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Mini-Abstract

The pathogenesis for low-trauma wrist fractures in men is not fully understood. This study found that these men have lower bone mineral density at the forearm itself, as well as the hip and spine, and has shown that forearm bone mineral density is the best predictor of wrist fracture.

Abstract

Purpose/Introduction

Men with distal forearm fractures have reduced bone density at the lumbar spine and hip sites, an increased risk of osteoporosis and a higher incidence of further fractures. The aim of this case-control study was to investigate whether or not there is a regional loss of bone mineral density (BMD) at the forearm between men with and without distal forearm fractures.

Methods

Sixty-one men with low-trauma distal forearm fracture and 59 age-matched bone healthy control subject were recruited. All subjects underwent a DXA scan of forearm, hip and spine, biochemical investigations, health questionnaires, SF-36v2 and FRAX. The non-fractured arm was investigated in subjects with fracture and both forearms in control subjects.

Results

BMD was significantly lower at the ultradistal forearm in men with fracture compared to control subjects, in both the dominant (mean (SD): $0.386g/cm^2$ (0.049) versus $0.436g/cm^2$ (0.054), $p<0.001$) and non-dominant arm (mean (SD): $0.387g/cm^2$ (0.060) versus $0.432g/cm^2$

(0.061), p=0.001). Fracture subjects also had a significantly lower BMD at hip and spine sites compared with control subjects.

Logistic regression analysis showed that the best predictor of forearm fracture was ultradistal forearm BMD (OR=0.871 (0.805-0.943), p=0.001), with the likelihood of fracture decreasing by 12.9% for every $0.01g/cm^2$ increase in ultra-distal forearm BMD.

Conclusions

Men with low-trauma distal forearm fracture have significantly lower regional BMD at the ultradistal forearm, which contributes to an increased forearm fracture risk. They also have generalised reduction in BMD, so that low-trauma forearm fractures in men should be considered as indicator fractures for osteoporosis.

Key Words

Forearm fracture, DXA, osteoporosis, male, bone density

Introduction

Male osteoporosis is a common condition resulting in compromised bone strength and increased risk of fractures with age. For men over the age of 50 years there is a 1 in 5 lifetime risk of fracture and men account for 20-30% of all fractures [1]. Life expectancy is increasing at a higher rate for men than for women and based on these demographics an 89% increase in hip fractures has been predicted by 2025 [2]. The standardised mortality ratio for all fractures compared with age-matched healthy subjects is higher in men than women [3, 4, 5]. Despite this there has been less research into male osteoporosis compared with women and male osteoporosis continues to be both under-diagnosed and under-treated.

Factors involved in the pathogenesis of distal forearm fractures in Caucasian men are of interest because they are considered an "early and sensitive marker of skeletal fragility" [6]. Men who have had a distal forearm fracture have a 2.7 fold and 10.7 fold increased risk for hip and vertebral fractures respectively compared with age-matched men who have not fractured [7]. In retrospective studies, low areal bone mineral density (BMD) was identified at the hip and spine with up to 42% of men with this type of fracture having osteoporosis [8, 9]. One of those studies found that approximately 50% of men with fractures had secondary causes for osteoporosis such as glucocorticoid use [8]. It is possible that varying rates of bone loss at different skeletal sites may predispose to particular fracture types. It is not known if men with distal forearm fractures have reduced BMD at the distal forearm. It has been demonstrated that about 60% of distal forearm fractures occur on the left [8, 10, 11] and it is speculated that this may be due to reduced BMD in the non-dominant arm. FRAX is a well-validated tool for identifying individuals at risk of hip and other major fractures [12, 13]. FRAX has not been tested for its ability to identify men at risk of forearm fractures.

There have been no studies of forearm BMD, health parameters and FRAX in men with distal forearm fractures. To address this deficiency we have undertaken a case-control study to

further investigate these fractures in men. The aim was to test the hypothesis that men with low trauma distal fractures have lower regional BMD at the forearm compared to control subjects without fracture.

Materials and Methods

Study design and participants

This investigation is an age-matched case-control study: the pathogenesis of Male distal foRearm Fracture study or the Mr F study. Subjects were recruited from one geographical area (catchment area of The James Cook University Hospital, Middlesbrough, UK and its environs) over a period of 28 months.

All subjects were Caucasian males 50 years and older as the majority of fractures in men under 50 years of age are due to high trauma or assault [8]. Written informed consent was obtained from all participants.

Subjects with low trauma distal forearm fracture (defined as fractures of the distal radius with or without fracture of the distal ulna) were identified within six months of their fracture from hospital databases. Age-matched control subjects without fracture were identified from the patient register of collaborating GP practices, which were from rural as well as urban areas to ensure that recruited control subjects were representative of the overall population in the catchment area of the hospital.

Subjects were excluded from participation if: they were unable to provide informed consent, were already receiving treatment for osteoporosis (including calcium and vitamin D) or received it after the fracture, had known metabolic bone disease. (e.g. Paget's disease, osteomalacia, osteopetrosis, hyperparathyroidism, treated hypogonadism), malignancy or fractures due to metastatic disease. Subjects with fracture were also excluded if: the fracture

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was not united at the time of the study visit, was the result of high energy trauma, road traffic accident or assault and if they had sustained bilateral forearm fractures or other major fractures at the time of the distal forearm fracture. Control subjects were also excluded if they had a history of low trauma fracture at any location (excluding digits) or had sustained a fracture in the last six months.

Study questionnaires

All potential participants were approached by mail and asked to complete a questionnaire, which could be returned even if they decided not to take part in the main study, to allow insight into differences between participants and non-participants. The baseline questionnaire collected the following data: name, date of birth, gender, weight and height (subsequently measured using a standard scale and stadiometer when attending for DXA), hand dominance, site of fracture (where relevant), mechanism of injury, history of previous fractures, risk factors for osteoporosis including current smoking and alcohol intake, medical history and medication. BMI was calculated as weight/height^2 in kg/m^2. Participants completed the SF36v2 health survey to provide a profile of functional health and well-being scores as well as a physical and mental health summary.

The 10-year percentage risk of fracture (major and hip) was calculated using the Fracture Risk Assessment Tool (FRAX) both with and without inclusion of the lowest femoral neck BMD [13]. For subjects with fracture a 'pre-fracture' and 'post-fracture' risk were calculated. The need for treatment was then established for all participants using the National Osteoporosis Guideline Group (NOGG) clinical guideline for the management of men and women at high fracture risk in the UK [14]. Those individuals with a sufficiently high fracture risk were seen in clinic and received treatment after completing the study protocol.

Biochemical Investigations

Participants had blood taken to detect abnormalities and look for secondary causes of osteoporosis or fracture. Participants with fracture were investigated at a minimum of six months following their fracture. Where possible subjects had their blood tests evenly distributed throughout the year, but due to the seasonal variation in fracture incidence this was not always achieved. All bloods were taken between 8.15am and 9.45am with the patient fasting. Two participants did not attend for blood tests.

The laboratory investigations included: full blood count, urea & electrolytes, bone profile (including ionised and albumin adjusted calcium, albumin, inorganic phosphate and alkaline phosphatase), liver function tests, ESR, CRP, fasting blood sugar, TSH, PTH, total 25 hydroxyvitamin D (25OHD), total oestradiol, bioavailable oestradiol, total testosterone and bioavailable testosterone. Details of the assays and analysers used are given in Online Resource 1. Vitamin D levels were defined as: deficient < 25 nmol/L, insufficient 25-50 nmol/L and sufficient as > 50 nmol/L [15, 16].

Dual energy X-ray absorptiometry (DXA)

All participants underwent a DXA scan to determine BMD at the lumbar spine (L2-L4), forearm (ultra distal and distal one third of the radius) and both hips (femoral neck and total hip sites). Subjects with fracture had a scan of the non-fractured forearm at three to six months after fracture whereas control subjects had both forearms scanned at the time of recruitment. At the lumbar spine lateral views for vertebral morphometry were also undertaken to assess for vertebral fractures, using the Genant and Wu semi quantitative approach to confirm [17-19]. All BMD measurements were performed on the same DXA scanner throughout (Lunar Prodigy Advanced, GE Healthcare Lunar, Madison, Wisconsin, USA, Version 13.6). To reduce bias the same, independent radiographer carried out all DXA

measurements and stability and accuracy were monitored daily using a manufacturer-supplied phantom. The coefficient of variation (CV), measured using a local spine phantom, were a mean of 1.24% and all were less than 1.5%. All quality assurance checks were well within manufacturer's tolerances throughout the study. T-scores were derived using the manufacturer's reference ranges for males at the lumbar spine and forearm and the NHANESIII reference database at the hip sites for males 20-39 years of age. Z-scores were also determined. T-scores at the hip sites were further developed using female reference databases from NHANESIII in light of the recent recommendations to use femoral neck BMD to calculate fracture risk and determine T-scores [20]. Osteoporosis was defined as per WHO definition [21] as a T-score $\leq$ -2.5 SD below the mean for a young person with osteopenia being between > -2.5 and < -1.0 SD and normal being $\geq$ -1.

Sample size calculation

As no data on BMD at the forearm was available for men, the sample size calculation has been based on the difference in BMD at the femoral neck in men with and without distal forearm fracture. Using data from Tuck et al. [8] 50 subjects were needed in each group to detect a mean difference of $0.103 g/cm^2$ with a standard error of 0.01 and standard deviation of 0.1107 in the fracture group and 0.1169 in the control group with a power of 90% at the 5% significance level. To allow for attrition 60 participants were to be recruited to each group.

Statistical analysis

Statistical analysis was performed using a standard software package (SPSS for Mac, V21). All significance tests were two-tailed and carried out at the 5% level. Missing data were not replaced. Subject demographic details and outcome measures were summarised by fracture

and control group with quantitative variables summarised by the mean, median, standard deviation, minimum and maximum and categorical variables summarised by the number of subjects and percentage in each category. All quantitative data were tested for normality and log transformation performed if data were not normally distributed at initial testing. Data were further analysed using paired- and independent t-test for normally distributed data or Wilcoxon Rank Sum Test for non-parametric data. Pearson correlation coefficients were determined to investigate the relationship between multiple factors and BMD. Values for dominant and non-dominant forearm were calculated using data from the available forearm from the fracture group with data from all control participants.

Multiple linear regression analysis using forward selection of variables was performed to further examine the association between correlated factors and BMD at all sites. For the analysis of BMD at the ultradistal and distal third forearm sites fracture subjects had only one set of measurements available, i.e. the non-fractured arm, whereas control subjects had measurements at both forearms, i.e. right and left. To allow comparison between all participants one value had to be chosen for the control group and the lower value of either right or left forearm was selected for each forearm site and compared with the available measurement for the fracture group.

To identify factors that increased the likelihood of fracture in the study cohort, clinically relevant factors and factors where there was a significant difference between groups, based on t-tests for continuous normally distributed and Mann-Whitney-U test for continuous not normally distributed variables, were chosen. A logistic regression model was fitted with independent variables using a forward selection method (based on the likelihood ratio test). Odd ratios (OR) and confidence intervals were reported. Due to the low magnitude of the numerical values for lowest ultradistal forearm BMD when entering them in g/cm^2, a new variable was created by multiplication with 100 to present a % change per $0.01g/cm^2$.

Results

Responses

Figure 1 illustrates the numbers of subjects approached, excluded and agreeing to take part. Ultimately, 61 fracture and 59 control subjects were recruited. There was no statistically significant difference in age between subjects who took part in the study and subjects who did not take part in either the fracture or control group. Subjects who only answered the questionnaire were older than subjects who took part in the study (mean age 68.7 and 65.3 respectively, p=0.015), but there were no statistically significant differences in height, weight, health and lifestyle factors. Two participants in the fracture group did not attend for blood tests and SF36v2 completion due to difficulties of attending an early morning appointment.

Subject characteristics

There were no significant differences in mean age and anthropometric indices between the fracture and control group as shown in Table 1. There was no difference in the proportion of fracture cases and control subjects with excess alcohol consumption (> 21 units per week), current smoking, prior fragility fractures, pre-existing co-morbidities which could impact on bone health or medical conditions. There was a statistically significant difference in the physical component score of the SF36v2 between fracture and control participants (p=0.045), but no difference in the mental component score (p=0.371) at a minimum of six months following the fracture. Although most of the participants in the fracture group were right hand dominant (88.5%), subjects were almost equally likely to fracture the non-dominant or dominant arm with (52.5% vs. 47.5%, p=0.789; Online Resource 2, Table 1).

The results of the FRAX estimates of 10-year fracture risk are given in Table 2. Prior to the inclusion of lowest femoral neck BMD or fracture there was no significant difference between the two groups. This became significantly different with higher risk estimates in the fracture group once BMD or fracture or both were included in the calculation. Using FRAX calculated after inclusion of fracture and femoral neck BMD 13 participants (21%) in the fracture group compared to no participants in the control group were above NOGG treatment thresholds and would require treatment based on their fracture risk.

Blood results

The results of biochemical and haematological laboratory investigations are shown in Table 2 of Online Resource 2. The only significant difference between the two groups was that the mean serum 25OHD concentration was higher in the fracture group compared with the control group (66.9 nmol/l vs. 53.0 nmol/l, p=0.003). This difference lost significance once adjustment for season in which the blood samples were taken had been made. There was no statistically significant difference between the groups when comparing vitamin D status (sufficient, insufficient, deficient) (X^2=3.512, N=118, p=0.173). Of note, there was no significant difference between the groups in PTH, renal function, alkaline phosphatase, adjusted calcium, oestradiol or testosterone.

Bone Mineral Density

There was significantly lower BMD at all sites in the fracture group compared with the control group except at non-dominant distal 1/3 forearm and the distal 1/3 forearm (Table 3). Notably, there was significantly lower BMD at the ultradistal forearm (both dominant and non-dominant arm) and distal 1/3 forearm (dominant arm only) in the fracture subjects compared with control subjects. Interestingly, there was no difference in BMD between the

dominant and non-dominant forearm in the control subjects at the ultradistal radius (p=0.304) and the distal 1/3 radius (p=0.080). At those sites where BMD was significantly lower the percentage reduction in the fracture group compared with controls varied between 5.1% and 11.5%, with greatest reduction being seen at the ultradistal forearm sites. As a result of the lower BMD the T- and Z-scores of these men (using male normative data) were significantly lower in the fracture subjects versus the control subjects as shown in Table 3 of Online Resource 2.

Using male normative data 11.5% per cent were found to be osteoporotic at the lumbar spine or hip sites in the fracture group and 5.1% in the control group (Fisher's Exact, p=0.324). This rises to 13.1% and 5.1% respectively if forearm sites are included (X^2=2.236, N=119, p=0.206). At the femoral neck alone these figures are 11.5% and 3.4% (Fisher's Exact, p=0.164). These differences were not statistically significant.

Using female reference data at the femoral neck to define osteoporosis [20] reduces the proportion of osteoporotic participants to just 3.3% in the fracture group and zero in the control group.

BMD at multiple sites was found to associate with: age, height and weight; adjusted calcium with the dominant ultradistal and both dominant and non-dominant distal 1/3 forearm, bioavailable oestradiol with the non-dominant ultradistal forearm, total oestradiol with the distal 1/3 forearm and finally TSH with the hip sites (Online Resource 2, Table 4). The observed differences in BMD between the two groups persisted at all sites after making adjustments for these factors.

Predictors of likelihood of fracture

The following clinically relevant variables that were found to be statistically significantly different between the fracture and control group (Table 1, Online Resource 2 Table 2) were

entered into a logistic regression analysis: Vitamin D, lumbar spine BMD, right femoral neck BMD, left femoral neck BMD, right total hip BMD, left total hip BMD, ultradistal and distal 1/3 forearm BMD. Vitamin D was adjusted for seasons and adjusted values entered into the regression model. Only ultradistal forearm BMD remained as a significant variable in the final model. The regression analysis (Table 4) shows that the likelihood of fracture was decreased by 12.9% for every $0.01 g/cm^2$ increase in ultradistal BMD.

Predictors of BMD

In order to determine the best predictors of BMD in all subjects, linear regression models were fitted with independent variables selected by forward selection for each individual site. Age, height and weight were seen as potentially predictive at all sites and were entered in all models. Further significantly correlated factors relevant to each site (Online Resource 2, Table 4) were added into the model relevant for the individual sites (Table 5).

The best fitting model at the lumbar spine BMD accounted for 5.5% of the variation and incorporated height and total oestradiol. For the right femoral neck the model included weight and TSH and explained 8.9% of the variation, whereas at the left femoral neck 13.8% was accounted for by a model incorporating age and height. At both total hip sites only weight was predictive producing model that explained 5.8% of the right and 5.2% of the left BMD. At the ultradistal forearm the best model used bioavailable oestradiol and adjusted calcium to predict 7.8% of BMD and at the distal one third this was height, age and adjusted calcium to account for 23.7% of the variance.

Discussion

This is the first study to examine forearm BMD in men with distal forearm fracture, finding significantly lower BMD in fracture subjects at the ultradistal and distal 1/3 of the non-

fractured forearm compared with the forearm BMD in control subjects. Regression analysis also showed that the likelihood of fracture decreases as BMD at this site increases. These findings are consistent with the study hypothesis and emphasise the importance of regional BMD in the pathogenesis if these fractures. Similar findings were reported in a study by Farr et al. [22], which showed that already in childhood and adolescence boys with low-trauma distal forearm fracture had skeletal deficits compared to control subjects.

As in previous studies BMD was also significantly lower at all sites at the hip and spine or the heel compared with age and gender matched control subjects [8, 9, 23, 24]. The significantly lower areal BMD persisted after adjustment for confounders. This suggests a higher future fracture risk at all sites, which Cuddihy et al. [7] confirmed with a 2.7 fold and 10.7 fold increased risk for hip and vertebral fractures respectively after a distal forearm fracture compared with age-matched men. Lower femoral neck BMD has also been identified as a risk factor for wrist fractures in an epidemiological study by Nguyen et al [25].

The greatest percentage reduction in BMD compared with controls was at the ultradistal site, which has previously only been observed in women with forearm fractures [26]. In men with vertebral fractures and hip fractures the greatest percentage reduction in BMD was observed at the lumbar spine and hip sites respectively [27, 28] and lumbar spine and hip BMD were the best predictors for fractures at these sites [28, 29]. This suggests that an element of regional bone loss may be contributing to the site of fracture occurrence. Furthermore, in control subjects there was no difference in BMD between the dominant and non-dominant forearm. This might explain why the men were equally likely to fracture the dominant or non-dominant forearm. By contrast, in women, lower BMD has been reported in the non-dominant forearm [30-32] and this difference has been hypothesised to explain why women are more likely to fracture the non-dominant arm.

Using male normative data the proportion of men with osteoporosis in at least one site (lumbar spine, femoral neck or total hip) was 11.5%, which rises to 13.1% if the forearms are included. This is much lower than the 42% seen previously by Tuck et al. [8] and the 23.3% found by Egund et al. in men over 65 years [9]. In the current study participants had very few medical problems or secondary causes (Table 1) and there were no differences between the groups. In contrast, Tuck et al. [8] and Egund et al. [9] found that up to 51% of subjects with forearm fractures and up to 37% of control subjects had secondary causes. Tuck et al. further reported a higher incidence of previous adult low trauma fracture with 47% in the fracture and 45% in the control group compared to 11.5% and 3.4% in our study cohort [8].

Overall predictors of BMD varied with different sites and included: age, height, weight, adjusted calcium, TSH and oestradiol. This is consistent with previously published studies [8, 27, 28]. The association between BMD and TSH has had conflicting results [33, 34], although Grimes et al. [33] found that men with very low TSH had low forearm BMD and argued that TSH may have bone protective properties. In the present study the strongest predictors of forearm BMD were bioavailable oestradiol and adjusted calcium for the ultradistal forearm and age, height and adjusted calcium for the distal 1/3 forearm. There was no association with TSH.

Interestingly, in our study population there was no difference in 10-year predicted fracture risk as calculated by FRAX until BMD and/or the fracture were included. It would therefore have not been possible to identify these male subjects as at risk prior to fracture during routine screening. FRAX is well validated for predicting major and hip fractures in both genders [35-39], but major fractures are all grouped together [12, 13] as there were too few fractures of any one type to develop an algorithm for them individually. The European Osteoporosis Study looked at Colle's fractures separately, but was unable to find any predictors for forearm fractures in men [39].

The strengths of the study are that the cohorts are very clearly defined by stringent inclusion criteria and there are very few confounders that could affect the outcomes. Subjects in fracture and control group were well and there are very few differences between the groups identified by questionnaire or blood tests. Study investigations have been carried out by the same individuals throughout the study, ensuring consistent data collection with accurate timing of follow-up assessments and taking of blood samples.

A limitation of this study is its small sample size with only 59 fracture subjects. A larger study may identify further important factors in the pathogenesis of these fractures in men. However, the study was adequately powered to detect the observed differences in BMD and included more participants than other published comparative studies [23, 24].

case-control design, which introduces potential recall bias from participants. Also only 58% of eligible participants in the fracture and 61% in the control group agreed to take part in the study, resulting in possible selection bias. The most common reasons for not wishing to take part in the study were a lack of interest in research, inability to attend study appointments (particularly for subjects in work), travel distance to the appointment and the belief that the study did not apply to them. However, comparing data from participating subjects and subjects who only provided questionnaire data revealed no significant differences.

Prior fragility fracture was an exclusion criterion for control but not fracture subjects, which could have potentially accentuated differences between the two groups. However, there were only 7 prior fragility fractures identified in the fracture group and 2 in the controls, a difference that was not statistically significant. Furthermore, the FRAX risk estimates were not significantly different between the two groups until BMD and/ or forearm fracture were added. It therefore seems unlikely that such a bias occurred.

Participants in the fracture group may have altered their activity levels and use of the injured hand, which could have affected regional BMD. The lower score in the physical domain of

SF36v2, even though not clinically significant, could be an indicator of this. However, the non-fractured forearm was scanned, which may on the contrary have been used more to compensate for the loss of function in the fractured arm. In addition there was no difference between groups in the activity level captured during their falls risk assessment. BMD changes also occur slowly, so that BMD measurement three to six months after fracture are unlikely to detect a significant reduction in BMD given the relatively minor nature of the fracture.

This study is the first to demonstrate significantly lower BMD at the forearm in fracture subjects compared with controls. The greatest percentage reduction in BMD compared with control subjects was at the ultradistal forearm and the best predictor of forearm fracture was ultradistal forearm BMD. FRAX could not identify these men at risk until they had fractured or had BMD measured so further factors may need to be found if these men are to be identified prior to fracture. We suggest that all men with low trauma distal forearm fractures should be considered at risk of osteoporosis and further fractures. Further work is required to understand their pathogenesis.

Statement of Human Rights

The study has been approved by the National Research Ethics Committee North East, UK (REC reference 10/H0908/15) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

References

[1] van Staa TP, Dennison EM, Leufkens HG, Cooper C. (2001) Epidemiology of fractures in England and Wales. Bone 29(6):517-522. doi: 10.1016/s8756-3282(01)00614-7

[2] Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA (1999) Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353(9156):878-882. doi: 10.1016/s0140-6736(98)09075-8

[3] Morin S, Lix LM, Azimaee M, Metge C, Caetano P, Leslie WD (2011) Mortality rates after incident non-traumatic fractures in older men and women. Osteoporos Int 22(9):2439-2448. doi: 10.1007/s00198-010-1480-2

[4] Wehren LE, Hawkes WG, Orwig DL, Hebel JR, Zimmerman SI, Magaziner (2003) Gender differences in mortality after hip fracture: the role of infection. J Bone Miner Res 18(12):2231-2237. doi: 10.1359/jbmr.2003.18.12.2231

[5] Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture (2010) National analysis of comedications, comorbidity and survival. Age Ageing 39(2):203-209. doi: 10.1093/ageing/afp221

[6] Haentjens P, Johnell O, Kanis JA et al (2004) Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men. J Bone Miner Res 19(12):1933-1944. doi: 10.1359/jbmr.040917

[7] Cuddihy MT, Gabriel SE, Crowson CS, O'Fallon WM, Melton LJ,3rd (1999) Forearm fractures as predictors of subsequent osteoporotic fractures. Osteoporos Int 9(6):469-475. doi: 10.1007/s001980050172

[8] Tuck SP, Raj N, Summers GD (2002) Is distal forearm fracture in men due to osteoporosis? Osteoporos Int 13(8):630-636. doi: 10.1007/s001980200085

[9] Egund L, McGuigan F, Önnby, K, Giwercman A, Akesson K (2016) High prevalence of osteoporosis in men with distal radius fracture: A cross-sectional study of 233 men. Calcif Tissue Int 99(3):250-258. doi: 10.1007/s00223-016-0142-6

[10] O'Neill TW, Cooper C, Finn JD et al (2001) Incidence of distal forearm fracture in British men and women. Osteoporos Int 12(7):555-558. doi: 10.1007/s001980170076

[11] Lindau TR, Aspenberg P, Arner M, Redlundh-Johnell I, Hagberg L (1999) Fractures of the distal forearm in young adults. An epidemiologic description of 341 patients. Acta Orthop Scand 70(2):124-128. doi: 17453679909011248

[12] Kanis,J A. on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report.

[13] World Health Organisation Collaborating Centre for Metabolic Bone Disease, University of Sheffield, UK. FRAX - WHO Fracture Risk Assessment Tool. http://www.shef.ac.uk/FRAX/. Accessed 24th September 2016.

[14] Compston J, Cooper A, Cooper C et al (2009) Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 62(2):105-108. doi: 10.1016/j.maturitas.2008.11.022

[15] Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications (2001) Endocr Rev 22(4):477-501. doi: 10.1210/er.22.4.477

[16] National Institute for Health and Care Excellence (2014) Vitamin D: increasing supplement use in at risk-groups. https://www.nice.org.uk/guidance/ph56?unlid=7843398020162310553. Accessed 23rd September 2016.

[17] Fuerst T, Wu C, Genant HK et al (2009) Evaluation of vertebral fracture assessment by dual X-ray absorptiometry in a multicenter setting. Osteoporos Int 20(7):1199-1205. doi: s00198-008-0806-9

[18] Wu C, van Kuijk C, Li J et al (2000) Comparison of digitized images with original radiography for semiquantitative assessment of osteoporotic fractures. Osteoporos Int 11(1):25-30. doi: 10.1007/s001980050002

[19] Genant HK, Jergas M (2003) Assessment of prevalent and incident vertebral fractures in osteoporosis research. Osteoporos Int 14 Suppl 3:S43-55. doi: 10.1007/s00198-002-1348-1

[20] Schousboe JT, Shepherd JA, Bilezikian JP, Baim S (2013) Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom 16(4):455-466. doi: 10.1016/j.jocd.2013.08.004

[21] World Health Organisatio (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. WHO Technical Report Series, No.843.

[22] Farr JN, Amin S, Melton LJ 3rd, Kirmani S et al (2014) Bone strength and structural deficit in children and adolescents with a distal forearm fracture resulting from mild trauma. J Bone Mineral Res 29(3):590-599. doi: 10.1002/jbmr.2071

[23] Oyen J, Rohde G, Hochberg M, Johnsen V, Haugeberg G (2011) Low bone mineral density is a significant risk factor for low-energy distal radius fractures in middle-aged and elderly men: a case control stud. BMC Musculoskelet Disord 12:67. doi: 10.1186/1471-2474-12-67

[24] Risto O, Hammar E, Hammar K, et al (2012) Elderly men with a history of distal radius fracture have significantly lower calcaneal bone density and free androgen index than age-matched controls. Aging Male 15(1): 59-62. doi: 10.3109/13685538.2011.593659

[25] Nguyen TV, Centre JR, Sambrook PN, Eisman JA (2001) Risk factors for proximal humerus, forearm, and wrist fractures in elderly men and women: the Dubbo Osteoporosis Epidemiology Study. Am J Epidemiol 153(6):587-595. No doi available.

[26] Kanterewicz E, Yanez A, Perez-Pons A, Codony I, Del Rio L, Diez-Perez A (2002) Association between Colles' fracture and low bone mass: age-based differences in postmenopausal women. Osteoporos Int 13(10):824-828. doi: 10.1007/s001980200114

[27] Scane AC, Francis RM, Sutcliffe AM, Francis MJ, Rawlings DJ, Chapple CL (1999) Case-control study of the pathogenesis and sequelae of symptomatic vertebral fractures in men. Osteoporos Int 9(1):91-97. doi: 10.1007/s001980050120

[28] Pande I, O'Neill TW, Pritchard C, Scott DL, Woolf AD (2000) Bone mineral density, hip axis length and risk of hip fracture in men: results from the Cornwall Hip Fracture Study. Osteoporos Int 11(10):866-870. doi: 10.1007/s001980070046

[29] Tuck SP, Scane AC, Fraser WD, Diver MJ, Eastell R, Francis RM (2008) Sex steroids and bone turnover markers in men with symptomatic vertebral fractures. Bone 43(6):999-1005. doi: 10.1016/j.bone.2008.08.123

[30] Borg J, Mollgaard A, Riis BJ (1995) Single X-ray absorptiometry: performance characteristics and comparison with single photon absorptiometry. Osteoporos Int 5(5):377-381. doi: 10.1007/bf01622260

[31] Taaffe DR, Lewis B, Marcus R (1994) Quantifying the effect of hand preference on upper limb bone mineral and soft tissue composition in young and elderly women by dual-energy X-ray absorptiometry. Clin Physiol 14(4):393-404. doi: 10.1111/j.1475-097x.1994.tb00398.x

[32] Walters J, Koo WW, Bush A, Hammami M (1998) Effect of hand dominance on bone mass measurement in sedentary individuals. J Clin Densitom 1(4):359-367. doi: 10.1385/jcd:1:4:359

[33] Grimnes G, Emaus N, Joakimsen RM, Figenschau Y, Jorde R (2008) The relationship between serum TSH and bone mineral density in men and postmenopausal women: the Tromso study. Thyroid 18(11):1147-1155. doi: 10.1089/thy.2008.0158

[34] Abe E, Marians RC, Yu W et al (2003) TSH is a negative regulator of skeletal remodelling. Cell 115(2):151-156. doi: 10.1016/s0092-8674(03)00771-2

[35] Ettinger B, Ensrud KE, Blackwell T et al (2013) Performance of FRAX in a cohort of community-dwelling, ambulatory older men: the Osteoporotic Fractures in Men (MrOS) study. Osteoporos Int 24(4):1185-1193. doi: 10.1007/s00198-012-2215-3

[36] Leslie WD, Berger C, Langsetmo L et al (2011) Construction and validation of a simplified fracture risk assessment tool for Canadian women and men: results from the CaMos and Manitoba cohorts. Osteoporos Int 22(6):1873-1883. doi: 10.1007/s00198-010-1445-5

[37] Leslie WD, Lix LM, Langsetmo L et al (2011) Construction of a FRAX(R) model for the assessment of fracture probability in Canada and implications for treatment. Osteoporos Int 22(3):817-827. doi: 10.1007/s00198-010-1464-2

[38] Schousboe JT, Vo T, Taylor BC et al (2016). Prediction of Incident Major Osteoporotic and Hip Fractures by Trabecular Bone Score (TBS) and Prevalent Radiographic Vertebral Fracture in Older Men. J Bone Miner Res 31(3):690-697. doi: 10.1002/jbmr.2713

[39] Silman AJ (2003) Risk factors for Colles' fracture in men and women: results from the European Prospective Osteoporosis Study. Osteoporos Int 14(3):213-218. doi: 10.1007/s00198-002-1364-1

References remove

[28] Kanis JA, Bianchi G, Bilezikian JP et al (2011) Towards a diagnostic and therapeutic consensus in male osteoporosis. Osteoporos Int 22(11):2789-2798. doi: 10.1007/s00198-011-1632-z

[29] De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA (1997) Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ 315(7102):221-225. doi: 10.1136/bmj.315.7102.221

[30] Ensrud KE, Taylor BC, Peters KW et al (2014) Implications of expanding indications for drug treatment to prevent fracture in older men in United States: cross sectional and longitudinal analysis of prospective cohort study. BMJ 349:g4120. doi: 10.1136/bmj.g4120

Figures

Figure 1: Flow Chart Participant Recruitment

Online Resource 1

Does regional loss of bone density explain low trauma distal forearm fractures in men (The Mr F study)?

Osteoporosis International

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Online Resource 1

Supplementary Material: Details of laboratory assays

U&E, bone profile, LFT, CRP and glucose were analysed on the Siemens automated Advia analysers (either Advia2400 or 1800) – Siemens Healthcare Diagnostics Inc. Sir William Siemens Sq. Frimley, Camberley UK. Intact parathyroid hormone (PTH) was measured in EDTA plasma on the Roche E411 analyser (Roche Diagnostics, Lewes, UK). The assay employs a Sandwich principle electro-chemiluminescence immunoassay (ECLIA). FBC (Full Blood Count) was measured using a Siemens Advia 120 analyser (Siemens Healthcare Diagnostics Inc. Sir William Siemens Sq. Frimley, Camberley UK) in EDTA whole blood. The ESR was measured in EDTA whole blood on the Starrsed Compact ESR analyser. This produces a true Westergren ESR result and therefore conforms to the recommendations of the International Council for Standardisation in Haematology (ICSH). The StaRRsed Compact ESR analyser is a fully automated analyser for the haematology laboratory made by Mechatronics Manufacturing BV in the Netherlands and marketed in the UK by: Vitech Scientific Ltd Huffwood Trading Estate Partridge Green West Sussex RH13 8AU. Total serum 25OHD was measured on an IDS-iSYS automated analyser (Immuno-Diagnostic Systems, Bolden, UK).

Oestradiol (E2) was measured by electro-chemiluminescence immunoassay (ECLIA) on the automated COBAS e601 system (Roche Diagnostics, Mannheim, Germany). The inter-assay CV was ≤1.5% between 18.4-15781 pmol/L with lower detection limit of 18.4 pmol/L. Testosterone measurement was carried out via LC-MS/MS analysis using a SCIEX API4000 mass spectrometry instrument coupled to an atmospheric pressure chemical ionization (APCI) source (Warrington, UK) with a Shimadzu Prominence UFLC XR LC-20AD HPLC system (Duisburg, Germany). The LC-MS/MS raw data were processed using Analyst software (version 1.5.1, SCIEX).

Online Resource 1

Bioavailable oestradiol (Bio-E2) and testosterone (Bio-T) were measured indirectly using a radioimmunoassay. Samples (400µL) were stripped of all steroids using activated charcoal (400µL of a 5% solution in phosphate buffer 1M pH 7.4). Charcoal stripped serum (200µL) was added to nitrogen-dried tritiated ^{3}H-testosterone or ^{3}H-oestradiol (20,000Dpm/50µL, Perkin-Elmer, Beaconsfield, UK) and incubated for 2hr at 37°C to allow binding with SHBG. The SHBG-bound ^{3}H-testosterone or ^{3}H-oestradiol were then precipitated using 200 µL of an ice-cold saturated solution of ammonium sulphate. A control tube (blank) containing 200 µL NaCl 0.9% was treated with each tritiated standard. The precipitated samples and controls were centrifuged at 4°C for 20 minutes at 3,500 x g. 200 µL of the supernatant containing the non-SHBG bound ^{3}H-testosterone or ^{3}H-oestradiol fractions were transferred to a scintillation vial. 3mL of scintillation liquid (OptiPhase, HiSafe-3, Perkin-Elmer) was added to each tube. Beta radiation activity was measured on a Hidex 300SL automatic scintillation counter (Turku, Finland) for 2 minutes per tube. The radioactivity ratio of the SHBG-unbound/bound fractions were expressed in percentage using the equation:

$$\%Bio - T \ (or \ E2) = \frac{average(sample \ counts)}{blank \ (NaCl \ control)} * 100$$

Concentrations of bioavailable testosterone and bioavailable oestradiol were given in nmol/L using $Bio - T(or \ E2) = total(T \ or \ E2) * \%Bio - T \ (or \ E2)$

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Supplementary Table 1: Site of forearm fracture by hand dominance.

	Right hand dominant	Left hand dominant	
Fracture dominant FA	23 (37.7%)	6 (9.3%)	29 (47.5%)
Fracture non-dominant FA	31 (50.8%)	1 (1.6%)	32 (52.5%)
	54 (88.5%)	7 (11.5%)	61 (100%)

FA=forearm

Supplementary Table 2: Blood results and male reference ranges over 50 years.

Investigation (reference range)	Fracture (n=61)	Control (n=59)	p-value
Hb g/L (13.0-18.0)	14.49 (1.17)	14.71 (1.13)	0.316+
WBC x10⁹/L (4-11)	6.10 (1.76)	5.69 (1.35)	0.164+
Platelets x10⁹/L (150-400)	254.41 (75.98)	237.00 (66.47)	0.188+
ESR mm/hr (2-10)	7.48 (10.33)	8.33 (16.60)	0.883*
Sodium mmol/L (133-146)	140.41 (1.67)	139.66 (2.04)	0.032+
Potassium mom/L (3.5-5.3)	4.21 (0.32)	4.28 (0.21)	0.128+
Creatinine µmol/L (50-120)	86.69 (12.85)	84.90 (14.08)	0.410*
Bilirubin µmol/L (0-21)	11.80 (5.52)	13.19 (4.77)	0.146+
Protein g/L (60-80)	71.39 (4.50)	71.95 (4.68)	0.509+
Albumin g/L (35-50)	43.81 (2.61)	43.39 (2.41)	0.362+
ALP U/L (30-130)	75.73 (19.31)	72.54 (16.38)	0.336+
ALT U/L (1-40)	27.39 (11.54)	26.16 (12.14)	0.412*
GGT U/L (0-70)	36.32 (29.74)	33.98 (23.59)	0.579*
Phosphate mmol/L (0.8-1.5)	1.01 (0.12)	1.00 (0.13)	0.647+
Adjusted calcium mmol/L (2.2-2.6)	2.32 (0.09)	2.32 (0.08)	0.700+
Glucose mmol/L (2.2-6.0)	5.59 (1.01)	5.59 (1.18)	0.967&
TSH mU/L (0.27-4.2)	2.05 (1.18)	2.06 (0.99)	0.524*
PTH ng/L (12-72)	48.37 (18.00)	51.13 (21.41)	0.776*
Vitamin D (nmol/L)	66.88 (27.58)	53.00 (21.27)	0.003+
Vitamin D seasonally adjusted	1.06 (0.41)	0.94 (0.38)	0.091+
Oestradiol (pmol/L)	98.34 (28.25)	105.28 (30.24)	0.202+
Bio-Oestradiol (pmol/L)	18.85 (7.30)	17.87 (5.46)	0.411+
Testosterone (nmol/L)	15.00 (5.19)	16.67 (5.33)	0.089+
Bio-Testosterone (nmol/L)	2.66 (0.98)	2.58 (0.91)	0.677+

Blood investigations - mean and SD; + t-test; * t-test on log-transformed data; & Mann-Whitney U Test

Supplementary Table 3: Comparison of T- and Z-Scores – mean and SD.

Site		Fracture	Control	p-Value
AP Spine L2-4	T-score Z-score	-0.389 (1.467) -0.097 (1.408)	0.289 (1.731) 0.620 (1.862)	0.023 0.019
Right femoral neck	T-score Z-score	-1.241 (0.878) -0.262 (0.749)	-0.766 (0.948) 0.253 (0.944)	0.006 0.001
Left femoral neck	T-score Z-score	-1.368 (1.009) -0.395 (0.866)	-0.840 (1.060) 0.197 (1.021)	0.006 0.001
Right total femur	T-score Z-score	-0.826 (0.960) -0.184 (0.841)	-0.262 (0.981) 0.424 (1.037)	0.002 0.001
Left total femur	T-score Z-score	-1.162 (0.994) -0.261 (0.911)	-0.309 (1.018) 0.374 (1.002)	0.002 <0.001
Dominant ultradistal FA	T-score Z-score	-0.916 (1.205) -0.258 (1.200)	0.297 (1.315) 0.953 (1.348)	<0.001 <0.001
Nondominant ultradistal FA	T-score Z-score	-0.900 (1.442) -0.400 (1.437)	0.195 (1.477) 0.866 (1.470)	0.001 0.004
Dominant distal 1/3 FA	T-score Z-score	-0.794 (0.826) -0.126 (0.784)	-0.305 (0.808) 0.371 (0.755)	0.008 <0.001
Nondominant distal 1/3 FA	T-score Z-score	-0.703 (0.785) -0.193 (0.761)	-0.417 (0.760) 0.261 (0.738)	0.100 0.008

FA=forearm

Reference population for lumbar spine and forearm sites: manufacturer's reference ranges for males

Reference population for hip sites: NHANES III reference for males 20-39 years of age

Supplementary Table 4: Correlation between BMD and clinically relevant variables.

BMD	Age	Height	Weight	Crea	adjCa	TSH	PTH	VitD	E2	Bio-E2	T	Bio-T
L24	**0.196** p=**0.032**	0.134 p=0.143	0.124 p=0.176	0.158 p=0.087	-0.025 p=0.789	0.059 p=0.523	0.040 p=0.668	-0.082 p=0.377	**0.190** p=**0.040**	0.095 p=0.306	-0.08 p=0.932	-0.043 p=0.648
RFN	**-0.197** p=**0.034**	**0.251** p=**0.007**	**0.269** p=**0.004**	0.065 p=0.492	-0.112 p=0.236	**0.223** p=**0.017**	-0.054 p=0.571	0.051 p=0.595	0.080 p=0.398	0.081 p=0.392	0.006 p=0.945	0.071 p=0.452
LFN	**-0.325** p<**0.001**	**0.290** p=**0.001**	**0.247** p=**0.007**	0.011 p=0.904	-0.124 p=0.184	**0.202** p=**0.030**	-0.031 p=0.740	0.002 p=0.983	0.017 p=0.854	0.056 p=0.550	-0.017 p=0.859	0.082 p=0.383
RTH	-0.112 p=0.232	0.111 p=0.237	**0.257** p=**0.005**	0.097 p=0.303	-0.146 p=0.121	**0.195** p=**0.038**	-0.019 p=0.840	-0.003 p=0.975	0.113 p=0.233	0.146 p=0.122	-0.061 p=0.516	0.000 p=0.997
LTH	**-0.195** p=**0.034**	**0.185** p=**0.045**	**0.246** p=**0.007**	0.051 p=0.589	-0.143 0.126	**0.193** p=**0.037**	-0.004 p=0.969	0.014 p=0.882	0.081 p=0.390	0.115 p=0.221	-0.022 p=0.813	0.072 p=0.441
DUDFA	-0.076 p=0.478	0.154 p=0.148	0.173 p=0.103	-0.026 p=0.810	**-0.228** p=**0.032**	0.120 p=0.263	0.027 p=0.799	-0.078 p=0.469	0.066 p=0.542	0.134 p=0.214	0.091 p=0.398	0.167 p=0.119
NDUDFA	-0.032 p=0.766	-0.001 p=0.993	0.150 p=0.161	-0.066 p=0.540	-0.160 p=0.137	0.026 p=0.811	-0.104 p=0.337	0.041 p=0.707	0.142 p=0.189	**0.285** p=**0.007**	-0.066 p=0.539	-0.011 p=0.918
D33FA	**-0.307** p=**0.003**	**0.401** p=**0.003**	**0.309** p=**0.003**	0.014 p=0.897	**-0.250** p=**0.018**	0.073 p=0.496	-0.021 p=0.843	-0.097 p=0.367	**-0.270** p=**0.011**	-0.047 p=0.661	-0.122 p=0.256	0.048 p=0.655
ND33FA	**-0.225** p=**0.035**	**0.377** p<**0.001**	**0.256** p=**0.016**	0.011 p=0.920	**-0.234** p=**0.029**	0.082 p=0.449	-0.139 p=0.200	0.164 p=0.131	-0.128 0.241	0.065 p=0.555	-0.061 p=0.574	-0.057 p=0.602
FAUD	-0.074 p=0.420	0.086 p=0.249	**0.209** p=**0.022**	-0.075 p=0.417	-0.176 p=0.057	0.075 p=0.421	-0.053 p=0.570	0.018 p=0.845	0.112 p=0.228	**0.236** p=**0.010**	-0.019 p=0.842	0.056 p=0.545
FA33	**-0.302** p=**0.001**	**0.400** p<**0.001**	**0.319** p<**0.001**	0.016 p=0.863	**-0.247** p=**0.007**	0.131 p=0.161	-0.084 p=0.367	0.108 p=0.248	**-0.184** p=**0.047**	0.030 p=0.748	-0.103 p=0.265	0.019 p=0.841

Pearson Correlation coefficient; L24=lumbar spine L2-4, RFN=right femoral neck, LFN=left femoral neck, RTH=right total femur, LTH=left total femur, DUDFA=dominant ultradistal forearm, NDUDFA=non-dominant ultradistal forearm, D33FA=dominant distal 1/3 forearm, ND33FA=non-dominant distal 1/3 forearm, FAUD= ultradistal forearm, FA33= distal 1/3 forearm, Crea=Creatinine, adjCa=adjusted Calcium, TSH=thyroid stimulating hormone, PTH=parathyroid hormone, VitD= 25 hydroxyvitamin D, E2=Oestradiol, Bio-E2=bioavailable Oestradiol, T=Testosterone, Bio-T=bioavailable Testosterone

Online Resource 2