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Mandibular bone structure, bone mineral density, and clinical variables as fracture predictors: a 15-year follow-up of female patients in a dental clinic

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Objective. To compare three mandibular trabeculation evaluation methods, clinical variables, and osteoporosis as fracture predictors in women.
Study design. One hundred and thirty-six female dental patients (35-94 years) answered a questionnaire in 1996 and 2011. Using intra-oral radiographs from 1996, five methods were compared as fracture predictors: (1) mandibular bone structure evaluated with a visual radiographic index, (2) bone texture, (3) size and number of intertrabecular spaces calculated with Jaw-X software, (4) fracture probability calculated with a fracture risk assessment tool (FRAX), and (5) osteoporosis diagnosis based on dual-energy-X-ray absorptiometry. Differences were assessed with the Mann–Whitney test and relative risk calculated.
Results. Previous fracture, gluco-corticoid medication, and bone texture were significant indicators of future and total (previous plus future) fracture. Osteoporosis diagnosis, sparse trabeculation, Jaw-X, and FRAX were significant predictors of total but not future fracture.
Conclusion. Clinical and oral bone variables may identify individuals at greatest risk of fracture. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:362-368)

Osteoporosis is a major public health problem. It affects approximately 75 million people in Europe, Japan, and the USA and leads to more than 2.3 million fractures yearly in Europe and the USA alone.[1] Apart from increasing health care costs, fractures are associated with high mortality and individual suffering.[2] Osteoporosis occurs when bone mass decreases faster than it is replaced. This results in a net loss of bone strength, with the skeleton becoming fragile. The risk of sustaining a fracture increases exponentially with age, due not only to a decrease in bone mineral density (BMD) but also to the increased rate of falls among the elderly. Osteoporosis is the best explored risk factor for future fracture, but as many as 73% of all fractures occur in individuals who are not osteoporotic when measured with dual energy X-ray absorptiometry (DXA) of the hip.[3]

BMD only partly explains bone strength.[4] Trabecular bone structure can be assessed by measuring trabecular volume, spacing, and connectivity.[5-11] Computed tomography and magnetic resonance imaging provide detailed insights into trabecular and cortical bone microstructure; however, these methods are expensive, technically challenging, and not intended for clinical practice. Most adults in Western countries have regular dental radiographic examinations. The trabecular structure is well-imaged in intraoral radiographs. When panoramic radiographs are available, the mandibular inferior cortex can be evaluated. The mandibular alveolar bone undergoes aging processes that are similar to other bones.[12] The trabeculae become thin and perforated, and the mandibular inferior cortices become more porous and thin focally.[13-15] In a dentate subject, a dense mandibular alveolar trabecular pattern is a reliable sign of normal BMD, whereas a sparse trabecular pattern indicates osteopenia.[16-18] Subjects with self-reported histories of osteoporotic fractures have increased resorption and thinning of the mandibular inferior cortex.[19] In longitudinal studies, both sparse trabeculation[20,21] and severely eroded inferior cortexes are significant predictors of future fractures.[20]

To maintain quality of life for the elderly, targeting individuals with high fracture risk is an important

Statement of Clinical Relevance

Sparse mandibular bone structure is, together with other clinical variables like previous fracture and gluco-corticoid medication, an indicator of future extracranial fracture. A holistic view on the patient in the dental clinic may include an assessment of fracture risk.

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challenge for health care planners. A number of clinical decision-making models for osteoporosis screening and/or fracture-risk assessment have been proposed. Among them the World Health Organization fracture risk assessment tool (FRAX) has been used in numerous studies.[22,23] To substantiate the grounds for fracture risk assessment and treatment regimes for osteoporosis, epidemiological studies of diverse populations are needed. Furthermore, comparisons of available clinical instruments are needed to present clinicians with a choice of readily available, valid, and reliable options. In that most people have yearly dental radiographic examinations (which contain useful information concerning trabecular bone), a dental clinic setting may be the ideal place for screening patients for fracture risk.

The primary aim of the present investigation was to compare three mandibular trabeculation evaluation methods, the FRAX tool, and osteoporosis (as assessed with dual-energy-X-ray absorptiometry) as fracture predictors in women. The secondary aims were to analyze clinical variables as predictors of fracture and to assess the fracture rate in a sample of women from a dental clinic.

MATERIALS AND METHODS

Patients

Women from a public dental clinic in Borås, Sweden participated in this project in 1996 ($n = 166$),[16] 2001 ($n = 131$),[17] and 2006 ($n = 42$).[18] Sixteen of 166 women were deceased in 2011. The remaining 150 women were each sent a questionnaire to obtain data on fractures, parental fractures, diseases, medications, and life styles.

One hundred and thirty-six women of 150 (90.7%) answered the questionnaire. In 2011, their mean age (±standard deviation) in years was 64.1 ± 11.2 (range = 35-94). Twenty-seven were premenopausal and 109 postmenopausal with a mean age at menopause of 50.1 ± 4.8 (range = 31-59).

A fracture in an elderly person is considered osteoporotic when it occurs as a result of minimal trauma (no more severe than that resulting from a fall from a standing height).[19] According to this definition, all fractures included in the study were classified as osteoporotic: e.g., either sustained by falling from a height equal to a standing height (slipped or tripped, stepped off sidewalk) or a minor trauma generated during normal daily activities (like stubbed toe)[19]; however, some falls occurred when skiing or bicycling.

Fractures are described as either a previous fracture (fracture before 1996), future fracture (fracture from 1996 up to 2011), and total fractures (all fractures including fractures before 1996 plus fractures after 1996 up until 2011). Whenever the term "fracture" is used, it refers to total fracture. Previous and future fractures are always denoted in this manner.

All participants received written and oral information before entering the studies. Furthermore, each signed a detailed informed consent form. The regional Ethics Committee of Gothenburg University approved the study.

Mandibular trabeculation

Visual radiographic index. Intra-oral radiographs from 1996 had been evaluated as sparse, sparse and dense, or dense trabeculation (Figure 1).[16-18] This classification was used in bivariate and multiple regression analyses and dichotomized for calculating the relative risk (sparse trabeculation = 1, non-sparse = 0).

Alveolar bone texture method. The radiographs from 1996 had been digitized with a resolution of 600 dpi by using Epson Perfection 4990 (Seiko Epson Corporation, US Affiliates, Long Beach, CA, USA). With a specially developed program developed in Matlab (MathWorks, Natick, MA, USA), the radiographs were analyzed and statistical descriptions of the bone texture determined.[17,18] The texture analyzed was mainly the transition from trabeculae to inter-trabecular spaces, edges and spots as previously described. The analyzed bone was selected with a rectangular tool in a standard area, between the premolars, halfway between the crest and the apical areas. In bivariate and multiple regression analyses, classes 3 and 4 were merged due to their small sizes. This classification was used in univariate and multiple regression analyses and dichotomized for calculating relative risk (bone texture class 1 [the sparsest trabeculation] = 1; classes 2-4 = 0).

Bone structure evaluation with the Jaw-X method. The software consists of two parts. In the first part, the digitized radiograph is imported as a JPEG-file (8-bit greyscale) into the computer software (Jaw-X, Crebone AB, Sundbyberg, Sweden). The software uses digital imaging algorithms to create a binary filtered image and analyses the trabecular structure in a region selected with a standardized trapezoid marker. The largest intertrabecular space is identified, thereafter the next largest and so on until the 20 largest spaces are found. The final resulting value represents the sum of the sizes and intensities of the spaces between the trabeculae. Values are between approximately 3000 (dense bone structure) and 9500 (sparse bone structure − large gaps between trabeculae). This value was used in the regression analyses and dichotomized for calculating relative risk. Values ≥6500 denoted risk of osteoporosis according to the manufacturer's manual (value = 1); values <6500 were assigned the value 0. The second part of the software consists of a questionnaire about sex, weight, previous fracture, parental

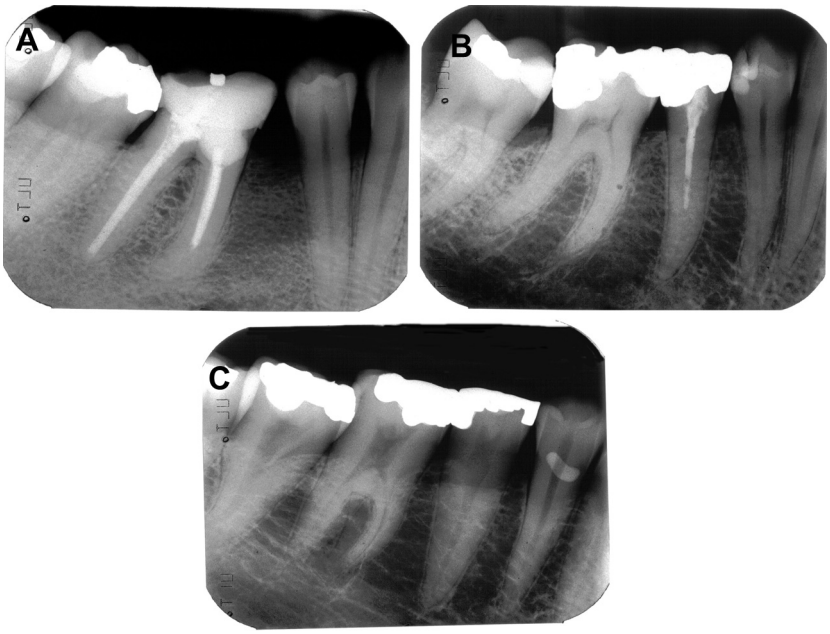

Fig. 1. Reference images. The radiographs present dense trabeculation with small intertrabecular spaces (**A**), mixed dense and sparse trabeculation with small intertrabecular spaces cervically and larger spaces more apically (**B**), and sparse trabeculation with large intertrabecular spaces and almost invisible trabeculae (**C**).

fractures, gluco-corticoid medication, smoking, and gastro-intestinal disease. The calculated value from the first part and the answers from the second part are used to calculate a probability for osteoporosis; probable risk = 1 or no probable risk = 0.

FRAX. The FRAX tool was developed by studying population-based cohorts from Europe, North America, Asia, and Australia.[22-24] The following clinical risk factors are included: age, sex, height, weight, previous fracture, parents with fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol (three or more units/day). "Secondary osteoporosis" indicates that the patient has type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism (premature menopause, <45 years), chronic malnutrition (malabsorption), or chronic liver disease. A value for BMD can be included, but the tool can be used without BMD. If a response(s) is missing, the tool calculates the probability of future fracture as if the response(s) were "no."

For the present study, the question of alcohol consumption was not asked. The women were all well known to the clinic, and it was estimated that few, if any, consumed three or more units of alcohol per day. No women reported parental hip fracture. The outcome of the FRAX tool is a 10-year probability of hip fracture and a 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). The latter was used because only one woman had experienced a hip fracture. The FRAX value was used in the regression analyses. To calculate relative risk, the value was dichotomized. Values $\geq$7% indicated increased probability for osteoporotic fracture (value = 1); values <7% were given the value 0.[24]

Osteoporosis

BMD had been assessed in 1996 with DXA of the non-dominant forearm. BMD was denoted as a *T*-score (number of standard deviations from the mean BMD for young women). The *T*-score is used as a working definition for osteoporosis and osteopenia because it is a relative value that is easily compared. Osteoporosis is defined as a *T*-score ≤ -2.5. The *T*-score was used in the regression analyses. To calculate relative risk, the *T*-score was dichotomized: *T*-scores ≤ -2.5 denoted osteoporosis (value = 1); *T*-scores > -2.5 were given the value 0.

Statistics

The Mann–Whitney *U*-test was used to test for differences. Relative risk was calculated using DJR Hutchon's calculator (www.hutchon.net/ConfidRR.htm) (Table I). Spearman's correlation coefficient was used for ordinal data and Pearson's for continuous data. Multiple linear regression analyses were performed to calculate the explained variance. The dependent variable was either total fracture or future fracture. The independent variables, BMD, visual trabecular pattern, bone texture, and

Table I. Relative fracture risk (RR and 95% CI) for oral radiographic bone variables, BMD, FRAX, and clinical variables

	Total fracture[†] *RR (95% CI)*	*Future fracture*[‡] *RR (95% CI)*
Bone texture	3.16 (1.27-7.86)*	4.74 (1.49-15.04)*
Sparse trabeculation	2.22 (1.06-4.61)*	1.52 (0.56-4.11)
Jaw-X with clinical variables	2.89 (1.29-6.48)*	2.20 (0.86-6.48)
Jaw-X without clinical variables	2.18 (1.01-4.72)*	1.87 (0.73-4.71)
BMD (*T*-score, underarm)	2.83 (1.39-5.78)*	2.37 (0.93-6.02)
FRAX with BMD included	2.59 (1.33-5.06)*	2.53 (1.13-5.63)*
FRAX without BMD included	1.95 (0.98-3.87)	1.34 (0.56-3.20)
Previous fracture ($n = 13$)	–	6.30 (3.17-12.55)*
Secondary osteoporosis[§] ($n = 26$)	3.67 (1.42-9.51)*	2.28 (1.01-5.14)*
Gluco-corticoid medication ($n = 13$)	3.43 (1.79-6.57)*	5.01 (2.44-10.29)*
Rheumatoid arthritis ($n = 15$)	2.74 (1.37-5.47)*	4.00 (1.88-8.53)*
Gastro-intestinal disease ($n = 19$)	2.62 (1.33-5.15)*	2.64 (1.57-6.02)*
Parent fracture ($n = 19$)[¶]	1.48 (0.73-3.01)	1.87 (0.83-4.18)
Estrogen ($n = 22$)	1.21 (0.51-2.87)	1.90 (0.61-5.92)
Current smoking ($n = 16$)	0.62 (0.16-2.38)	0.39 (0.06-2.73)

*$P < .05$.
[†]Fractures before and after 1996.
[‡]Fractures after 1996.
[§]Insulin dependent diabetes ($n = 1$), osteogenesis imperfecta in adults ($n = 0$), untreated long-standing hyperthyroidism ($n = 0$), hypogonadism ($n = 0$) or premature menopause (<45 years) (10), chronic malnutrition ($n = 0$), or malabsorption ($n = 19$), and chronic liver disease ($n = 0$).
[¶]No parent hip fracture recorded.

Jaw-X were used separately in bivariate correlation analyses, and together with clinical variables in multiple regression analyses. FRAX was used with and without BMD. Results with *P* values <.05 were considered significant. Statistical analyses were performed with Epi Info version 3.5 (Center for Disease Control, Atlanta, GA, USA).

RESULTS

Fracture

Fracture rate increased from 9.6% in 1996 to 19.1% in 2011 ($n = 13 \rightarrow n = 26$). Out of 26 women with one or more fractures in 2011, 10 women had sustained 2 fractures, one women 3 fractures, and one 4 fractures—for a total of 41 fractures: 27% were hand fractures (all falls were from standing heights, but 2 occurred on icy roads, and 1 while skiing), 50% leg (2 did not fall but tripped; the rest were falls from standing heights, but 3 falls occurred on icy roads, and 1 while dancing), 14% arm (all were falls from standing heights, 1 fall occurred while skiing), 7% rib (2 were due to falls from bicycles and 1 while skiing), and 2% had a hip fracture (she tripped, did not fall). No fracture occurred due to metastatic disease, and no vertebral fracture was recorded.

Relative risk for fracture

Relative risks for total fracture and future fracture are shown in Table I. Previous fracture, gluco-corticoid medication, bone texture, rheumatoid arthritis, gastro-intestinal disease, FRAX with BMD, and secondary osteoporosis were significant indicators of total and future fracture. Jaw-X, osteoporosis diagnosis, and sparse trabeculation were significant indicators of total fracture number. Height, weight, BMI, smoking, estrogen, and parent fracture were not significant predictors.

Fracture and bone trabeculation

Visual sparse trabeculation was found in 15% of the women. Bone texture class 1 was found in 24.1% of the women. Jaw-X risk was found in 34.2% of the women (part 2 with clinical variables included). All three methods showed significantly more women with a fracture experience in the group with the sparsest trabeculation compared with the other groups (Table II).

Fracture and FRAX

Fifteen women (11%) had a new fracture in the period 1996-2006, and 20 women (14.7%) in the period 1996-2011. The 10-year probability of major fracture including BMD, predicted by FRAX, was 6.1 ± 6.01; range: 1.2-35.0; FRAX probability for future fracture, without BMD, was 5.0 ± 3.6; range: 1.2-21.0.

Fracture and osteoporosis

The women with fractures in 2011 had significantly lower BMDs in 1996 (*T*-score: -1.48 ± 1.16; range: -3.2 to 2.2) than the women with no fracture (*T*-score: -0.86 ± 1.05; range: -4.0 to 1.3; $P = .008$). Six women with fractures (23.1%) had osteoporosis (*T*-score ≤ -2.5), twelve women (46.1%) had osteopenia ($-2.5 \geq$ *T*-score > -1.0), and eight women (30.8%) had normal BMDs (*T*-score ≥ -1.0) in 1996. This means that of all women with fractures in 2011, 76.9% did not have osteoporosis in 1996.

Multiple linear regression analyses

In bivariate linear regression analyses, BMD, bone texture, and FRAX including BMD were significantly

Table II. Percentage of women with a fracture experience (left), and bone mineral density (BMD) (right) in the groups with sparse and non-sparse trabeculation presented for all three mandibular bone trabeculation variables

	Fracture experience %		*BMD T-score*	
Visual method	Sparse	Non-sparse	Sparse	Non-sparse
	35%*	15.8%*	−1.96 ± 1.23†	−0.79 ± 0.97†
			Range: −4.0 to 2.2	Range: −3.2 to 1.3
Texture	Sparse (class 1)	Non-sparse (2-4)	Sparse	Non-sparse
	36.8%*	11.7%*	−1.67 ± 1.05†	−0.79 ± 0.97†
			Range: −3.3 to 0.4	Range: −3.2 to 1.3
Jaw-X‡	Risk	Non-risk	Risk	Non-risk
	30.0*	10.4%*	−1.15 ± 1.07; ns.	−0.86 ± 1.11; ns.
			Range: −3.1 to 2.2	Range: −4.0 to 1.3

ns = not significant.
*$P < .05$.
†$P < .001$.
‡Jaw-X with included clinical variables.

Table III. Correlation coefficients *r* and *P* values for oral radiographic bone variables, BMD, and FRAX

	Total fracture r *(P)*	*Future fracture* r *(P)*
BMD (*T*-score, underarm)	−0.35 (<.001)	−0.24 (.003)
Bone texture	−0.35 (.002)	−0.28 (.011)
FRAX with BMD included	0.30 (<.001)	0.17 (.04)
FRAX without BMD included	0.22 (.010)	ns
Jaw-X with clinical variables	0.22 (.019)	ns
Jaw-X without clinical variables	ns	ns
Visual trabeculation	−0.20 (.017)	ns

ns = not significant.

correlated to both future fracture and total fracture (Table III); FRAX without BMD, Jaw-X with included clinical variables, and visual trabeculation were significantly correlated to total fracture, but not to future fracture (Table III).

In regression analyses where all variables were included separately and the non-significant variables were eliminated one by one, 54% of the variation in total bone fracture was explained by only two significant variables: previous fracture ($P < .001$) and gluco-corticoid medication ($P < .001$).

Similarly, 32% of the variation in *future* fracture was explained by the same two variables: previous fracture ($P < .001$) and gluco-corticoid medication ($P < .001$). Whenever previous fracture was included in a model for future fracture, all other variables (BMD, FRAX tool, bone variables, gastro-intestinal disease, etc.) changed from significant predictors to non-significant ones, and only gluco-corticoid medication remained significant.

Subgroup without previous fracture 1996

In the final model for total fracture for this subgroup ($n = 123$), the following independent variables: gluco-corticoid medication ($P = .035$), gastro-intestinal disease ($P = .006$), and mandibular bone texture ($P = .001$) explained 27% of the variance. Twelve percent of the variance for future fracture was explained by gluco-corticoid medication ($P = .050$) and mandibular bone texture ($P = .033$). The contribution of rheumatoid arthritis (together with mandibular bone texture) was similar to that of gluco-corticoid medication ($P = .050$).

DISCUSSION

The findings in this investigation showed that the three oral bone variables, BMD, the FRAX tool, and most separate FRAX variables were significant predictors of total fracture. The best predictors of future fracture (fracture after 1996) were previous fracture and gluco-corticoid medication followed by alveolar bone texture, rheumatoid arthritis, gastro-intestinal disease, FRAX with BMD, and secondary osteoporosis.

A visually sparse mandibular trabecular pattern and Jaw-X were significant predictors of total bone fracture, and alveolar bone texture was a significant predictor of both total and future fractures. In large prospective studies with 38-year fracture follow-up, mandibular visually sparse trabeculation predicted future fracture both in peri-menopausal and older women: 70% of women with sparse trabeculation had a new fracture in the follow-up period from 1968-2006.[20,21] The older the participants the better was the fracture prediction.[20,21]

In the present study, visual trabecular pattern was only useful for total fracture prediction. The reason may be a bias attributable to the given osteoporosis information, but probably the main cause was the small sample size of only 136 participants. A longer follow-up, exceeding 15 years, may yield a different result. The alveolar bone texture method was more sensitive than the visual one and was useful even for future

fracture prediction. The Jaw-X method has not been used previously as a predictor of fracture; here it predicted equally well as visual evaluation, BMD, and FRAX. When the clinical variables were included (part 1 plus part 2), the Jaw-X prediction was slightly better than without them. The second part of the Jaw-X software is constructed so that a previous fracture automatically signals probable risk. The present results do support a highly increased risk for a new fracture in women with a previous fracture.

Mandibular bone structure was evaluated in the premolar region with three different methods, but the same area of bone was not assessed with the methods. The visual method assessed the largest area and alveolar bone texture the smallest bone area.

Most participants were informed twice and 42 participants three times about osteoporosis and the importance of nutrition and physical exercise. It is not possible to estimate the influence that this information had on fracture rate, and it may in some degree have biased the outcome; however, in the five-year follow-up, 12.5% of the participants increased their BMDs more than 3% by improving their diets, intakes of calcium and D-vitamin, and by increasing physical activity.[17]

It has been demonstrated that from puberty to middle-age adulthood, mandibular trabecular bone becomes denser.[25] In an investigation of 1003 individuals with 36-year fracture follow-up, some older women had dense trabeculation and thick inferior mandibular cortexes, but most had decreased visual trabecular coarseness and cortical thickness with aging.[19] In another study, it was determined that mandibular bone becomes denser with age, and it was suggested that mandibular bone not be used for BMD prediction.[26] Local factors such as strong masseter muscles and large numbers of occluding teeth may influence the distal area of the mandible, which may become denser than extracranial bones[27]; however, if the trabeculation is *sparse* in areas with occluding teeth (areas under bridge pontics excluded), mandibular trabecular bone structure can be useful for fracture prediction.

Several on-going projects have used the mandibular inferior cortex for osteoporosis prediction with promising results.[14,15] Only a few have reported results for which the mandibular cortex was used as a predictor of fracture: two with significant results,[19,20] and another without significant results.[28] In one study with significant results, the group with severely eroded cortexes was found to increase from 0.5% in the youngest subjects (38-year-olds) to 75.4% in the oldest subjects (78-year-olds), and after the age of 50, the group with severely eroded cortexes included 64% of all fractures (previous + future fractures).[20] Bone changes may be seen early on dental radiographs because the bone formation rate (a measure of bone turnover) is high in the mandibular alveolar process. This has been demonstrated in mature dogs. In dogs the bone formation rate decreases with age in the femur while remaining elevated in the jaws with a mandibular bone formation rate two times higher than in the maxilla.[29] These findings may support the use mandibular trabecular and cortical bone for fracture prediction. Although this may be different in humans, this would be difficult to demonstrate.

Most findings in the present study are in agreement with the results of large studies using the FRAX tool,[22] for which the highest probability for future fracture for men and women were found if they had sustained a previous fracture followed by having oral glucocorticoid medication. In the present study, smoking was not a significant predictor of fracture. In Sweden few women smoke, and in our study, women who smoked were physically active, with most women being employed in hospitals as nurses, assistant nurses, and such. Similarly, in the FRAX study,[22] current smoking had the same 10-year probability for fracture as having no clinical risk factor; this indicates a rather low influence of smoking on future fracture.

As discussed above, the FRAX tool was useful for prediction of total bone fracture. The ten-year probability of fracture was the same order of magnitude as the percentage of sustained future fracture. It is a conservative tool that slightly underestimates the 10-year fracture incidence, but it is not surprising that there is some discordance when comparing a probability with an incidence of fracture in a small study.[30] FRAX has been evaluated with positive results in many studies but some investigators have expressed concern with FRAX because the logarithm (used in FRAX calculations) is based on research cohorts for which not all questions were posed.[31]

The gold standard for fracture risk is DXA BMD measurement of the proximal femur, but the present study used BMD of the forearm. Both the forearm and the mandible have approximately 80% cortical and 20% trabecular bone,[32] so it is reasonable to expect similar results with both types of BMD measurements.

There are strengths and limitations of this study. Strengths are the prospective design and high follow-up participation rate. The most serious limitation is that the number of participants was relatively small and few new fractures occurred. If a larger number of women with a higher mean age had been followed and/or the women had been followed for a longer period, the bone variables and the FRAX tool may have been significant predictors for future fracture as well as for total fracture. Furthermore, the fracture-history questionnaire may not be accurate, but the same questionnaire had been used in the same sample twice before (1996 and 2001); therefore, the answers could be compared and partly validated.

The result from this investigation and from large population studies and meta-analyses show that previous fracture is a serious risk factor[22]; however, waiting for the first fracture to occur before intervention is not fully ethical.

CONCLUSION

Assessment of the mandibular bone structure and the FRAX variables are easily accessible, economical, and effective in identifying individuals at greatest risks for subsequent fractures.

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