confounders nor significant predictors.

A number of strengths and limitations of this study may be considered. The advantage of this study is the prospective design, the relatively large, representative study population, and a high participation rate. Fractures were carefully checked from questionnaires and hospitals and as far as we know it is the first longitudinal study using mandibular trabecular pattern as a predictor of future fracture. The limitations are mainly that panoramic radiographs are less sharp than intra-oral radiographs and BMD measurements were not available. Very few private medical practices in Sweden possess X-ray equipment which means that nearly all fracture treatments require hospital contact. The advantage of using a hospital register is that a precise date is obtained, which is seldom the case when using questionnaires. However, most studies involving osteoporotic fractures have similar limitations since all persons who sustain a fracture do not automatically have contact with health care, especially concerning vertebral osteoporotic fractures. Further studies are needed using BMD measurement and objective methods on intra-oral radiographs, in order to further clarify whether mandibular trabecular pattern can perform as well or even better than BMD measurements for fracture prediction.

Panoramic radiographs are not ideal for assessing trabecular pattern; they cannot be taken at all dental clinics and fail to show clearly the fine details of the trabeculation, compared to “ordinary” dental intra-oral radiographs available at all dental clinics. However, they show approximately the same features as the intra-oral radiographs [22]. The densitometric measurements were the only objective method we could use on the trabecular bone. The objective methods used previously in our research [11–13] were developed using intra-oral radiographs. Similarly, advanced imaging techniques [9,23–26], were not initially designed for trabecular bone in panoramics though images of the mandibular ramus has been analyzed in one study [26].

We have studied the degree of erosion of the inner endosteal compact bone using Klemettis index [27,28], and the results are not published yet. Due to the erosion of the endosteal compact bone we found it difficult to measure accurately the thickness of the compact bone on the panoramics of the oldest participants. Other researchers have developed and validated an automated measurement of cortical thickness concerning osteoporosis [29], and compared this automated assessment together with clinical variables with the FRAX index without BMD [30].

When comparing our results with other studies, we observe that the rates of sparse trabeculation observed in 1968/69, when the population was 38–54 years old, are similar to rates observed in more recent studies [10–12]. Thus, although the baseline data are over 4 decades old, they may be relevant to contemporary middle-aged female populations. Our results are supported by findings from cross-sectional studies, using computed tomography, showing that impaired bone architecture is associated with fracture, partially independent of BMD [31,32], and resistance to fracture depends not only on the total amount of bone but also on the size and distribution of the trabeculae [33]. The increased distances between adjacent trabeculae account for more than twice the age-related bone loss compared to the decrease in trabecular width, and loss of connectivity has more deleterious effect on bone strength than thin but well-connected trabeculae [33].

We excluded cases with severely resorbed edentulous mandibles. The main observation in the excluded edentulous material was that the radiographic basal bone was mostly dense. Basal bone seems to react differently to aging than alveolar bone. It is possible that severe alveolar resorption is followed by a reinforcement of the remaining trabecular structures in the basal bone in order to compensate for the loss in vertical dimension. Our observation is supported by other investigators [34–36]. Data from questionnaires in 2000 showed that 3–13% of the population was edentulous [37] and fewer have a severely eroded alveolar process, especially in Sweden where implants are rather common. Our findings are applicable in dentate individuals and in partial edentulous individuals with well preserved alveolar bone. The exclusion of non-dated fractures was due to the selected methods: the Cox proportional hazards modeling and the Kaplan–Meier survival curve. We were focused on future fractures and time to fracture.

Previously mentioned prospective research demonstrated that osteoporotic women have more fractures compared to women with normal BMD [1], but that the osteoporotic group is small (14.5%) [1]. In fact, women without osteoporosis had 73% of fractures while only 27% occurred in women with osteoporosis [1]. Thus, our results may make it possible to also identify non-osteoporotic women at future risk and refer them to medical care. Our previous study showed that mandibular trabecular pattern is a better correlate of fracture than BMD, identifying 48% of all previous fractures compared to the 19% identified using BMD [13].

Conclusions

The unique feature of the present study, compared with most previous publications, is the long observation period and prospective design. We found that the trabecular pattern was a highly significant predictor of future fracture risk both in perimenopausal and in older women: the older the individual, the more effective the mandibular trabecular pattern as a fracture predictor. Given that 20% of 38–54 year old women in this study had sparse trabeculation and similar rates are seen today, a large fraction of the population could potentially benefit from the knowledge that they are at risk. In conclusion, our findings imply that dentists can use ordinary dental radiographs as a rough tool to identify women at high risk for future fractures in mid-life, often many years before the first fracture occurs.

Contributions

LL, CB and GJ designed the study; LL, CB, MA and MH are the principal investigators of The Prospective Population Study of Women in Gothenburg; GJ coordinated, and with MA collected the data. VS and GJ performed the statistical analyses; GJ wrote the first draft of the report; all authors interpreted the results, revised the text, and approved the final text.

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Table 3

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<tr>
<th>Observer A</th>
<th>Observer B</th>
<th>Observer C</th>
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<tr>
<td>0.92</td>
<td>0.84</td>
<td>0.73</td>
</tr>
<tr>
<td>0.76</td>
<td>0.72</td>
<td>0.65</td>
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Kappa values for intra and inter-observer agreement for trabecular pattern.
Role of the funding source

The study sponsors had no role in the design, in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. The opinions, results, and conclusions are those of the authors and all authors have full access to all data.

Conflicting interest

All authors declare no conflict of interest.

References